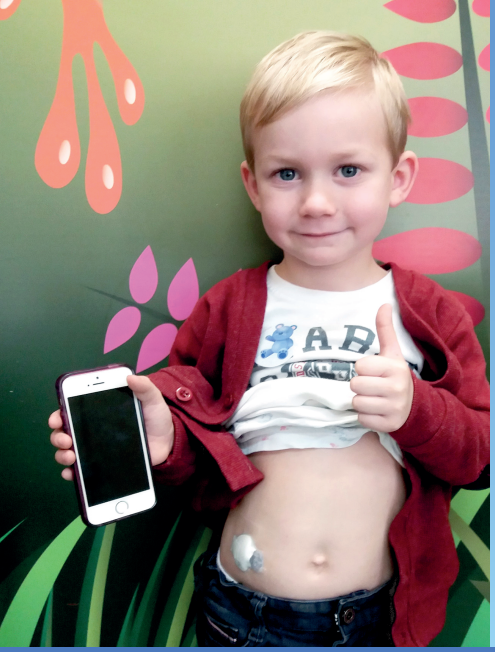

PEDIATRIC ENDOCRINOLOGY AND DIABETES

2018 UPDATE

Editors:

Iulian P. VELEA
Corina PAUL
Stuart J. BRINK

EDITURA MIRTON

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ENDOCRINOLOGY AND DIABETES
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Authors: Iulian P. VELEA,
Corina PAUL,
Stuart J. BRINK

Descrierea CIP a Bibliotecii Naţionale a României
Pediatric endocrinology and diabetes 2018 update /
ed.: Iulian P. Velea, Corina Paul, Stuart J. Brink.
- Timişoara : Mirton, 2018

ISBN 978-973-52-1799-0

I. Velea, Iulian (ed.)
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Stuart J. BRINK

Editura Mirton
Timişoara
2018

Contributors:

Stuart J. BRINK, MD
Senior Endocrinologist, New England Diabetes and Endocrinology Center (NEDEC), Waltham MA, USA
Associate Clinical Professor of Pediatrics, Tufts University School of Medicine, and Clinical Instructor, Harvard Medical School, Boston, MA, USA

Cristina CĂPĂȚÂNĂ, MD, PhD
Assistant Professor "Carol Davila" University of Medicine and Pharmacy, Endocrinology Department, Bucharest, Romania
Senior Endocrinologist "C.I. Parhon" National Institute of Endocrinology,

Andra CARAGHEORGHEOPOL PhD
Principal Chemist, Doctor in Chemistry
Principal Scientific Researcher,"C.I. Parhon" National Institute of Endocrinology, Bucharest, Romania

Agata CHOBOT
Clinical Hospital No 1 in Zabrze, Poland
Grazyna Deja Dept. of Children's Diabetology, Medical University of Silesia, Katowice, Poland

Przemysława JAROSZ-CHOBOT MD, PhD
Head of Department of Children's Diabetology and Pediatrics
School of Medicine in Katowice, Medical University of Silesia
The Independent Public Clinical Hospital no.6 of the Medical University of Silesian in Katowice, John Paul II Upper Silesian Child Health Centre, Katowice, Poland

Vasilie CIUBOTARU, MD, PhD
"Bagdasar Arseni" Clinical and Emergency Hospital, Neurosurgery Department, Bucharest, Romania

Anda DUMITRAȘCU, MD, PhD
Assistant Professor, Department of Imagery & Radiology, C.I. Parhon National Institute of Endocrinology, Bucharest, Romania.

Wojciech FENDLER
Department of Biostatishics and Translational Medicine, Medical University of Lodz, Poland

Iuliana GHERLAN
Assistant Professor "Carol Davila" University of Medicine and Pharmacy, Endocrinology Department, Bucharest, Romania
Senior Endocrinologist "CI Parhon" National Institute of Endocrinology, Bucharest, Romania

Maia KONSTANTINOVA, MD, PhD
Professor, Leader of the Diabetic department in the University Pediatric Hospital – Sofia (Bulgaria)
President of the Bulgarian National Society of Pediatric Endocrinology

Mihai D. NICULESCU, MD, PhD
Founder & CEO, Advanced Nutrigenomics, Hillsborough, USA
Research Associate Professor, The "Victor Babes" University of Medicine and Pharmacy, Timişoara, Romania

Corina PAUL, MD, PhD
Lecturer, Department of Pediatrics, "Victor Babeş" University of Medicine and Pharmacy Timişoara.
Senior Pediatrician, Specialist Endocrinology, Clinic II Pediatrics, "Pius Branzeu" Clinical County Hospital, Timisoara, Romania

Catalina POIANĂ, MD,PhD,
Professor in Endocrinology "Carol Davila" University of Medicine and Pharmacy, Endocrinology Department, Bucharest, Romania
Senior Endocrinologist "CI Parhon" National Institute of Endocrinology, Bucharest, Romania

Joanna POLAŃSKA
Data Mining Division, The Silesian University of Technology, Gliwice, Poland

Camelia PROCOPIUC, MD, PhD
Senior Endocrinologist "CI Parhon" National Institute of Endocrinology, Bucharest, Romania

Eliza SKAŁA
Dept. of Children's Diabetology, Medical University of Silesia, Katowice, Poland

Dana STOIAN, MD, PhD,
Associate Professor, Department of Obstetrics-Gynecology, "Victor Babeş", University of Medicine and Pharmacy Timisoara, Romania,
Consultant endocrinologist, "Pius Branzeu" Clinical County Hospital, Timisoara,

Iulian P. VELEA, MD, PhD
Professor of Pediatrics
"Victor Babeş" University of Medicine and Pharmacy Timişoara.
Senior Pediatrician at Clinic II Pediatrics, "Pius Branzeu" Clinical County Hospital Timisoara, Romania

Mădălina VINTILĂ, MD, PhD
Assistant Professor "Carol Davila" University of Medicine and Pharmacy, Endocrinology Department, Bucharest, Romania
Endocrinologist "CI Parhon" National Institute of Endocrinology, Bucharest, Romania

Preface

The increasing prevalence of endocrino-metabolic diseases, as well as their impact on the health of the population from the very early age, requires the training of pediatricians in endocrinology and pediatric diabetes.

Pediatric endocrinology is, unfortunately, not a recognized medical specialty in our country as it is in most of the developed country.

That is why, the diabetes and endocrinological diseases of children and adolescents are shared between adult endocrinologists,diabetologists, and some pediatricians with interest in this pathology.

Respecting the purpose of "ENDOPED", to the implicate in the professional training of all physicians who are in contact to the pediatric patient, we offer participants at the 5th National Congress of Diabetes Nutrition and Pediatric Endocrinology a new volume with "Pediatric Endocrinology and Diabetes – 2018 Update".

Professor Iulian P. Velea MD, PhD
Presdient of
Romanian Society of Diabetes, Nutrition and Pediatric Endocrinology

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DIAGNOSIS & MANAGEMENT of TYPE 1 DIABETES MELLITUS in CHILDREN, ADOLESCENTS & YOUNG ADULTS

Stuart J. Brink

GOALS OF TREATMENT[1,2,3]

The **primary goals** for the treatment of type 1 insulin-dependent diabetes mellitus (IDDM) are achievement of as near normal blood sugar levels as possible, normal growth and development for children and adolescents, and emphasizing avoidance of severe hypoglycemia.

Secondary goals include avoidance of the long-term complications associated with type 1 diabetes: microvascular abnormallities such as retinopathy, neuropathy and nephropathy as well as macrovascular problems/atherosclerotic events such as heart attacks, stroke and circulatory blockage in keeping with research studies such as the now classical DCCT[4].

Overall goals of treatment[5] must take into account: (1) The age of the patient and how well he or she understands the management concepts. (2) How much endogenous insulin remains available. (3) Individual caloric needs for normal growth and avoidance of obesity. (4) Activity patterns and their unique fuel requirements. (5) Home glucose and ketone monitoring needs, what's available and affordable and perhaps which particular brands are covered by health care insurance. (6) Insulin choices, affordability and availability, restrictions by health care providers, delivery, kinetics, absorption idiosyncrasies and adjustment guidelines. (7) Psychosocial factors including financial and family issues, learning problems, language barriers, distance from health

care providers, local customs re: traditional health care providers vs "scientific" medicine.

DIABETES TREATMENT TEAM

The goals of therapy usually are best achieved using a multidisciplinary[1-4] approach to optimally deal with all of these complex issues. Ideally, a well-trained and experienced pediatric diabetologist should supervise the team for children and adolescents and an internist diabetologist should do the same for adults. The diabetologist should be in charge of the diabetes team, which includes interactions with primary health care providers (pediatricians, internists or family physicians) as well as nurse specialists and nurse practitioners, dieticians, social workers, psychologists, psychiatrists, and, if available, exercise specialists. All such members of the diabetes team should have not only their specific specialty training but also special interest and training vis-à-vis diabetes as well as idiosyncrasies of dealing with growing and developing children and family interactions. If specific complications exist, other subspecialists (i.e., ophthalmologists, cardiologists, neurologists, nephrologists, gastroenterologists) may be extremely helpful, particularly if they have experience with diabetes-related pathology as well as pediatric and adolescent age groups. For school-age youngsters this may also include teachers, school nurses, coaches and after-school workers as well as school administrators as well as baby-sitters. If other members of the team are not available or there are no resources for their provision[5], then the physician must also assume these roles since nutrition, activity and psychosocial factors remain key ingredients of the successful equations for care of any patients with this chronic illness and such enormous potential but avoidable morbidities. In places of the world where there are no such teams and no chronic care model of medical care – and then this was brought the area – young children, teenagers and adults all stop dying and the numbers of people with "chronic" type 1 diabetes who are alive and thriving increase enormously - all because they are no longer just dying from DKA or concomitant infections concordant with DKA - at home or on arrival to emergency facilities any longer.[6] The critical component of a multidisciplinary diabetes care team is not only having health care providers with diabetes-specific knowledge regarding younger patients but also having consistent messages about goals, motivational interviewing and empowerment

techniques so that mixed-messages to the patient and family members are minimized.[7,8]

THE AGE OF THE PATIENT

How old is the patient is rather critical information and makes a great deal of difference in treatment guidelines, targets as well as how the health care professional approaches the problem of type 1 diabetes. Very young children[9] are particularly vulnerable since general practitioners and pediatricians usually do not think about diabetes when a young child presents ill, but rather focus on acute problems such as infectious diseases. As a result, often there are inordinate delays in making a diagnosis so that hyperglycemia, ketonemia and ketoacidosis may present in more dire circumstances since the delay in diagnosis often is associated with more severe clinical presentation or even coma and death. Some research also suggests that the younger the child, the more vulnerable the brain and nervous systems is to either hypoglycemia, hyperglycemia or both with some associations with cognitive dysfunction reflecting by younger age at onset.[10] All of the teaching and training about diabetes with young children is done through the parent or parents although sometimes older siblings or grandparents may also be involved. As the child is older, and particularly when able to read, education efforts need to occur for both parents and caretakers as well as the child themselves. This takes more time and as might be expected needs to be focused at the appropriate level for optimal understanding without overwhelming young children. Some are more agile and able to assume more responsibility while it is generally safe to assume that most young child still require a great deal of adult assistance and direction with diabetes tasks. As the young child matures further, they may assume some more limited self-care as long as there is appropriate adult supervision ongoing: ie. blood glucose testing, retrieving insulin administration equipment and even helping to enter blood glucose results into a color-coded logbook. Even if able to do some of these tasks, adult supervision will persist to ensure continuity and appropriate decisions are continuing. Ongoing education should also occur adapted for age appropriateness every year and for individual circumstances, learning styles while listening for questions and concerns not only from the developing child but also family members. Being sure to involve fathers as well as mothers, grandparent and other caregivers and specifically

inviting siblings and peers to patient visits is a valuable endeavor and encourages support back home and at school. With further maturation, more of such daily tasks may be assumed with appropriate education and similar efforts at re-education at regular intervals appropriate for the level of interest, involvement and needs of an individual child and family. When the child goes to school, some of these tasks must be self-administered but often with the assistance of either teachers or school nurses if such school nursing staff, are available and trained as well as willing to participate. In middle school and high school, further independent self-care behaviors can be assumed but there is some risk that more errors will occur without adult supervision and some risk of handing off too much diabetes self-care too early. In the pre-teen and teenage years as well as the young adult years, regimen nonadherence[11] produces extra concerns and often there is deterioration of glycemic control not only because of inherent hormonal differences moving through puberty but also with more independence and time away from family and home. Studies of diabetes self efficacy have illuminated our understanding of some of these issues.[12] Discussing such concerns openly, reviewing effects of alcohol, marijuana, drugs and sexual concerns including condoms and contraception in an appropriate fashion for the circumstances also become extremely important to minimize problems and interference with diabetes self-care. Paying particular attention to such psychological and family systems potential problems and linking professional understanding of the diabetes health care team to A1c results, frequency and severity of hypoglycemia all become important aspects of provision of care for youngsters as they grow and develop.

INITIAL APPROACH TO THE PATIENT: PRESENTATION AND DIAGNOSIS

The classic manifestations of type 1 diabetes mellitus include:

Hyperglycemia secondary to insulin insufficiency.

Polyuria. As high glucose in the bloodstream is filtered through the kidneys, osmotic balance causes excess urination. Nocturia (and enuresis especialy in younger children but sometimes also in older kids too) reflects this same mechanism driven by glycosuria. This is a critical fact to emphasize [5] since in many parts

of the world where dehydration is secondary to overwhelming gastroenteritis, sepsis, meningitis or malaria, the normal kidney functions to save the body from dehydration by the opposite of its function with hyperglycemia and glycosuria associated polyuria. When such patients present for evaluation, if there is concomitant polyuria, then a blood glucose level should be the next immediate request and the diagnosis of diabetes would be confirmed. (If there are ants or other insects near the site of urination, this too is an important "clue" to thinking about diabetes ("ants in the backyard") and not other conditions associated with excess urination where specific laboratory facilities are not always present.

Polydipsia. As more water is excreted, the body requires more water intake and, because thirst mechanisms are intact, thirst increases.

Loss of weight: clinical dehydration: hypotension

This occurs more commonly in those with the most acute insulin deficiencies; however, most type 1 patients lose some weight in comparison with the more typical weight gain associated with the diagnosis of type 2 diabetes. Loss of water as well as loss of muscle mass and fat mass all contribute to acute or subacute weight loss at the time of diagnosis of type 1 diabetes mellitus. With more type 1 diabetes patients diagnosed during antibody screening programs or with more knowledgeable patients showing up earlier, there may be less acute weight loss at diagnosis than in the past. For diabetes to be diagnosed early enough to avoid ketoacidosis and coma, health care professionals,parents and the generalpublic must be aware of the differential diagnoses and presentation of diabetes so that early rather than late diagnosis becomes more common. This is as true in parts of the world where HIV/AIDS and malaria are thought more common than type 1 diabetes/DKA and equally true in the parts of the world where viruses and other conditions may confuse earlier type 1 diabetes diagnosis. Nevertheless, excess weight loss, clinical dehydration, hypotension and severe DKA still occur through the developed world as well as in parts of the world with limited health care access and limited medical resources. The more extensive and the longer these go on, the more severe the presentation and in many parts of the world, new DKA and type 1 diabetes continues to go on unrecognized and needless deaths still occur.

Fatigue and weakness probably occur as a result of decreased glucose utilization and subtle electrolyte and/or mineral abnormalities as well as clinical and subclinical dehydration in addition to muscle catabolism.

Type 2 vs Type 1 diabetes

With the obesity epidemic around the world, it is important to distinguish between type 1 and type 2 diabetes in children, adolescents and young adults[13] where type 2 diabetes is also epidemic. Members of US minority populations (i.e., African Americans, American Indians, Latinos and Asian Americans), but also Caucasian populations, are all at risk, especially if there is concomitant acanthosis nigricans, polycystic ovarian syndrome, irregular menses or overt hirsutism (hyperandrogenism). The same ethnic groups in their own countries or in countries to which they have migrated are also presenting with type 2 diabetes at younger ages, as they become more obese and more sedentary (indigenous populations such as Canadian First Nation, Australian aboriginal folk, for example). Classical type 2 diabetes in children and adolescents sometimes presents with ketoacidosis, but almost always with moderate to severe insulin resistance because of obesity. This is different than classical maturity onset of diabetes in youth (MODY)[14], with a different pattern of family history, and different pathogenesis. Treatment of type 2 diabetes in younger patients, after any initial DKA presentation and treatment, focuses on weight loss, increasing caloric expenditure and the same host of oral agents classically available for the older patient with type 2 diabetes, ie. metformin as well as other, newer medications even if such newer medications are not officially authorized for treatment. Sometimes, insulin is needed either at bedtime or in combination with oral agents if weight loss does not occur. If insulin is needed initially in type 2 diabetes, it often can be quickly discontinued within several weeks of diagnosis as insulin resistance decreases. More recently, combinations of autoimmune based type 1 diabetes with obesity related insulin resistance and type 2 diabetes have been described and labeled “double-diabetes” or “type 1½” diabetes and may be more common in African-American or other ethnic populations [15].

LABORATORY FINDINGS IN TYPE 1 DIABETES MELLITUS

Fasting blood glucose. If the value is greater than 126 mg/dL (7 mmol/L) on 2 or more separate days, the diagnosis of diabetes mellitus can be confirmed according to the latest diagnostic classification. **Random blood glucose** values greater than 200 mg/dL (~11 mmol/L) are also diagnostic.

A1c testing. If available and clinically meaningful elevated results occur, some studies suggest that this can replace blood glucose testing or blood glucose screening and, if abnormally high, utilized for diagnosis per se.

Glucose tolerance test (2-hour). If the diagnosis is still in doubt, then perform a glucose tolerance test (usually not necessary):

(1) Give at least 150 to 200 g carbohydrate daily for 3 days prior to test.

(2) Overnight fast.

(3) Have patient drink 75 g of glucose dissolved in 300 mL of water within a few minutes.

(4) Measure serum glucose levels at 30-minute intervals for 2 hours. Usually it is not necessary to measure (expensive) insulin levels automatically but extra tubes of blood should be drawn and stored appropriately (usually frozen), in case this is needed once actual blood glucose levels are reviewed.

Autoantibodies and genetic testing

A variety of islet-related autoantigens can now be measured commercially or in research laboratories, including islet cell antibodies (ICA), glutamic acid decarboxylase-65 antibodies (GAD-65), insulin antibodies (IA2) and zinc-transporter 8 antibodies (ZnT8). In combination, such autoantibodies are positive at least 60% to 80% of the time in classical cases of children and adolescents with type 1 diabetes mellitus since type 1 diabetes is thought to be an autoimmune disorder. Adults and older teenagers are less likely to have positive antibodies but, if present, make type 1 rather than type 2 diabetes more likely. Very young children also are less likely to be antibody-positive. Other populations such as those with Asian forebears may frequently be antibody-negative but require insulin rather than oral agents (ie. those from Japan, Singapore, China, Bangladesh, India, Pakistan). Adults with positive

antibodies will likely need insulin eventually, but early in the course of what is called latent autoimmune type 1 diabetes (LADA) they may only be treated with typical type 2 diabetes treatment protocols, starting with metformin and then adding other medications depending on blood glucose monitoring results and agreed-upon blood glucose treatment goals. In patients with obesity and polycystic ovary syndrome (PCOS), antibody levels may also be helpful in determining insulin vs other diabetes related medications. Such autoantibodies may also be helpful in an already diagnosed patient to help distinguish between type 1 and type 2 diabetes or to determine if insulin is needed although it must be acknowledged that antibody levels usually are in highest titers at the beginning or near presentation of type 1 diabetes with titers decreasing over time. HLA testing and other forms of genetic testing remain research procedures, although haploidentity suggests higher risk in sibling studies, particularly if coupled with antibody testing to predict the likelihood of development of diabetes.

New genetic tests for **monogenic diabetes** can help identify rare cases of neonatal or early childhood diabetes associated with potassium channel or sulfonylurea receptor abnormalities.[16] These youngsters may present with severe DKA at diagnosis, often as infants or very young children who are very sick and need insulin as well as electrolyte and fluid management. Such patients can be elegantly managed days or weeks later (if diagnosis is confirmed genetically) without insulin (insulin withdrawal program) but with sulfonylurea medications to the amazement of staff and family coupled with actual significantly improved glycemia despite not needing insulin.

C-Peptide is not affected by antibodies to exogenous insulin, so that measurement may be helpful in classification of diabetes in an already diagnosed patient when drawn either fasting, postprandially (especially if concomitant with elevated blood glucose levels), or after glucagon or Sustacal® stimulation testing. C-peptide is thought to be secreted by the beta cell in equimolar concentrations so that higher levels would seem to reflect ongoing insulin secretion, be helpful in better biochemical definition of endogenous insulin production/availability and be helpful in defining the honeymoon period or a period of resumption of insulin production when it was previously absent or minimal.

In the occasional patient with very prolonged honeymoon phase and exceptionally stable glycemic variability, c-peptide

measurements confirm the continued production of endogenous insulin even when insulin treatment is continued.

Similarly, in patients on insulin who may have been mistakenly diagnosed with T1DM when they actually have T2DM, c-peptide measurements may be helpful diagnostically as well.

Diabetic ketoacidosis (DKA)[17]

DKA, is a severe metabolic derangement produced as a result of insulin deficiency and concomitant fluid and electrolyte imbalance associated with counterregulatory hormones outweighing the effects of waning or absent insulin. The potential life-threatening consequences of DKA often reflect severe and/.or unrecognized fluid, electrolyte and acid-base disturbances not treated properly.

Three key factors all increase morbidity and mortality associated with DKA:[1] delay in considering the diagnosis in those without prior history of diagnosis,[12] in the very young since DKA is not suspected because of the relative rarity of diabetes in infancy and [3] chronic poor self-care management (frequently associated with omitted insulin doses in those already diagnosed but with long-standing extremely poor glycemic control. Some studies have suggested a risk of DKA of 8 per 100 person-years with increased frequency in teenagers, those already with higher A1c levels as well as prescribed higher insulin doses, inadequate health insurance coverage and the presence of psychiatric co-morbidities. In some studies length of hospital stay for DKA has decreased with improved professional educational focus and efforts. In circumstances where access to medical care or medical knowledge and sophistication is less than ideal, DKA may be completely missed, mistaken for other more common condition (ie. in Africa, cerebral malaria or HIV-AIDS).

DKA never even come into question, of course, if presentation is at a late stage with severe dehydration and coma or the patient may arrive and quickly die before testing can be undertaken. Because the general public is not aware of the common Symptoms and signs of diabetes like polyuria, polydipsia, unexplained weight loss, unexplained new onset enuresis, medial attention may also be delayed. In those already diagnosed with diabetes, not only omitted insulin and chronic diabetes mellitus out-of-control (DMOOC) but also misapplication of lack of knowledge of sick day guidelines contribute to morbidity and mortality associated with DKA events.

Lack of professional medical and nursing experience with DKA, lack of awareness and following DKA treatment protocols in emergency rooms and hospital also contribute to preventable DKA morbidity and mortality. An elegant study documented double the cost and increased readmission rate for DKA if generalists rather than diabetes specialists provided the DKA care.[18]

The goal of DKA therapy is not returning glucose levels to absolutely normal values but rather the reversal of the underlying ketoacidotic state – and the avoidance of cerebral edema. Effective DKA therapy requires attention to the pathophysiologic changes caused by insulin deficiency in the first place and the enormous secondary consequences of this deficiency: hyperglycemia, glycosuria and osmotic diuresis, sodium and water losses, total body potassium deficit, glycogenolysis and protein and fat catabolism generating hyperglycemia, ketonuria, ketonemia and eventually ketoacidosis. Prompt institution of appropriate fluid and electrolyte replacement along with appropriate insulin administration should produce slow and steady corrections of such imbalances, thereby preventing or minimizing known complications associated with DKA and its treatment (cerebral edema, cardiac arrest, death).

If not treated prudently and with extremely close, ongoing and coordinated follow-up and care by the medical team, coma and death can result. DKA is not yet uniformly defined and definitions in various reference sources differ vis-à-vis carbon dioxide levels, serum bicarbonate results, pH and glycemia making some comparisons particularly difficult. The exact degree of morbidity and mortality thus cannot be pinned to specific values as a result of such difficulties and even the term “diabetic coma” in the medical literature often can be misleading since most DKA patients re not necessarily “unconscious.” DKA can occur in patients on any insulin treatment regimen and with insulin pump patients, there may be special risks because interruption of insulin completely removes all insulin – and the conditions where such interruptions from rare electromechanical pump failures occur unbeknownst to the patients as well as the more common but more subtle catheter blockade with interruptions in insulin delivery all can result in DKA.

With appropriate monitoring, of course, any and all of such conditions should respond to education and awareness training since DKA is not an instantaneous emergency but rather comes on over a period of hours or days during which time blood glucose

monitoring by fingerstick or sensors as well as ketone testing would alert the patient and family members to such a possibility.

During intercurrent illnesses such as viral, bacterial, parasitic or fungal infections or other medically known conditions such as glucocorticoid treatment, appendicitis, DKA risks also increase as insulin demands can be unmet. DKA does not occur because of overeating or other "dietary indiscretions" nor does it occur following alcohol or other substance abuse although such conditions often result in chronic hyperglycemia and long-standing poor self-control of a chronic illness like diabetes that increases ultimate deterioration when another factor (ie. an infection) presents itself or is associated with omitting insulin itself.

Sick day guidelines (see Table 1.1.)

Are listed as taught at NEDEC and purposefully kept with the daily insulin algorithm in addition to the hypoglycemia treatment protocol – all in one place and thus less likely to be lost.

Initial education shortly after diagnosis and periodic re-education and review is very important for family members and for the patients particularly as the patient gets older and takes on more self-care responsibility. Most illnesses can be managed at home although there are exception for more severe episodes that require emergency room or hospital admission and treatment.

Frequent monitoring of glucose and ketones allow for identification of events that could result in DKA and under which circumstances home care needs to be increased to include professional contact either by telephone or in person in the hospital. With CGMS providing more frequent glucose results, alarms and even automatic pump responses to such alarms could potentially be extremely helpful if patient response takes place.

At home blood ketone testing also is available and relatively inexpensive with some studies documenting earlier detection of deteriorating ketonemia, ketonuria so that earlier treatment may take place.[19]

Recurrent DKA

Chronic omitted insulin is almost always the explanation for recurrent episodes of DKA. The extremely "brittle" or "labile" child or adolescent who presents with recurring DKA, often from a tumultuous family environment associated with insufficient adult supervision of the patients, demands more professional attention and follow-up in an effort to reverse the situation. In large diabetes

practices, recurrent DKA may occur in approximately 2% of the patient population. Usually this occurs with pre-teens and teenage patients as well as young adults and their parents may have problems with finances, substance abuse, anxiety and depression just as the patient themselves may have such similar problems. Some such problems are already well known but some are often hidden and never discussed until the crisis of recurrent DKA brings them to the surface. Sexual and physical abuse, mental abuse and neglect are common co-morbidities in such situations and intensified psychiatric and social work interventions are required to change these situations.

DKA management protocol (see Table 1.1, page 28).

The NEDEC DKA low dose insulin infusion protocol has been used successfully for many years and works in Africa, India, Bangladesh and China as well as throughout North, Central and South America and European sites. Attention must be made to local conditions and availability of personnel as well as testing and treatment facilities. Also, attention must be made to common conditions that may co-exists or confuse differential diagnoses: cerebral malaria, HIV-AIDS, overwhelming sepsis, gastroenteritis must be considered with appropriate testing while diabetes is not forgotten as a possibility.

Delay in arrival for medical care, financial constraints and/or lack of medical sophistication all are potential contributors to higher morbidity and mortality under such conditions.

In wealthier parts of the world, many cases of DKA continue to occur where the patient actually had contact with medical personnel one or several times in the days or hours prior arrival in the emergency room but nobody thought about DKA or diabetes as a possibility.

Sodium and water management

Sodium The severity of mental status changes is likely related to serum amorality. The weight of the patients can be used for initial calculation of replacement fluids on the assumption that dehydration is mainly reflected by acute body weight loss. Surface area estimations are often best to reflect the differences in infancy, childhood, adolescent and adulthood maintenance needs.

The severity of the signs and symptoms of clinical dehydration reflect extracellular fluid loss with minimally clinically detectable

dehydration approximating 3-5% lost body weight. With 20% acute volume depletion the patient is, by definition, in profound shock and often moribund. It must also be remembered with newly diagnosed patients that some of their weight loss, however, is not necessarily acute but reflects days, weeks or months of hyperglycemia and glycosuria causing such negative fluid balance and some of their weight loss as well as lost muscle and fat.

Fluid losses should be estimated and initial replacement accomplished with normal (0.9%) saline given of the first 1-2 hours with more severe presentation.

This effectively removes the patient from the immediate consequences of potential or overt shock and does not cause any delay searching for special or expensive intravenous solutions. Maintenance water, sodium and potassium can estimated according to standard guidelines based on surface area estimations: water ~1500-2000 cc/m^2/24 hours; sodium 30-60 mEq/m^2/24 hours; potassium 30-50 meq/m^2/24 hours.

Total body deficits can be enormous with such electrolytes changes not always well reflected in initial laboratory measurements so that sequential sodium and potassium as well as acid-base determinations are always required.

Most centers suggests the use of normal saline intravenously over the first 1-4 hours but more recently because of the chance that cerebral edema is more common than appreciated in severe DKA, recommendations to continue normal saline for a longer time period, perhaps 24 hours, rather than switch to half-normal saline, have become more common.

Attention to kidney function is also important because of the total sodium deficit or volume deficit is severe enough, glomerular filtration and renal function can be compromised presenting with oliguria or acute tubular necrosis. This is uncommon, however. In adults with known cardiac or renal compromise or when the patient is unconscious or moribund on presentation, central venous catheters or dialysis may be required but this is extremely rare in children or adolescents.

Potassium

Because of the acidosis, potassium is usually driven out of the intracellular space while a state of kaliuresis exists as the kidney attempts to save sodium (Bunge effect\t).

Initially, serum potassium levels can be either normal, elevated or low.

Total body potassium is always depleted. As hydration is corrected with normal saline, lactic acid production decreases and some potassium begins to shift back intracellularly fostering peripheral hypokalemia.

With lowered ketoacid production as insulin becomes more available, the same process accelerates. Sequential bedside electrocardiogram rhythm strips for T or U wave changes or cardiac monitoring allows identification of potential dangerous hypokalemia necessitating an increase in potassium replacement. This may be more important in adults than in children and particularly in those with pre-existing cardiac and/or renal dysfunction.

If initial hypokalemia is present at diagnosis this usually portends a more prolonged prodrome time period and there is a more ominous prognosis because of cardiac arrhythmias problems. Usually potassium is not added in the first intravenous solutions of normal saline but sometimes under these circumstances, earlier potassium is needed. As soon as reliable history or documented urination occurs, this may be the optimal time to add potassium.

In youngsters who are otherwise heart-healthy, potassium can be replaced at a rate of 40 mEq per liter of solution with danger of a rapid rise in blood levels.

The potassium can be provided as potassium chloride or half as potassium chloride and the other half as potassium phosphate since there also is total body phosphate depletion in DKA. This helps ensure not overwhelming the calcium/phosphate balance with excessive phosphate.

After 6-12 hours, all the potassium replacement can be changed to just potassium chloride again to attempt to not cause disruption in the calcium/phosphate total body balance.

Bicarbonate

Since acetoacetate and β-hydroxybutyric acid are metabolizable anions, restoration of serum bicarbonate concentrate will follow insulin administration in the absence of treatment with alkali containing solutions. Acidosis results from a combination of (1) release of fatty acids secondary to insulinopenia, (2) generation of “ketone bodies”, (3) starvation from poor food intake, fat breakdown since glucose and glycogen are not available to the cells, nausea and vomiting, (4) excessive lactic acid production from plasma volume depletion, poor tissue perfusion and an increase in anaerobic glycolysis in muscles.

Concerns for consequences of severe metabolic acidosis have

been balanced by fears of cerebral edema, respiratory arrest and death when bicarbonate is replaced "too quickly."

Worsening and life threatening hypokalemia as potassium returns back into the cell with beginning DKA treatment as well as worsening tissue hypoxia can be added to the list of possible bicarbonate treatment complications that may be associated with increased cerebral edema risk.

Therefore, treatment is generally restricted to patients with severe metabolic acidosis as indicated by an arterial pH of 7.0-7.1 or less or a bicarbonate value of less than 5 mEq/L.

Rapid infusions of large amounts over a short time span should not be automatic and should reserved for acute and life-threatening cardiorespiratory arrest situations.

If sodium bicarbonate is given, the amount of sodium should be subtracted from the amount of sodium contained in the replacement fluids to avoid exacerbation of the (already) hyperosmolar state.

When sodium bicarbonate is used, it should be given by slow intravenous infusion over several hours rather than as an emergency "push" if possible.

Frequent pH and/or bicarbonate determinations should be obtained sequentially so that any bicarbonate given can be discontinued when the pH is approximately 7.2-7.25. Favorable results using low dose insulin infusion protocols without bicarbonate have been reported around the world that seem to avoid the paradoxical cerebrospinal acidosis associated with bicarbonate administration. Cerebral vasodilatation and an increase in cerebral blood volume may contribute to an increase in cerebrospinal pressure and cerebral edema as well as account for the changes in levels of consciousness in patients receiving sodium bicarbonate previously.

Calcium and Phosphate... and Oxygen

Patients with DKA sustain intracellular phosphate depletion. Serum phosphate often follows a pattern similar to that of potassium. Initial phosphate values may be normal or elevated but within 4-6 hours of insulin treatment, these may fall dramatically as glycogen deposition resumes.

The consequences of hypophosphatemias may be reflected in red blood cell levels of 2,3 diphosphoglycerate (2,3 DPG) thereby altering the affinity of hemoglobin for oxygen and compromising oxygen delivery to tissues. Recommendations for phosphate

depletion are listed above with half of the initial potassium losses providing potassium phosphate and the other half as potassium chloride for the first 6-12 hours of electrolyte therapy accordingly.

Some recommendations, especially in adults, in recent years but perhaps also applicable vis-à-vis preventing cerebral edema in younger patients have therefore promoted not only slower or no bicarbonate administration but always providing some nasal oxygen to help ameliorate this potential danger and hopefully help decrease cerebral edema. If bicarbonate were given to raise the pH rapidly, the protective Bohr effect allowing oxygen to be released in the face of acidosis may not take place. This could all worsen tissue hypoxia and may explain the deterioration of some patients receiving bicarbonate on cardiac or neurologic function.

Oxygen is therefore recommended at low flow rates in the early stages of all DKA treatment.

Insulin in DKA

The best route of administration and the dose of insulin necessary for treatment of DKA remains unknown. Successful results have been published with differing insulin regimens although most experts prefer continuous low dose insulin infusion over subcutaneous or intramuscular administration.

All patients with DKA have an immediate need for insulin no matter which protocol is followed. Fluid and electrolyte replacement as well as recognition of underlying, precipitating events must remain high on the list of priorities to decrease morbidity and mortality.

Close and repeated clinical as well as laboratory observations are mandatory to enable the wisest and safest therapeutic approaches and to allow for their modification once therapy ensues.

The giving of "enough" insulin should be one's therapeutic goal. This should be guided by initial and follow-up glucose levels as well as by clinical follow-up. At least one physician must at all times be in charge and delegated to know the time of insulin administration, be responsible for oversight of clinical and lab flow chart reviews as well as specifically being aware of all fluid and electrolyte orders and changes. The flow sheet may be the single most important tool once the diagnosis is established and treatment started because of the dynamic state of affairs present in DKA and how much it can change with treatment itself. There is no substitute to replace close hour-to-hour direct observation of the patient's clinical as well as biochemical status for the treating

physician and his or her hospital team.

Follow-up neurologic, cardiovascular and renal status goes hand-in-hand with follow-up lab parameters to document problems and success.

Blood acetoacetate and acetone levels may rise initially despite a much greater fall in β-hydroxybutyrate as a result of acid-base changes and insulin treatment with its fat metabolic effects.

If only urinary ketones are measured, this may produce an expected overall rise initially until equilibrium occurs with all ketoacids taken into account. Knowing that this is expected should not produce an erroneous increase in insulin administration so that excessively rapid decreases in glucose are avoided.

Rapid-acting lispro and aspart as well as glulisine insulin as well as semi-synthetic human regular insulins can all be used to treat DKA depending on local costs and availability although it makes sense to use the purest fast-acting insulins (lispro, aspart or glulisine) to minimize any (rare) allergic phenomenon. All these insulin can be used intravenously, intramuscularly or subcutaneously.

An increase insulin dose in DKA treatment is expected when insulin resistance is already present or expected (obesity), in a known patient on very high usual daily doses, with longer duration of diabetes, with more severe infections as well as with more severe acidosis and dehydration.

Decreased doses would be expected in a newly diagnosed patient never before treated with insulin, a patient not unconscious, an extremely high initial glucose level (so that too rapid decrease may be ameliorated), in a very thin person, in much younger infants or children, in those with a known history of omitting insulin, in those with a known history of insulin sensitivity, where renal insufficiency co-exists, hypokalemia is present or those with extreme hyperosmolality. In those with known significant cardiac disease, not expected with children, adolescents and young adults, slower and lower insulin doses also would be expected to be somewhat safer.

The new “epidemic” of extremely overweight adolescents presenting in DKA but who soon revert to more typical type 2 diabetes present unique challenges because they may require enormous amounts of insulin originally; after the insulin resistance wane, more rapid decrease in insulin then are needed and sometimes no insulin at all but a transition to typical type 2 medications after the acidotic crisis is finished.

SQ and IM insulin DKA protocols

When subcutaneous regular insulin was all that was available, it was not uncommon to receive relatively large initial subcutaneous dose of 2-10 units for small children and pre-adolescents while teenagers and adults would commonly receive 25-100 units; because of these large subcutaneous doses, sometimes no other insulin was needed for many hours because of their relative excess dosage. Earlier reports advocated changing from subcutaneous to intramuscular insulin because this provided faster absorption than the subcutaneous route, especially if there was concomitant vascular perfusion problems.

Intramuscular insulin was in vogue for a while on an hourly basis with a loading dose of ¼ unit per kilogram of body weight followed by 0.1 units per kilogram per hour intramuscularly. For adults or older teens, this involved intramuscular follow-up doses of 5-20 units hourly. The benefits of intramuscular treatment over intravenous plus subcutaneous treatment was ease of protocol understanding by staff, no need for complex apparatus to deliver the insulin, no need for complicated calculations of insulin dose, little risk of late hypoglycemia because of the less elevated blood insulin levels achieved, smoother fall in acidosis and ketone parameters with smaller and slower potassium flux and decreased potential for cerebral edema because of the slower changes in glucose, pH, sodium, potassium and phosphate as well as slower osmotic changes.

The biggest problems with intramuscular protocols was the inadvertent decrease in attention to intravenous access so that rehydration and electrolyte corrections were less emphasized. Both SQ and IM insulin DKA protocols also have an advantage in parts of the world where intravenous access cannot be guaranteed for any reasons.

Table 1.1. NEDEC DKA low dose insulin infusion protocol

1. Maintain airway, breathing and circulation. Document baseline vital signs including neurologic status. Consider low flow nasal oxygen especially if possible cardiovascular compromise, known previous cardiac disease etc.
2. Confirm diagnosis of diabetic ketoacidosis at bedside and consider infections, surgical emergencies and other possible precipitants.
3. Start intravenous infusion with normal saline 10-20 cc/kg to run over 1-2 hours
4. Lead II EKG for potassium status (full EKG in adults to rule out myocardial infarction)

5. Start flow sheet: weight, height, surface area calculations, pulse, BP, respiratory rate and effort, neurologic status including fundoscopy, baseline glucose, urine glucose and ketones, urine specific gravity, serum electrolytes, calcium, phosphate, acid-base data and renal functions
6. Determine estimated maintenance and deficit for electrolyte and fluid orders. Usually not necessary to rapidly correct low pH unless concomitant several abnormal neurologic state but ongoing acid-base determinations should continue to double-check treatment choice without automatically hurrying to correct low pH
7. Attach piggyback short acting insulin infusion system to existing intravenous line:

A. prepare 100 units regular or fast-acting analog insulin (1 cc) in 100 cc normal saline (not NPH, glargine, detemir or other basals

B. preflush intravenous tubing to allow adherence of insulin to plastic before connecting to saline IV line; no need for albumin

C. set up piggyback system into existing intravenous line using available pump or pediatric set-up

D. give 0.1-0.2 units/kg of body weight as intravenous push (bolus) of fast-acting insulin

E. start 0.1 unit/kg body weight/hr intravenously by continuous infusion

F. expect initial drop from rehydration and then approximately 10% of blood sugar hourly (50-70 mg/dl or about 3-4 mmol/L)

G. monitor blood glucose at 1 hour and then every 2-4 hours to ensure expected response or change protocol

H. monitor urine for ketones at least every 3-4 hours or, if available, blood β-hydroxybutyric acid sequentially every 2-4 hours

I. check infusion sites/lines; double rate of infusion or switch to alternative insulin delivery protocol if no response

J. calculate estimated time when blood glucose will reach 250 mg/dl (approximately 14-17 mmol/L) and inform staff so everyone is aware of estimated time to consider adding glucose to infusion orders

K. stop insulin infusion when glucose reaches 250 mg/dl (approximately 14 mmol/L and change intravenous solution to contain 5% dextrose in addition to existing electrolytes

8. After initial 1-2 hours of normal saline infusion, change intravenous solution to 40 meq/l of potassiumusing20 meq/l KCl plus 20 meq/l K_2HPO_4 to avoid iatrogenic hypokalemia in either 0.5 or 0.9 normal saline
9. Check electrolytes at 2-4 hours and again as necessary according to clinical monitoring requirements, patient status and prior levels to adjust type of fluids and rate of administration. Evaluate abdominal pain appropriately and consider surgical consultation if no better or worsening
10. Give subcutaneous insulin or intramuscular insulin 15 minutes before intravenous insulin is discontinued or if line no longer operational because of short half life of intravenous insulin to avoid recurrent ketoacidosis. Adjust dosage according to newness of T1DM, degree of ketosis and/or

acidosis, age of patient, known sensitivity or other factor which affect amount of insulin needed (pregnancy, renal failure, infection etc.)
11. Identify and treat any underlying problems (ie. continue antibiotics as needed for urinary infection, streptococcal disease etc.)
12. Keep flow sheet up-to-date and reassess frequently
13. Pay attention to vital signs, abdominal exam, neurologic status (including follow-up examination of the optic disk) and electrolyte changes; detect and treat cerebral edema
14. Educate patient and family appropriately to prevent recurrence: identify contributing psychosocial issues

Intravenous low dose continuous infusion DKA protocols

IV low dose insulin infusion has become the standard recommendation for treating DKA to replace the earlier, larger boluses with SQ or IM doses. These produced an even slower and more predictable decrease in blood glucose thought to be important for deceasing cerebral edema risks and especially when already present cardiovascular or renal problems existed as long as access could be set up and sustained.

Table 3 presents a typical low dose continuous intravenous insulin infusion protocol producing an approximately 10% hourly decrease in glucose values once the initial “dehydrated” blood sugar is corrected with the first few hours of hydration.

Correction of the many metabolic abnormalities also occurs at a slower and steadier pace and it is hoped that this would decrease co-morbidities and mortality. Any kind of regular animal, human semi-synthetic or the newer rapid-acting analogs can all be used, again based on local finances and availability and there is no difference in efficacy since absorption differences from the subcutaneous or intramuscular depot are not apparent when these are used intravenously. It must be directly observed by staff that the intravenous catheter is in place correctly, that infusion is correctly ongoing and that the insulin is actually connected correctly and flowing properly since obvious errors of these kind produce worsening and no improvement since no insulin is administered. When glucose levels fall to about 250 mg/dl (~14 mmol/L), 5% dextrose is added to the intravenous fluids and subcutaneous insulin can be stared and intravenous insulin infusions discontinued.

Another potential error commonly occurs when intravenous infusion of insulin is discontinued but subcutaneous insulin is forgotten to be ordered or given so staff needs special attention to

such common potential problems to minimize their occurrence.

The key benefit of the intravenous low dose insulin infusion is the slower, more predictable return to lower values of all DKA abnormalities at the same time there is less likelihood of cerebral edema. In the extremely severely dehydrated patient or in the very small and very young child, intravenous access is a potential barrier. An added advantage with intravenous insulin routes is that dose titration is an almost instantaneous process because of the very short plasma half life of insulin and the fact that no depot insulin is in the subcutaneous or intramuscular tissue. Intravenous insulins usually are connected in piggyback fashion to the already existing intravenous fluid line but with separately controlled infusion rate systems.

With any treatment of DKA, physician and medical staff complacency must be avoided. Staff should have more time to consider precipitating factors and ongoing processes as well as devoting more attention to the fluid and electrolyte abnormalities. It would be difficult to argue that the low dose treatment methods now favored are more effective than others but they appear to be simpler to use, easier to teach and for these reasons, better treatment for DKA.

Once the DKA emergency is over and the patients feels better, looks better and laboratory parameters document such improvement, resumption of oral liquids and then food coupled with a transition to subcutaneous insulin must be instituted.

Depending on local preferences, some kind of basal insulin (NPH, glargine, detemir, degludec) must be provided coupled with some kind of prandial insulin (regular, aspart, glulisine, lispro). All such choices as described in this chapter can be started with appropriate monitoring of blood glucose as well as ketones to aid decision making as nutrition is resumed and then subsequent education processes started for patient and family (see below).

DKA treatment is often associated with frequent errors and specific associated complications:

1. delay in diagnosis,
2. delay in instituting therapy,
3. inadequate fluid replacement,
4. over-emphasis on insulin,
5. unrecognized hypokalemia,
6. overzealous bicarbonate usage,
7. hypoglycemia especially during staff shift changes with loss

of continuity of care (“changing of the guard”),
8. recurrent ketoacidosis from omitting follow-up insulin coverage (another example of “changing of the guard”),
9. overzealous phosphate replacement with resultant hypocalcemia,
10. aspiration,
11. unrecognized cerebral edema and neurologic problems,
12. unrecognized acute tubular necrosis,
13. peripheral or pulmonary edema (insulin edema vs fluid overload),
14. not treating the precipitating cause of the DKA (eg. missed appendicitis or bacterial pneumonia),
15. severe neurologic handicap (stroke),
16. coma and death.

Missing the underlying precipitating factors whether they are lack of knowledge concerning home recognition of impending DKA, lack of following sick day guidelines, psychosocial turmoil at home or at school are of utmost importance to consider particularly in the patient with recurring DKA. Gastric lavage should be considered for any patient truly unconscious because of the frequent association of gastric atony with ketoacidosis. Used judiciously, nasogastric tubes can certainly help to prevent aspiration in these most critically ill patients. Abdominal pain can be diffuse and severe with DKA and perhaps suggests the need for surgical considerations. Amylase elevation, usually of pancreatic origin, is common with DKA and sometimes extremely high whereas serum lipase values are often not abnormal and may be helpful in differential diagnostic discussions. Leukocytosis also can be extreme with DKA "stress" causing concerns about underlying sepsis of bacterial infection while most often resolves spontaneously as the metabolic acidosis, dehydration crisis is corrected. More rapid DKA treatment has sometimes also been associated with insulin edema, is higher with long standing poor glycemic control prior to the DKA episode itself and usually abates spontaneously over the first few days.

Cerebral edema

Cerebral edema is the leading cause of death in children present in DKA and occurs in about 0.2-1% of cases. Newer cases had a higher risk than in those already known to have diabetes with as much as 24% mortality and 35% serious morbidity (persistent neurologic deficit) in those who survived the cerebral edema itself.

While major treatment errors in fluid, electrolyte or insulin administration occur and can be associated with cerebral edema, most cases of cerebral edema remain unexplainable with some presumptions that younger age, longer duration and worse severity of presenting symptoms are contributing factors to be considered. Actual clinical and laboratory parameters, however, often cannot be directly correlated with the overall severity of the coma episode. Staff must become intensely aware of the (sometimes subtle) symptoms and signs of cerebral edema:

(1) progressive CNS deterioration despite improvement of laboratory parameters including
   - new or worsening headache,
   - increasing lethargy,
   - failure to regain consciousness,
   - increased CSF pressure,

(2) abnormal reflexes; eye changes including (a) papilledema, (b) unequal intraocular pressure, (c) increasing intraocular pressure, (d) decreasing pupillary light reflexes;

(3) hyperpyrexia;

(4) hypertension;

(5) diabetes insipidus;

(6) abnormal electroencephalogram;

(7) abnormal computerized tomography or magnetic resonance imaging consistent with cerebral edema. Dillon first proposed in 1936[20] and Rosenbloom[21] suggested that approximately 50% of their cases of cerebral edema during DKA had "a premonitory period when development, in retrospect, could be suspected on the basis of clinical symptoms or signs" that were missed. Any delay in diagnosis, error in treatment or worsening of acid-base, fluid or electrolyte status, if left unrecognized or if treated incorrectly, could be invoked as possible explanations for inadequate oxygen delivery to the brain. Brain infarction can occur with or after cerebral edema and autopsy findings thought to be similar to those seen in brains of victims of asphyxia and cerebral anoxia have been reported. Too rapid osmotic changes have also been implicated so that slowing down replacement fluid recommendations, being less aggressive with bicarbonate treatment of the acidosis itself, providing oxygen to all seem to have contributed to lessening the risks of cerebral edema in recent years. Research studies have also suggested that all

patients with DKA have some neurologic abnormalities all of the time so that fundoscopy at the bedside has now become a mandatory part of the clinical evaluation. If the emergency team cannot perform such fundoscopy with a hand-held ophthalmoscope, then an emergency ophthalmology, neurology or neurosurgical consultation should be obtained to guarantee that the very beginnings of cerebral edema are not missed. Treatment of cerebral edema is supportive and includes consideration for corticosteroids to reduce intracranial pressure and the use of other measures such as mannitol (1 gram/kg intravenously or 10-20 g/m^2) for induction of therapeutic osmotic diuretic effects at the same time that intravenous fluid infusion rates are decreased. Hyperventilation may also be of some help as well.

DKA is at true medical emergency. Prevention of DKA decreases morbidity and mortality. Teaching the patient and his or her family to recognize early symptoms and signs of impending DKA should be a high priority with the teaching of appropriate sick day guidelines and when to contact the medical team for further advice. Similarly, focusing on DKA treatment for nursing and physician staff also remains an equally high priority.[17]

Hyperglycemia without dehydration

If dehydration is not present at diagnosis and there is no vomiting, insulin can be started on an outpatient basis at the same time that preliminary meal planning and home blood glucose monitoring are taught if professional availability of the doctor and/or his or her team is established in such a way to manage such timely demands.

For young children, parents assume direct responsibility for such meal planning and ambulatory monitoring, whereas more mature older children and adolescents as well as adults assume self-monitoring responsibilities with the assistance of family members, spouses, or significant others. Frequent telephone contact and office visits are mandatory for the first 1 or 2 weeks if hospitalization is to be avoided at diagnosis or the start of insulin therapy. Telephone contact is also important and psychosocial support must be provided at the same tine that giving insulin is taught and mastered, beginning meal planning takes place, home monitoring is taught and mastered with record keeping tasks established and formalized.

Insulin treatment[1,2,3,5,22,21,24]

Intensive ("aggressive") insulin treatment[23] using basal-bolus concepts (MDI: multidose insulin) can be started as soon as possible in an attempt to "rest" the damaged islet cells and help to "induce" a remission ("honeymoon," see below). Evidence suggests that "quicker" normalization and maintenance of blood sugars may allow for some recovery to assist in prolonging pancreatic function. No adverse effects have occurred when youngsters (or adults) with type 1 diabetes are begun on such intensified multi-dose insulin programs at or soon after diagnosis. Any insulin that is affordable and available can be used to help lower such initial hyperglycemia/ketonemia but analogs such as glargine (Lantus® or Abasaglar®) or detemir (Levemir®) insulins can provide basal insulin, coupled with bolus doses of fast acting analogs [lispro (Humalog®), aspart (Novolog® or glulisine (Apidra®)) around meals and snacks at the same time hypoglycemia is decreased compared to older regular and NPH animal-based or synthetic human-types of insulin. Insulin degludec (Tresiba®) is also a newer basal insulin alternative to glargine and detemir with a somewhat flatter and more predictabele sowhat flater and more predictable basal pattern shown to be useful in several studies. Cost and availability of these new analogs in many parts of the world remains a huge burden. Prandial insulin provided by rapid acting insulin premeals and presnacks offers flexibility combined with carbohydrate counting and insulin correction algorithms and seems preferable to pre-mixed combinations of insulin. The newer analogs provide quicker more physiologic action to counter initial hyperglycemia at the same time they decrease faster than older insulins and therefore produce less hypoglycemia hours afterwards. This is true for the fast acting as well as the slower acting insulins. Basal insulin can be provided as in the past with overlapping doses of NPH (two, three or four times a day) if the newer analogs are too expensive or otherwise not available or with these newer "flatter" basal analogs (glargine, detemir, degludec). Detemir is almost always given twice-a-day while glargine and degludec are usually needed only once-a-day at bedtime especially in early days after diagnosis of type 1 diabetes. Many youngsters will nevertheless need glargine also on a twice-a-day regimen presumably because of smaller total dose requirements and less mass-action that ends up decreasing duration effects. Exact doses and proportions of day vs nighttime dosing are extremely varied and must be individualized based upon frequent blood glucose test results; dogmatic rules and formulas should be

avoided but with time, experienced practitioners can have a strong sense of initial dose estimates and the changes to reach such treatment goals safely. Other advantages of analog-based multidose insulin regimens include the following:

(a) Hypoglycemic reactions may be decreased significantly in number or severity because smaller doses of insulin are needed at any one dose time;

(b) More physiologic match of insulin to meals is achieved; and it may be easier to teach abstract concepts, such as balancing insulin with food and activity, particularly when using the three rapid acting insulin analogs (lispro, aspart and glulisine insulin) 15 minutes prefood;

(c) Newer even more–rapid acting prandial analogs (or inhaled fast acting analogs) are being studied or will soon be available that may even avoid the need for dosing 15 minutes preprandially to accomplish similar goals; these are currently too new or not yet fully available to have reliable and full confidence;

(d) Because 80% to 90% of children will have "total diabetes" within 2 to 5 years of diagnosis, it seems prudent to initiate a two, three, or even four or five times a day shot MDI schedules using very small and minimally painful pen tip needles attached. Such needle tips are disposable and attach to very easy to use insulin pens instead of vials of insulin administered by syringes – if these are available and affordable. If this is done early in treatment, it minimizes some of the initial fears and hassles while at the same time helps to improve psychological acceptance and teach the concept of matching insulin to activity and food effects. Teaching insulin pen use often takes just a few minutes compared to 30-60 minutes for teaching older, syringe based administration but pens are often significantly more expensive than syringes and such financial issues, of course, needs to be considered.

Other considerations also need to be thought about regarding insulin therapy. Insulin analogs (lispro, aspart and glulisine) are the most physiologic rapid-acting insulin preparations and can be given immediately before or after eating to mimic previous endogenous insulin delivery. However, waiting about 15 minutes prior to eating, seems to allow optimal matching of food absorption, prandial glycemia and absorption of insulin given subcutaneously thus minimizing both hypoglycemia as well as hyperglycemia so pre-meal insulin analog prandial insulin has become our most common recommendation to optimize results and minimize hypoglycemia accordingly.

Regular (human or animal-based) insulin takes longer to be absorbed, reaches a peak after injection later than such rapid-acting insulin analogs, and often has a more prolonged "tail effect" causing delayed hypoglycemia hours after use.

Analogs also can be used in combination with intermediate-acting insulins in any patient with diabetes who demonstrates postprandial hyperglycemia after meals and/or snacks, with overlapping NPH providing basal insulin function. Better still, they can be used with the longer sustained analogs like glargine and detemir as well as more recently also with insulin degludec, but must be given using different syringes or pens, since these longer-acting insulins have a different pH and do not readily mix with faster acting insulins.

In a three shot-per-day older and less expensive regimen, prebreakfast, presupper, and bedtime insulin is given. This most commonly involves regular insulins plus an intermediate-acting insulin prebreakfast, analog or regular insulin alone presupper, and intermediate-acting insulin alone at bedtime. This has a major benefit of decreasing peak early nocturnal insulin effects between 2 AM and 4 AM from suppertime NPH. Sometimes combinations of two types of insulin are used at two or three of these injection times based on actual blood glucose readings. Here too it must be stressed that twice-a-day older regular and NPH regimens provide fewer injections and allow mixing in a syringe of the regular and NPH preparations but at a cost of decreasing food and activity flexibility and increasing hypoglycemia risks. This must be weighed based on availability and all these other factors, of course.

Prandial analog insulin doses with a pre-bedtime intermediate or long-acting insulin work best for some patients with type 1 diabetes (four-or five-shot regimen). This regimen tends to provide greater flexibility with changing patterns or inconsistent food provision/food insecurity; changing activity also may respond better under such circumstances offering improved dosing flexibility. Overlapping doses of intermediate-acting insulins can be combined with any or all of these four injection times based on blood glucose data but with the expectation that these older less expensive NPH insulins would still have significant peak effects and more variability than the newer basal analogs.

Glargine (Lantus® and Abasaglar® and detemir (Levemir®) insulins as well as newer degludec (Tresiba®) insulin significantly help decrease hypoglycemia and in many parts of the world have become the preferred basal insulins. Usually glargine as a basal

insulin can be started alone at bedtime and this has been the time-tested substitute for NPH to avoid NPH peaks and the shorter NPH duration compared to glargine. In very young children, glargine sometimes is given only at breakfast. Most youngsters, however, need glargine insulin twice-a-day to prevent a waning effect at the sixteenth to twenty-fourth hours.

Detemir insulins as a basal insulin is almost always used via a twice-a-day regimen but, as with all insulin regimens, is often started alone at bedtime and a morning dosage added based on actual blood glucose results in an individual patient rather than with preconceived rules. Such decisions should be determined by pre and postprandial glucose levels as well as levels through the night to individual basal insulin needs for any given patient. Degludec with a somewhat flatter and longer duration effect usually is administred just once-a-day for basal insulin effect but there are more adult research studies involving degludec than in children and adolescents even though there is no theoretical reason to suspect that the same benefits wouldn't accrue with younger patients. More clinical experience should answer such questions in the coming years especially with more sophisticated continuous glucose monitoring to help determine the ups and downs and insulin peak patterns, help with safety concerns etc. Lente and ultralente insulins have generally been discontinued although are still available in some parts of the world. Both have significant peak effects and significant variability from day-to-day compared to the newer “flatter” analogs, glargine, detemir and degludec.

In general, insulin doses with fast-acting prandial analog insulin should be given about 15 minutes immediately before meals to best match food absorption and insulin absorption characteristics. If older, somewhat slower, regular insulin is used, it should be given 30 to 60 minutes before food but this is rarely sustained because of its inconvenience. For very young children where food intake is unpredictable, the newest fast acting analogs (lispro, aspart and glulisine) can be given immediately *after* food is consumed so that less guessing and food-battling occurs. This is less physiologic but better balances food inconsistencies and therefore helps to decrease hypoglycemia when insulin has been given but the child "refuses" food.

Also, actual insulin absorption may be different in different parts of the body. This may occur because of more physical activity and muscle action affecting the skin of arms and legs compared to buttocks and abdominal sites but also can be unique in any

individual patient as well. Different manufacturers use different buffers in their insulin preparations and this may contribute to insulin–food mismatches if brands change frequently. Ideally, the same brand of insulin should be used unless a specific reason exists to change from one manufacturer to another or availability of insulin is problematic. Insurance companies who periodically force changes in brands do not do so based on medical science but only for economic reasons and frequently disrupt patient care in addition to wasting valuable medical time needed for re-training and reassurance. Insulin absorption is most consistent in the abdominal and buttocks regions compared with the extremities presumably because there is less activity variability. Exercise-related changes themselves can contribute to poor glucose control because of changing absorption when there is changing activity of the arms and legs during the day.

Hypertrophy

Insulin lipohypertrophy, while much less common and less intense than years past, occurs when the same site is overused and is more common with animal-based insulin preparations, synthetic human insulin modified from animal-based insulin precursors than the newest synthetic analog insulins.

Individual sensitivity to hypertrophy predisposes some patients more than others even when sites are varied. Any insulin lipohypertrophy interferes with insulin absorption consistency and contributes to erratic hyperglycemia as well as hypoglycemia because of the subcutaneous scar tissue and changes inflammatory processes as well as blood absorption characteristics. Improved purity of insulin has likely helped decrease hypertrophy problems first as we moved to more pure preparations of animal-based insulins, then as we learned how to synthesize human insulin and more recently as this has moved into the insulin analog current phase of “designer” insulin which alter uptake and duration characteristics as well as action curves.

Lipoatrophy

With improved manufacturing of newer insulins, insulin lipoatrophy now is rarely seen with current highly purified animal or human insulin preparations and even less so with the newest analog insulins despite the fact that this was a common and disfiguring complication of insulin injections in the past.

Insulin doses[3,12]

Most youngsters at diagnosis need approximately 1.0 U/kg per day. With MDI (multidose insulin) regimens, about 50% of total dose is given as basal insulin. Usually this would entail about 80-90% as bedtime glargine and 10-20% as breakfast glargine but with varying amounts and individualized proportioning if detemir is used instead of glargine. About 10% of patients, particularly younger patients, need a "reverse" distribution with more in the morning dose of glargine and less at bedtime (sometimes none at all at bedtime in toddlers). The prandial analogs (lispro (Humalog®), aspart (Novolog®) or glulisine (Apidra®) would constitute the other 50% distribution with about 20% prebreakfast, 10% prelunch and 10% predinner plus the remaining 5-10% presnacks utilizing the most up-to-date multidose insulin (MDI) regimens to gain maximum flexibility, decreasing hypoglycemia and optimizing overall glycemic control in the process.

As with all insulin regimens, individual food and activity preferences are extremely important just as a non-dogmatic approach should be fostered based upon pre- and post-prandial actual blood glucose data rather than automatic assumptions. With certain individuals eating larger lunches than breakfast (ie. Mediterranean style food distribution) this would demand larger insulin coverage in the middle of the day rather than at breakfast or evening meals.

Because of overnight cortisol and growth hormone effects, the morning "dawn phenomenon" may also be seen and this requires relatively larger boluses than would be needed at other times of the day. Reverse dawn phenomena, however, also occurs not infrequently. An elegant study doing continuous glucose monitoring in insulin pump treated patients collected sophisticated data and defined four distinct insulin dose patterns that can be applied to patients using any type of insulin administration system coupled with some blood glucose monitoring to identify which pattern best fits their individual circumstances.[24]

The remission stage *("honeymoon" phase*) results from a partial recovery of islet cell function (as documented by C-peptide as well as relative ease of control and stability of treatment seen in blood glucose results from day-to-day). It occurs within 1 to 3 months after diagnosis and can last from weeks to a few months, during which time insulin requirements fall drastically to less than 0.3 U/kg per day and, in some (rarely), to no requirement for insulin at

all. This honeymoon phase happens more often in adolescents and young adults who, while antibody positive, seem to have a different time course of their diabetes natural history. However, insulin administration usually is not discontinued during this time because of potential development of insulin allergy (see below), as well as the need to reinforce the concept that type 1 IDDM is a lifelong illness without potential for true remission with current treatment. Remission phases last longest in older teenagers and young adults compared with toddlers and school-aged children but also in certain non-Caucasian ethnic groups. If significant obesity and/or polycystic ovary syndrome with insulin resistance occurs, this too may influence residual insulin availability and thus external insulin needs so should be taken into account. There is some theoretical consideration for "resting" the damaged beta cells shortly after diagnosis and this is also used as a strategy for continuing even small doses of insulin.

Eventually, most pre-pubertal youngsters require between *0.6 and 0.8 U/kg per day.* On a twice-a-day insulin regimen, two thirds of a total dose given as a mixture of regular plus NPH a half-hour before breakfast (in a ratio of about 1 unit rapid acting insulin for every 3 to 4 units of NPH plus one third of the total dose given as a mixture of rapid-acting insulin plus NPH a half-hour before supper (in a ratio of 1:1–2). Using an intensified multidose insulin (MDI) regimen which frequently has replaced a twice-a-day regular plus NPH overlap, small bursts of insulin analogues (i.e., lispro, aspart or glulisine insulin) are used about 15 minutes prior to meals (and often before snacks too), with some type of basal insulin provided either at bedtime alone, bedtime plus breakfast or in overlapping doses (if using NPH) throughout the day and night. This can be started at diagnosis or introduced when treatment goals are modified and intensified. Ratios are usually 50% basal plus 50% prandial boluses. Teenagers may need as much as *1.0 to 1.5 U/kg per day* during the rapid growth spurt at or around puberty; in subsequent years they return to lower insulin requirements.

If there is concomitant or subsequent obesity, such dose: weight ratios increase since there is also usually significant insulin resistance with a need for higher doses to accomplish the same glucose lowering effect.

The ratio of faster acting insulins to NPH insulin as well as basal analog insulins can vary according to the activity of the patient and the type and amount of carbohydrate ingested. NPH, lente, and ultralente insulin are absorbed somewhat more

inconsistently on a day-to-day basis and thus produce more peak effects in a much more variable fashion than faster acting, lower-peak and longer-lasting analog insulins like detemir, glargine and degludec. Glargine and detemir as well as the newest basal insulins such as degludec produce somewhat more predictable insulin effects from day-to-day and also do so with lower peaks to explain improve glycemic variability, efficacy and lowered hypoglycemia. This is especially well documented with reductions in nocturnal hypoglycemia – times when someone is usually asleep and therefore less likely to be aware of hypoglycemia. While supposed to be peakless, glargine and detemir sometimes will have a (small) peak effect at 12-16 hours after being given and this can be determined by careful round-the-clock glucose monitoring or with the newest continuous glucose monitoring sensors. Under most circumstances, glargine, detemir and deludec insulin are associated with less hypoglycemia and better more consistent basal delivery characteristics.

Insulin doses at lunchtime and mid-afternoon, and the number of insulin injections, varies depending on activity intensity and consistency as well as food ingestion, glycemic effect and which type of basal insulin is utilized.

Many youngsters do extremely well with overlapping doses of analog insulin and NPH prebreakfast, prelunch, predinner, and NPH at bedtime if the more expensive degludec, detemir or glargine basal insulin is unavailable or not used. Some with large afternoon snacks and relatively little afternoon activity also need presnack analog insulin to keep predinner blood glucose levels in target range. Identifying specified and individual blood glucose goals allows for optimal choice of insulin type and dosing. Insulin doses must be individualized according to food and activity patterns as well as individual insulin absorption characteristics. (see also insulin pump section below). A template used at NEDEC for prandial insulin dosing is shown in Table 2 (which also includes advice for some food adjustments, activity adjustments, and sick day as well as hypoglycemia treatment).

Table 1.2. NEDEC algorithms, sick-day advice, and hypoglycemia information

INSULIN ALGORITHM - (how to adjust or **VARY INSULIN** for high and low BGs) - this intensified insulin system only works if you know BG level and then allows adjustments for food, activity, stress....

FOR_____DATE_____

BLOOD GLUCOSE	BREAKFAST BOLUS	LUNCH BOLUS	AFTERNOON BOLUS	DINNER BOLUS	BEDTIME SNACK BOLUS	
<69 (JUICE)						
70–100						
101–150						
151–200						
201–250						
251–300*						*=check ketones even if not sick
301–350*						
351–400*						
401–450*						
451–500*						
>501*						
BASAL INSULIN						

DAY-DAY GLYCEMIC INDEX ADJUSTMENTS: approximately 1:15 insulin:carbohydrate coverage ratio (DIFFERENT FOOD EFFECTS ON BG LEVELS: USE_____MORE HUMALOG, APIDRA OR NOVOLOG INSULIN FOR HIGH GLYCEMIC INDEX FOODS SUCH AS: CORN PRODUCTS, POTATO PRODUCTS, ROLLS, CHINESE FOOD, PASTA, PIZZA AND MOST "FAST" FOOD. IF MERELY OVEREATING, DECIDE IF YOU NEED MORE HUMALOG, APIDRA OR NOVOLOG TO "COVER" BG EFFECTS.

BUT **DECREASE** HUMALOG. APIDRA OR NOVOLOG INSULIN BY_____UNITS OR ADD EXTRA SNACK FOR PLANNED **ACTIVITY**

NEDEC SICK DAY ADJUSTMENTS: *CHECK BG EVERY 2–3 HOURS INCLUDING OVERNIGHT BGS*

1. GET WEIGHED AT LEAST THREE TIMES EACH DAY . WEIGHT LOSS MEANS POSSIBLE DEHYDRATION. DRINK MORE SALTY FLUIDS LIKE SOUP/BROTH.

2. CHECK KETONES AT LEAST EVERY 3–4 HOURS. IF +, MORE INSULIN NEEDED IF BG LEVELS ARE ALSO HIGH.
3. EXTRA INSULIN **(SICK DAY BOOSTER)** IS BASED ON 10–20% OF TOTAL DAY'S INSULIN DOSE ( ) IF YOUR BLOOD GLUCOSE WAS 100. THIS 10–20% SICK DAY BOOSTER IS GIVEN EVERY 3–4 HOURS DAY & NIGHT. THIS IS MUCH MORE THAN USUAL ALGORITHM CHANGES

   →10% SICK DAY BOOSTER IF BG >240 & KETONES NEGATIVE: ☐ **EXTRA HUMALOG OR NOVOLOG OR APIDRA**

   →20% SICK DAY BOOSTER IF BG >240 & KETONES POSITIVE: ☐ **EXTRA HUMALOG OR NOVOLOG OR APIDRA**

4. CALL IF NOT BETTER, SYMPTOMS DO NOT GO AWAY , SEVERE HEADACHE OR ACTING STRANGE, VOMITING DOES NOT STOP OR WEIGHT LOSS CONTINUES OR IF NOT SURE WHAT TO DO
5. RARELY , WITH ILLNESS, INSULIN NEEDS TO BE DECREASED - WHEN BG <100.

6. USUALLY, EVEN IF NOT EATING WELL, ILLNESS BLOCKS INSULIN SO THAT EXTRA INSULIN IS NEEDED.

NEDEC HYPOGLYCEMIA RECOGNITION & TREATMENT: IF POSSIBLE, CHECK GLUCOSE

A. DECIDE IF EXTRA FOOD NEEDED AT BEDTIME SNACK FOLLOWING INCREASED AFTERNOON OR EVENING ACTIVITY

   TO PREVENT OVERNIGHT (NOCTURNAL) HYPOGLYCEMIA!!!

B. NEVER GO TO BED WITHOUT KNOWING YOUR BLOOD GLUCOSE LEVEL.

C. REMEMBER THAT MANY EPISODES OF HYPOGLYCEMIA DO NOT PRODUCE SYMPTOMS. CHECK YOUR BLOOD GLUCOSE LEVEL BEFORE A NAP.

D. IF ABLE TO TALK AND RESPOND, GIVE 4–6 OZ OF JUICE OR SUGAR-CONTAINING SODA OR 2–3 GLUCOSE TABLETS OR 7 LIFESAVERS ® OR GLUCOSE GEL OR HONEY OR REGULAR TABLE SUGAR. RARELY THIS NEEDS REPEATING. (NOT CHOCOLATE **or other high fat foods**: TOO SLOW ACTING AND ALSO EXCESSIVE CALORIES)

E. DURING DAYTIME, USUALLY NO NEED FOR EXTRA SNACK AFTER TREATING REACTION; JUST JUICE OR OTHER SIMPLE CARBS.

F. IF MIDDLE OF THE NIGHT , BE SAFER AND GIVE AN EXTRA SNACK: 1 BREAD + 1 PROTEIN W/FAT.

G. IF LIMP , HAVING A CONVULSION OR SEIZURE, UNCONSCIOUS OR NOT ABLE TO TALK→THEN DO NOT PUT ANYTHING IN THE MOUTH, USE GLUCAGON SHOT $^1/_4 - ^1/_2 - 1$ MG IN MUSCLE. IF NOT BETTER BY 15 MINUTES, CALL US - ANY TIME DAY OR NIGHT - SO WE CAN DISCUSS AMBULANCE, EMERGENCY ROOM EVALUATION AND INTRAVENOUS GLUCOSE

Types of insulin

Human analog insulin is preferred at the time of diagnosis to reduce the likelihood of future allergic problems such as itching, burning, redness, and hives. Because purity of insulin seems to be related to lipoatrophy at injection sites, such atrophic sites may be completely avoided with the use of either pure pork or human insulins. Lipoatrophy was very commonly seen up to the late 1970s but is extremely rare due to the availability of purer insulin preparations and improved quality-controlled preparations, except in parts of the world where insulin purity is less than ideal.

Analogs have continued this trend of vastly improved purity and fewer side effects although some patients still demonstrate some scarring/hypertrophy at injection sites that are overused without optimal site rotation. If costs were taken out of the equation, it is likely that all insulin would be of the highest purity, human rather than animal based, analog rather than other formats. While the situation is improving all the time, this ideal situation does not exist around the world and there still exist many patients who simply have no insurance, no government support and therefore no availability of insulin unless it is donated by such fabulous programs such as Life for a Child (LFAC) or Changing Diabetes in Children (CDIC).

Insulin allergy

Local allergy to insulin itself is now extremely rare. It may occur minutes to hours after injection and may manifest with redness, pruritus, swelling, and heat as well as urticaria. It usually occurs within the first few weeks of therapy and can be self-limiting. Intradermal insulin injections caused by poor technique sometimes can cause similar problems but such technique problems when corrected "solve" the "hives" and discomfort.

Smaller and finer needles on syringes and needle tips on insulin pens allow for optimizing administration for the individual patient such that there are 4 mm, 5 mm, 6 mm, 8 mm and 12.7 mm needle tips, for instance, that are attached to insulin pens to help minimize discomfort (and needle phobia) as well as optimize depth of injection. (There also are devices which “hide” sight of the needles especially for very young children or for those especially fearful of needle use (i.e. Inject-Ease®) Even more rarely, systemic allergy to insulin occurs with manifestations of total body urticaria, angioneurotic edema and frank anaphylaxis especially in an

otherwise allergy-prone individual. This type of insulin allergy may be related to prior intermittent use of insulin as may occur during the honeymoon phase or when gestational diabetes needs change after delivery so that insulin is discontinued but then later, insulin is resumed. In parts of the world where purity of insulin is in question or where there is intermittent insulin availability because of financial barriers, this too produces similar potential allergic problems that may otherwise be avoided.

The immediate systemic reaction is more likely IgE mediated (local allergy tends to be IgG mediated). Insulin desensitization is the required preventive measure. Insulin allergy desensitization kits can be obtained from most insulin manufacturers on special request or in consultation with diabetes specialty groups although such severe allergic phenomena related to insulin is more and more rare.

Administration of shots

Some problems may occur when overemphasis is placed on children younger than 10 to 12 years measuring insulin doses and administering their own shots. In general, adults should retain the major responsibility for diabetes care during this time and often even directly supervising teenagers. Gradual transfer of this responsibility is begun when the child with diabetes demonstrates age-appropriate readiness to accept the day-to-day burden of self-care coupled with mature self-responsibility and honesty. Forcing such self-care too early may result in falsified blood glucose results and/or insulin omission on the part of a child wanting to "save face" about dietary, testing, or insulin difficulties. Automatic injection or pen delivery systems may be preferred for children on MDI regimens especially if school-time doses are needed and optimal adult supervision is not available (i.e., no school nurse present or teachers reluctant to provide such supervision). Such devices often decrease dosing errors and are more comfortable being used in front of peers.

Omitted insulin may occur up to 30% of the time in adults as well as in children and adolescents [3] when prescribed insulin doses are compared with actual pharmacy vials distributed.

Lack of comprehension of the importance of glucose control, eating disorders, depression and anger in patients, and patients feeling overwhelmed by the difficulties of modern diabetes treatment all contribute to insulin omission.

A form of anorexia nervosa which we coined as "diabulimia"[13]

in 1979 exists where, instead of omitting food or purposeful vomiting to allow binge eating but not weight gain, insulin is surreptitiously omitted causing chronic hyperglycemia, urinary caloric losses and sometimes dangerous and recurring DKA. Often there is significant psychological distress including sexual abuse or other types of severe trauma that is the basis for such problems but played out through diabetes.

Fear of hypoglycemic reactions[25] what we coined "hypophobia")[26] in the 1980's) is another reason for purposeful but unacknowledged insulin omission.

If insulin omission occurs frequently or excessively, not only is glucose control compromised, but ketoacidosis and death may result when cases are extreme. If glucose control is elusive and/or grossly elevated A1c levels persist, having responsible adults actually draw up and administer all insulin doses (and actually directly supervise or do blood glucose testing at home and also at school) frequently "solves" the problem.

Assistance with psychosocial parameters of care with social workers, therapists and/or psychologists and psychiatrists when there is significant or persistent hypophobia or other psychological disturbances such as physical or sexual abuse, post-traumatic stress disorders, substance abuse, executive dysfunction and/or attention deficit disorders can be invaluable.

All health care workers involved with a chronic illness such as diabetes where food, self-care behaviors and chronicity interact to such a degree, must be educated and sophisticated sufficiently to consider such concomitant factors particularly when actual care defined by blood glucose monitoring results, unbelievable blood glucose monitoring results, rising A1c or recurrent DKA are taking place.

HOME MONITORING

Home blood glucose monitoring (SMBG) or self blood glucose monitoring (SBGM)[1,2,3,5,21,27,24]

The best and most accurate home monitoring system involves the use of capillary blood glucose determinations. Automatic lancet injectors (eg: Monojector® Penlet®, Autolance®, Autolet®) are available for skin puncture to minimize trauma and discomfort using short and very fine disposable lancets. One of the best ways to lessen initial fear that our team has learned, especially with children, but, in fact, with all patients at diagnosis, is actual initial

demonstration of fingerstick technique and such monitoring with the health care professional doing this on themselves while explaining the process and the minimal discomfort to the child and family members present. These devices also effectively "hide" the lancet needle helping to decrease fears of the needle itself. The very small drop of blood obtained is placed at or next to a reagent strip and usually the blood is "sucked" into or placed onto the strip whereupon colors are read with the use of a colorimetric meter or with meters reading blood glucose levels via electrical impedance. In the early days of self blood glucose monitoring, there also were visually read blood glucose test strips but these are no longer available. Reflectance meters and electronic meters (Bayer's Contour® series, LifeScan's Ultra®, UltraMini®, Profile® and Verio®, Abbott's Precision Xtra® and Free Style® series; Roche's AccuChek® series meters; Nipro® meter and so forth) are widely used because of increased accuracy and ease of administration with some more recent comparisons between these meters documenting the improved accuracy, specificity and sensitivity.

Many diabetologists and patients as well as parents prefer memory meters, which can also be downloaded into home as well as office computers and more recently to cell phones. This all facilitates ongoing data analysis and graphic displays to help analyze patterns of glucose control and helps patients and family members become not just reactive to the BG results but also more proactive (see below). The newest meters use minute amounts of capillary blood (1-5 uL) to decrease pain and discomfort as well as semi-automatic capillary filling characteristics of their test strips. These features lead to more accurate testing. The newer meters also auto-calibrate when strips are inserted further decreasing user errors. Some but not all meters can be programmed to automatically send results to insulin pumps and to have such data incorporated into the pump computer analysis downloaded data simultaneously (see below). The newest will use blue tooth technology to send data for storage and analysis more and more automatically. Some separate computer and mobile telephone-based applications such as Glooko®, Diasend® , Diabetes Log®, Glucose Buddy®, Log for Life® and many others) download blood glucose meters (as well as insulin pumps and continuous glucose monitors) and can be shared with other family members and health care provider automatically for home analysis between visits to health care providers. Meters, of course, are also used to assist in calibrating continuous glucose monitoring sensors (CGMS) such as

those that are manufactured by Medtronic Minimed®, DexCom® Abbott's Navigator® series and others to come. More recently, CGMS systems such as DexCom-5® no longer require predetermined capillary glucose calibrations and it is expected that this will be true for all such CGMS within the coming years.

Table 1.3. NEDEC Home blood glucose monitoring protocol [a]

	Check prior to							
Interval	Breakfast	Mid-Morning	Lunch	After-noon	Dinner	Bed-time	11 PM-MN	3-5 AM
"Profile" 3 days each month[b]	bG	bG	bG	bG	bG	bG	bG	bG
Daily	bG		bG	bG	bG	bG		
Every 8 days (awake profile)	bG	bG	bG	bG	bG	bG		

[a] bG, blood glucose.

[b] On sick days, follow this profile for testing, sometimes more often, and remember to **check for acetone** whenever blood glucose level is more than 240 mg/dL.

Problem-solving profile should be obtained whenever there is a question of dosage needing adjustment or change. Many patients can obtain 3–4 blood glucose measurements each day. Keeping written records is important so that patterns can be identified. 240 mg/dL. than more is level glucose blood whenever

Blood sugar monitoring should ideally be done every 2 to 3 hours around the clock and this includes preprandial as well as postprandial assessments. Such monitoring is expensive and often deemed impractical by many patients especially overnight monitoring.

An example of NEDEC's suggested monitoring is shown in Table 1.3 that separates day-to-day monitoring for prandial dose decisions, periodic overnight monitoring and both pre and post prandial checking for more intensified problem solving especially just prior to follow-up visits so that both patient, family and diabetes team can have access to more information for education and "detective" work. Government as well as private health care insurers do not "like" to cover such frequent monitoring costs without tedious appeals and rationalizations. Newer but expensive continuous glucose monitoring sensor (CGMS) capabilities (see below) can provide up to 288 daily glucose values (ie. automatically

every 5 minutes) and there is convincing published research confirming that if such data is used correctly and in ongoing fashion, rather than only intermittently, overall glycemic control can improve at the same time A1c is lowered and hypoglycemic events can be identified and minimized.[28] Attaching such CGMS to insulin pumps to provide semi-automated feedback will effectively help "close the loop" and move towards a hybrid or truly artificial pancreas in the not too distant future and there are more and more ongoing research trials evaluating such devices, how they might be used and under what circumstances, which patients are good candidates and which are not from a behavioral and psychological as well as educational standpoint, what types of problems can be expected and what types of solutions need to be considered medically, psychologically, behaviorally etc.

Low glucose suspend features of CGMS connected to insulin pumps already exist and have documented better control, less severe and less frequent hypoglycemia.

Automatic basal pump adjustments based on CGMS also has more recently been shown to move towards the "hybrid" artificial pancreas systems, predicting rising as well as falling glycemia and thus avoiding more sustained glycemic aberrations Computer mathematical models for such adaptations are now more available and help to sustain such improvements.

The more frequent the actual blood glucose monitoring, the more data are available not only for pattern analysis but also for adjustments of food and/or insulin in what is deemed "reactive" adjustments (after the fact). Daily monitoring for type 1 diabetes is usually recommended before and after breakfast, before and after lunch, before and after dinner and at bedtime.

Occasional middle-of-the-night BGs are also needed for specific problem solving and to identify asymptomatic hyperglycemia as well as nocturnal hypoglycemia. Here, to, CGMS automatically provides such information without the need to set middle-of-the-night alarms but identifying potentially risky situations such as asymptomatic nocturnal hypoglycemia or even patterns of hyperglycemia that would otherwise go unrecognized. All such monitoring is more expensive as more testing supplies are needed, often impractical (especially overnight) or only done on intermittent occasions with capillary BG testing.

Many patients can be encouraged to do such monitoring but do not seem able to sustain these efforts. Another group of patients seem to be able to monitor in an intensive fashion and even keep

logbooks of data - but do not have the necessary mathematical skills to analyze the data obtained and this may be more common than appreciated. Some will utilize computer downloading programs to assist in this analysis task but then discontinue such efforts as too cumbersome or time-consuming or just too difficult. (see Table for an example of a SMBG protocol).

Most recently, there are also studies utilizing CGMS in patients not using insulin pumps but MDI or other non-pump treatment regimens but still interested in more frequent monitoring, overnight monitoring or because of problematic or too frequent hypoglycemic episodes as well as hypophobia.[29]

On rare occasions, such as sick days assessing hyperglycemia or for specific problem solving, blood glucose monitoring every 1 to 2 hours has been used to identify subtle hypoglycemia and/or its after-effects (see below) as well as fine-tuning basal-bolus MDI regimens and insulin pump delivery with growth, activity and schedule changes etc. CGMS facilitates such data collection since it is semi-automatic and requires SMBG for calibration but not as frequently on a day-to-day basis. Efforts to create CGMS sensors wich are factory calibratded and do not need at home calibration are on the horizon and beginning to be produced and authorized by health care authorities.

There have been no significant problems with local cellulitis, abscess, or excess callus formation using this protocol in patients as young as neonates as long as reasonable common sense, site rotation and hygienic technique is used. However, localized infections can and do occur and need standard antibiotic treatment usually for typical staphylococcal and/or streptococcal infection. Almost always these occur with poor hygiene or poor technique. Routine alcohol swabbing is no longer recommended although obvious handwashing to keep food particles and obvious dirt out of the path of the sterile lancet remain appropriate with periodic reminders and discussions at follow-up visits. Many patients re-use their lancets until they are dull and hurt but this is not the “official” recommendation because of sterility concerns.

With CGMS the potential for localized infections also exists but, similarly, with reasonable technique and hygiene at the sites, this is not a major dilemma although a significant minority of patients continue to have localized allergic problems from the catheter itself or, more commonly, from the taping adhesives designed to keep the sensor from movement or falling out while in use. Localized anti-inflammatory glucocorticoid steroid water-based

sprays usually used for allergic rhinitis have proved to be very helpful if sprayed on before placement in such patients to minimize localized redness, itchiness and irritation.

Urine glucose testing[5]

Double-voided urine testing allows assessment of both sugar and acetone in a semi-quantitative fashion. It should be realized that urine glucose testing is less accurate than blood glucose testing because of changes in renal threshold, fluid intake and output. In certain circumstances where costs or availability prohibit SMBG such urine glucose testing should not be automatically discounted since some information provided in this fashion is certainly better than no information at all. However, the actual costs of urine test strips is still expensive and availability as well as cost may still make such testing prohibitive in many regions. Because these can be visual strips, there is no added costs of a meters and batteries, however, so that should be taken into account accordingly. Combination systems such as Chemstrip uGK® and Keto-Diastix® allow identification of glucose and ketone spillage. These are the standard urine testing systems for use on sick days and on days when blood sugars are either running high (>250 mg/dL) or are not being otherwise checked. In parts of the world where blood glucose monitoring is too expensive or otherwise unavailable, urine glucose testing with strips or reusable test tubes with Benedict's solution also may provide information for some daily monitoring of insulin, food and sick days.

Ketone testing[10,21,24]

Urine testing for ketones remains extremely valuable during sick days or whenever ketoacidosis may occur. Combination systems, such as Chemstrip uGK® or Keto-Diastix®, can be used, or, alternatively, simple ketone testing urine systems, such as Chemstrip uK® or Ketostix®, can be used. If these are unavailable, older nitroprusside powder can also be used. All such systems test for acetone and acetoacetate, but not for *β*-hydroxybutyric acid, and provide guidance regarding the need for extra insulin under such circumstances.

Ketone capillary blood systems (Precision Extra® meters) also now are available that will test specifically for blood *β*-hydroxybutyric acid and may eliminate the need for nonspecific urinary acetone and acetoacetate testing while also providing earlier

data about ketonemia but at higher expense and the need for a dedicated meter (and batteries) to read the ketone strips. When used appropriately, they help decrease ketoacidosis and perhaps save significant emergency room and hospitalization costs and do so somewhat earlier and more reliably than the older acetone and acetoacetate systems. Because any such ketone testing systems are only used intermittently, repetitive teaching/training and reminder-teaching is needed (at least annually, ie. pre-winter flu season) to document that supplies are current and not out-dated and that techniques are remembered including specific sick-day guidelines (see *Table 1*).

SBGM with insulin and carbohydrate algorithms

Better decisions regarding insulin, food amounts, and food choices, as well as exercise, may result from using insulin algorithms (see Table 2). These provide a basis for flexibility with insulin analogs or even with MDI-based regular insulin. *Strict blood sugar goals* including setting target goals to achieve near-normal blood sugar levels - about 100 mg/dL (~5.5 mmol/L) - *without frequent episodes of (severe) hypoglycemia* throughout the day and night and concomitantly to sustain A1c levels below 7.5 % (some would say below 7.0%) safely in an effort to mimic DCCT-level results, thus mitigating or avoiding short and long term diabetes-related complications (see below). An overall target of 70 to 140 mg/dL (~4-8 mmol/L) preprandially and lower than 160 to 180 mg/dL (~9-10 mmol/L) postprandially. A1c levels <7-7.5% to approximate DCCT-level goals while minimizing significantly hypoglycemia. Some consideration in achieving blood sugar goals would need to be individualized with smaller amounts for younger children, higher amounts for those moving through puberty, presumably related to pubertal hormone changes, and then somewhat decreased considerations post-puberty: usually 0.5 to 1.0 U of fast-acting analog or regular insulin decreases blood sugar levels by 40 to 50 mg/dL (~2-3 mmol/L) for patients taking 20 to 40 U/d if blood sugar levels are below 240 mg/dl (~13 mmol/L); above 240 mg/dl (>13 mmol/L), the patient may need proportionately more insulin to accomplish the same goal (1 to 2 U to decrease 40 to 50 mg/dL (2-3 mmol/L). Using insulin pump terminology even for non-pump-treated patients, this produces what is called an *insulin correction factor* (or insulin sensitivity factor) with those needing very small total amounts of insulin each day (youngest infants and children) often having an insulin correction factor (CF)

of 1:100 whereas those with somewhat higher doses needing the more typical CF of 1:50. Those with insulin resistance and needing proportionately higher insulin doses, presumably associated with obesity or other factors such as pubertal hormone increases would need a CF of 1:25-30. In very young children and in those who are extremely sensitive to insulin, u100 preparations can be diluted (make u10 or u20 insulin with diluent supplied by manufacturer or with normal saline). Then algorithms can be created using 0.1-to 0.2-U increments. SMBG pre and post prandially (or CGMS) is used to double-check and adjust the algorithms being applied to avoid over-corrections and excessive hypoglycemia as well as under-correcting. Improvement (or lack of) is confirmed by hemoglobin A_{1c} (HbA_{1c}) measurements every 4 to 6 weeks as performed in the DCCT (Diabetes Control and Complications Trial) (see below). Although many people do not recommend getting A1c levels more than every 3 months, we believe that more frequent contact, more frequent discussions, more frequent interactions and review may be key to achieving DCCT-style success so generally see patients every 1-2 months with A1c levels checked at each follow-up visit: monthly or more frequently if problems persist and every 2 months if no problems occur and target goals are being met.

Dietary compliance issues should be part of specified education[30] not only at diagnosis but periodically and regularly reviewed and updated to include family-specific food and meal planning knowledge particularly carbohydrate counting and glycemic excursions after different types of meals high or low in fat, high or low in fiber, simple or otherwise complex carbohydrates. This should all be periodically reviewed (at least annually in a formal session) with reasonable timing of meals in relation to insulin injections and aiming for optimal consistency of day-to-day activity schedule as much as possible. Easy-to-obtain and often virtually freee telephone applications (“aps”) such as Lose-It®) (and many others) are excellent for teaching and confirming carbohydrate counts, fat content and calorie content to assist with mealplanning so that guessing about food intake is decreased or eliminated. Helping patients and family members learn about reading food labels also can be invaluable since most of us (and our patients, too) eat similar foods quite frequently and so these can be "learned." One may specifically establish and confirm carbohydrate algorithms in a similar fashion (i.e., how much fruit or bread must be changed to bring about an increase or decrease in blood sugar, which foods have what type of glycemic effect, effects of high fiber or

high fat on food absorption, what types of adjustments with food are needed for different types and intensity and timing of activities).

Problems with SBGM include nonacceptance of need for ongoing, frequent blood glucose surveillance and frustration when diabetes remains difficult to control. Occasionally SBGM results will be misleading when done improperly so this must be discussed and appropriate education and re-training provided including attention to behavioral issues and compliance, embarrassment in front of peers or in public places etc. Financial constraints can include general unavailability of testing supplies as well as actual costs. Results can be falsified because of fears of being "caught omitting insulin, overeating or just making mistakes." Keeping logbooks or figuring out ways to analysis large amounts of data can be difficult as a task, difficult to accomplish because of competing tasks such as school work, peer relations, embarrassment at results or other psychological and family as well as personal factors. A surprising number of people have mathematical "dyslexia" (dyscalculia) that is unacknowledged or unrecognized yet such specific numeric analysis skills are a key part of current diabetes management utilizing blood glucose results for pattern identification and then not only being reactive to such results but being proactive to analyze them and therefore minimize or prevent future problems accordingly. A good number of our patients believe that just doing the blood glucose results is all that is required so strategies that emphasize again the psychological, behavioral, cognitive skills needed for not only ongoing testing but also analysis are important for patient and family members involved with diabetes care. Those who do this, usually are in the group that succeed at keeping lower A1c results, minimizing or eliminating severe hypoglycemic events and thus leading a healthier life with fewer long term complications and better quality of life ongoing.

MEAL PLANNING[1,2,3,5,21,24,31,32,33]

Dietary prescriptions must take into account the individual and ethnic preferences as well as the family habits of the child, teenager or adult with type 1 diabetes mellitus. Types and timing of food intake are probably more important with type 1 IDDM patients than total calories as long as obesity is not an associated problem. If weight excess co-exists or enters into the situation, then more activity and/or fewer calories also needs to be considered and this

is as difficult as with any type of weight or obesity situation but made that much more complicated because insulin dosage also needs to be adapted and balanced concomitantly. Old diabetes treatment guidelines “forcing” snacks three times a day are less necessary with modern, multidose insulin regimens or insulin pump treatment that is designed to increase choice, increase flexibility, allow different times to eat under differing situations rather than force food intake against insulin peaks. Most of the dietary dogmas of years past have not stood the test of better scientific study but newer recommendations still are mostly offered by scientific consensus rather than with long term prospective studies of large numbers of patients. Individualizing dietary recommendations is also de rigueur. Mobile phones or tablets with free or very inexpensive applications (ie. Lose It ®) are increasingly prolific and useful in assisting not only learning about meal-planning and carbohydrate counting but also in helping to track dietary compliance and choices as they allow scanning of labels, photographic portion control and ease of use.

Carbohydrates

The total carbohydrate content of the diabetic meal plan is usually about 50% to 60% of total calories. If there is significant obesity in an adolescent or young adult, Atkins-style low or "no carbohydrate" meal plans can also be considered with appropriate adjustments downward for prandial insulins while balancing basal insulin regimens by injection, pen or pump based on BG data. Significant decreases in prandial insulin should be expected with such carbohydrate restrictions and often very much easier weight loss occurs and can be sustained with such changes when simple caloie restriction has been elusive or simply failed to produce desired results. Concentrated sugars generally are avoided or minimized in most diabetes meal planning recommendations except for management of short-activity bursts or actual hypoglycemia treatment. Ten to fifteen grams of fast-acting sucrose or glucose (i.e., 4 to 6 oz of orange or apple juice or regular carbonated soda, seven small hard candies such as Lifesavers®), or 10 to 15 g of a variety of prepackaged dextrose preparations (Monogel®, BD Tablets®, Instant Glucose®, Glutose®) is generally adequate treatment. Simple granular sugar (or packets) can also be used if less expensive and other sources are unavailable or just too expensive. Some diabetes specialists now recommend only concentrated carbohydrates during daytime hypoglycemic episodes,

whereas others suggest that extra carbohydrate or protein also be given not just in the middle of the night but during the daytime hours as well. This author suggests that simple carbohydrates be used for most episodes of hypoglycemia except overnight when more caution should be exercised. This helps eliminate excess calories and also provides the fasting type of simple carbohydrates to promote faster absorption and efficacy. Higher fat chocolate or peanut butter products are not optimal to treat acute episodes of hypoglycemia because the fat tends to slow down the absorption of the simple sugars thus delaying hypoglycemic correction; on the other hand, high fat high carbohydrates such as ice cream may be ideal for such circumstances based on documented overnight BG monitoring to detect post-evening exercise nocturnal hypoglycemia. Complex high-fiber carbohydrates (bran, whole-grain cereals and breads, legumes, vegetables, and whole fruit) generally are encouraged. The particular type of carbohydrate or how it is complexed to protein or fat may be more important in its effects on postprandial glycemic excursions than the quantity of sugar in a particular food or meal. Individual patients' responses also need to be learned and considered based on individual blood glucose results and monitoring.

A small minority of diabetologists and nutritionists now are beginning to recommend a very low-carbohydrate/high-protein approach to meal planning on a routine basis and not just for promoting weight loss in those who are overweight or obese. This was, in fact, what was available pre-insulin and in some parts of the world where insulin remains unavailable, still the only treatment in such sad circumstances. This Atkins-like approach is theorized on the basis that less insulin may be needed and has been documented in some research studies and therefore it may be easier to counterbalance food and insulin needs under such circumstances. Basal insulin is still required (pump or injection methods) but at lower dosage compared to higher carbohydrate intakes. Such approaches are more often recommended for adults than for children and adolescents, and more often associated with type 2 rather than type 1 diabetes or with those who need or want weight loss but have not been successful. Our initial use of such very low carbohydrate intake has been very positive but requires a lot of re-teaching and re-training to change prior concepts of nutrition (often that we taught) while the concepts of reducing insulin when reducing carbohydrates has been significantly easier to teach and make happen.

Carbohydrate counting concepts provide added flexibility and decrease the previous restriction on individual carbohydrates by allowing exchanges among all sources of carbohydrates but also require specific individualized learning based on SMBG results pre and postprandially to identify which foods needs which type of insulin response, how this may better balance different types, intensities and durations of activity etc. Paying individual attention to glycemic index variabilities allows for more appropriate adjustment of insulin according to different types of foods and snacks (ie. prolonged pasta effects vs rapid post-potato, corn or rice effects; extended bolus options available via insulin pumps for high fat foods, for bagels or for pizza that seem different than the mere carbohydrate calculations might otherwise predict).

In those with concomitant celiac disease (gluten sensitivity), occurring in the range of 5-10% of type 1 diabetes patients in many parts of the world, wheat and gluten restrictions demand changes to more rapid-acting types of carbohydrates with concomitant need for relatively higher doses of prandial insulin to cover these expected and earlier peak hyperglycemic surges associated with simpler carbohydrate choices. This too needs to be considered, documented with individualized SMBG results and then adaptations created and learned.

Protein

The total protein content of the diabetes meal plan is usually about 15% to 20% as recommended by most dieticians and diabetologists. It may be prudent to limit animal source protein rather than vegetable or fish source protein for general cardiovascular and/or renal benefit but this too is coming into question more recently with carbohydrate restriction showing more promise in reducing obesity and hyperlipidemia compared to prior recommendations to restrict saturated fats. Protein and fat may be very helpful in the bedtime snack to help prevent overnight hypoglycemia since they slow absorption of carbohydrates, and therefore may provide a “lente” carbohydrate effect (i.e., ice cream). This is less important when using "peakless” glargine, detemir or degludec insulin or insulin pump treatment compared to previous intermediate acting (NPH) basal regimens. With insulin pumps, adjustment of overnight insulin can also be accomplished in much more physiologic fashion compared to injected basal insulins and so this too may be more adaptable under such circumstances.

Sugar-containing high-fat ice cream may be an ideal bedtime

snack because the protein and fat content in such ice cream preparations allows for slower glycemic availability throughout the night-time hours and thus decreases the chances of overnight hypoglycemia. Uncooked cornstarch mixed with liquids or solid foods may also provide a source of long-acting carbohydrates to prevent overnight hypoglycemia. In some, but not all patients, the fat in peanut butter also can produce similar effects. In those who are drinking large quantities of milk, decrease in total protein intake (also true if decreasing milk-based cholesterol saturated fats for lipid problems) often includes recommendations to restrict milk intake or change to skim milk rather than low fat or whole fat products. Attention also should be paid to adequate calcium and vitamin D intake with concomitant reductions in milk so that appropriate supplementation can occur.

Fats

Total fat content usually should be no more than 25% to 30% of total calories. Saturated animal fat intake in general should be reduced for improved cardiovascular health especially if there is already known positive family history of high cholesterol and/or cardiovascular or circulatory problems or where there is documented hyperlipidemia in the patient. Specific intake of unsaturated fats-particularly those from vegetable sources - should not necessarily be restricted unless there is also a weight issue. In many surveys of youngsters with type 1 diabetes, lipid values are increased particularly in the subset of patients whose glucose remains out of control. This may occur in as many as 40% of such youngsters as well as adults with type 1 diabetes. Most such abnormalities reflect higher triglyceride values postprandially but, more importantly, higher low-density lipoprotein (LDL) and total cholesterol values as well as well as non-HDL cholesterol compared with age-and sex-matched cohorts without diabetes (using the 75th through 90th percentile values for age as appropriate cutoff points).

The following are traditional guidelines for mealplanning regarding which fats should be used: skim or low-fat milk ideally to help reduce milk-based saturated fats; margarine may not be any different than butter in terms of saturated fat content or its blood level enhancing effects, so both should be decreased; decrease red and brown meats; increase poultry, tofu, fish, and vegetable-based oils; encourage skim milk–based cheeses; eggs (yolk) previously were also restricted but newer scientific evidence suggests that there are some other antioxidant potential benefits from eating eggs

so that egg restrictions are not as rigorous as in the past until new data becomes available. With documented hypercholesterolemia and/or hypertriglyceridemia, more restrictions in dietary saturated fat and trans-fatty acids may be important – perhaps also supplemented by lipid lowering medications (plant stanols and sterols, bile acid sequestrants, statins, yet add another dietary restriction to the general dietary plan of those with diabetes. As indicated above, there are new scientific studies countering these decades-old saturated fat recommendations that document improvements in weight excess, lipid excess and hypertension associated with significant reduction in total amounts of carbohydrates while having no limits on amount of types of fats from red meats, cheese and eggs. With such restrictions on cereal, fruit, juices, breads, bagels, pasta, rolls, potatoes, corn, peas, beans the focus (stricter carbohydrate restrictions), less insulin is required particularly at meal times but also for basal needs.

At the same time, hunger can be "treated" with no limits on green, high fiber, high water-content vegetables as well as no restrictions with any protein/fat content.

More daily water and/or broth (“bone broth”) helps also solve the carbohydrate cravings that occurs initially as well as the sense of being deprived of food for the first few weeks while giving almost immediately positive benefits with lowered glycemic excursions, lowered weight, lowered blood pressure and lowered lipid levels simultaneously.

In some studies inflammatory markers like c-reactive protein also are significantly reduced. More studies are needed to document this effect, its durability and sustainability in adults as well as children but initial results look extremely promising.

The prolonged and slower carbohydrate absorption that occurs when carbs are ingested at the same time as significant fat from any source is ingested (ice cream, peanut butter, added margarine or butter, high-fat meat products, eggs) is likely a reflection of the slower stomach emptying associated with this fat intake. This is easiest counterbalanced with “square or dual wave” extended pump boluses but MDI can also partially mimic such insulin counterbalancing to hold down post-prandial glycemic excursions accordingly.

General dietary considerations

Total calories are guided by body habitus and general appetite. Frequent complaints of hunger and forced overfeeding should be

avoided.

General rule of thumb: Start with 1,000 kcal/d for a 1-year-old and increase by about 100 kcal/yr thereafter. For boys, keep increasing calories to about 2,600 to 2,800 kcal for a base diet, but a 3,000-to 3,500-kcal daily may be needed for coverage of prolonged and regular athletic sports activity or several weeks at camp. Late adolescent males and young adult males usually require <2,500 kcal/day except if increased physical activity continues. Girls usually need to start calorie restriction at about age 10 to 12 years (usually associated with early puberty than for boys) so that meal plans are increased to about 1,800 to 2,000 kcal/d until this stage and then decreased to 1,100 to 1,700 kcal/d according to metabolic needs, activity patterns, and desired weight, with 1,200 to 1,400 kcal being the mean. With more girls and young women participating in vigorous sports activities, lowered insulin and/or increased calories are needed for counterbalancing and hypoglycemia prevention just as with active boys and young men. If overweight or frankly obese, caloric restriction plus increasing activity will be needed although difficult to encourage, enforce and sustain behaviorally for many with (or without) diabetes. Correct insulin adjustments will also be needed under such circumstances. Consideration for carbohydrate restriction potential under circumstances where weight loss is not occurring and/or lipid and blood pressure problems co-exists should be another possible approach to review but will require a lot of discussions and support since most patients and family members will reject the idea outright or simply decide *a priori* that it would be too difficult to consider. With support, however, this too may be changeable and worth a "therapeutic trial".

To counterbalance extra activity, extra food can be provided or insulin doses should be downwardly adjusted in anticipation of such extra activity demands. Teaching proactive decisions helps decrease hypoglycemia. Supporting more learning through more SBGM (or CGMS) helps to learn about individualized needs. Specific teaching efforts should focus on ways to identify early signals of hypoglycemia with SMBG so that appropriate quick-acting carbohydrate (without fats or being used as an excuse for overeating) may be used. Holidays and special events often associated with extra food like birthdays or special family events can be allowed with appropriate extra insulin (or activity) counterbalanced. For special religious fast days (e.g., Yom Kippur or Ramadan), education should be used to minimize hypoglycemia

with appropriate monitoring and reduction of insulin and activity during such periods when less food is provided. Facilitating individual cultural needs for such changes can occur more readily with those in good control, those using MDI or CSII and those more knowledgeable about their options with appropriate discussions, educations, practice sessions and training opportunities with staff. CGMS can be especially useful since it provides an automatic data set for analysis around-the-clock.

Exercise[1,2,3,5,21,24]

Although it may be difficult to incorporate activity programs into a young child's routine, the goal of modern diabetes treatment includes consistent daily activity with the hope of establishing more formal and regular aerobic exercise programs by late adolescence and adulthood. The burst activity so commonly seen in younger children often disrupts rather than assists patients with type 1 diabetes. Some with exercise will have an accentuated, early adrenalin-like hyperglycemic effect while others will show hypoglycemia mid-activity compared to more prolonged and delayed hypoglycemia hours after the activity has been completed. There is a tendency for such patterns to be rather consistent in any one patient under certain circumstances and, if learned, such patterns can be better identified and counter-balanced to optimize glycemia and minimize future hypoglycemia problems.

Burst activity

Short burst activity usually needs extra short-acting carbohydrate intake just before or just after such activity whereas prolonged exercise often needs less insulin for a longer period of time as well as an increase in carbohydrates, proteins, and fats. Here too, individual patterns of metabolic needs exist and should be recognized; some patients need extra food at the start of bursts of activity, whereas others need extra food provided only after the activity is completed. This is true for toddlers, school-age, teen-age, and adults with type 1 diabetes. With increased intensity and/or duration of activity, more delayed hypoglycemic effects can be expected, ie. several hours after the activity. Some exercising also produces an immediate adrenalin-associated rise in glucose only to have a subsequent fall at the end of the activity or for hours later. One response to this particular pattern is a more intensive burst of activity early in the activity to counter-act the adrenal hyperglycemic rise and then the usual reduction in insulin and/or

extra food thereafter for the activity-produced aftereffects of hypoglycemia later on. Blood glucose monitoring should be used to document such effects and learn what works as counterbalancing measures, ie. food changes vs insulin changes or both**.**

Prolonged, planned activity

The longer the activity (and the more aerobic), the more likely it is to cause a delayed hypoglycemic effect (accentuating insulin effect several hours afterward); recognizing this phenomenon allows for additional food to be provided several hours after the activity is completed or for appropriate reductions in insulin working at those times (ie. basal changes). Fattier ice cream or chocolate products or uncooked cornstarch (available in some special "bars"), as well as foods generally higher in protein and fat (eg. meats, peanut butter), may be used to counterbalance such prolonged activity effects on sugar levels, presumably through changes in liver and muscle insulin receptors and timing differences in food absorption. If the activity is planned, then one may decrease the amount of insulin taken, especially that peaking several hours after activity. As with all other aspects of diabetes care, such prolonged activity effects should be detected via blood glucose monitoring (SMBG and / or CGMS) so that individualized adjustment can be more proactive rather than just reactive.

Activity related general considerations

In theory, it should not matter whether a patient reduces insulin in anticipation of activity or compensates with extra food in an attempt to balance energy expenditure. However, because as many as 20% to 30% of female teenagers with type 1 diabetes are more than 120% above ideal weight (in some recent studies even more), it may be prudent to avoid additional calories under such circumstances. Males, of course, also are not exempt from the problems of calorie excess and adiposity. Sport should be encouraged for all. Close friends and family members especially for adolescents and adults can be taught about hypoglycemia recognition, signs and symptoms and appropriate treatment; some friends and siblings will even volunteer to learn blood glucose testing and glucagon so all this should be encouraged and discussed openly. Supervisory personnel at school or at a park or camp must be made aware of the presence of a person with diabetes and be provided with a source of quick-acting carbohydrate to manage hypoglycemia should it occur; guidelines must be given so

that hypoglycemia can be recognized and avoided. Decisions about glucagon use and availability should be openly discussed and individual advice provided. All schools should have teachers and nurses, if they are available, taught and ready to intervene under emergency circumstances rather than refuse to care for such children while at school or in other community-based programs. Good Samaritan laws should be invoked to allow appropriate emergency care. Newer intranasal glucagon will soon become available eliminating need for injetions of glucagon and decreasing fears associated with less common availability, storage etc.

Medic-Alert tags must be worn in case of emergencies in all children and teenagers as well as adults who take insulin so that emergency personnel called will know that intravenous glucose and/or glucagon (intravenous, intramuscular or nasally administered) will be needed and perhaps life-saving without delay.

TYPE 1 DIABETES SPECIAL CONSIDERATIONS AND DIABETES RELATED COMPLICATIONS[34, 35]

Hemoglobin A1c (glycohemoglobin (GHb), HbA_{1c})

This test is an indicator of blood sugar control during the previous 1 to 3 months time period, the approximate life span of the red blood cell hemoglobin. Blood is assayed after saline washing to detect the relative percentage of "stable" glycosylated hemoglobin present that is associated with ambient glycemic levels.

Modern systems are adjusted to the DCCT standard HbA_{1c} methodology, and most currently used systems provide comparable results although quality control must be emphasized and maintained.

Because glucose attaches to hemoglobin in a mostly irreversible fashion throughout the life span (120 days) of the red cell, at any moment, a sample of blood will represent a collection of newly "born," middle-aged, and "dying" cells such that the glycohemoglobin level obtained represents an integrated glucose value that is reflective of the glucose environment confronting the red cell over its lifespan. There does, however, seem to be an over-representation of the most recent 2-4 week period of glycemic in most A1c assays.

The most reliable methods use high-pressure liquid chromatography or gel electrophoresis, and separate out the subfraction called HbA_{1c}; alternatively, HbA_{1a+b+c} (total glycosylated

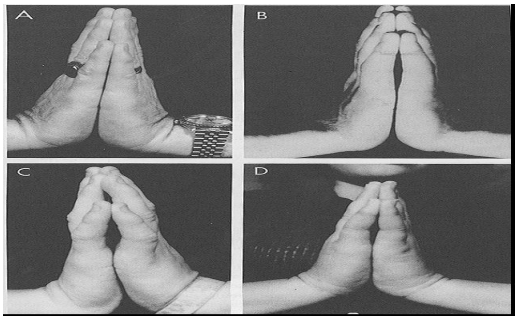
hemoglobin, total HbA_1, or glycohemoglobin fractions) can be separated as an index of blood glucose control. Either HbA_{1c} or total GHb can be used to estimate the average blood sugar present for the past few months. Values less than 7.5% for HbA_{1c} are acceptable, whereas values less than 7% are more optimal as long as excessive or severe episodes of hypoglycemia do not occur. According to the DCCT, the higher the HbA_{1c} value and the longer duration the HbA_{1c} stays out of ideal range, the more likely will be the long-term eye, kidney, and neurologic complications of diabetes as well as the more likely cardiovascular problems.

HbA_{1c} determinations can serve as an ongoing index of relative control and select out those patients who require more intensive medical, psychosocial intervention or both. Providing patients with HbA_{1c} results often helps motivate improved overall glycemic control – but not always. In patients with anemias or other hemoglobinopathies, alternatives such as fructosamine assays can serve similar purposes. A minimum of every 3 month A1c results should be available for all patients with type 1 diabetes mellitus. In the DCCT, A1c results were available to staff and to patients on a monthly basis and this provided a feedback approach to allow problem identification and discussions for amelioration that we, as investigators in the DCCT believed was part of the success of maintaining the study for such a long time across multiple research centers with so many patients. Figuring out a way to teach about A1c results in a non-pejorative fashion while still allowing it to remain a focus of relative objective glucose control remain key to successful diabetes health care teams working with patient and their family members.

LIMITED JOINT MOBILITY
(LJM, joint contractures, diabetic hand syndrome)[36]

LJM is present in as many as 15% to 30% of adolescents with type 1 diabetes and we believe may predict a subset of (young) people who are at 400% to 600% greater risk for developing the complications associated with hyperglycemia such as retinopathy, nephropathy, hypertension, and neuropathy. LJM probably reflects collagen glycosylation based on long-standing ambient glucose concentrations in the body. As originally described by Rosenbloom[37], the patient places the hands together in prayer position with the forearm parallel to the floor. Normal placement allows for juxtaposition of all fingers as well as the palm. The

earliest abnormality appears to be a sclerodermatous, tight, waxy skin consistency. The fifth finger is most often the initial finger to become less than fully extendable although all fingers and joints potentially can be involved. The Brink-Starkman classification used at NEDEC is as follows:



stage 0: no abnormality (A);
stage I: skin thickening without contractures;
stage II: bilateral fifth finger contractures (B);
stage III: other fingers involved bilaterally (C);
stage IV: fingers plus wrist involvement bilaterally (D);
stage V: fingers, wrist, and other joint involvement.

The higher the stage, the worse the LJM and the higher the risk of complications. LJM is a unique, absolutely free method of analysis of long term complications risk and probably reflects a combination of genetic predisposition in any particular family as well as long term glycemic exposure setting up the tissue glycosylation process that can be visible and associated with tissue glycosylation in proportionate fashion. Recomandation: document assessment of LJM at least every 6 months including teaching patients and family members about such results and their implications if negative or if positive. It may be the first actual "abnormal" finding that a patient himself or herself can see since most complication-related abnormalities either show up without concomitant symptoms aware to the patient or family or by lab testing.

SICK-DAY GUIDELINES AND KETOACIDOSIS

Special attention because of potential acute insulin resistance and associated dehydration is required during illnesses with more blood glucose monitoring, blood or urine ketone monitoring as well as weight checks several times each day to assess acute changes in hydration status. Unless there is a major vomiting component to the illness, more rapid acting analog or regular insulin is given every 2 to 4 hours (calculated by adding up the total daily insulin requirement and using a sick-day booster dose of 10% to 20%) with each dose. This is either added to the usual insulin dose or given as a supplemental dose until the added stress of such infection

subsides. With insulin pump treatment, basal doses can temporarily also be increased quite easily but with MDI regimens, it is usually sufficient to boost the fat-acting insulins without having to make major increases in the basal injected insulins. Antiemetic medications have been questioned because of reports associating these types of medicines with Reye syndrome, but prochlorperazine (Compazine®) or trimethobenzamide (Tigan®) suppositories, as well as bismuth-salicylic acid (PeptoBismol®) liquid preparations or other similar medications can be used to reduce nausea and vomiting safely and inespensively. The provision of large amounts of salty fluids (soups and broths or electrolyte solutions such as Gatorade® or Lytren®) is perhaps more important than extra insulin in preventing hospitalization from dehydration caused by the osmotic effects of excessive glycosuria. Sugar or sugar-free carbonated sodas can also provide needed water and salt with some darker drinks (colas) also having some extra potassium as well if other types of salty liquids are unavailable or not tolerated. Obtaining frequent weight measurements, several times each day, is a simple technique for assessing overall hydration status at home and gives family members an indication of how much additional fluid may be required; acute weight loss over a 1-to 2-day period is attributable almost completely to fluid loss and if it persists, requires either a phone call or an office/emergency room/hospital evaluation rather than let DKA progress to coma or death associated with water and/or electrolyte acid-base imbalance deterioration. SMBG (or more frequent attention to CGMS) is a critical part of home monitoring during sick days but must be coupled with urinary ketone testing or blood β-hydroxybutyric acid levels; blood sugar levels greater than 180 to 240 mg/dL (~10-13 mmol/L) associated with ketonuria or increasing levels of β-hydroxybutyric acid demand 10% to 20% more insulin given every few hours throughout the day as well as throughout the night to prevent hyperglycemia and dehydration from progressing to decompensated ketoacidosis, coma and death. CGMS can provide similar glycemic evaluatipn.

Ketonuria can be present because of relative lack of food (starvation ketosis) as well as insulin deficiency. Blood sugar levels lower than 180 mg/dL (10 mmol/L) with ketonuria do not automatically call for additional insulin; instead, liquids containing carbohydrates should be added to the treatment program at home (i.e., Gatorade®, sweetened juices, and sugar-containing carbonated

soda) and alternated with salty fluids. This more typically occurs with gastrointestinal illnesses whereas hyperglycemia and DKA more typically occurs with respiratory or other infections.

Uncontrolled diabetes mellitus and recurrent DKA

Children and teenagers who require frequent hospitalization and intravenous fluids generally are those not properly supervised by adults, those not routinely testing (or falsifying) either blood or urine results at home, and/or those who "forget" to take their insulin. Omission of insulin is a frequent cause of recurrent ketoacidosis in adults and some adolescents. If interventions with the patient themselves cannot reverse this, then insisting and facilitating responsible adults in actually not just observing but actually giving all insulin will almost always stop the recurrence of such DKA. Enmeshed families, however, often with parents having similar psychosocial problems as the index child/teen, make such cases extremely frustrating and difficult and often hospitalization and in-patient interventions are required to turn things around and return safety considerations to the forefront. Noncompliance and psychosocial problems (dysfunctional families; sexual, physical and/or emotional abuse and neglect; alcohol and / or sunstance abuse; severe depression, eating disorders, diabulimia etc) are major causes of recurrent ketoacidosis. Hypophobia usually is not associated with recurrent DKA although it is associated with chronic, significant hyperglycemia and elevated A1c levels because pf purposeful lowering or omission because of purposeful lowering or omission of insulin to "prevent hypoglycemia".

Hypoglycemia

Most episodes of hypoglycemia are predictable and preventable[38]. Very young children may be at higher risk for severe hypoglycemic reactions (unconsciousness or seizures) because of their inability to recognize and/or communicate subtle symptoms of hypoglycemia. Hypoglycemia usually occurs for obvious reasons associated with mistakes: late meals, missed snacks, incorrect insulin doses, incorrect timing of insulin dosage, exercise incorrectly compensated with lowered insulin and/or increased food intake, illness (especially nausea, vomiting and/or diarrhea viral illnesses). While mild hypoglycemia (self-care and treatment possible) cannot always be completely avoided, *moderate hypoglycemia* (needing assistance of others) and *severe*

hypoglycemia (not only needing assistance of others but needing intravenous glucose or glucagons because of loss of consciousness and/or convulsions) should be preventable in almost all circumstances. Recurrent episodes of hypoglycemia should require the diabetes health care team to seek out specific reasons (noncompliance, timing errors, alcohol, other psychological or behavioral problems with the patient and/or family etc.) Rarely, celiac disease, adrenal insufficiency (see below) or severe gastroparesis (associated with severe autonomic neuropathy) are the explanation for such recurrent moderate or severe hypoglycemia.

Since episodes of hypoglycemia are common events in T1DM in everyday life, education can focus on identifying such events and appropriately changes in monitoring, doses or information as to when (telephone) contact with the health care team (or emergency facilities) should be considered for more specific advice. MDI successfully taught and CSII both have documented decreased A1c values and decreased hypoglycemia just as insulin analog use is associated with significantly less hypoglycemia as well. CGMS added to MDI as well as CSII has shown similar decreases in hypoglycemia in many studies around the world as pumps and sensors have continued to improve in sensitivity and specificity / accuracy parameters. The combination of alcoholic beverages with insulin (usually in teenagers or adults) can produce long-lasting and very severe (eg. 2- 6 AM) hypoglycemia hours after alcoholic intake; such information must be made available to teenagers and adults with type 1 diabetes so that prevention is possible. There is a common misperception that alcohol produces hypoglycemia. Alcohol, however, does not specifically cause hypoglycemia; but, if hypoglycemia occurs when there is already significant alcohol in the system, the liver is “too busy” metabolizing the alcohol to be able to respond with glycogenolysis and glucose production - so that whatever hypoglycemia occurs, can not receive the normal compensatory response either from the muscles or the liver. Thus what might have been only mild hypoglycemia (post sports, post dancing or other activities) could instead become moderate or severe hypoglycemia with alcohol in the body.

All patients of any age should have hypoglycemia emergency education and appropriate family members and/or friends should be identified who may assist in an unexpected hypoglycemia emergency situation.

Glucagon should be available to be given in age and size

appropriate dosage (approximately ¼-½ mg for a very small child, ½ - 1 mg for a school age child and 1 mg for an older child, adolescent or adult).[21,24] Doses should be individualized by the health care team and if glucagon cannot be available because of financial constraints or lack of insurance coverage, appropriate advice provided for emergency care and attention. Glucagon emergency kits which currently provide a way for emergency administration of intramuscular or subcutaneous administration of glucagon by trained school staff or family members/friends and can be stored up to a year in a normal refrigerator. If medical or nursing personnel are present, these same glucagon kits can also be administered intravenously too. Special cool facilities for such storage (usually a refrigerator) may need to be used but in places where refrigeration and/or electricity is unavailable or unreliable, clay pot water storage buried in a hole in the desert can also be used effectively. Soon to be available will be stable powder preparation for intranasal glucagons administration that may solve the problems associated with temperature instable glucagons preparation previously utilized as well as remove the fear of injectable medication through ease of use.[39] Mini-dose glucagon [40] (0.1 – 0.3 mg SQ) has also been very helpful during episodes of gastrointestinal illness, usually viral, when intake of food is not occurring and this boosts the glucose levels sufficiently to avoid hospitalization for intravenous nutrition. Such small doses can be repeated as needed through the course of the day and night for a few days quite successfully.

Purposeful insulin overdose is being recognized as a form of suicidal gesture by the adolescent or adult with severe but often unsuspected depression and/or severe family turmoil (i.e., physical, emotional, or sexual abuse).

Recent studies suggest a frequent and early abnormality of counterregulatory response in many patients with diabetes which may account for prolonged and unpredictable hypoglycemiav – probably a common and very early from of autonomic neuropathy often not fully appreciated by professional staff, patient or family members. With the advent of continuous glucose monitoring systems, the enormous frequency of unrecognized hypoglycemia overnight and even throughout the daytime hours is simultaneously very scary and heightens the importance of optimizing glycemic control while at the same time providing high focus on prevention of as much hypoglycemia as possible.

Hypoglycemia unawareness is associated with recurrent and severe episodes of hypoglycemia with little recognition of symptoms

by the patient**.** Frequent blood glucose monitoring, sometimes including daily nocturnal monitoring, often is required to prevent periods of unconsciousness or convulsions induced by such hypoglycemia. Research documenting very promising CGMS with predictive alarms as well as automatic low glucose suspend (LGS) systems to help decrease and prevent severe episodes of hypoglycemia have been successful (see below) without concomitant increases in overall glycemic levels or A1c results. Recurrent hypoglycemia begets more severe episodes of hypoglycemia with further abnormalities of counterregulation as the normal counterregulatory systems fail more and more. Efforts to minimize hypoglycemia under such circumstances focus on retraining (called *hypoglycemia awareness training* (HGAT) or blood glucose awareness training (BGAT)[41]. HGAT and BGAT utilize frequent monitoring and focus on relearning early warning signals that presage additional, more severe episodes. If severe episodes of hypoglycemia occur, evaluation for celiac disease, adrenal insufficiency, thyroid disorders, and growth hormone deficiency should be considered even though fairly uncommon. (see also CGMS section and insulin pump section) More recent experience with insulin pumps and especially with continuous glucose monitoring have documented how common is hypoglycemia between meals and snacks and especially overnight.

Approximately 30% of daytime hypoglycemia remains asymptomatic although may be recognized by family members or close friends - if taught**.**

Even more worrisome, similar data analysis from CGMS suggest that *overnight hypoglycemia may be asymptomatic in about 50% of patients* with type 1 diabetes and both these examples of hypoglycemia unawareness may be the earliest diabetes complication from autonomic neuropathy.

Somogyi phenomenon (rebound effect)

The Somogyi phenomenon is a series of events caused by overinsulinization and its attendant episodes of hypoglycemia – with or without symptoms. It is probably less commonly occurring with increased MDI and CSII in recent years and perhaps also with CGMS offering predictive alarms, low threshold suspend and now also automatic basal dose responses. As the insulin dose is increased beyond the amount required for any given portion of the day, the effect of the excessive insulin is to cause either overeating or frank hypoglycemia; but the hypoglycemic event is not always

symptomatic or recognized particularly if it occurs nocturnally or if hypoglycemia unawreness is present. This excessive insulin effect elicits an excessive counterregulatory hormone response followed by "rebound" hyperglycemia from adrenalin, cortisol and/or growth hormone among other factors raising the glucose levels and then often exceeding normal levels because of background insulin deficiency. Some cases of uncontrolled diabetes may actually be caused by this counterregulatory response so that wide glucose excursions are seen and this also may represent an early form of autonomic neuropathy.

In its most common form, relatively minor hypoglycemia from any cause or combination of causes (inadequate meals or snacks, excess activity, unopposed insulin, alcohol) contributes directly to subsequent hyperglycemia which may last for 8 to 24 hours (although Somogyi's original description commented on rebound hyperglycemia lasting as long as 72 hours after hypoglycemia). In rare instances, this counterregulatory response is so excessive as to produce not only ketonuria but also full-fledged DKA. Recognition of the possibility that some episodes of high blood sugar levels might be caused by too much rather than too little insulin, especially in the middle of the night, leads to the correct conclusion that reduction of insulin can correct some causes of fasting hyperglycemia by avoiding the nocturnal hypoglycemic event in the first place. Somogyi problems, however, are not as commonly seen as previously thought, and most morning hyperglycemia is caused by a waning effect of free insulin availability (the dawn effect, compounded by increased overnight cortisol and/or growth hormone) rather than overnight "Somogyi-ing". Blood glucose testing should be used to diagnose, confirm or refute such patterns. CGMS helps automatically identify such overnight hypoglycemia and rebound hyperglycemia but only if the CGMS data is seen and if there is a response to such episodes – not just at follow-up office appointments but at home between visits.

Dawn phenomenon

Many patients with type 1 diabetes mellitus demonstrate an early-morning (4 to 10 AM) rise in glucose levels that is aggravated by intake of food at breakfast (but not due to it) and that tends to peak in midmorning. It often occurs because of waning insulin availability plus concomitant increase in growth hormone and cortisol overnight effects.

The Dawn Phenomenon appears to be unrelated to food intake

or activity, and whether it represents an increase in hepatic glucose production or decreased peripheral utilization (or both) is not known. It does indicate a further requirement for basal insulin levels that may be ideally treated with continuous subcutaneous infusions such as those provided by insulin pumps.

With CSII, basal insulins can be automatically raised, ie. from 4 AM to 10 AM without having to concomitantly provide extra basal insulin at midnight or 2 am or throughout the remainder of the day. The basal analogs glargine, detemir and degludec among others with less peaking effects help to better counterbalance such needs as well compared to previous ultralente, lente or even NPH insulin formulations.

The dawn phenomenon may be confused with the Somogyi phenomenon since both show up as hyperglycemia otherwise unexplained by food or too little insulin. Sampling of glucose levels throughout the night should help differentiate the two conditions with appropriate education efforts and attention by patients and/or family members. Some have recommended an earlier injection in the morning (5 AM to 6 AM), and most suggest a late-evening (before bedtime) injection of intermediate-acting NPH insulin if an insulin pump is not being used or basal analogs are not being used or available.

With an insulin pump, increasing the basal insulin in an effort to counterbalance the dawn phenomenon is usually successful, just as the new, long-lasting insulin analogs (glargine, detemir or degludec insulins) or degludec insulin all provide smoother (relatively peakless) insulinization without concomitant overnight peaks.

Insulin needs

Reverse dawn phenomenon where supper or evening insulin needs exceed those of the predawn breakfast hours occurs in up to 10-20% of youngsters.

Other patients exist who have no dawn or reverse dawn phenomenon but relatively "flat" basal needs; some with a small dinnertime insulin need and others with an early afternoon peak requirement.

CGMS or other intensified monitoring allows identification of such alternative needs and once identified, the options for food and/or insulin change become more apparent.

Growth[42]

Percentile grids for height and weight must be used for the correct monitoring of growth in children and teenagers. Weight and height must be obtained at least quarterly and actually **plotted** either on a paper growth chart kept for each child or teenager or a computer based systems must be established that does the same and "notifies" the practitioner that there is a potential problem height velocity aberration, weight gain or loss etc.). Decreased growth velocity appears to be more common in males than in females with type 1 diabetes mellitus, and may be as common as 5% to 10% in large pediatric and adolescent cohorts. Extreme growth failure can be associated with pubertal delay and hepatomegaly (*Mauriac* syndrome) caused by severe and chronic diabetes mellitus out of control as a result of long-standing lack of insulin or insulin underutilization. This still is seen in parts of the world where insulin is not consistently available, too expensive or when insulin is purposefully/surreptitiously omitted. It also can occur if temperature conditions are such that insulin degradation may be common (ie. sub-Saharan Africa where clay pots with water can be used to provide temperature stability even in the desert or when no reliable or affordable refrigeration or electricity is available). With such chronic diabetes mellitus out of control, reintroduction of control demands close attention to the retina so that unexpected severe retinopathy does not develop unchecked.

In the subset of children and adolescents prone to obesity (family history, bulimia and binge eating, inactivity etc.), attention to body mass index (BMI) will help identify those in need of special dietary and/or psychosocial support.

With reasonable (not even optimal glucose control), growth and pubertal progression should be very close to that of the control population cohort and this should be the expectation to be documented and tracked

Teenage and adult pregnancy

The teenager who has diabetes and becomes pregnant has many added burdens affecting both herself and the child. The first trimester is often associated with increasing episodes or severity of hypoglycemia, while the second and third trimesters are usually associated with rapidly increasing insulin resistance, and therefore insulin doses rise dramatically. Discussions about contraception and birth control options must become part of the repertoire of professionals responsible for diabetes care with anticipatory

guidance automatically provided so that unplanned pregnancies hopefully may be avoided or decreased. Patients ready to conceive must be made aware that improving blood sugar control at-or ideally *before* conception-reduces the risks of congenital anomalies, as well as prematurity and its associated complications. At the same time, maternal risks when pregnant also may be avoided or decreased with appropriate advance planning and discussions. Fetal monitoring and close collaboration with high-risk obstetric teams is extremely valuable.

THYROID DYSFUNCTION AND OTHER AUTOIMMUNE ENDOCRINOPATHIES[43]

Thyroid problems often coexist with type 1 autoimmune diabetes mellitus. In the type 1 diabetes population, 5% to 10% have a variety of thyroid dysfunction including euthyroid goiters, hyperthyroidism, and hypothyroidism. Hypothyroidism (low T4, low free T4, elevated TSH) or compensated hypothyroidism (normal T4, normal free T4 but elevated TSH) should be treated as should hyperthyroidism and treatment is the same with or without diabetes co-existing. Simple goiters may or may not need hormone treatment without symptoms or changing hormone levels – also not different with or without concomitant T1DM. The vast majority of thyroid problems seen in association with type 1 diabetes are secondary to chronic Hashimoto thyroiditis consistent with the concept that type 1 diabetes mellitus, to a large extent, is an autoimmune disorder. Thyroid antibodies may be positive in 20% to 40% of young type 1 patients depending upon antibody assays and cutoff points for normal and abnormal results utilized. Therefore thyroid antibodies should be checked yearly along with thyroid function tests (if available and affordable) but euthyroid Hashimoto's thyroiditis by itself with no clinical symptoms or signs does not automatically require immediate hormone treatment. After a period of several years, if antibody levels are persistently negative (or positive), less frequent monitoring of actual antibodies may be reasonable but guidelines differ since there are no long term prospective studies to optimize conclusions, only “expert consensus opinions.” Similarly, exactly how often should TSH, total or free T4 levels be checked and under what conditions (family history, prior normal values for how long, prior abnormal values or intermittently abnormal values) should rechecking occur is unknown. This author checks total T4

and TSH annually until about 10 years after diagnosis; if the levels remain absolutely normal and if antibody levels are persistently negative, then less frequent checking would be reasonable, ie. every 2-3 years. Later onset of thyroid problems is known to occur in a T1DM (as well as T2DM) population so such considerations should be entertained at least annually. If there is an actual abnormality especially a persistent intermittent pattern or a steadily worsening set of lab results, one with some consistency, then open discussions about the risks and benefits of treatment would be appropriate. The risks of untreated hypothyroidism or untreated compensated hypothyroidism vis-à-vis cardiovascular complications and abnormal bone mineralization suggest that this should be important information to have, if possible.

Achlorhydria and mild iron deficiency related to possible iron malabsorption may occur (associated with positive gastroparietal antibodies). Folic acid and vitamin B12 deficiency also is more common with positive **gastroparietal antibodies** and often with minimal or no symptoms. If thyroid antibodies are positive and especially if there is concomitant clinical hypothyroidism or hyperthyroidism documented, it is prudent to then also check gastroparietal antibodies as well as obtain baseline folic acid, vitamin B12, iron and ferritin levels. Exactly how often such gastroparietal antibodies and these other factors should be checked also is unknown so that clinical decision making on an individual basis and costs/availability of such testing must come into consideration.

Adrenal insufficiency (**adrenalitis**) may co-exist with type 1 diabetes with adrenal insufficiency associated with autoimmune (positive adrenal antibodies) dysfunction that may be life-threatening and occurring more commonly in the subset of type 1 diabetes patients who also have other evidence of autoimmunity, ie. celiac or thyroid related antibodies, or overt thyroid or bowel dysfunction. Routine adrenal antibody determination does not seem to be cost-effective because it occurs in less than 5% of this T1DM population in several studies. However, routine adrenal antibody determination in the subset with transglutaminase and/or thyroid antibodies, produces a higher yield and seems to be worthwhile so that his author recommends such testing where available and affordable followed by more definitive testing (cortisol and ACTH levels or stimulation testing) if positive results occur. Treatment with of such Addison`s disease follows standard

treatment protocols usually with hydrocortisone but sometimes with prednisone or dexamethasone as alternatives. Similarly, some but not all will also have concomitant need for fludrocortisone for salt retaining needs.

Celiac disease with positive transglutaminase, endomysial and/or other gluten related (gliadin) antibodies is also significantly more common in many cohorts of patients with type 1 diabetes, particularly in those populations with ancestry in or around the Mediterranean Sea. Estimates suggest positivity in about 6-10% of a type 1 diabetes population particularly Caucasians. The celiac disease may be symptomatic, severe or mild or asymptomatic and may often be associated with mineral and vitamin malabsorption especially with hypovitaminosis D and its associated osteopenia and osteoporosis problems. Calcium, iron and trace mineral deficiencies can occur under such circumstances and all such antioxidant effects may be terribly important vis-à-vis potential diabetes related complications and even psychological and otherwise asymptomatic patients. While gasiness and diarrhea would be expected, about 10-20% of celiac patients complain of constipation or infrequent bowel movements and another subset of diagnosed celiac patients will have no symptoms whatsoever.

Gonadal (testicular or ovarian) antibodies also are available and even less commonly seen than celiac or adrenal antibodies. As with all such autoimmune endocrinopathies, the risks of having more than one positive increase as the number of positive antibodies and the clinical seriousness of the autoimmune disorder increases. Detailed attention to family history of autoimmune dysfunctions may also facilitate risk assessment and discusions. If persistent, highly positive antibodies occur, then clinical assessment including specific hormone testing, is warranted and appropriate treatment can then be determined accordingly for any documented testosterone or estrogen deficiencies.

Vitamin D, Osteopenia or Osteoporosis.

Prevalence and incidence in type 1 diabetes is unknown but there are some research reports suggesting increases in this population (as well as in those with type 2 diabetes). Increased prevalence and incidence of osteopenia is known if celiac disease co-exists even if the celiac disease is asymptomatic. Baseline and follow-up bone density DXA scanning may be important to follow

sequentially with increased calcium and vitamin D supplementation as well as consideration of other vitamin and mineral factors affecting bone mineralization.

Vitamin D insufficiency (hypovitaminosis D) in mild, moderate or severe degrees is often very common and likely somewhat worsened in a type 1 diabetes cohort in this author's experience. Since vitamin D has important effects on some of the same tissues that are affected by chronic hyperglycemia, it is not surprising that correcting (asymptomatic) hypovitaminosis D is likely to help reduce long term microvascular and macrovascular complications of diabetes and even has been reported to help reduce respiratory infections, cancer incidence and help with executive dysfunctioning, attention deficit disorders and learning problems as well as anxiety and depression.

Measurement of blood total vitamin D. Particularly if levels are low and/or levels don't improve with supplementation (usually supplement noncompliance), then baseline DXA scans should be considered with appropriate follow-up DXA scans about every 3-4 years to track results.

COMPLICATIONS[44,45,46,47,48]

Hypertension and nephropathy

Blood pressure shouldbe obtained lood pressure should be obtained at least every six months in all patients from diagnosis onbwards and documented in the medical record. Hypertension should be treated aggressively in an effort to reduce morbidity and mortality associated with diabetic complications. Most of the time this will not start until adolescence or early adulthood, however.

Essential hypertension can occur in any youngster or young adult with type 1 diabetes and detailed family history of hypertension and cardiovascular disease should be reviewed since this obviously increases the possibility in the younger patient too. Most cases of hypertension are associated with diabetic nephropathy but in many instances hypertension may occur without changes in blood urea nitrogen, creatinine or any evidence of albuminuria. Some cases of early hypertension suggest that hyperglycemia in association with a genetic predisposition to hypertension produces such hypertension earlier than would otherwise be the case. With hypertension, BUN, creatinine should be assessed and a baseline microalbumin, microalbumin: creatinine ratio and total protein assessment should also be obtained either

with a timed overnight sample or a random sample depending on local preferences.

Thiazide diuretics and other diuretics can be safely used in most cases to control hypertension. Beta-blockade can also be used but with some caution because of the potential to mask symptoms of hypoglycemia. Angiotensin-converting enzyme (ACE) inhibitors play a role not only in normalizing mild hypertension but also in reducing glomerular hyperfiltration and microalbuminuria. Therefore, ACE inhibitors may be the medication treatment of choice if hypertension exists and these are generally the medication of choice for this author although sometimes there is an annoying cough as a side-effect when using ACE inhibitors that forces other medications to be considered instead. Other antihypertensive agents all have a place particularly in the patient who appears to be resistant to one or more anti-hypertensive agents and additional options should be considered. All such medications seem safe to use without any special precautions in a diabetes population. With movement through puberty and into adulthood it is not so uncommon to need more than a single blood pressure medication depending upon family history, sensitivity to treatment, compliance, weight, exercise and other confounding variables such as smoking, drug use or abuse, salt sensitivity and hypovitaminosis D. During pregnancy, pre-eclampsia or overt eclampsia and edema also may require blood pressure and/or diuretic control to protect fetus and mother with particular attention to choosing those less likely to cause fetal side effects.

Sequential evaluation of renal function with blood urea nitrogen (BUN), creatinine, overnight or 24-hour urine protein, and creatinine clearance are helpful in early detection of nephropathy. Microalbuminuria (>7-20 mg being used as cutoff points in various research studies over the years for children and adolescents) obtained in overnight or 24-hour collections as well with random screening sampling utilizing microalbumin:creatinine ratios) may identify subpopulations at risk for diabetic nephropathy. If abnormal, protein intake may need to be restricted (to as low as 12%), although this is a difficult meal plan prescription for many to follow.

ACE inhibitors also have been helpful under circumstances when microalbuminuria or proteinuria occurs even when hypertension is not present.

Controlling hyperglycemia is most important to slow down kidney damage and possibly reverse such abnormalities. Smoking

cessation is also helpful.

Onset of proteinuria and hypertension during the first 10 years of type 1 diabetes mellitus should not be automatically considered as indicative of diabetic nephropathy (uncommon in the first 10 years of diabetes mellitus), and its etiology should be vigorously pursued despite the fact that all such retinopathy and neuropathy and eventually hypertension may be effectively treated with ACE inhibitors. As with retinopathy and neuropathy, the DCCT and the follow-up EDIC studies documented elegantly and persistently over 30 years of follow-up of the original DCCT cohort, metabolic memory effects and persistence of the importance of glycemic control over time being incredibly important.[39,40,41,42]

Lipids

Fasting blood levels should be obtained for total cholesterol, triglyceride, and HDL cholesterol, as well as direct or calculated LDL cholesterol values at least every 6 to 12 months to identify which patients require further dietary lipid control as well as more intensified insulin therapy. Calculated non-HDLc levels also can be helpful for assessment of current and future cardiovascular risks. Remember that the 75thn 90th and 95th percentile cutoff for lipid levels in children and adolescents is significantly lower than in adults and that such age-appropriate standards should be utilized when making decisions bout what is normal or abnormal and when intervention may be considered. If fasting triglycerides are normal, then nonfasting direct LDL measurements plus HDL and total cholesterols can be done non-fasting to make timing of testing easier. This author stops checking triglycerides after two or three sets of results fasting are normal but continues with periodic directly measured LDL, HDL and total cholesterol with a calculated non-HDL cholesterol value being followed.

Anti-lipid medications, including sterols, stanols, resins such as cholestyramine and colestipol as well as gemfibrozil and statin medications (e.g., simvastatin, fluvastatin atorvastatin and rosuvastatin) can be used in conjunction with insulin treatment based on family risk analysis and individualized lipid data even in children and adolescents quite safely. The biggest problem may be with compliance and omitted doses especially since this is yet another asymptomatic situation to consider. Plant sterols and stanols also can be safely prescribed especially if there is documented chemical myositis or liver dysfunction with statins although they are not as helpful in many patients compared to the

statin medication family. Statins remain the mainstay of treatment of elevated LDL and total cholesterols with older less expensive generic formulations useful before the newer, more expensive versions are utilized. Concomitant provision of co-enzyme Q10 with statins may help prevent and /or treat liver or muscle side effects of statins.Pediatric studies have documented about the same degree of side effects of midland more severe degree as in adults and with the same amount of nonpredictability.[49] Surveillance and heightened awareness of such potential problems should be openly discussed and ongoing if treatment is recommended including periodic liver and muscle enzyme analysis. Newer but significantly more expensive lipid medications are under consideration but without sufficient longitudinal experience for specific recommendations at present.

Ophthalmologic evaluation and diabetic retinopathy[1,2]

Baseline ophthalmology evaluation, including fundus photographs, is recommended within the first 2 to 3 years of developing diabetes and might be repeated at 1-to 2-year intervals after 5 years duration of type 1 diabetes mellitus (or age 10 years) to pick up early vascular changes in the retina and to assess cataract risk or presence. Less expensive screening fundus photography may be reasonable soon after diagnosis before any serious retinopathy is expected to be present. Fluorescein angiograms may show the earliest abnormalities of diabetic retinopathy years before dilated-eye examinations or fundus photography and may be especially valuable in the cohort with the highest HbA_{1c} values or with other risk factors such as obesity, lipid abnormalities, smoking or substance abuse or significant family history as well as highest A1c results or already present or worsening limited joint mobility (LJM). Poor glycemic control is clearly associated with earlier and more severe types of retinopathy with the DCCT[39,40,41,42] elegantly documenting this and established the concept of metabolic memory where even a relatively short period of improvement in glycemic control (or poor control in the opposite sense) lasts for decades. Very rapid improvement of chronic very poor control is also associated with retinopathy and sometimes rather fast and dangerous changes in vision. In any patient known to have terrible glycemic control – for any reason – and in whom fast improvement is documented, close direct eye examinations are important to identify retinal changes that might require laser therapy or other ophthalmologic intervention. Laser treatment of retinopathy saves

vision. Duringpregnancy, one or two specific dilated eye exams may also be helpful for reassurance as well as documentation of any deterioration especially if there had been a period of poor glycemic control with rapid improvement. Cataracts, too, are extremely rare in children and adolescents but in some young adults, beginning cataract formation can be detected and in some studies this is directly linked to overall glycemic control.

Neuropathy

Significant neuropathy is often not seen in the child or adolescent unless there has been prolonged lack of insulin because of unavailability or psychosocial disturbance with associated conditions such as Mauriac Syndrome, recurrent DKA or simply insulin omissions.

Alcohol, substance abuse, nicotine abuse all may exacerbate neuropathy and compromised self-care because of attention deficit, anxiety and/or depression all are contributors to this and all other complications accordingly.

Symptomatic diabetic neuritis is fairly rare but may show up after 5-10 years of high A1c levels and especially if exacerbated by alcohol, drug use, smoking, untreated hyperlipidemia or combinations of such risks. Symptomatic diabetes neuritis can include autonomic neuropathy with abnormal counter-regulation and abnormal hormone responses to hypoglycemia, burning pain, absent reflexes and other autonomic dysfunction such as gastroparesis with severe gut motility problems.

Gastroparesis can be relatively asymptomatic but interfere with insulin adjustments to food because of unpredictability of food leaving the, diarrhea, constipation or any such combination. Treatment is problematic because most treatments available are not ideal. Significant and recurring severe episodes of gastroparesis is associated with both unpredictable hyperglycemia and hypoglycemic convulsions, bloating and abdominal discomfort. Neuropatic pain treatment is especially problematic if diabetic neuritis occurs affecting peripheral nerves and even narcotics do not often provide ideal relief. It is rare for significant diabetic neuropathy to occur without significant glycemic elevations and concomitant prolonged periods of time of A1c abnormalities.

Often there is also significant limited joint mobility so most such complications are not unexpected nor are they discordant from the diabetes control history. The DCCT and especially EDIC also show that optimizing glucose control at any point in time either

helps prevent and/or treat diabetic neuropathy in much the same fashion and intensity as for retinopathy and nephropathy. [39, 40, 41, 42]

Cardiovascular and macrovascular complications

These are extremely rare in those under 21 years of age and are often linked in type 1 diabetes patients with much longer duration as well as other concomitant risk factors such as obesity, hyperlipidemia and/or smoking history. When the relatively young cohort of the DCCT were followed for more than 20 years, the original dearth of macrovascular problems after the initial 7 year study follow-up period showed significant increases. Macrovascular risks showed similar patterns to the well known microvascular risks earlier identified[39,42].

The same metabolic memory effects comparing the intensively treated with the control group also were demonstrated. Knowledge and periodic review of detailed family history for cardiovascular events - and especially lipid abnormalities amenable to medical treatment – can be invaluable for assessing suspected higher risk subgroups and assiting with motivation for improvements and / or treatment decisions. Other research has identified gender-specific increased of cardiovascular risk factors in children and adolescents studied in a large computerized T1DM data base. [50]

INTENSIFIED THERAPY AND TREATMENT

Continuous glucose monitoring systems (CGMS)

As discussed previously, CGMS is now available, although expensive, with results usually produced at 5 minute intervals by most sensors (ie. Enlite ®, Guardian ®, DexCom®, Navigator®, Libre ®). Initial systems were useful for trend analysis but had error rates in the 20-30% range for individual values and the original sensors were especially problematic when registering hypoglycemia. Newer models have a reduced error rate to the 5-10% range compared to capillary blood glucose readings and continue to be most helpful to identify decreasing as well as increasing glycemic trends. This allows potentially earlier corrections of both high and low glucose readings whether treated by MDI or CSII and may be especially helpful for those with hypoglycemia unawareness or recurrent seizures as well as those with recurring nocturnal problems. CGMS remains very expensive and to many patients burdensome so that compliance suffers. Several research studies of CGMS have documented lowered A1c levels, decreased glycemic variability and

most importantly less severe and fewer episodes of hypoglycemia, especially loss of consciousness and coma episodes – but only if the CGMS continuous to be utilized over time.

When patients discontinue CGMS, the benefits disappear. Parents using CGMS with younger children and young adults using CGMS generally use it more frequently and profit more from such increased use compared to adolescents and young adults where compliance issues predominate.

Newer systems download directly to mobile telephones as well as internet servers and can be accessible via tablets and computers at home, school, office and for diabetes team assessment.

CGMS systems which provide 288 blood glucose equivalent values each day identify information that would otherwise escape detection, allow for better food and activity flexibility and improve glycemic control concomitant with not only identifying asymptomatic hypoglycemia but also reducing the most severe episodes of hypoglycemia such as those that such as those that nocturnally occur when asleep.

Insulin pumps, intensified MDI therapy, and new devices leading up to the artificial pancreas projects[51,52,53]

While totally implantable artificial endocrine pancreases and pancreas transplants (partial and β-cell) continue to be investigated, insulin pumps (continuous subcutaneous insulin infusion (CSII) systems)[54, 55] coupled with extensive SMBG and now CGMS are being used in adults and children more frequently than ever. While SMBG is expensive, CGMS is even more expensive but the potential benefits warrant paying attention to risk: benefit ratios and trying to optimize candidate selection and specific conditions that would benefit patients with type 1 diabetes based on published, well-designed, unbiased and, if possible optimally randomized prospective multicenter scientific studies.

CSII and MDI therapy has been applied successfully in research settings and in clinical practice in association with multidisciplinary health professional teams and optimized education/re-education.

Such intensified treatment efforts following the incredibly positive results of the DCCT with its potential for capitalizing on glycemic memory have documented positive and beneficial effects in teenagers. [56] Development of improved implantable and noninvasive glucose sensors is on the horizon and likely will continue to revolutionize current diabetes care. Sensors can be coupled to

internally or externally situated programmable insulin delivery systems that potentially feed appropriate amounts of insulin adjusted frequently according to glucose fluctuations in the blood or interstitium. Current CGMS units are available that communicate directly with CSII[57] but are not yet fully automatic but with rapid progress occurring. At this time, Medtronic ® leads the field with such interconnected sensors and pumps (530G, 630G, 670G) but other companies (Insulet ®, Abbott ®, T-Slim ®) have similar units under investigation. Automatic low glucose suspend (LGS) systems[58] are available and such systems not only provide predictive alarms for rate of glucose decline and rise as well as absolute hypoglycemia and hyperglycemia limits, but also automatically suspend insulin delivery at set values (ie. <60 mg/dl, approximately 3.3 mmol/L). All such alarms can be turned on or off, can be set for individual needs and provide additional safety when striving for tighter glycemic control and lower average glucose levels as well as improved A1c results. Systems which document, alarm and automatically reset basal insulin rates are also available responding to rising as well as falling glucose levels with mathematical algorithms created to identify such patterns (Medtronic 630G and 670G ® HCL, hybrid-closed-loop, devices) [59] in addition to notifying the patient and his or her parnts or family members. Better, smaller, more accurate and more sophisticated devices are on the horizon. Pumps that provide insulin alone as well as combination pumps with both insulin and glucagon[60] are also available and being researched. Efforts to decrease hyperglycemia also include efforts to decrease glycemic variability. While some of the complications may be related to glycemic exposure, there may be some genetic contribution towards glycosylation of varying tissues and this may be expressed not only in variable glycosylation of hemoglobin but also of the macro and microvasculature. Research exploring such possibilities and potential medical intervention show promise.

Continuous subcutaneous insulin infusion (CSII).

Insulin pumps are being prescribed with improved success more and more frequently for appropriate candidates. Selection and education efforts[61] are becoming more sophisticated in helping make transition to pump therapy easier and less problematic as well as increasing success with such patients over longer periods of time. Insulin pump treatment can be started in ambulatory fashion as well as during short hospitalizations for conversion to insulin

pump treatment depending more upon staffing situations and saving significant health care expenditure if done on an outpatient basis. Young children, teenagers, and adults can be treated successfully with insulin pumps. CSII may be the preferred treatment modality for infants and toddlers because of ability to immediately turn off delivery and for fine-tuning adjustments but diluted insulin is often necessary because of small dose requirements. New models are water resistant fully waterproof. They include alarms for occlusion as well as runaway delivery, empty catheters, and battery failure. Earlier black and white screens now have been replaced by color-screens and more of the pumps are truly waterproof.

Technical problems may be increased in youngsters in comparison with adults and especially in adolescents because of compliance issues. With appropriate adult (parental) supervision, success is likely and many centers around the world are using subcutaneous insulin pumps with good clinical results in large numbers of children and teenagers (as well as adults) without problems.

Similarly, family members (ie. spouses) must be supportive in adults using insulin pumps.

Hypoglycemia may be decreased with successful use of insulin pumps, particularly when insulin analogs are used in conjunction with automatic sensors. With such pump use, A1c improvements using CSII are lowered by 0.5-2.0% in many large studies around the world while at the same time decreased number and severity of hypoglycemia is well documented. Newer and smaller pump models have dose calculators and carbohydrate counting wizards as well as built-in meters to facilitate dosing decisions. Wireless devices and catheter-less "pods" improve acceptance and ease-of-use of CSII for patients who do not like the ideas of long tubes for insulin delivery (Omnipod ®).

Insulin basal and bolus distributions are similar to MDI algorithms with subsequent individualized adjustments based upon pre and post-prandial SMBG or CGMS profiles but data analysis is still required in all but the most sophisticated pump systems. Connections to night-stand monitors for parents or other family members and automatic downloading not only to network data centers but also to individual mobile telephones have been developed with significant improvement in sharing glucose and pump data but also reviewing glycemic results, providing warning alarms and assisting in the overview of large amounts of glucose

and insulin data. More and more combinations of glucose sensors communicating with insulin pumps and coupled with interactive mathematical response algorithms will continue to proliferate and likely bring us closer to full artificial pancreas devices[62]. A key barrier remains analysis of glucose data looking proactively as well as responding reactively to this information so that ongoing efforts to automate such analyses continue to be promising to overcome what is often the psychological burden of living with diabetes and constantly needing to be aware and responsive to so many different variables without any "vacation."

Intensive MDI therapy.

Where CSII uses analog (or regular) insulin delivered in small boluses over 24 hours with larger pre-food boluses given as needed, MDI uses basal-bolus algorithms of subcutaneous insulin in a variety of programs. Some examples are the following:

Glargine or detemir insulin before breakfast and again at bedtime with additional analog (or regular) insulin before meals and snacks as needed (BID long-acting insulin with premeal boluses).

Analog (or regular insulin) given before breakfast, before lunch, and before supper with glargine or detemir insulin at suppertime. (Bedtime long-acting insulin with premeal boluses).

Glargine insulin prebreakfast with prandial analogs often used in pre-schoolers who do not need any bedtime insulin.

Analog or regular insulin plus NPH before breakfast; analog or regular alone before supper; and NPH alone at bedtime [BID NPH with premeal boluses].

Analog or regular insulin plus NPH before all three meals, plus NPH alone at bedtime. [Overlapping NPH with premeal bolus mixtures.]

Same as example, but also with analog insulin before afternoon snack (when there is no afternoon activity).

Analog or regular insulin given before breakfast, before lunch, and before supper with ultralente insulin at suppertime or bedtime in circumstances where ultralente remains available. (Ultralente basal insulin plus prandial boluses.)

insulin given before breakfast, before lunch, and before supper with ultralente insulin at suppertime or bedtime in circumstances where ultralente remains available. (Ultralente basal insulin plus prandial boluses Analog or regular)

Same as example as above but with degludec instead of other basal insulins in association with prandial fast-acting insulins.

The principles of insulin adjustment are similar to those for CSII and demand frequent SMBG each day to provide data to adjust insulin, food, and exercise accordingly using prospective as well as retrospective analyses. The major benefits of MDI over CSII are that (a) no pump need be worn and (b) there are no added costs for purchasing the pumps or maintaining them. Some studies suggest similar positive effects in combining CGMS with MDI to avoid wearing an insulin pump but still providing additional glycemic information more often than intermittent SMBG.

Inhaled insulin may replace injected bolus insulin in MDI but still must be coupled with injected basal insulin analogs or overlapping intermediate-acting insulins. Inhaled insulin is presently not-approved for pediatric use, however, and remains expensive but has the advantage of avoiding some insulin injections. Short term pulmonary safety has been established but long term pulmonary safety remains unknown.

Ongoing education, peer, and parent support groups, empowerment and motivational interviewing.

Diabetes education

Education is a critical component of diabetes care[17].

If there is no acute decompensation (DKA), then it can take place on an ambulatory basis as long as the patient and family members live close enough and can afford and arrange to get to the facility for the frequent time needed to complete such "survival" education: what is diabetes, how does it happen, how to administer insulin and blood glucose as well as ketone testing, meal planning, record keeping, sick day rules, emergencies, preventing long term complications etc.

If the presentation is too severe, if there is no possibility for outpatient visits because of finances or distance, then inpatient education must occur at enormous added expense. Initially it was felt around the world that all such education could only take place as an inpatient but more and more this has been changed and well documented that outpatient education can and should occur, has benefits in addition to lowering costs and making learning about diabetes "more normal"[22,3,63] It should include these survival skills shortly after diagnosis and evolve into a continuous and on-going process with periodic updating and review by the health care team

at a minimum annually. Details should be documented in the medical records. The patient's entire family (parents, siblings, grandparents and other caregivers for children and adolescents; spouses for young adults) should be included and urged to participate fully in the process. As children get older and especially when they are teenagers, inviting friends to participate in office sessions and education reviews is also often very helpful since it expands the support network for the patient. Diabetes camping programs[64] are an extension of diabetic education while encouraging independence and self-esteem. Adult weekend programs use the same principles of education and support as childhood and adolescent summer, weekend, and winter camping programs with similar benefits. Special programs for babysitters as well as grandparents also have taken place and family camping programs or hotel resort programs are extremely popular and productive sometimes for the first time including both mothers and fathers as well as siblings who can meet others in similar circumstances and learn in group settings.[57]

Teaching manuals such as those written by Hanas[24] and also by Chase[21] are superb in providing up-to-date information in an accessible manner in English, Spanish, French and other language editions.

Disney and Eli Lilly Pharmaceuticals have also produced superb illustrated booklets highlighting a new character (chimpanzee), Coco, who has type 1 diabetes and must interact with Mickey, Minnie, Goofy and friends at school, at a sleep-over, at camp and do so in a positive and helpful manner. These are increasingly available not only in English but in Spanish, French, Hebrew, Arabic, Chinese, Korean, Japanese, Romanian, Portuguese, Italian and Turkish language editions and freely distributed.

Other teaching tools made available by NovoNordisk, Sanofi-Aventis and local medical establishments and diabetes programs are also increasing to aid in such education and support endeavors especially in parts of Africa, Bangladesh and India as well as Latin America. Life for a Child has a website devoted to such efforts where these materials can be freely shared.

For adolescents and young adults, three specific books written not only to provide information and educational but also designed to help support better self-care efforts and reduce the emotional burden of a chronic disease like diabetes are also excellent: Adam Brown's *Bright Spots and Landmines: the Diabetes Guide I Wish Someone Had Handed Me* [27], Gary Scheiner's *Think*

Like a Pancreas[65] and Michael Weiss and Martha Funnell's *Little Diabetes Book* [66]among others.

Peer and parent support groups

Groups provide an opportunity to complement office visits. Groups can be informational, supportive, and therapeutic. Joining organizations such as the International Diabetes Federation (IDF) or the Juvenile Diabetes Research Foundation (JDRF) provides not only support but also an avenue for lobbying for better health care insurance and care, better education, less discrimination, and support for research into both treatment and cures. Instructional publications include *Diabetes Forecast* and *Countdown* from the American Diabetes Association and similar educational support websites and mailings from many local and national diabetes organizations around the world also provide such ongoing support. The Internet has many sites (eg: www.childrenwithdiabetes.com; myglu.com; diatribe) available for a similar purpose and will continue to develop an expanding role for education and support internationally.

Diabetes Health and other excellent publications are produced privately but also bring up-to-date research reports and support. Organizations such as the International Society for Pediatric and Adolescent Diabetes (ISPAD) have websites where consensus guidelines are published and updated (www.ispad.org) and where programs such as Changing Diabetes in Children (CDIC) can foster cooperation, insulin and meter supply donation and structured assistance for economically distressed parts of the world. Life for a Child (LFAC) is another organization which sponsors such assistance in addition to promoting mentoring relationships with diabetes experts worldwide for teaching and care support where needed. Both LFAC and CDIC have worked closely with ISPAD and IDF as well as local diabetes facilities in improve the life of young patients with diabetes, improve access to insulin and testing supplies and provide needed emotional support.

Socioeconomic status, anxiety and depression, attention disorders and learning problems, quality of life[67]

It would seem rather obvious that poverty, food insecurity, family disruption all would have some impact on living with a chronic and time-demanding illness like diabetes. Education of parents and other caretakers not only concerning diabetes-specific issues but in general also have an impact on who can do what and

assist with diabetes care needs. If there is concomitant family-based emotional turmoil of any kind (alcohol parents, substance abuse, safe living issues, then this also has an impact on diabetes tasks and compliance. Specific issues for the patient him or herself with anxiety and depression, ADhD or ADHD, dyslexia or dyscalculia all "participate" in such compliance factors. If appropriate medical or psychosocial treatment exists but is not utilized or if it is not sufficient, then diabetes care usually suffers. Similarly, quality of life is directly associated in many studies with overall diabetes care and outcomes of diabetes treatment regimens.

School and after-school care issues[68]

One of the key differences in dealing with youngsters with type 1 diabetes is that they have families and their family members have to understand and often assume most if not all of their diabetes related care. As children grow, they are expected to attend school and the responsibility for diabetes care shifts somewhat more to the child but more specifically to the adults in charge at or after school: teachers and nursing staff.

Unfortunately, not all teachers understand the intricacies about a chronic illness with such frequent demands like diabetes and many are also scared of having to assume such responsibilities. Some are also worried that they could be held legally liable for wrong decisions under such circumstances even when there are "good samaritan" laws protecting them.

Similarly, after-school activities, sports and field trips also increase kids' time away from the security of home and family supervision. Teachers as well as after school supervisors express concern about their insufficient training particularly to identify or handle emergency situation related to diabetes. Parents as well express concerns about perceived inadequacies of school and after-school personnel abilities regarding diabetes supervision and care even when laws exist that mandate such training and care be provided to minimize discrimination against a child with a chronic condition like diabetes. In the US and many other countries, federal and local laws mandate such responsibilities to school and related staff under anti-discrimination regulations.

As with parents, teacher and other staff training needs to be specific to the circumstances including the age of the patient, self-care efficacy and skills, interest and skills of bus drivers, coaches, librarians, secretaries, counseling staff and administrative staff as well as school volunteers. With intensification of T1DM treatment

following the DCCT and with more MDI and more electronic based diabetes related care devices (meters, pumps, sensors), demands during school time have increased accordingly. Insulin pens, also have replaced syringes in many parts of the world but this actually eases the administration of insulin compared to the vagaries of syringe administration. Nevertheless, supervision still is often required and different degrees of supervision needed for young children, middle-aged children and adolescents. As a result, diabetes care plans have evolved created by the child or teenager, parent(s) and the diabetes health care team to be passed along to the school staff and created yearly, adapted to the needs of the child/teen and their independence vis-à-vis diabetes self-care. This may involve accepting that blood glucose testing and insulin administration can be done in the classroom or the lunchroom instead of only at the nursing station, what to do if there are not nurses always available, who will help with hypoglycemic events or sick days and how to contact the diabetes team and parents if questions or problems ariseSimilarly, issues with snacking, lunch choices and sports participation that requires changes in either insulin and/or food provision need to be addressed with as much "normalcy" arranged as is possible to ensure safety of all. In high school, all this may translate into merely agreeing to allow the high school student independence with their own self-care whereas for a toddler in day-care or a very young child or a child with limited intellectual abilities (ie. Down Syndrome concomitant with T1DM), specific and designated staff must be able to provide the needed care as agreed upon and needed. Glucagon should be provided by patient/family annually and be stored in an agreed upon site usually in the nursing office. When tests take place, specific arrangements for blood glucose testing, snacking or appropriate treatment of hypoglycemia as well as provisions to retake examinations if hypoglycemia occurs during them (without penalty or embarrassment), all need to be prearranged and agreed upon by school staff too. The same for university students although as they are older and more responsible for their own care, they bear some of the burden of carrying out such discussions, asking for specific authorization from the diabetes health care team and otherwise discussing their individual needs, professors etc. NEDEC has template school authorization forms for such circumstances as does the American Diabetes Association and the Juvenile Diabetes Foundation. Many schools systems also have developed their own similar forms in similar style to many other national and local

diabetes groups and these can be shared with patients and families or your own forms created.

Other issues about school involve not just hypoglycemia interference with school productivity and emergency issues but also about research that links school performance with A1c levels, glycemic control and perhaps indicating a subtle, but common and unrecognized complication of long-standing diabetes.[69]

Empowerment and motivational interviewing

Changing professional attitudes and adaptation of modern psychosocial constructs for education are important new ideas to facilitate life with a chronic illness such as type 1 diabetes.

Adjustments in choice of words and phrases, approaches to behavioral change, discussions of life and death issues in a manner which promotes proactive decision making and acknowledges thedifficulties when negative consequences occur help in this process. (For instance, not calling someone ”a diabetic” but rather a PWD: person with diabetes, is le pejorative and more positive and uplifting to many. Multidisciplinary team support, consistent goals, adapting goals to individual patient and family circumstances coupled with positive rather than negative reinforcement often will help bring about clinical improvement and change in health care choice.[3]

Summary

Efforts to provide ongoing education and support for the patient with type 1 diabetes should be aimed at obtaining blood sugar levels as close to normal as possible without causing excessive hypoglycemia. With attention to the psychological needs of the child, teenager and family members, and with a positive, nonpunitive empowering attitude on the part of the health care team, more patients should be able to live better, happier and longer lives free of the complications of IDDM.

References

1. American Diabetes Association. *Children and adolescents*. Section 12 in: Standards of Medical Care in Diabetes -2017. Diabetes Care, 2017; 40 (suppl 1): S105-113
2. *ISPAD Clinical Practice Consensus Guidelines 2014*. Sperling MA, Acerini C., Craig M.E., de Beufort C., Maahs D.M., Hanas R. Eds Pediatric Diabetes 2014: 15 (suppl 20) : 1-290

3. Brink SJ and Serban V, eds. *Pediatric and Adolescent Diabetes*. 2004: Timisoara, Romania: Brumar
4. Brink SJ, Moltz K. *The message of the DCCT for children and adolescents*. Diabetes Spectrum 1997;248–67
5. Brink SJ, Lee WRW, Pillay K, Kleinebreil L. *Diabetes in Children and Adolescents. Basic Training Manual for Healthcare Professionals in Developing Countries*. 2011, NovoNordisk, Denmark
6. Abdullah M. *ISPAD Annual Scientific Congress, Henri Lestradet Award Lecture*, 2012.
7. Cameron FJ, de Beaufort C, Aanstoot HJ, Hoey H, Lange K, Castano L, Mortensen HB, Hvidoere International Study Group. *Lessons from the Hvidoere International Study Group on childhood diabetes: be dogmatic about outcome and flexible in approach.* Pediatr Diabetes 2013; 14: 473-480.
8. De Beaufort CE, Lange K, Swift PGF, Aman J, Cameron F, Castano L, Dorchy H, Fisher LK, Hoey H, Kaprio E, Kocova M, New A, Njolstad PR, Phillip M, Schoenle E, Robert JJ, Urakami T, Vanelli M, Danne T, Barrett T, Chiarelli F, Aanstoot HJ, Mortensen HB and on behalf of the Hvidoere study Group. *Metabolic outcomes in young children with type 1 diabetes differ between treatment centers: the Hvidoere Study in Young Children* 2009. Pediatr Diabetes 2013; 14:422-8.
9. Brink SJ. The Very Young Child with Diabetes. In: Brink SJ and Serban V, eds. Pediatric and Adolescent Diabetes.2004: Timisoara, Romania: Brumar, 189-232.
10. Ryan CM. Why is cognitive dysfunction associated with the development of diabetes early in life? The diathesis hypothesis. Pediatric Diabetes 2006; :289-97.
11. Iannotti RJ, Nansel TR, Schneider S, Hayne DL, Simons-Morton B, Sobel DO, Zeitzoff L, Plotnick LP, Clark L. Assessing regimen adherence of adolescents with type 1 diabetes. Diabetes Care 2006;29:2263-7.
12. Grossman HY, Brink SJ, Hauser ST. Self efficacy in adolescent girls and boys with insulin dependent diabetes mellitus. Diabetes Care 1987; 10:324-9.
13. Brink SJ. How should children and youth with type 2 diabetes be treated? In: Velea IP, Paul C, Brink SJ, eds. Theoretical and Practical Update in Pediatric Endocrinology and Diabetes. 2014, Timisoara, Romania: Editura Mirton, 89-125.
14. Cret V. Maturity onset diabetes of the young (MODY): clinical characteristics, diagnostic and therapeutic approaches. In: Velea IP, Paul C, Brink SJ, eds. Pediatric Endocrinology and Diabetes 2016 Update. Timisoara, Romania: Editura Mirton, 147-64.
15. Pozzilli P, Buzzetti R. A new expression of diabetes: double diabetes. Trends Endocrinol Metab 2007; 18:52-7.
16. Hattersley AT, Ashcroft FM. Activating mutations in Kir6.2 and neonatal diabetes: new clinical syndromes, new scientific insights and new therapy. Diabetes 2005;54:2503-13.
17. Brink SJ. Diabetic ketoacidosis. In: Chiarelli F, Dahl-Jorgensen K, Kiess W. (eds) Diabetes in Childhood and Adolescence 2005, Basel: S. Karger, 94-121.
18. Levetan C, Passaro MD, Jablonski KA. Effect of physician specialty on outcomes in diabetic ketoacidosis. Diabetes Care 1999; 11:1790-5.

19. Laffel LMB, Wentzell K, Loughlin C, Tovar A, Moltz K and Brink S. Sick day management using blood 3-hydroxybutyrate (3-OHB) compared with urine ketone monitoring reduces hospital visits in young people with T1DM: a randomized clinical trial. Diabetic Medicine 2005; 23:278-84.
20. Dillon ES, Riggs HE, Dyer WW. Cerebral lesions in uncomplicated fatal diabetic acidosis. Am J Med Sci 1936; 192:360 - 5.
21. Rosenbloom AL. Intracerebral crises during treatment of diabetic ketoacidosis. Diabetes Care 1990; 13:22-33.
22. Brink SJ. 2015: Insulin past, present and future. In: Velea IP, Paul C and Brink SJ, eds. Update in Pediatric Endocrinology and Diabetes, 2015, Timisoara, Romania: Editura Mirton, 61-96
23. Hirsch IB, Farkas-Hirsch R, Skyler JS. Intensive insulin therapy for treatment of type I diabetes. Diabetes Care 1990; 13:1265–1283.
24. Holterhus P-M, Odendahl R, Oesingmann S, Lepler R, Wagner V, Hiort O, Holl R, The German/Austrian DPV Initiative and the German Pediatric CSII Working Group. Classification of distinct baseline insulin infusion patterns in children and adolescents with type 1 diabetes on continuous subcutaneous insulin infusion therapy. Diabetes Care 2007; 30:568-73.
25. Chase HP. Understanding Diabetes. A handbook for people who are living with diabetes. 2006, Children's Diabetes Foundation at Denver, Denver, CO.
26. Brink SJ. Pediatric and Adolescent Diabetes Mellitus. 1987, Chicago-London, Year Book Medical Publishers.
27. Brink SJ. Insulin treatment and home monitoring for type 1 diabetes mellitus. In: LeRoith D, Taylor SI and Olefsky JM. (eds) Diabetes Mellitus. A Fundamental and Clinical Text, Third Edition, 2004, Philadelphia: Lippincott Williams & Wilkins, 683-700.
28. Hanas R. Type 1 Diabetes Mellitus. A Guide for Children, Adolescents, Young Adults – and their Caregivers. 2005, New York, NY: Marlowe & Company
29. Garg SK, Voelmle MK, Beatson CR, Miller HA, Crew LB, Freson BJ, Hazenfield RM. Use of continuous glucose monitoring in subject with type 1 diabetes on multiple daily injections versus continuous subcutaneous insulin infusion therapy. Diabetes Care 2011, 34: 574-9.
30. Brink S, Siminerio L, Hinnen-Hentzen D, et al. Diabetes Education Goals. 1995, Alexandria, VA: American Diabetes Association.
31. Brink SJ. Pediatric and adolescent IDDM meal planning 1992: our best advice to prevent, postpone and/or minimize angiopathy. In: Weber B, Burger W, Danne T, eds. Structural and functional abnormalities in subclinical diabetic angiopathy. *1992,* Basel: Karger, 156–169.
32. Brown A. Bright Spots and Landmines: The Diabetes Guide I Wish Someone Had Handed Me. 2017, San Francisco, The diaTribe Foundation.
33. Dorchy H. Nutritional Management for Young People with Type 1 Diabetes Mellitus. In: Brink SJ, Serban V, eds. Pediatric and Adolescent Diabetes, Revised Edition. 2004, Timisoara, Romania: Brumar, 211-240.
34. Dorchy H. What glycemic control can be achieved in young diabetics without residual secretion of endogenous insulin? What is the frequency of severe hypoglycemia and subclinical complications? Arch Pediatr 1994;1:970–981
35. Brink SJ. Complications of type 1 diabetes mellitus in children and teenagers. In: Cheta D (ed) Vascular Involvement in Diabetes. Clinical,

Experimental and Beyond. 2005, Basel: S. Karger, 375-388.
36. Brink SJ. Limited joint mobility. In: Brink, SJ, ed. Pediatric and Adolescent Diabetes Mellitus 1987, Chicago – London, Year Book Medical Publishers, 305-12.
37. Rosenbloom AL. Limited joint mobility in childhood diabetes mellitus indicates increased risk for microvascular disease. N Engl J Med 1981, 305:191-4.
38. Gonder-Frederick L, Cox D, Kovatchev B, Clarke W. A biopsychobehavioral model of risk of severe hypoglycemia. Diabetes Care 1997;20:661–669.
39. Sherr JL, Ruedy KJ, Foster NC, Piche CA, Dulude H, Rickels MR, Tamborlane WV, Bethin KE, DiMeglio LA, ox LA, Wadwa RP, Schatz DA, Nathan BM, Marcovina SM, Rampakakis E, Ming L, Beck RW for the T1D Exchange Intranasal Glucagon Investigators. Glucagon nasal powder: a promising alternative to intramuscular glucagon in youth with type 1 diabetes. Diabetes Care 2016;39:555-62.
40. Haymond MW, Schreiner B. Mini-dose glucagon rescue for hypoglycemia in children with type 1 diabetes. Diabetes Care 2001;24 (4);643-5.
41. Clarke WL, Cox D, Gonder-Frederick L, Kovatchev B. Hypoglycemia. In: Brink SJ, Serban V, eds. Pediatric and Adolescent Diabetes, Revised Edition. 2004, Timisoara, Romania: Brumar.
42. Velea I, Paul C. Growth in the child with diabetes mellitus. In: Velea IP, Paul C, Brink SJ, eds. Clinical Issues in Pediatric Endocrinology 2012, Timisoara, Romania: Mirton, 75-100.
43. Hughes J.W., Riddlesworth T.D., DiMeglio L.A., Miller K.M., Rickels M.R., Mc Gill J.B., for the T1D Exchange Clinic Network. Autoimmune disease in children and adults with type 1 diabets from the T1D Exchange Clinic Registry. J Clin Endocrinol Metab 2016, 101 (12) : 4931-7
44. Brink SJ. Complications of type 1 diabetes mellitus in children and teenagers. In: Cheta D (ed) Vascular_Involvement in Diabetes. Clinical, Experimental and Beyond. 2005, Basel: S. Karger, 375-388
45. DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329:977–986.
46. DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Beneficial effects of intensive therapy of diabetes during adolescence: outcomes after the conclusion of Diabetes Control and Complications Trial (DCCT). Pediatrics 2001; 139:804–812.
47. DCCT/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 2000; 342:381–389.
48. Nathan DM, Zinman B, Cleary PA., Becker D, Orchard T. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Modern day clinical course of type 1 diabetes mellitus after 30 years' duration: the Diabetes Control and Complications/Epidemiology of Diabetes Interventions and Complications and Pittsburgh Epidemiology of Diabetes Complications experience (1983-2005). Arch Intern Med 2009;169:1307-16.
49. Belay B, Belamarich PF, Tom-Revzib C. The Use of Statins in Pediatrics: Knowledge Base, Limitations and Future Directions. Pediatrics 2007;119:370-80.
50. Schwab KO, Doerfer J, Marg W, Schober E, Holl RW. DPV Science Initiative

and the Competence Network Diabetes Mellitus. Characterization of 33,488 children and adolescents with type 1 diabetes based on the gender-specific increase of cardiovascular risk factors. Pediatr Diabetes 2010;11:357-63.
51. Maahs D.M., Buckingham B.A., Castle J.R., Cinar A., Damiano E.R., Dassau E., DeVries J.H., Doyle F.J., Griffen S.C., Haidr A., Heinemann L., Hovorka R., Jones T.W., Kollman C., Kovatchev B., Levy B.L., Nimri R., O`Neal A.N.D., Philip M., Renard E., Russell S.J., Weinzimer S.A., Zisser H., Lum J.W. – Outcome measures for artificial pancreas clinical trials > a consensus report. Diabetes Care2016, 39:1175-9
52. Kovatchev B., Tamborlane W.V., Cefalu W.T., Cobelli C. – The artificial pancreas in 2016: a digital treatment ecosystem for diabetes. Diabetes Care, 2016; 39:1123-6.
53. Brink SJ. Insulin pumps and continuous glucose monitoring systems en route to the artificial pancreas 2017. In: Pediatric Endocrinology and Diabetes 2017 Update. Velea IP, Paul C, Brink SJ, Krzisnik C, eds. 2017, Timisoara, Romania: Editura Mirton, 85-112.
54. Chase HP. Understanding Insulin Pumps & Continuous Glucose Monitors. 2007, Children's Diabetes Foundation at Denver, Denver, CO.
55. Danne T and Tamborlane WV, eds. Insulin Pumps in Childhood Diabetes. In: Pediatric Diabetes 2006;7 (S4): 1-50.
56. White NH, Cleary PA, Dahms W, Goldstein D, Malone J, Tamborlane WV. Beneficial effects of intensive therapy of diabetes during adolescence: outcomes after the conclusion of the Diabetes Control and Complications Trial (DCCT). J Pediatr 2001: 139:804-12.
57. Bergenstal RM, Tamborlane WV, Ahmann A. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. N Engl J Med 2010; 363:311-20.
58. Buckingham BA, Raghinaru D, Cameron F, Bequette BW, Chase HP, Maahs DM, Slover R, Wadwa RP, Wilson DM, Ly T, Aye T, Hramiak I, Clarson C, Stein R, Gallego PH, Lum J, Sibayan J, Kollman C, Beck RW for the In Home Closed Loop Study Group. Predictive low-glucose insulin suspension reduces duration of nocturnal hypoglycemia in children without increasing ketosis. Diabetes Care 2014;38:1197-1204.
59. Ly T.T., Roy A., Grossman B., Shin J., Campbell A., Monirabbasi S., Liang B., von Eyben R., Shanmugham S., Clinton P., Buckingham B.A., - Day and night closed-loop control using the integrated Medtronic hybrid closed-loop system in type 1 diabetes camp. Diabetes Care 2015; 38 1205-11.
60. Russel S.J., El-Khatib F.H., Sinha M., Nathan D. – Outpatient glycemic control with a bionic pancreas in type 1 diabetes. N Engl J Med 2014; 371 : 313-25
61. Kaufman FR, Westfall E. Insulin Pumps and Continuous Glucose Monitoring. A User's Guide to Effective Diabetes Management. *2012,* Alexandria, VA. American Diabetes Association.
62. Skyler JS. T1DM in 2014: progress towards a bionic pancreas. *Nat Rev Endocrinol* 2015;11:75- 6.
63. Siminerio LM, Charron-Prochownik D, Banion C, et al. Comparing outpatient and inpatient diabetes education for newly diagnosed pediatric patients. Diabetes Educ 1999;25;895–906.
64. Brink SJ. Diabetes camping. In: Werther G, Court J, eds. Diabetes and the Adolescent. 1998, Melbourne, Australia: Miranova Publishers, 281–294.
65. Scheiner G. Think Like a Pancreas. A Practical Guide to Managing

Diabetes with Insulin. 2011, Boston, DaCapo Press.
66. Weiss MA and Funnell MM. The Little Diabetes Book 2007, Philadelphia, Running Press Book Publishers.
67. Hassan K, Loar R, Anderson BJ, Heptulla RA. The role of socioeconomic status, depression, quality of life, and glycemic control in type 1 diabetes mellitus. J Pediatr 2006; 149:526-31.
68. Siminerio L and Brink SJ. Diabetes School Issues. In: Brink SJ and Serban V, eds. Pediatric and Adolescent Diabetes. 2004: Timisoara, Romania: Brumar, 27-44.
69. Schoenle EJ, Schoenle D, Molinari L, Largo RH. Impaired intellectual development in children with type 1 diabetes: association with HbA1c, age at diagnosis and sex. Diabetologia 2002;45:108-14.

STUART J. BRINK, MD
Senior Endocrinologist, New England Diabetes and Endocrinology Center (NEDEC), Waltham MA, USA
Associate Clinical Professor of Pediatrics, Tufts University School of Medicine, and Clinical Instructor, Harvard Medical School, Boston, MA, USA
Address correspondence to: New England Diabetes and Endocrinology Center (NEDEC), 52 Second Avenue, Suite 2800, Waltham MA 02451-1127 USA.
E-mail: stuartbrink@gmail.com

February 2018

EPIDEMIOLOGY OF DIABETES MELLITUS IN CHILDREN AND YOUTH

Przemysława Jarosz-Chobot, **Agata Chobot**, **Wojciech Fendler**, **Joanna Polańska**, **Eliza Skała**

Basic epidemiological definitions

Epidemiology, as the science of the occurrence, causes and effects of health phenomena in defined populations, is the basis for their understanding and, at the same time, the necessary basis in the field of public health. In practical terms, it uses the obtained data to reduce the occurrence of a specific health problem in the population. It also helps to shape clinical practice and health policy.[1]

In the paediatric population, epidemiological studies on diabetes cover the most common type 1. But epidemiological studies are carried out worldwide on virtually all types of diabetes in children. In Poland epidemiological research covers mainly type 1 diabetes and recently also monogenic diabetes.

In epidemiology, cross-sectional/observational analyses are performed most frequently (both retrospectively and prospectively), but also experimental studies are carried out, which allow to assess the effectiveness of selected therapeutic and preventive interventions.

Particular attention should be paid to the fact that in epidemiology the observation time is very important for conclusions - the longer it is, the more correct it is [1-3]

The basic concepts in the field of epidemiology are presented below [1-3]

Incidence

It is a measure of the likelihood of a disease or condition occurring in a population and over a period of time. It determines the number of new cases that have been reported for the population in the observed period. It can be expressed in absolute terms, but it is more useful to express it in relative terms, either as incidence rate or as cumulative incidence rate. Both are calculated on the basis of the number of persons constituting the population exposed – those that could acquire the disease in the given period of time (according to the formulae below) [2]

$$\text{Incidence ratio} = \frac{\text{number of new cases in a defined period of time}}{\text{total of time periods, when each person of the population is exposed}} 10^6.$$

$$\text{Cumulative incidence ratio} = \frac{\text{number of new cases in a defined period of time}}{\text{size of the population exposed at the beginning of the observation}} 10^6.$$

The incidence rate expresses the number of new cases per all person-years in observation or more frequently per 100 000 person-years (also person-days, etc).

The cumulative incidence rate represents the number of new cases over a defined period of time divided by the size of the population exposed at the beginning of the observation. For example, the cumulative incidence of type 1 diabetes among children under the age of 15 in Poland between 2007 and 2012 of 18.94/100 000/year means that for every 100 000 children under 15 years of age, around 19 at that age have developed the disease during that period and in the region.

Prevalence

It defines the proportion of all cases of a given disease or health event (new and ongoing, which started before the observation period) in a chosen population and over a defined period of time. Prevalence, just as incidence, can be expressed in absolute terms or by means of a relative factor. The prevalence rate is calculated from the formula below [2]:

Prevalence = total number of people with a defined disease/ condition in a specified time period x-10^6 the number of people at risk of developing the disease during this period (alternatively, in the middle of the period considered)

The result is usually expressed per 100 000 persons of the exposed population. Therefore, the prevalence of type 1 equaling 138/100 000 means that there are 138 kids with this disease per 100 000 children (newly diagnosed and lasting).

Incidence and its rates are used in cause-and-effect considerations. The usefulness of prevalence rates is low for these purposes, but they are used to identify health care needs and to plan health and social policies.

Mortality

Crude mortality rate defines the total number of deaths in a defined period to the size of the whole population. More reliable are the mortality rates calculated for a chosen group from the society, identified by age, race, gender or health status (ie. Population of people with diabetes), job or geographic region.

Number of all deaths in a defined population/cohort in a certain period of time

Mortality = ---------- 100%

Size of this population/cohort

Diabetology, for example, defines the mortality rate in diabetes patients - the number of deaths (due to diabetes and its complications as well as those not related to diabetes) relative to the whole population of patients with diabetes.

Fatality

It is a measure of the severity of a disease and is calculated by dividing all deaths due to a specific disease or its complications by the number of all diagnosed cases of this disease or events over a specific period of time. [2]

Number of disease-related deaths per period of time

Fatality = ----------X100%

Number of cases of this disease in the same period

The fatality of type 1 diabetes or the fatality of diabetes ketoacidosis at the diagnosis of diabetes can therefore be calculated.

Life expectancy

It is a frequently used synthetic measure of population health. It defines the average number of years that a person of a given age has still a chance to live. This indicator can also be calculated for individual patient populations. An example is the calculated average life expectancy of 58.8 years for children aged 10 who were diagnosed with type 1 diabetes between 1965 and 198.[2,3]

Structure indicators

They present the percentage share of a given variable in the study group (e.g. occurrence of particular types of late complications in children and adolescents with diabetes).

Standardized and crude rates.

Crude rates are numbers from registers or data sets. Their standardization allows to compare values between data sets with different distributions of basic features. Standardization may be made by age, sex or another characteristic and shall determine what the factors in the study group would be if the distribution of the chosen parameters (age, sex, etc.) was that of the 'standard' population. In diabetes rates are most often standardized by age and gender, in order to exclude the impact of these two important parameters (in particular, in paediatrics).[1-3]

Absolute risk.

A measure of the strength of the relation between the exposure and occurrence of the disease. It is the difference between incidence rates of the exposed and not exposed population.[1-3]

Relative risk.

A better than absolute risk indicator of the strength of the relation between exposure and occurrence of the disease, as it allows taking into account the basic prevalence of the disease/condition in question. It is the ratio of the risk of disease occurrence in the exposed to the risk in the not exposed group.[1-3]

Type 1 diabetes mellitus epidemiology

Worldwide data

Type 1 diabetes mellitus (T1D) is currently one of the most common chronic metabolic diseases in children. According to the latest IDF (International Diabetes Federation) report from 2017, the number of children below the age of 20 suffering from T1D worldwide reached almost 1 106 200 [4]. Moreover, it is estimated that about 96 000 (under 15 years of age) and 132 600 (under 20 years of age) new cases of this type of diabetes are reported annually (*Table 2.1.*).

Table 2.1. Global estimates for T1D in children and adolescents (< 20 yrs) for 2017.

IDF region	
Population (<15 years)	1.94 billion
Population (<20 years)	2.54 billion
Type 1 diabetes in children and adolescents (<15 years)	
Number of children and adolescents with type 1 diabetes	586,000
Number of new cases of type 1 diabetes per year	96,100
Type 1 diabetes in children and adolescents (<20 years)	
Number of children and adolescents with type 1 diabetes	1,106,200
Number of new cases of type 1 diabetes per year	132,600

IDF Diabetes Atlas - 8th Edition

Worldwide epidemiological data on T1D prevalence, based on longstanding observations (DERI, WHO-Diamond and EURODIAB studies), show a wide global variation. In European countries, in the Caucasian population, T1D is diagnosed in over 90% of all cases of diabetes in children/young people and over 50% of cases are diagnosed by the age of 14. The incidence rates vary from country to country, from region to region within countries, as well as from ethnic to ethnic population living in the area. Of the total T1D population, about 25% is from Europe and about 22% from North America and the Caribbean. [4]

In most high income countries the majority of children and adolescents who develop DM have T1D.

The table 2.1. shows the number of patients and the incidence of T1D in the countries where these rates are highest, IDF 2017 data.[4]

Table 2.2.a. i 2.2.b. - Number of patients with T1D < 15 years of age and incidence rates of T1D and number of patients with T1D<15 year of age/ 100 thousand/year] - data 2017, IDF Diabetes Atlas 2017

2 a).

Rank	Countries	New cases
1	United States	14,700
2	India	11,300
3	Brazil	7,600
4	China	4,100
5	United Kingdom	3,300
6	Russia Federation	3,100
7	Algeria	2,900
8	Saudi Arabia	2,800
9	Nigeria	2,400
10	Germany	2,400

2b.

Rank	Country	Incidence rates with type 1 diabetes
1	Finland	57.2
2	Kuwait	44.5
3	Sweden	39.5
4	Saudi Arabia	33.5
5	Norway	29.8
6	Algeria	26.0
6	Morocco*	26.0
8	United Kingdom	25.9
9	Ireland	24.3
10	Denmark	23.0

(*)The data for Marocco is extrapolated from Algeria

A significant epidemiological phenomenon characteristic for the last few decades is the fact that we are constantly observing a tendency to increase the number of new cases - the average increase of the annual incidence rate is 3% with a strong indication of geographic differences.[5] The fastest growth rate is observed in developing countries and in countries which have recently undergone significant economic changes, e.g. in the countries of Central and Eastern Europe, including Poland. [6] In Romania (2017), the number of children and adolescent with T1D is estimated as 2,623 and the incidence ratio 7,2 per year and per 100 000 children and adolescent. [7]

The global incidence of T1D is well illustrated on the map published in IDF Atlas, 2015 – Fig 2.1. [8]

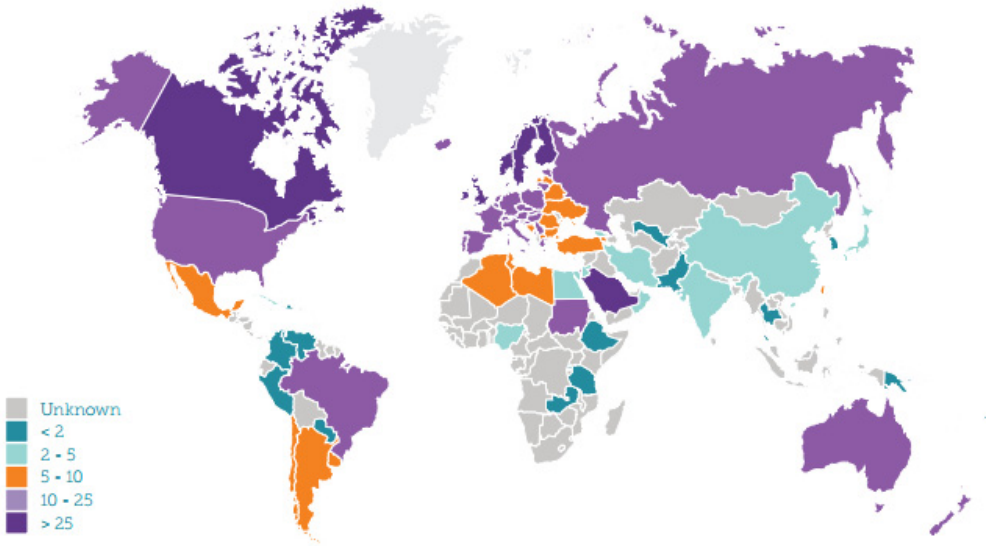


Fig. 2.1. - T1D incidence rate among children and adolescents <15 years old / 100 000 children, data 2015 - IDF Diabetes Atlas

Factors determining the incidence of T1D:

1. *Family history.*

The risk of developing T1D increases in families with a positive history. Taking into account the degree of relationship, the risk is as follows:

- 40 % for identical twins,
- 6-17% for siblings (depending on common HLA haplotypes predisposed to the disease, increases with age, is potentially higher in the case of early diabetes),
- 1-4% in the offspring of mothers with diabetes mellitus
- 3-8% in the offspring of fathers with diabetes mellitus
- 30% in the offspring of both parents with diabetes.

Current epidemiological studies indicate a high increase of these rates - overall, the risk of developing T1D in burdened families can be estimated to be 15 times higher than in unburdened families.[9]

2. Seasonality

In many studies the seasonal variability of T1D was estimated. The peak of the diagnosis of disease in autumn-winter months and the changing seasonality were described year by year, which was mainly explained by coincidence with a variable number of infections, mainly viral. Seasonality is mainly observed in older children.[5]

3. Migration

Is the most significant confirmation of the role of environmental factors - often after a change of residence representatives of populations with previously lower incidence rates start to become diabetic more frequently, as compared to the population living in a given region.

4. Periodicity of the disease

Also suggests a significant role of environmental factors - several recent reports from various parts of the world (including Poland and Australia) have provided evidence of several-year (5-year periods) fluctuations in the number of new cases in the paediatric population.[10]

Mortality

Over the years, since the introduction of insulin therapy, especially intensive therapy based on self-regulation of glycaemia, and due to the generally rapidly improving diabetes care, the survival of T1D patients has been steadily increasing. In general, the survival time of patients compared to the general population is shorter - according to the latest data by about 12 years.[11]

What is very important, a trend of significant, systematic decrease of this difference has been observed recently.

However we should be aware, that patients with type 1 diabetes diagnosed less than 15 years of age had 3 times the mortality risk of the general population. Over half of the deaths were related to acute or chronic complications of diabetes.

Mortality is associated with acute and chronic complications of diabetes, such as hypoglycaemia, ketosis, infections, micro-vascular/macrovascular complications, and is very diverse around the world. In the general population of T1D patients, cardiovascular diseases continue to be the main cause of death. Factors increasing the risk of premature death in T1D include: poorer metabolic control of diabetes, arterial hypertension, lipid disorders, multiple incidents of severe hypoglycaemia.[12]

Thanks to a significant improvement in the treatment of diabetes in general, in recent decades, the incidence of complications in all diabetes patients, leading to death has been significantly reduced - for example, the current trend of changes observed in the USA is shown in Fig. 2.2. [12.]

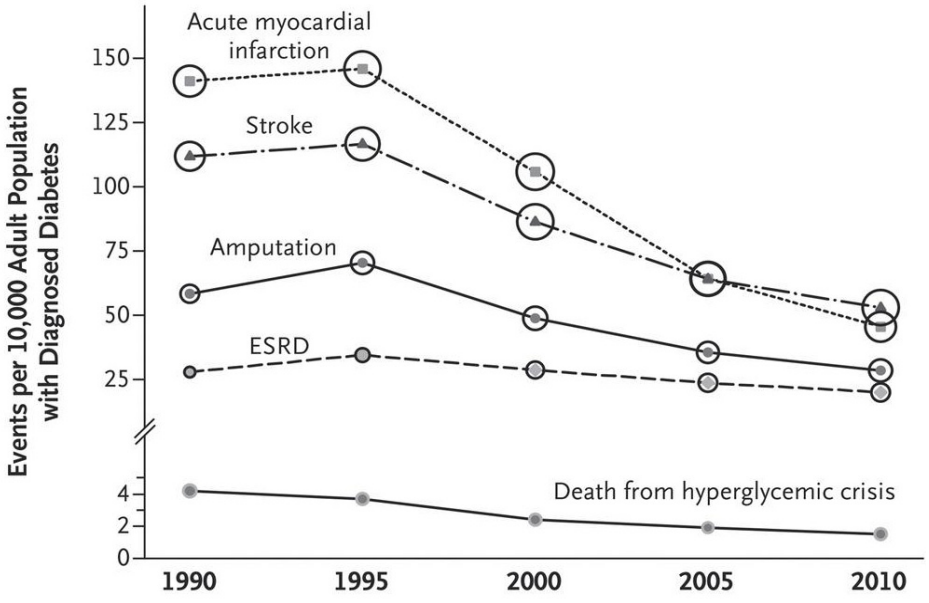


Fig. 2.2. - Number of diabetic incidents over the past 20 years - US health care data.[12]

Prediction for the future

The global outlook for children's T1D incidence looks very appalling for the coming years. A few years ago, a study by the EURODIAB group assessing the incidence of T1D in 23 European countries, based on the assumption that the current trend of disease growth continues, predicts a doubling of the number of sick children below the age of 5 and an increase of 70% in the number of new cases of children below the age of 15 within a decade. [5]

Type 2 diabetes mellitus epidemiology

Worldwide data

Type 2 diabetes mellitus (T2D) is classically associated with adult onset, however epidemiological data from the last 2-3 decades indicate a significant increase in the prevalence of T2D in children, especially in selected ethnic groups, in some countries.[1]

However, T2D occurs in persons of all races, but as mentioned above, with a significant prevalence in persons not belonging to the Caucasian population, including in the case of persons with a significant prevalence of T2D: Africans, indigenous peoples of North America (Indians), Latin American (Mexican), Asian or South Asian (India) and Pacific Islands origin.[13]

In European countries, including Poland, T2D still occurs relatively rarely, although there is also a noticeable increase in the incidence of the disease due to the rapidly increasing prevalence of obesity.

Data information of the prevalence, its trends of youth-onset type 2 diabetes based on population studies are limited. However, the prevalence of T2D in children and adolescents in the United States is approximately 12:100000, while it is still rare in Europe (approximately 2.5:100000). The majority of young people diagnosed with type 2 diabetes mellitus was found in specific ethnic subgroups such as African-American, Hispanic, Asian/Pacific Islanders and American Indians being highest in Pima Indians (22.3/1000 in 10 - 14-year-old children). Furthermore, screening studies in obese adolescents (considering obesity as a high risk factor of T2D) have reported a prevalence of 0.4% up to 1% of type 2 diabetes mellitus in obese children ≥ 12 years.[14]

The interesting picture, based on SEARCH study results, clearly illustrates the differences in incidence of T1D and T2D in children and youth among the races (*Fig.2.3.*) was published by Mayer-Davis et al.[15]

The incidence of T1D was assessed among participants (0-19yrs of age) and the incidence of T2D among participants who were 10 - 19yrs of age. P-values are for the linear trend test in each racial or ethnic group according to type of DM. Significant results suggest a positive annual rate of increase during study period (2004-2012).[15]

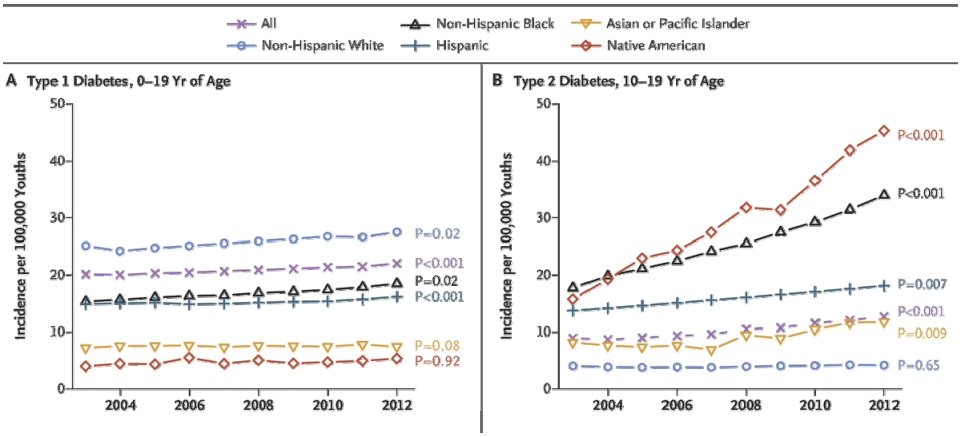


Fig. 2.3. Model-adjusted incidence estimates per 100,000 youths – SEARCH study.

Factors determining the incidence of T2D

1. Obesity: in Europe and the Americas, almost the entire T2D youth population has BMI > 85 pc for age and gender; this is not typical of Asian countries: 50% of Indian and Taiwanese children and 15% of Japanese children with T2D have normal body weight.

2. Insulin resistance - the disease rarely manifests itself before puberty, usually coexists with the peak of physiological insulin resistance during puberty, usually the symptom confirming its existence is acanthosis nigricans.

3. Diabetes mellitus in relatives - a strong positive effect of family history is observed (45-80% of patients, according to various sources, have parents or relatives with T2D); the risk is 6 times higher than that of persons whose parents do not have T2D, and the incidence of the disease is also observed.

4. Female sex - a significant predominance of the female sex is found, especially in endangered ethnic groups.

5. In some girls T2D is associated with coexisting *polycystic ovarian syndrome.*

6. Environmental factors: poor nutrition, sedentary lifestyle - adverse changes in lifestyle in the same vulnerable ethnic groups result in a significant increase in the incidence of T2D.

7. Prenatal factors - malnutrition during the fetal period can cause metabolic and hormonal changes that can promote the increase of obesity and insulin resistance at puberty age.

Mortality

Young-onset T2DM is the more lethal phenotype of diabetes and is associated with a greater mortality, more diabetes complications, and unfavorable cardiovascular disease risk factors when compared with T1DM.

Australian population-based study shows for a median observation period of 21.4 and 23.4 years for the T2D and T1D cohorts, respectively, 71 of 824 patients (8.6%) died. A significant mortality excess was noted in T2D. Death for T2D occurred after a significantly shorter disease duration and at a relatively young age. There were more cardiovascular deaths in T2DM. Despite equivalent glycemic control and shorter disease duration, the prevalence of albuminuria and less favorable cardiovascular risk factors were greater in the T2DM cohort, even soon after diabetes onset. Neuropathy scores and macrovascular complications were also increased in T2DM – *Fig. 2.4.*[16]

Prediction for the future

As an example, projections for US population suggests that the number of youth with T2D can reach 4-fold increase between years 2010-2050.[17]

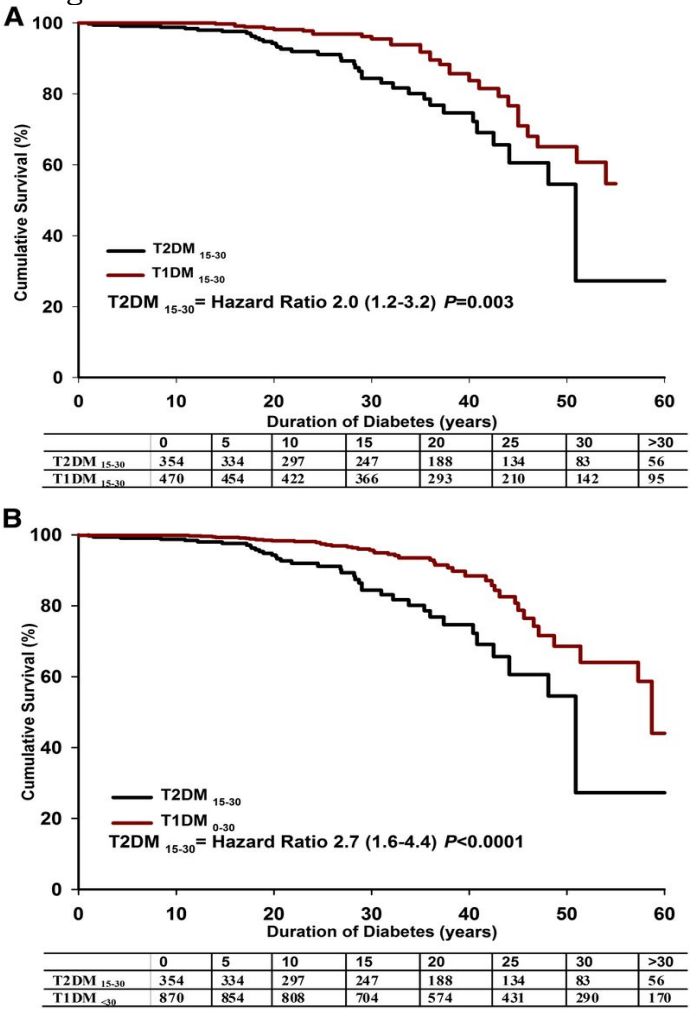
Epidemiology of other forms of diabetes: monogenic and related to cystic fibrosis.

The prevalence of monogenic diabetes (MD) is difficult to estimate. Several factors can be mentioned which have a very significant impact on this fact.

1. MD is a rare clinical problem, which results in insufficient awareness of the clinical phenotype of the disease among the medical staff (often the only feature of MODY is moderate asymptomatic hyperglycaemia, which means that there are no symptoms of the disease, and this means that the patient is not diagnosed).[18,19]

2. The lack of molecular diagnosis can be justified by the observed unequal access to expensive genetic tests. Available publications provide information that more than 80% of patients with clinical features indicating monogenic diabetes are not subject to molecular diagnosis due to the above mentioned reasons.[20]

3. Another reason for the underestimation of MD is the criteria for the inclusion of patients in molecular diagnosis. Shields et al. states that by extending the existing recruitment criteria for genetic tests it was possible to make a diagnosis of MD in 47% of patients more than the guidelines would indicate.[21,22]



	0	5	10	15	20	25	30	>30
T2DM 15-30	354	334	297	247	188	134	83	56
T1DM 15-30	470	454	422	366	293	210	142	95

	0	5	10	15	20	25	30	>30
T2DM 15-30	354	334	297	247	188	134	83	56
T1DM <30	870	854	808	704	574	431	290	170

Fig.2.4. Kaplan-Meier survival curve for T2DM (n = 357) and T1DM 15–30 (n = 470) patients.[16]

Epidemiology of the most common forms of monogenic diabetes: MODY and neonatal diabetes.

The most common forms of heterogeneous and genetically determined defects of beta cells are: diabetes described with the acronym MODY (Maturity Onset Diabetes of the Young) and neonatal diabetes mellitus (NDM).

MODY-type diabetes

MODY-type diabetes is found in Europe in 1 - 2%, in Poland in 3.1 - 4.2% of patients with diabetes, of which 70-80% are: GCK-MODY type diabetes (formerly MODY 2) associated with glucocinase gene mutation and diabetes associated with HNF1A gene mutations (MODY-3). The prevalence of these two forms of MODY varies from country to country. Literature data generally indicate that MODY GCK diabetes is more common in Southern European countries (UK 10-20%, France 46-56%, Italy 41-61%, Spain 25-80%, Czech Republic 31%, Norway 12%, Denmark 10%), while diabetes associated with HNF1A gene mutations is more prevalent in Northern Europe.[19,20,21]

Table 2.3. - Frequency of currently known MODY diabetes mellitus

Type MODY	Gen	Frequency of occurrence
1	*HNF4A*	~5%
2	*GCK*	70-80%
3	*HNF1A*	
4	*IPF1*	rare <1%
5	*HNF1B*	~5%
6	*NEUROD1/BETA2*	very rarely
7	*KLF11*	very rarely
8	*CEL*	very rarely
9	*PAX4*	very rarely
10	*INS*	very rarely
11	*BLK*	very rarely
12	*ABCC80*	very rarely

Newborn diabetes

Newborn diabetes is a very rare cause of neonatal hyperglycemia. Two forms of neonatal diabetes are clinically distinguished: transient neonatal diabetes mellitus (TNDM) and

persistent neonatal diabetes mellitus (PNDM). The prevalence of PNDM is estimated at 1:90,000-300,000 live-born newborns. TNDM at 1:400,000 - 500,000 which is 50-60% of neonatal diabetes mellitus (NDM). [23,24,25]

Cystic fibrosis related diabetes (CFRD) epidemiology

Due to the constant progress in the treatment and care of patients with cystic fibrosis, the quality of life is improving and significantly extended, which results in an increased incidence of complications. The most common disease coexisting with cystic fibrosis is diabetes. Although CFRD can occur at any age, its frequency increases with age (5%/year in patients ≥10 years old and 9.3%/year in patients ≥20 years old). The disease occurs mostly in advanced cystic fibrosis, therefore it concerns mainly sick teenagers and adults.

The European Register of Cystic Fibrosis Patients of the European Society for Cystic Fibrosis (ECFS) shows that about 5% of children and adolescents with CF aged 10-14 have diabetes, up to 13% of adolescents aged 15-19. Data from systematic screening centers using the OGTT study in patients ≥6 years of age report that CFRD is observed in 2% of children, 19% of teenagers and 40-50% of adult patients. In the Irish report of 2007 this percentage was 19% for adult patients and 1% for children.

It is estimated that about 53% of CF patients aged over 20 years and about 70-90% of CF patients aged over 40 years will have diabetes mellitus.[26,27,28]

References:

1. Basic Epidemiology. Beaglehole R, Bonita R, Kjellstrom T. - World Health Organization, Geneva, 1993.
2. http://www.pzh.gov.pl 28.03.2018
3. http://www.cdc.gov/ophss/csels/dsepd/ss1978/28.03.2018
4. Atlas IDF 2017 http://www.diabetesatlas.org/IDF_Diabetes_Atlas_8e_interactive_EN/28.03.2018.
5. Patterson CC1, Dahlquist GG, Gyürüs E, Green A, Soltész G; - EURODIAB Study Group. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. Lancet. 2009; 13; 373(9680): 2027-33.
6. Jarosz-Chobot P, Polanska J, Szadkowska A, et al. - Rapid increase in the incidence of type 1 diabetes in Polish children from 1989 to 2004, and predictions for 2010 to 2025. Diabetologia. 2011; 54:508-15.

7. Sandu M, Protasiewicz D, Firanescu E, Lacatusu E, Bicu M, Mota M. - Data regarding the prevalence and incidence of diabetes mellitus and prediabetes. Rom J. Diabetes Nutr Metab.Dis 2016; 23 (1), 95-103.
8. Atlas IDF 2015 https://www.idf.org/e-library/ epidemiology-research/diabetes-atlas/13-diabetes-atlas-seventh-edition.html 28.03.2018
9. Parkkola. A, Härkönen. T, Ryhänen. S.J, Ilonen. J, Knip.M, - The Finnish Pediatric Diabetes Register, Extended Family History of Type 1 Diabetes and Phenotype and Genotype of Newly Diagnosed Children. Diab. Care 2013; 36(2): 348-54.
10. Chobot. A, Polanska. J Brandt. A, Deja Glowinska-Olszewska. B, Pilecki Szadkowska. A, Mysliwiec. M, Jarosz-Chobot. P. - Updated 24-year trend of Type 1 diabetes incidence in children in Poland reveals a sinusoidal pattern and sustained increase. Diabet Med. 2017;34(9):1252-58
11. Petrie. D, Lung.T.W, Rawshani. A i wsp. - Recent trends in life expectancy for people with type 1 diabetes in Sweden. Diabetologia. 2016; 59(6):1167-76.
12. E. W. Gregg, Y. Li, J. Wang. - Changes in Diabetes-Related Complications in the United States, 1990–2010, N Engl J Med 2014; 370:1514-1523.
13. Fazeli Farsani. S,Van der Aa.M, Van der Orst. M et al. - Global trends in the incidence and prevalence of type 2 diabetes in children and adolescents: a systematic review and evaluation of methodological approaches. Diabetologia, 2013, 56:1471–88.
14. Reinehr. T. - Type 2 diabetes mellitus in children and adolescents World J Diabetes. 2013; Dec 15; 4(6): 270–81.
15. Mayer-Davis .E.J, Lawrence. J.M, Dabelea. D, Divers. J, Isom. S, Dolan. L, Imperatore. G, Linder. B, Marcovina. S, Pettitt. D.J, Pihoker. C, Saydah. S, Wagenknecht .L. - Incidence Trends of Type 1 and Type 2 Diabetes among Youths, 2002–2012. N Engl J Med 2017; 376:1419-29
16. Constantino. M.I, Molyneaux. L, Limacher-Gisler. F, Al-Saeed. A, Luo. C, Wu. T, Twigg. S.M, Yue. D.K, Wong. J. - Long-Term Complications and Mortality in Young-Onset Diabetes. Type 2 diabetes is more hazardous and lethal than type 1 diabetes Diab. Care 2013; 36:3863-69.
17. Dabelea. D, Mayer-Davis. E.J, Saydah. S, Imperatore. G, Linder. B, Divers. J, - Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. Jama 2014; 311 (17), 1778-86
18. Heuvel-Borsboom. H, De Valk H. W, Losekoot M, Westerink. J. Maturity onset diabetes of the young: Seek and you will find. Neth J Med. 2016;74(5):193-200
19. W. Fendler, M. Borowiec, A. Baranowska-Jazwiecka, A. Szadkowska, E. Skala-Zamorowska, G. Deja, P. Jarosz-Chobot, I. Techmanska, J. Bautembach-Minkowska, M. Mysliwiec, A. Zmyslowska, I. Pietrzak M. T. Malecki, W. Mlynarski. - Prevalence of monogenic diabetes amongst Polish children after a nationwide genetic screening campaign. Diabetologia 2012; 55:2631–35.
20. Rubio-Cabezas O, Hattersley AT, Njølstad PR, Mlynarski W, Ellard S,White N, ChiDV, CraigME. - The diagnosis and management of monogenic diabetes in children and adolescents. ISPAD Clinical Practice Consensus Guidelines 2014 Compendium. Pediatric Diabetes 2014: 15 (Suppl. 20): 47–64.
21. Shields B. M, Hicks S, Shepherd MH, Colclough K, Hattersley A. T, Ellard S. - Maturity-onset diabetes of the young (MODY): how many cases are we missing? Diabetologia 2010; 53: 2504-08.

22. Thanabalasingham G, Pal A, Selwood MP et al. - Systematic assessment of etiology in adults with a clinical diagnosis of young-onset type 2 diabetes is a successful strategy for identifying maturity-onset diabetes of the young. Diab. Care 2012; 35: 1206-12.
23. Naylor RN, Greeley SA, Bell GI, Philipson LH. Genetics and pathophysiology of neonatal diabetes mellitus. J Diabetes Investig. 2011; 5;2(3):158-69
24. Esquiaveto-Aun A.M, De Mello M.P, Paulino M.F, Minicucci W.J, Guerra-Júnior G, De Lemos-Marini S.H. A new compound heterozygosis for inactivating mutations in the glucokinase gene as cause of permanentneonatal diabetes mellitus (PNDM) in double-first cousins. Diabetol Metab Syndr. 2015; 18, 7:101.
25. Priyadarshi A, Verge CF, Vandervliet L, Mackay DJ, Bolisetty S. Transient Neonatal Diabetes Mellitus followed by recurrent asymptomatic hypoglycaemia: a case report. BMC Pediatr. 2015; 2:15:200.
26. Siwamogsatham O, Alvarez JA, Tangpricha V. Diagnosis and treatment of endocrine comorbidities in patients with cystic fibrosis. Curr Opin Endocrinol Diabetes Obes. 2014; 21(5): 422-29.
27. A. Kelly, A. Moran. Update on cystic fibrosis-related diabetes. J Cyst Fibros. 2013;12(4):318-23.
28. Ode KL, Frohnert B, Laguna T, Phillips J, Holme B, Regelmann W, Thomas.W, Moran.A. Oral glucose tolerance testing in children with cystic fibrosis. Pediatr Diabetes. 2010; 11(7):487-92.

PRZEMYSLAWA JAROSZ - CHOBOT MD, PhD
Head of Department of Children's Diabetology and Pediatrics
School of Medicine in Katowice, Medical University of Silesia
The Independent Public Clinical Hospital no.6 of the Medical University of Silesian in Katowice, John Paul II Upper Silesian Child Health Centre, Katowice, Poland
E-mail: Przemka1@o2.pl

February 2018

GLYCEMIC VARIABILITY. PARAMETER TO BE FOLLOWED IN THE CHILD WITH DZ?

Iulian P. Velea, Corina Paul

Introduction

Epidemiology data show an upward trend in the incidence of Type 1 DZ in children regardless of country or continent and an increase in newly diagnosed cases at lower age. This situation involves a long duration of exposure to the disease in periods of maximum vulnerability of the child (growth, puberty, adolescence) and implicitly increases the risk of installing chronic complications at younger age.

Once the diagnosis of type 1 DM has been established, the patient (the child and his or her family) should understand that in the case of chronic illness such as DM the course of the disease can not be changed, but the perception of the disease can be changed respecting the therapeutic goals promoted by ISPAD and IDF:

- good metabolic control at <7.5%
- normal physical and psychosocial development
- optimal quality of life
- prevention of acute and late complications

PHYSIOLOGY[1,2]

Typically, blood glucose (the main energy substrate of the body) is maintained, regardless of the momentary conditions, at

constant values: 70-110 mg% (a jeun) and 120-140 mg% (postprandial).

Glucose from food is either used and under excess conditions storage in the form of lipids or glycogen.

Under fasting conditions (hunger), glucose deficiency requires production from other alternative energy sources. At this stage, the effects of hyperglycemic counter-regulation hormones with concomitant inhibition of insulin secretion increase.

So the serum level of glucose is not linear, but has a rhythmical variability of meals but also by hyperglycemic hormone discharges. These are:

- Glucagon that preferentially works on the liver stimulating hepatic gluconeogenesis and on the other hand favors lipolysis,
- catecholamines act preferentially at the muscle level, triggering glycogenolysis.
- glucocorticoids activate hyperglycemic mechanisms due to stimulation of gluconeogenesis,
- thyroid hormones, and growth hormone works by an indirect glucose regulation mechanism.

It is important to note that hormones have a daily (circadian) discharge rate in circulation at certain hours that can not be influenced. So:

- the growth hormone is discharged in the first part of the night (after the first two hours of sleep, ie from 24.00 to 3.00 at night);
- cortisol (hormone secreted by the adrenal gland) begins to discharge at 3.00 in the night, reaches the maximum concentration in the morning at 8.00 - 9.00 after which it starts to decrease to have the lowest value at 20.00.
- Thyroid hormones are discharged from the morning;
- catecholamines are mostly discharged under stress conditions;
- glucagon, the insulin antagonist hormone (secreted by alpha cells in the Langerhans islands) is not affected in diabetes and plays a role in fighting hypoglycaemia.

Regarding hormonal secretions, we must remember that there is also a monthly rhythm of these secretions, better known as the rhythm of sex hormones, which, starting from puberty, influences the glycemic balance of adolescents with type 1 DM;

Numerous studies have shown that there is also an annual rate of discharge of hormone secretions, a rate influenced, apparently, by exposure to light. It has been shown that the insulin requirement in the non-diabetic patient is lower in summer than in the winter, being influenced by the secretions of other hormones whose blood concentration is lower in summer than in the winter.

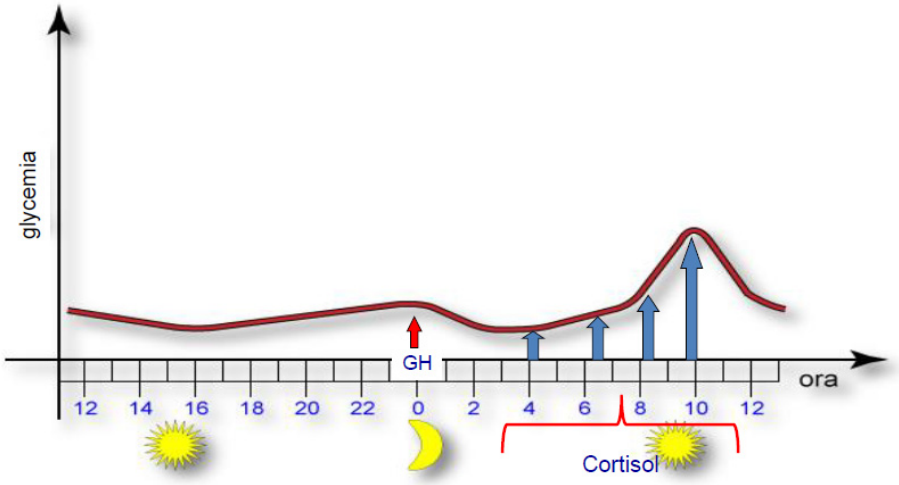


Fig. 3.1. - Circadian blood glucose variability rhythmic by the counter-hormone

PREVENTION IN TYPE 1 DM

At present, the notion of prevention in type 1 DM involves 3 steps: primary prevention addressing specifically the genetic background and possible factors triggering the autoimmune process of pancreatic beta cell destruction, secondary and tertiary prevention to be triggered by the medical team once the diagnosis It was established.

If primary prevention is still theoretically speaking, today there are many arguments that show the importance of the medical team in secondary prevention that involves the application of all methods and means of obtaining and maintaining objective euglicaemya that once fulfilled and maintained removes in time the risk of installing corneal complications. In the case of complications, the tertiary prevention must be triggered in order to prevent the installation of disabilities that will impinge on the quality of life of the patient with type 1 DM.

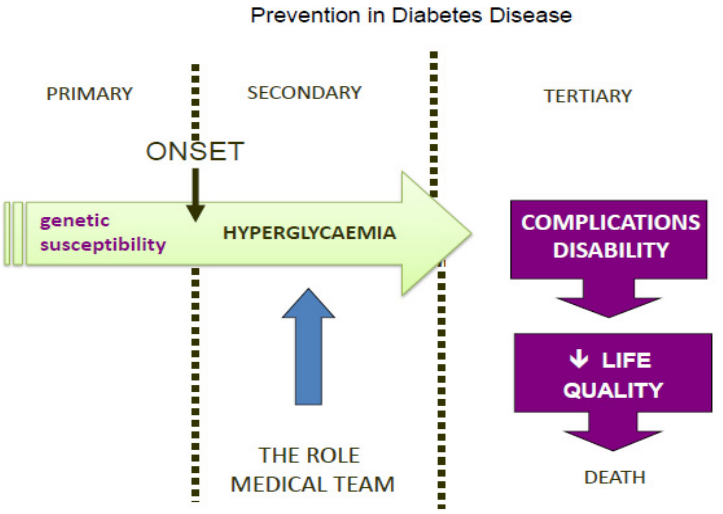


Fig. 3. 2 – Prevention in diabetes mellitus

Starting from these problems, Type 1 DM should be seen as an ambivalent both acute illness (due to events and actions to be taken daily: blood glucose, insulin administration, carbohydrate counting, etc) and chronic (due to the spectrum of corneal complications)

Taking into account these issues, standards of medical care in Type 1 DM promote the need for optimal glycemic control, i.e., as close as normal (nondiabetic) control, consisting of:

- HbA1c <7.5%,
- blood glucose value = 90-145 mg / dl,
- postprandial blood glucose = 90-180 mg / dl,
- bedtime glycaemia = 120-180 mg / dl,
- fasting blood glucose = 80-160 mg / dl.[3]

It is widely accepted that the therapeutic elements of type 1 DM (insulin, nutrition, physical exercise, specific medical education) are subject to the intervention / action of numerous and various factors: environmental, family, social, group of friends etc. Under these conditions, a patient with type 1 DM can lead a normal active life, provided regular blood glucose measurement and lifestyle changes with adequate diet and daily physical activity.

Making an effective insulin substitution assumes glycemic self-control with at least 4 determinations / day.

However, many studies have shown that the evolution of glycaemia between these determinations is different (hypoglycemia, dawn phenomenon, hyperglycemia etc.)

It is proven that the relative risk of installing chronic complications increases as glycemic and metabolic control is suboptimal and HbA1c is higher.

A relevant study in this regard is the one conducted by Anderzen et al who evaluated how HbA1c (in adolescents with type 1 DM) influences the installation of microvascular complications in young adults. On a group of 4,250 people (children aged between 13 and 18 and adults registered in the Swedish national diabetes registry in 2011 and 2012), logistic regression analysis showed that the risk of developing macroalbuminuria as a young adult was significant higher in the group of children with HbA1c> 9.3% (p <0.05). Of the patients with HbA1c> 9.3% both children and adults, there was a significantly higher proportion of those who had retinopathy, microalbuminuria (p <0.001) and / or macroalbuminuria (p <0.01) HbA1c under 7.5% in both batches.[4]

Taking into account recent DCCT confirmations, childhood maximal childcare efforts should be stepped up to reduce the risk of developing complications in adults.

In the last 20 years, the glycemic control value is given by the HbA1c value.[5] There is currently a universal agreement that HbA1c is the gold standard for the primary clinical target. There is, however, no consensus that other proposed glycemic determinations may provide additional clinical data or whether there should be additional targets besides HbA1c dosing.

HbA1c determines the long-term metabolic balance but can not identify short-term hypoglycemic / hyperglycaemic events during one day can not lower glycemic variability.

It is proven that people with the same HbA1c may have different fluctuations in blood glucose.[6]

With regard to glycemic variability, there are more and more voices who claim with pertinent arguments that this is an independent risk factor for complications of diabetes.[7-10,11]

The concept of "glycemic variability" (GV) is a "measure" that draws attention more and more simply being defined as the degree to which the blood glucose level of the patient fluctuates between high (peak) and low levels to achieve targets glycemic in a safe scenario.[12] The concept of glycemic variability is a complex phenomenon because it introduces the idea that multiple fluctuations in blood glucose in the same individual may be more

damaging than a simple episode of acute hyperglycemia or chronic stable hyperglycaemia.[13]

The idea that investigated the variability of glucose fluctuations is that, as with hyperglycemia, the high variation in serum glucose levels may lead to: increased mortality, increased oxidative stress, [14] neural distress, mitochondrial distress and activation coagulation. Monnier (2006), Brownelee (2005), Egi (2009), (Hermanides) 2010 have shown that rapid fluctuations in blood glucose increase oxidative stress to a greater extent than stable hyperglycemia. Hence, it has gone into investigating the variability of glycaemia and setting as a therapeutic target its avoidance.

Under these circumstances, it is necessary to identify: the reasons for the variability of blood glucose levels and especially the levels of variation to be avoided.

The reasons for the variability of blood glucose levels

The underlying cause seems to be related to the absorption of insulin, since interindividual variations and intra-individual variations (from one day to the next) exist in reaching the maximum peak as well as the duration of action.

The most important factors that influence insulin absorption are:

- *age.* In the younger age, subcutaneous cellular tissue is less well represented and consequently absorption is faster;
- *subcutaneous fat* richly represented as well as lipohypertrophy slow down absorption;
- *the dose (volume) of insulin*. The higher the insulin dose (amount) than the slower the absorption rate
- Injection area. The fastest absorption is done after insulin injection into the abdomen.
- *the depth of the injections*. Deep injection (closer to the muscle) induces a faster absorption. Ultrasonography has shown that 30% of children using 12.7 mm needles and some of those using 8 mm needles injected insulin intramuscularly, which accelerates absorption and increases the risk of hypoglycaemia.
- body *temperature* and even ambient temperature influence the absorption rate. A hot bath or sun

exposure of the area where the injection was made causes blood vessel dilatation, better irrigation of the area and consequently a faster absorption of insulin with increased risk of hypoglycaemia.

- *Local massage* and intense physical activity of the region where insulin has been injected can act as local warming accelerates absorption. Important information on the day when he has a gym or going out to play!
- *Insulin injection technique*. Rotation of injection sites within the same area.

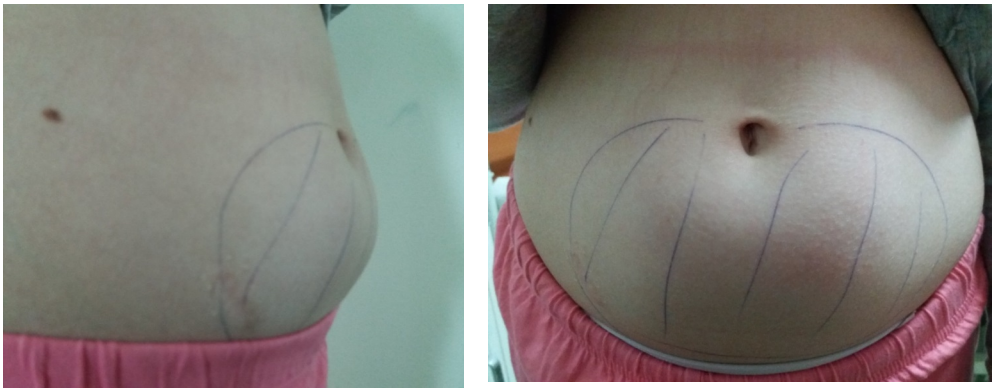


Fig. 3.3 - Lipo-hypertrophy

Non-adherence to therapy

Failure to insulin treatment, diet and monitoring leads to family conflicts, denial, and anxiety.

Non-adherence to treatment should be considered in all children and adolescents who have inadequate metabolic control being a characteristic of adolescents.

In the case of small children, the responsibility for supervising lifestyle in type 1 DM belongs to parents.

Presence of psychiatric disorders such as depression, lack of motivation, loss of interest.

In daily activity, loss of hope will accentuate non-adherence to treatment.

Unstable or fragile diabetes (brittle diabetes) [15]

It is defined as diabetes characterized by glycemic instability with extreme variations in blood glucose, regardless of cause (frequent CAD episodes and hypoglycemia), quickly installed and unpredictable, which disrupts the daily existence of patients with repeated or prolonged hospital admissions. Although the adjective "fragile" was "invented" and promoted by Woodyatt (1934), there are still no established diagnostic criteria and no effective therapeutic protocol, and production mechanisms are still controversial.

Classification

- The unstable type 1 DM and the causes and mechanisms of instability appear to be intrinsic (of the disease)
- Unstable false type 1 DM - glycemic variability has obvious causes.

Table 3.1.- Causal factors in unstable type 1 DM

Organic Factors	Psychosocial factors
- Food disorder - Disorder in physical activity - Alcohol abuse and drug abuse - Somogyi effect - Dawn effect - occult infections: dental, otic, sinus, urinary, respiratory, etc. - endocrine disorders: hyperthyroidism, hypocorticism - gastrointestinal disorders: celiac disease, gastroparesis - hyperglycemic medication: corticosteroids, diuretics, etc.	- Auto-induced treatment errors (compulsive attitudes, unconscious, over- / underinsulination (for fear of hypoglycemia) - Emotional stress followed by decision errors on treatment administration - Disorders of eating behavior - omission of insulin injection - Behavioral disorders, inducing instability: ketoacidosis factitiae * and hypoglycemia factitiae * (Factitiae = intentional self-provocation) - Educational disorders (difficulties in processing information and decision-making) - Patient communication disorders – physician - Handler behavior

Diagnosis of unstable diabetes [15]

In front of a patient suspected of having an unstable DZ, it is necessary to evaluate the patient in order to identify the possible causes of recurrent hypoglycemia and / or hyperglycemia:

Possible causes of recurrent hypoglycemia:

- kidney failure
- the absence of hypoglycemic alarm signs
- hypoadrenalism,
- celiac disease,
- Gastroparesis,
- hypoglycemia factitiae,
-

Possible causes of recurrent ketoacidosis:

- eating behavior disorders
- psychosocial problems,
- "unpleasant" events of life,
- adolescence,
- omission of insulin injections,

In case of suspicion of unstable diabetes, it is necessary to quantify the instability of glucose by determining some indices that have to answer two questions:

- which is the glycemic variability, depending on the rate of insulin injections, meals and exercise;
- what is the degree of glycemic variability from day to day under identical conditions of treatment, nutrition and exercise.[16]

EVALUATION OF GLYCEMIC VARIABILITY BY CGMS

The answer to the above questions is currently possible through continuous glycemic monitoring.

Besides the objection of hypoglycemia and hyperglycemia, the glycemic sensor also allows for the evaluation of glycemic variability in a much more precise manner than the classic self-monitoring glycemic methods, which is of great importance for the diagnosis of brittle diabetes. There is a possibility of calculating some variability indexes (which can be used by a physician) within a day, on different days, to evaluate postprandial glycemic excursions and the risk of hypoglycaemia.[17,18]

Glycemic variability: triggers programmed cell death

There is increasing evidence that glucose fluctuation in the DM patient plays a negative role on the various organs, including the brain.

Stable hyperglycemia causes programmed cell death (also known as "apoptosis"). But it has been shown that cell death was triggered even more when cells were exposed to fluctuating glycaemia (from hypo to hyperglycemia and inverse). In the experimental study conducted by Russo and all, the metabolic disorder of GV in neuronal cells was mimicked by exposure of SH-SY5Y neuroblastoma cells to constant glucose or fluctuating cycles (i.e., 6 hours) for 24 and 48 hours. Fluctuating glucose levels have had a greater negative effect on neuronal cellular energy regulation mechanisms than elevated or low glucose levels. [19]

Glycemic variability: increases oxidative stress

Glycemic variability triggers oxidative stress to a greater degree than chronic hyperglycemia. [13,20] Exposure to glycemic variability stimulates overproduction of free oxygen radicals. (Quagliaro et al.)[21]

The same is done in conditions of hypoglycemia that leads to the generation of free oxygen radicals by decreasing the efficacy of the mitochondrial system.[22] The same glycemic variability appears to be responsible for the worsening of multiple osteoarthritis in critical patients in intensive care units (Singh et al.)

Glycemic variability: trigger inflammation

GV leads to overproduction of nitrogen-based molecules ("oxidative stress") and induces cell damage and inflammation, including plaque accumulation in the arteries.[23]

Endothelial dysfunction and "oxidative stress" were significantly higher when exposed to fluctuating glucose. (Ceriello et al.) [22]

Inflammation associated with glycemic variability may lead to thickening of artery walls

Glycemic variability: is atherogenic

Adhesion of monocytes to vascular cell mucosa is among the first atherosclerosis or thickening of arterial walls.[24]

PPG fluctuations promote binding of monocytes to blood vessel lining to a greater extent than stable blood glucose.[24] GV promotes

monocytes to endothelial cells - one of the oldest events in the development of atherosclerosis.[25]

GLICEMIC VARIABILITY EVALUATION INDICATORS [26]

The mean Amplitude Glycemic Excursion (MAGE) is an index of glycemic variability during a day. Calculate as the arithmetic mean of the differences between the peaks and the lowest values of the glycemic profile, provided that these differences are greater than the DS. It has the advantage of being independent of the average daily blood glucose and quantifying large variations with the exclusion of small ones. The proposed algorithm also eliminates the manual identification and measurement errors of the counts in the CGM data to estimate MAGE. It can also be used to calculate MAGE from "rare" blood glucose measurements, such as those collected in blood glucose monitoring.[27]

The average daily risk range (ADRR) aims to provide a better balance between glycemic elevations and decreases, as most of the indexes tend to overrate the hyperglycemic excursions.

From the clinical point of view, ADRR can provide significant data on patients' risk for hyperglycemia and hypoglycaemia that can not be only available from Hba1c determination. Determining the daily risk score can help clinicians identify patients who can overcome blood sugar levels, evolving with very high or low values. In order to expand the usefulness of ADRR, future research should examine the validity of existing cutoff risk scores for pediatric patients, determine whether ADRR cutoff scores should be modified for continued glycemic monitoring data, and investigate whether patient ADRR scores are related to chronic complications (retinopathy and microalbuminuria.[28,29]

Average Daily Difference (MODD: Mean Of Daily Differences) measures glycemic variability between days. It is calculated as the mean of the absolute differences in glycemic values at the same time for two consecutive days.

Mean Indications of Meal Excursions (MIME)

Evaluates glycemic excursions related to food intake. It uses three elements: time to postprandial peak (AT), glycemic difference between pre- and postprandial value (AG) and return to preprandial glycemic level one hour after postprandial glycemic peak (RB).

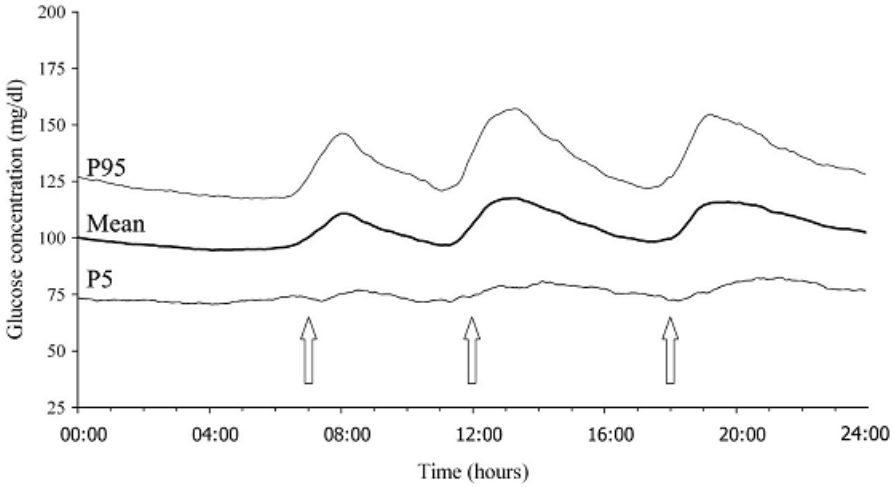


Fig. 3.4. Daily glucose profile in healthy subjects, assessed by continuous glucose
Monitoring. The center line is the average, P5 = percentile 5 and P95 (95th percentile). The arrows indicate the moments of three meals over a day. (after the American Diabetes Association).

You can also calculate:

The Low Blood Glucose Index (LBGI) and

The High Blood Glucose Index (HBGI), as the weighted mean of the glycemic values that have been converted, where the high and low glycemic ratios are higher.

Conclusion

Although many measures have been proposed to quantify glycemic variability, there is still no consensus on what is most useful in clinical practice.

Several clinical trials combined the mean amplitude of glycemic excursions (MAGE) in combination with glycosylated hemoglobin (A1C) to assess the efficacy of diabetes treatment.

Considering the suggested association between postprandial hyperglycemic and cardiovascular complications, MAGE can become the standard for assessing daytime variability.

In line with the initial definition, most users have applied a graphical approach to estimating MAGE, which is operator-dependent and consumes long to analyze the results of continuous

glucose monitoring (CGM) from a large number of patients. In order to allow for the automatic analysis of the data obtained in Continuous Glycemic Monitoring (CGM) and to avoid the imprecision associated with the initial approach to MAGE evaluation, in clinical practice, a computer program for a standardized patient-independent computation is needed.

References

1. Guyton and Hall - *Textbook of Medical Physiology*, 13th Edition, 2015. Author: John E. Hall Ed. Saunders, ISBN 9781455770052
2. Francis S. Greenspan, David Gardner, Dolores Shoback - *Basic & Clinical Endocrinology, Ninth Edition* (LANGE Clinical Medicine) 9th Edition, 2011.
3. IDF/ISPAD – Global Guideline for diabetes in Childhood and adolescent. 2011, 50 – 60
4. Anderzén J., Samuelsson U., Gudbjörnsdottir S., Hanberger L., Åkesson K. - *Teenagers with poor metabolic control already have a higher risk of microvascular complications as young adults.* J Diabetes Complications. 2016 Apr; 30(3):533-6. doi: 10.1016/j.jdiacomp.2015.12.004. Epub 2015 Dec 8.
5. *Diabetes Control and Complications Research Group. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus. J Pediatr 1994: 125: 177 – 188.*
6. Zaccardi F, Pitocco D, Ghirlanda G. Glycemic risk factors of diabetic vascular complications: the role of glycemic variability. Diabetes Metab Res Rev. 2009 Mar;25(3):199-207
7. Siegelaar SE, Holleman F, Hoekstra JB, DeVries JH: Glucose variability; does it matter? Endocr Rev 31:171-182, 2010
8. Kilpatrick ES: Arguments for and against the role of glucose variability in the development of diabetes complications. J Diabetes Sci Technol 3:649-655, 2009
9. Kilpatrick ES, Rigby AS, Atkin SL: For debate: glucose variability and diabetes complication risk: we need to know the answer. Diabet Med 27:868-871, 2010
10. Nalysnyk L, Hernandez-Medina M, Krishnarajah G: Glycaemic variability and complications in patients with diabetes mellitus: evidence from a systematic review of the literature. Diabetes Obes Metab 12:288-298, 2010
11. Kilpatrick E.S. – "Arguments for and against the role of glucose variability in the development of diabetes complications". *J Diabetes Sci Technol 3:649-655, 2009.*
12. Bergenstal R.M. – Glycemic variability and diabetes complication: does it matter ? simply put, there are better glycemic markers ! Diabets Care, 2015, aug 38(8): 1615-21 doi: 10.2337/dc15-0099.
13. Antonio Ceriello, Eric S. Kilpatrick - Glycemic Variability: Both Sides of the Story. Diabetes Care 2013 Aug; 36(Supplement 2): S272-S275. https://doi.org/10.2337/dcS13-2030
14. J.Hans deVries : Glucose Variability: Where It Is Important and How to Measure It. Diabetes , 2013, 62:1405–1408.

15. Şerban V., Sima A. – Diabetul zaharat tip 1 instabil (brittle diabetes) in: Serban V. Tratat Roman de Boli Metabolice, vol 1, Editura Brumar, p 455-460, 2010.
16. Choleau C., Aubert C., Cahane M., Reach G. – High day-to-day glucose variability: A frequent phenomenin in children and adolescents with type 1 diabetes attending summer camp. Diabetes and Metabolism 34 (2008), p.46-51
17. Hans deVries J. – *Glucose Variability: Where It Is Important and How to Measure It. Diabetes 62:1405–1408, 2013*
18. Sunghwan Suh, Jae Hyeon Kim. *Glycemic Variability: How Do We Measure It and Why Is It Important?* Diabetes Metab J 2015; 39:273-282
19. Vincenzo C. Russo, Sandra Higgins, George A. Werther, Fergus J. Cameron E. - *Effects of Fluctuating Glucose Levels on Neuronal Cells In Vitro*. Neurochemical Research, August 2012, Volume 37, Issue 8, pp 1768–1782
20. Yoshifumi Saisho. Glycemic Variability and Oxidative Stress: *A Link between Diabetes and Cardiovascular Disease?* Int. J. Mol. Sci. 2014, 15, 18381-18406; doi:10.3390/ijms151018381
21. Quagliaro L., Piconi L., Assaloni R., et al. - *Intermittent high glucose enhances ICAM-1, VCAM-1 and E-selectin expression in human umbilical vein endothelial cells in culture: the distinct role of protein kinase C and mitochondrial superoxide production.* Atherosclerosis 2005; 183:259–267pmid:16285992
22. A.Ceriello. - *Glycemic variability: a new therapeutic challenge in diabetes the critical care setting.* Diabetologia, Volume 26, Issue 4, August 2010, Pages 222-225
23. Tanaka Atsushi, Koichi Node - Amelioration of arterial pressure lability: an unmissable target for diabetes management. Journal of Human Hypertension, 2017, 40, 629–631, doi:10.1038/hr.2017.35
24. Azuma K, Kawamori R, Toyofuku Y, Kitahara Y, Sato F, Shimizu T, Miura K, Mine T, Tanaka Y, Mitsumata M, Watada H. *Repetitive fluctuations in blood glucose enhance monocyte adhesion to the endothelium of rat thoracic aorta. Arterioscler Thromb Vasc Biol* 2006; 26: 2275–2280.
25. Gert Fritzsche, Klaus-Dieter Kohnert , Peter Heinke, Lutz Vogt, Eckhard Salzsieder - The Use of a Computer Program to Calculate the Mean Amplitude of Glycemic Excursions. Diabetes Technology & TherapeuticsVol. 13, No. 3. https://doi.org/10.1089/dia.2010.0108
26. Peter A. Baghurst. - Calculating the Mean Amplitude of Glycemic Excursion from Continuous Glucose Monitoring Data: An Automated Algorithm. Diabetes Technology & Therapeutics, 2011, Vol. 13, No. 3 Published Online:27 Feb 2011https://doi.org/10.1089/dia.2010.0090
27. Peter A. Baghurst. - Calculating the Mean Amplitude of Glycemic Excursion from Continuous Glucose Monitoring Data: An Automated Algorithm. Diabetes Technology & Therapeutics, 2011, Vol. 13, No. 3 Published Online:27 Feb 2011https://doi.org/10.1089/dia.2010.0090
28. Susana R. Patton, Mark A. Clements. - *Average Daily Risk Range as a Measure for Clinical Research and Routine Care*. Journal of Diabetes Science and Technology, Volume 7, Issue 5, September 2013

29. Susana R. Patton, L. Kurt Midyett, Lawrence M. Dolan, Scott W. Powers - A Comparison of Average Daily Risk Range Scores for Young Children with Type 1 Diabetes Mellitus Using Continuous Glucose Monitoring and Self-Monitoring Data**.** Diabetes Technology & Therapeutics, 2012, Vol. 14, No. 3. Published Online:27 Feb 012https://doi.org/10.1089/dia.2011.0169

Iulian P. Velea, MD, PhD
Professor of Pediatrics
University of Medicine and Pharmacy "V. Babeş" Timisoara, Romania
Senior Pediatrician, Clinic II Pediatrics, Clinical County Hospital Timisoara, Romania
E-mail : ivelea56@yahoo.com

April, 2018

THE ROLE OF TRANSGENERATIONAL EPIGENETICS IN THE EARLY ONSET OF INSULIN RESISTANCE AND TYPE 2 DIABETES

Mihai D. Niculescu

Introduction

Type 2 diabetes (T2D) is one of the most prevalent chronic metabolic diseases, with numerous complications that are often difficult to manage.

While solid epidemiological data exist for the prevalence of T2D in adults (more than 8.5% worldwide, and more than 9% within US),[1] less is known about the incidence and prevalence of early onset T2D or insulin resistance. Limited data suggest that, during the last 15 years, there is a dramatic increase in the incidence of T2D at younger ages.

Among youths 10 to 19 years old, the incidence of T2D was estimated in 2012 at 12.5 cases per 100,000 youths per year, with an annual increase of 7.1% since 2002.[2]

In Romania the prevalence of T2D in children was estimated at around 3,000 cases in 2016,[3] although the accuracy of this data could not be verified independently by the author.

Not only T2D is a major public health burden, but the associated cost of treatment is also staggering. The lifetime direct medical costs of treating T2D and diabetic complications in the U.S. was estimated at between $54,700 and $130,800 per patient, with an age–gender weighted average of the lifetime medical costs of $85,200 per patient (2012 US dollars).[4] Within the complex milieu

of gene-environment interactions that contributes to the onset of T2D and insulin resistance, epigenetic mechanisms and alterations have been associated with the risk for T2D, including those related to parental epigenetic influences, or to early epigenetic alterations in the offspring due to parental environmental exposures, including nutrition.

Gene structure variations (*Fig. 4.1*) have a decisive contribution to shaping the phenotypes in humans, including in the case of T2D and insulin resistance.

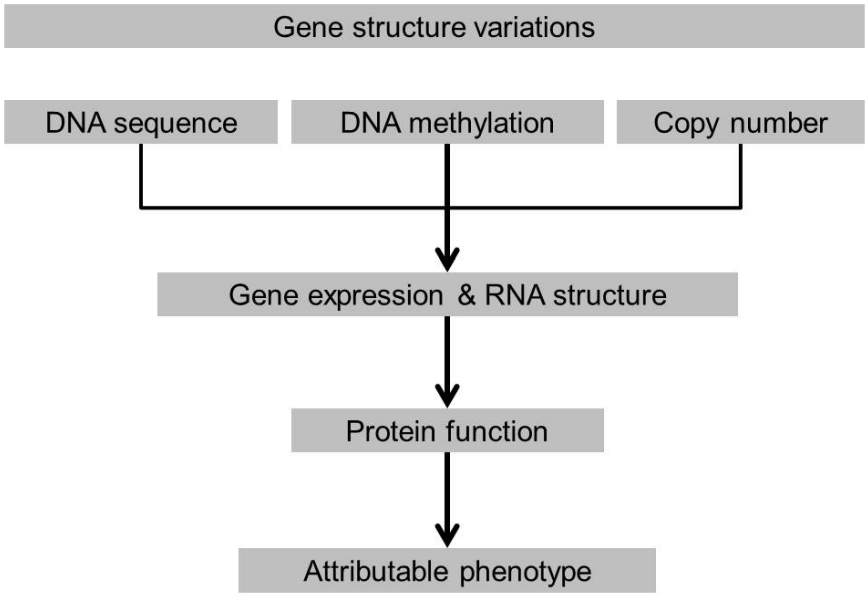


Fig. 4.1. - The relationship between gene structure variations and the attributable phenotype.

Epigenetics refers to molecular events, other than alterations in DNA sequence, which control and establish heritable patterns of gene expression that are stable throughout cell division.[5] Such mechanisms include (but are not limited to) DNA methylation, histone modifications, and the modulation of gene expression by noncoding RNA.[6]

Nutrition, health and transgenerational epigenetics

During the last two decades numerous studies have indicated the importance of parental nutritional in shaping the epigenetic

status in offspring. Nutrients such as folates, choline, niacin, flavonoids, or selenium are but a few examples.[7]

The macro-nutrient composition of a diet is also responsible for epigenetic modifications, as shown by studies indicating that high-fat diets and/or maternal protein restriction had a negative impact on the DNA methylation in offspring.[7]

Many studies, using various experimental models, demonstrated that parental nutritional status can alter the epigenetic profiles within subsequent generation, increasing the risk of disease, and including an increased mortality attributed to T2D.[8-11]

In humans the availability of various nutrients altered their epigenetic profiles, which can be inherited by subsequent generations.[8,12,13] But the use of animal models was decisive in revealing the molecular mechanisms responsible for such epigenetic changes. However, it is not clear whether exact same mechanisms are involved in humans or not, due to obvious ethical limitations of human studies.

For instance, the administration of an obesity-promoting, calorie-dense maternal diet in primates, epigenetically altered fetal chromatin structure *via* covalent modifications of histones.[14] When mice were exposed to different diets in the post-weaning period, they exhibited epigenetic alterations associated with phenotypic changes.[15]

Human studies indicated that parental food availability is also important for the health trajectory of their children and grandchildren. Data collected from the Dutch famine cohort suggested that maternal food restriction during pregnancy induced alterations in DNA methylation status in children, and that some of the epigenetically altered genes were involved in the pathogenesis of obesity and T2D.[13] In a different study looking at transgenerational influences over three generations, Kaati *et al.* indicated that mortality rates due to cardiovascular events and T2D in grandchildren were associated with the nutritional status of their grandparents, in a gender-specific manner (grandfather to grandsons, and grandmothers to granddaughters, respectively).[8]

Only recently the transgenerational influences upon epigenetic status and T2D were better understood, when parental influences were dissected into more specific maternal and paternal cues, respectively, using animal models (reviewed in.[16] As such it is important to differentiate between *transgenerational epigenetic inheritance* that involves the inheritance of specific DNA methylation patterns throughout at least four generations and *transgenerational*

(parental) cues that alter DNA methylation in the offspring, which may not necessarily represent proof of epigenetic inheritance (discussed in [16])

While transgenerational epigenetic inheritance has been demonstrated in animal models (especially mice), only very recently it has been strongly suggested that epigenetic alterations could be also inherited in humans.

Using a model of Mendelian inheritance for the methylation of CpG sites, *Zaghlool et al.* have identified, for the first time to our knowledge, that the DNA methylation patterns in humans are inherited in a Mendelian fashion for at least 955 CpG loci.[17] Whether this might be the case in humans for transgenerational effects with epigenetic consequences related to T2D and insulin resistance, it remains to be established further.

Transgenerational influences for the epigenetics of T2D

The epigenetics of beta-cells development

The first human study looking at DNA methylation profiling in pancreatic islets from T2D and non-diabetic donors indicated that 276 CpG sites within the promoters of 254 genes displayed differential DNA methylation in diabetic islets.[18] These changes were specific to the islets, as similar modifications were not found in the blood cells of the participants. Moreover, some of these epigenetic alterations were associated with concordant transcriptional changes.

The importance of epigenetic regulation of beta-cells was independently confirmed by Dayeh *et al.* who suggested that the DNA methylation machinery is required for proper beta-cell function. The study found that approximately 48% of single nucleotide polymorphisms (SNPs) associated with T2D were also associated with alterations in DNA methylation in the islets, which would indicate that genetic disturbances could alter the function of beta-cells *via* failure of maintaining the required epigenome in these cells.[19]

Another component of the epigenetic machinery, represented by histone modifications, was studied extensively in animal models, where alterations in histone acetylation/de-acetylation revealed interesting consequences upon the development of beta-cell mass (BCM). Several examples are presented. When cultured rat pancreatic buds, obtained on embryonic day E13.5, were treated *in vitro* with different histone deacetylase (HDAC) inhibitors, the net results were a decrease in exocrine, and an increase in endocrine,

pancreatic progenitors.[20] Inhibiting class-I and class-II HDACs with trichostatin A resulted in an increase of endocrine progenitor cells and beta-cells, whereas the inhibition of class-I HDACs with valproic acid specifically enhanced the endocrine progenitor and alpha-cell pool.[20]

However, expression of class-IIa HDACs was present only in beta and delta cells, and not in alpha and acinar cells. In the same study, deletion of HDAC5 and HDAC9 was associated with an increased number of beta and delta cells, possibly due to increased differentiation. [20]

Using animal models, studies have shown that early dietary manipulation impacts upon the epigenome, inducing alterations in both DNA methylation and histone methylation/acetylation, with measurable consequences upon longevity and metabolic status (discussed in [6,7])

In humans, obvious ethical considerations limit the extent to which epigenetic mechanisms can be interrogated. However, the argument that early nutritional cues can alter the epigenome in next generation became stronger after results from a study exploring the Dutch Hunger Winter (1944-1945) were published: people exposed to famine in utero during that period had altered methylation in several genes, including the *Igf2* gene in white blood cells as adults.[13]

In a rat model of intrauterine growth retardation (IUGR), by restricting fetal nutrition using a bilateral utero-placental insufficiency (UPI) model, it has been shown that the offspring had reduced BCM, decreased expression of *Pdx1*, and a T2D phenotype in adulthood.[21] Later studies elucidated the mechanisms behind these associations. The epigenetic landscape of the *Pdx1* gene revealed reduced H3 and H4 acetylation at the *Pdx1* locus, with progressively lower H3K4me3 levels, and associated with decreased *Pgx1* expression.[22,23] As a consequence, the upstream transcription factor (USF)-1, which regulates *Pdx1* transcription, does not bind anymore to the *Pdx1* promoter in UPI animals.[23] Conversely, administration of the HDAC inhibitor trichostatin A to 2-week-old islets allowed for partial restoration of *Pdx1* expression in UPI islets.[22] These results suggested that epigenetic alteration at the *Pdx1* promoter may be predictive of T2D development later in life, while the reversal of such epigenetic changes might prevent the later T2D onset.

Another example is the transcription factor hepatocyte nuclear factor 4-alpha (Hnf4a), which is also involved in beta-cell replication

in response to metabolic stress and glucose homeostasis alterations. Chromatin immuno-precipitation (ChIP) analysis revealed that maternal diet decreased the levels of activating acetylated H3 and mono-methylated H3K4, and increased the level of repressive di-methylated H3K9 and tri-methylated H3K27, related to the enhancer and P2 promoter regions.[24]

These examples show that the epigenetic landscape can change with age and in response to modified fetal nutrient supply, and that epigenetic mechanisms are involved in the pathogenesis of T2D.

Intergenerational influences upon BCM programming

Many animal studies have confirmed by now the deleterious effects of malnutrition (either over-nutrition or under-nutrition), during fetal and perinatal development, upon the glucose metabolism of F1 offspring later in life. There is also evidence of alterations in glucose metabolism in the F2 offspring as well as grand-offspring (F3) of in utero malnourished F1 females, even in the presence of well-nourished F1 and F2 females.[25,26] In a model where F0 females were exposed to a low protein diet during pregnancy and lactation, the F1 males exhibited hyperglycemia and impaired glucose tolerance (IGT) with ageing, and altered glucose-stimulated insulin secretion. The F2 offspring from either F1 males or females also developed glucose intolerance.[27] These findings suggest that intergenerational influence on glucose intolerance can come from both parental lines.

Because the intergenerational inheritance of disease risk may be mediated by non-genomic mechanisms such as epigenetic mechanisms and metabolic imprinting (the direct influence of maternal metabolism upon the fetus), it is important to understand that not all transgenerational influences upon T2D risk are epigenetic. For instance, the continuous exposure of the fetus to maternal metabolic cues does not represent a mechanism of transgenerational epigenetic inheritance. As discussed elsewhere,[7,16] nutritional cues that exist in the F0 generation can influence the epigenetic status in the offspring (F1) in two distinct ways:

(1) *via* direct metabolic signaling, where the epigenetic status in the offspring is a direct result of metabolic impairments in F0, and

(2) *via* transgenerational epigenetic inheritance, where epigenetic alterations existing in F0 are inherited by the next

generation(s). However, in order to prove such epigenetic inheritance, one has to prove that the epigenetic marks exist in a generation of offspring even in the absence of a direct influence from F0. This is necessary because the primordial germs cells, from which the offspring develops, should not be influenced directly by the metabolic disturbances in the F0 generation. Therefore, the first offspring generation that is not directly influenced by the F0 generation is the F3.[6]

To our best knowledge, no human study has been able to demonstrate clearly that the transgenerational effects upon the epigenetic status in offspring is are due to epigenetic inheritance, in spite of convincing animal studies. As discussed elsewhere, this was not yet made possible due to numerous challenges in the experiment design, as well as funding limitations.[28]

Present challenges

Although robust animal models have already demonstrated that transgenerational epigenetic inheritance is a reality, less is known about how relevant this process is in humans, in relationship with disease onset, including T2D. Clearly, it is strongly suggested this might be the case, but the ultimate proof is still elusive. Two main roadblocks must be overcome in order to demonstrate the role of epigenetic inheritance:

1. First, an experiment design encompassing four generations (F0 to F3) is the only type that would prove that the inheritance of a phenotype, and associated epigenetic alterations, are due to inheritance and not merely because of direct metabolic influences upon the epigenetics of primordial stem cells. This would require a design across four generations, with a duration probably of at least 60-70 years. Presently, there are no reliable DNA human samples obtained before World War II. For such design to be successful in the future, the paradigm of funding should also be changed, and such studies allowed to progress over a very long period.
2. But in order for such studies to be successful, another pre-requisite should also be fulfilled. While animal models make abundant use of in-bred strains, which have little genetic drift, and which is measurable, the genetic heterogeneity of humans makes such an endeavor more difficult. In order to demonstrate that an inherited phenotype (e.g. insulin resistance) is due to inherited epigenetics, one must

demonstrate that there are no genetic variations that could act as confounders or drivers for both the phenotype and epigenotype. As discussed above, genetic variations can drive epigenetic disturbances but in such cases, the epigenetic alterations are consequences arising from genetic variability. Therefore, in order to demonstrate the role of epigenetic inheritance upon disease onset or risk, one should filter out the influences brought by genetic variations. One example is the Rett syndrome, a disease mediated purely by epigenetic disturbances for MECP2, but which is driven by genetic mutations for this gene (29). In the rare cases of inheritance, the epigenetic alterations (due to MECP2 dysfunction) can seem inherited, but the actual inheritance is purely genetic.

Conclusions

With the increasing frequency of the early onset of insulin resistance and T2D, more research has focused on unraveling the relationship between early environmental cues (including nutrition), and their roles in the epigenetic component of this metabolic impairment. Animal studies have clearly shown that the epigenetic alterations induced by either maternal or paternal cues are clear contributors to the early onset of the disease, and such epigenetic alterations can be inherited.

In humans, although there is a strong suggestion that similar epigenetic mechanisms could have same roles, existing roadblocks are still challenging the concept of epigenetically inherited alterations as contributors to the early onset of T2D. These challenges can be addressed by studies encompassing at least four generations, and by adequate funding that should be available over a long period of time.

Meanwhile, significant knowledge gaps still exist in understanding how early epigenetic modifications contribute to the T2D phenotype, and therefore what could be the derived therapeutic applications that would include epigenetic interventions, either in the affected individuals or in their parents.

References

1. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS medicine. 2006;3(11):e442. Epub 2006/11/30.

2. Mayer-Davis EJ, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, et al. Incidence Trends of Type 1 and Type 2 Diabetes among Youths, 2002-2012. N Engl J Med. 2017;376(15):1419-29. Epub 2017/04/14.
3. Temneanu OR, Trandafir LM, Purcarea MR. Type 2 diabetes mellitus in children and adolescents: a relatively new clinical problem within pediatric practice. Journal of Medicine and Life. 2016;9(3):235-9.
4. Zhuo X, Zhang P, Hoerger TJ. Lifetime direct medical costs of treating type 2 diabetes and diabetic complications. American journal of preventive medicine. 2013;45(3):253-61. Epub 2013/08/21.
5. Skinner MK. Role of epigenetics in developmental biology and transgenerational inheritance. Birth Defects Res C Embryo Today. 2011;93(1):51-5. Epub 2011/03/23.
6. Niculescu MD. Nutritional Epigenetics. ILAR Journal. 2012;53(3-4):270-8.
7. Niculescu MD, Lupu DS. Nutritional influence on epigenetics and effects on longevity. Curr Opin Clin Nutr Metab Care. 2011;14(1):35-40. Epub 2010/11/23.
8. Kaati G, Bygren LO, Edvinsson S. Cardiovascular and diabetes mortality determined by nutrition during parents' and grandparents' slow growth period. Eur J Hum Genet. 2002;10(11):682-8. Epub 2002/10/31.
9. Nicolaidis S. Prenatal imprinting of postnatal specific appetites and feeding behavior. Metabolism. 2008;57 Suppl 2:S22-6. Epub 2008/09/23.
10. Bruce KD, Hanson MA. The developmental origins, mechanisms, and implications of metabolic syndrome. J Nutr. 2010;140(3):648-52. Epub 2010/01/29.
11. McAllister EJ, Dhurandhar NV, Keith SW, Aronne LJ, Barger J, Baskin M, et al. Ten putative contributors to the obesity epidemic. Crit Rev Food Sci Nutr. 2009;49(10):868-913. Epub 2009/12/05.
12. Stoger R. Epigenetics and obesity. Pharmacogenomics. 2008;9(12):1851-60. Epub 2008/12/17.
13. Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. PNAS. 2008;105(44):17046-9.
14. Aagaard-Tillery KM, Grove K, Bishop J, Ke X, Fu Q, McKnight R, et al. Developmental origins of disease and determinants of chromatin structure: maternal diet modifies the primate fetal epigenome. J Mol Endocrinol. 2008;41(2):91-102. Epub 2008/06/03.
15. Waterland RA, Lin JR, Smith CA, Jirtle RL. Post-weaning diet affects genomic imprinting at the insulin-like growth factor 2 (Igf2) locus. Hum Mol Genet. 2006;15(5):705-16. Epub 2006/01/20.
16. Jimenez-Chillaron JC, Ramon-Krauel M, Ribo S, Diaz R. Transgenerational epigenetic inheritance of diabetes risk as a consequence of early nutritional imbalances. Proc Nutr Soc. 2016;75(1):78-89. Epub 2015/11/18.
17. Zaghlool SB, Al-Shafai M, Al Muftah WA, Kumar P, Gieger C, Waldenberger M, et al. Mendelian inheritance of trimodal CpG methylation sites suggests distal cis-acting genetic effects. Clin Epigenetics. 2016;8:124. Epub 2016/11/30.
18. Volkmar M, Dedeurwaerder S, Cunha DA, Ndlovu MN, Defrance M, Deplus R, et al. DNA methylation profiling identifies epigenetic dysregulation in pancreatic islets from type 2 diabetic patients. EMBO J. 2012;31(6):1405-26. Epub 2012/02/02.

19. Dayeh TA, Olsson AH, Volkov P, Almgren P, Ronn T, Ling C. Identification of CpG-SNPs associated with type 2 diabetes and differential DNA methylation in human pancreatic islets. Diabetologia. 2013;56(5):1036-46. Epub 2013/03/07.
20. Haumaitre C, Lenoir O, Scharfmann R. Histone deacetylase inhibitors modify pancreatic cell fate determination and amplify endocrine progenitors. Mol Cell Biol. 2008;28(20):6373-83. Epub 2008/08/20.
21. Stoffers DA, Desai BM, DeLeon DD, Simmons RA. Neonatal exendin-4 prevents the development of diabetes in the intrauterine growth retarded rat. Diabetes. 2003;52(3):734-40. Epub 2003/02/28.
22. Park JH, Stoffers DA, Nicholls RD, Simmons RA. Development of type 2 diabetes following intrauterine growth retardation in rats is associated with progressive epigenetic silencing of Pdx1. J Clin Invest. 2008;118(6):2316-24. Epub 2008/05/10.
23. Qian J, Kaytor EN, Towle HC, Olson LK. Upstream stimulatory factor regulates Pdx-1 gene expression in differentiated pancreatic beta-cells. Biochem J. 1999;341 (Pt 2):315-22. Epub 1999/07/07.
24. Sandovici I, Smith NH, Nitert MD, Ackers-Johnson M, Uribe-Lewis S, Ito Y, et al. Maternal diet and aging alter the epigenetic control of a promoter-enhancer interaction at the Hnf4a gene in rat pancreatic islets. Proc Natl Acad Sci U S A. 2011;108(13):5449-54. Epub 2011/03/10.
25. Benyshek DC, Johnston CS, Martin JF. Glucose metabolism is altered in the adequately-nourished grand-offspring (F3 generation) of rats malnourished during gestation and perinatal life. Diabetologia. 2006;49(5):1117-9. Epub 2006/03/25.
26. Aerts L, Van Assche FA. Animal evidence for the transgenerational development of diabetes mellitus. The international journal of biochemistry & cell biology. 2006;38(5-6):894-903. Epub 2005/08/25.
27. Zambrano E, Martinez-Samayoa PM, Bautista CJ, Deas M, Guillen L, Rodriguez-Gonzalez GL, et al. Sex differences in transgenerational alterations of growth and metabolism in progeny (F2) of female offspring (F1) of rats fed a low protein diet during pregnancy and lactation. The Journal of physiology. 2005;566(Pt 1):225-36. Epub 2005/04/30.
28. Niculescu MD. Challenges in nutrition-related DNA methylation studies. BioMolecular Concepts. 2012;3(2):151.
29. Kyle SM, Vashi N, Justice MJ. Rett syndrome: a neurological disorder with metabolic components. Open biology. 2018;8(2). Epub 2018/02/16.

Mihai D. Niculescu, MD, PhD
Founder & CEO, Advanced Nutrigenomics,
206 Stockbridge Pl., Hillsborough, NC 27278, U.S.A.
Research Associate Professor, The "Victor Babes" University of Medicine and Pharmacy, Timişoara, Romania
Square E. Murgu 2, 300041 Timisoara,
E-mail: mihai.niculescu@gmail.com

February 2018

APPROACH OF GRAVES'DISEASE IN CHILDREN

Corina Paul, Dana Stoian, Iulian P. Velea

Introduction

Graves` Disease (GD) is a disorder quite rarely encountered in the pediatric age group but, still, it is the main cause of hyperthyroidism (thyrotoxicosis) in children and adolescents. First described by Robert Graves in 1835, GD is an autoimmune disease caused by the stimulation of the thyroid gland by the TSH receptor antibodies (TRAb), leading to excessive production of thyroid hormones and the clinical features of hyperthyroidism.

Epidemiology

In children, GD is an uncommon diseases, accounting for only 1 - 5% of all patients with GD and almost 15% of childhood thyroid disease.[1,2] The incidence of GD has an ascending trend, the actual literature data showing a GD prevalence, for children under 15 years of age, between 1/10.000 (in the USA) and 1/100.000 person-years (in the UK and Ireland).[3] Like other thyroid diseases, GD is much more frequent in females.[4,5] The disease may affect children of all ages, even the newborn babies, but, its frequency increases with age, peaking in adolescence. [2]

Like any other autoimmune disease, GD is associated more frequently in children with other autoimmune diseases (diabetes mellitus, celiac disease, vitiligo) or genetic syndromes (Down or Turner Syndromes) and in children with family history of autoimmune thyroid disease.[6-8]

Etiopathogeny

The pathogeny of GD is not completely clear yet, but it is known that the disease is the result of an interaction between a genetic background, the immune system and some environmental factors. It seems that the genetic background accounts for 80%, while the environmental factors for 20%, of the susceptibility to Graves`disease.[2,9]

Genetic susceptibility for GD is associated with the HLA genes (DR3, DQ2 şi DQ A1*0501), the cytotoxic T lymphocyte antigen 4 (CTLA-4) and the PTPN22 (lymphoid tyrosine phosphatase) gene. [2,4]

The pathogenesis of GD involves an imbalance between suppressor and helper T lymphocytes, responsible for the occurrence and severity of the disease.

For unknown reasons, the suppressor T lymphocytes decrease in number and function, leading to excessive production of antibodies (TSH receptor antibody, TRAb) that stimulate the thyroid gland. These antibodies are immunoglobulins, which bind to the TSH receptor, causing thyroid stimulation. Consequently, the follicular thyroid cells are growing, vascularity of the gland increases, with increased thyroid hormones synthesis and secretion. The antibodies mimic TSH action, most of them having a stimulatory effect. However some antibodies, bind to the receptor, without stimulating it, blocking the binding of TSH to the receptor and exerting, thus, an inhibitory effect (Thyroid stimulation blocking antibodies).[2,4]

The secretion of the thyroid hormones will depend on the balance between the two types of actions (stimulation-blocking), explaining somehow the variability of the thyroid hormones, encountered in some of these patients. The thyroid gland shows lymphocytic infiltration, local inflammation and tissue remodeling. [2,4,9,10]

Regarding the environmental factors that trigger the autoimmune process in GD, there are some data sustaining the involvement of infections (viral or Yersinia enterocolitica) in the onset of GD, including the increased incidence in spring and autumn (when viral infections are frequent) and the presence of Yersinia enterocolitica antibodies in many patients presenting GD.[11-13]

Clinical aspects

The clinical features of Graves` disease represent the consequence of the excessive thyroid hormones and their effects on the target tissues. In older children and adolescents with GD, the clinical aspect is quite similar to that encountered in adult, with some age-related features, while in the newborn and infant, it might be difficult to confirm the diagnosis sometime, especially if the history of the mother is missing.

The clinical onset in adolescents and school aged children is, usually, non-specific, which is why, it might not be noticed by the medical professionals right from the beginning. The patients present general signs like: emotional lability, behavioral changes, agitation, irritability, nervousness, incapacity to focus on school, sleep disturbances/insomnia, fatigue.

Palpitations, tremors and excessive sweating are associated with weight loss, despite increased appetite and adequate caloric intake. The intestinal movements are accelerated, with frequent stools (false diarrhea). This variety of non-specific signs brings the patient to various other pediatric services (neuropsychiatry, cardiology or pediatric gastro-enterology) before being consulted by a pediatric endocrinologist.

A symmetrical, firm, smooth, painless goiter might be present (*figure 5.1.a*). A local palpable thrill may be detected, which reflects the increase in the thyroid blood flow. If the goiter is voluminous, it may cause symptoms through cervical compression: dyspneea, dysphagia, cough.

In most patients, the thyroid is only slightly increased in volume, which is why, the goiter may go unnoticed by the physicians.

Infiltrative ophtalmopathy is rare in children but, eye involvement can be observed in most cases. Ophthalmic abnormalities are milder than in adults, producing less long-term consequences, being due to soft tissue involvement: staring eyes, caused by the lid retraction, sometimes proptosis, with retraction of upper lid and a wide palpebral apperture.[14] Most common symptoms are due to conjunctival or corneal irritation, including photophobia, tearing, pain, burning or „sandy" sensation. (*Figure 5.1.b*).

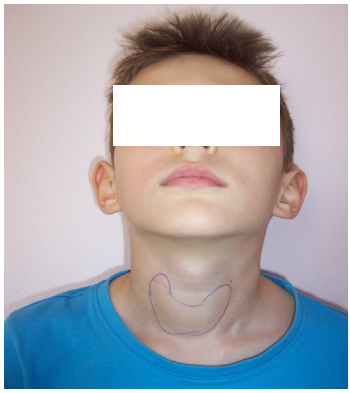


Fig. 5.1.a. – goiter;

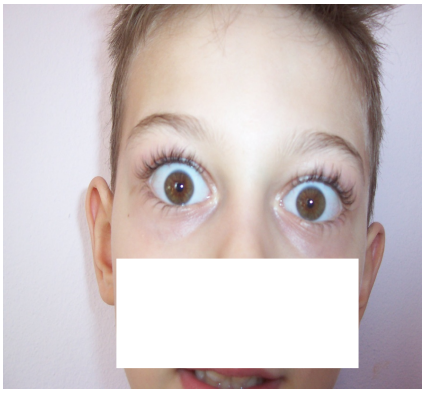


Fig. 5.1b - infiltrative ophtalmopathy

Among the major cardiac clinical signs in pediatric GD, tachycardia is representative, but other symptoms like increased blood pressure (hypertension), a precordial thrill and/or an ejection murmur due to a functional insufficiency of the mitral valve, may also be noticed.

Increased growth velocity with increased height and advanced bone age are revealed, with the longer the exposure to thyroid hormone excess.

Because of the strong influence of the thyroid hormones on bone metabolism, the excess of thyroid hormones is responsible for a high bone turnover, with an uncoupling between the resorbtive and the anabolic phase, which may result in a net bone loss and, thus, over the years, in osteoporosis. This phase is, fortunately, short in children, if promptly diagnosed and treated, so that, bone loss completely recovers in the first two years after completing therapy and achieving the euthyroid state.[4,15]

Severe neurological signs like chorrea, athetosis, ataxia are rare in children.[16] Pretibial myxedema and thyreotoxic crisis are, also, extremely rare in this age group.

Other clinical signs that may be present, mainly in the adolescents with GD are: muscular weakness, decreased muscular mass, particularly of the proximal muscles, with reduced muscular force, alopecia areata.[4] Boys may present gynecomastia (due to estrogen excess - increased steroids metabolism and their aromatization to estrogens) while girls may have dysregulation of the menstrual cycle or, even amenorrhea.

Neonatal GD may have a major impact on gowth and mental development, if undetected. The clinical features of GD in the neonate include: low birth weight for gestational age/premature birth, triangular facies, frontal bossing, microcephaly, craniosynostosis, warm and moist skin, staring and tendency to exophtalmos (*Figure 5.2*).

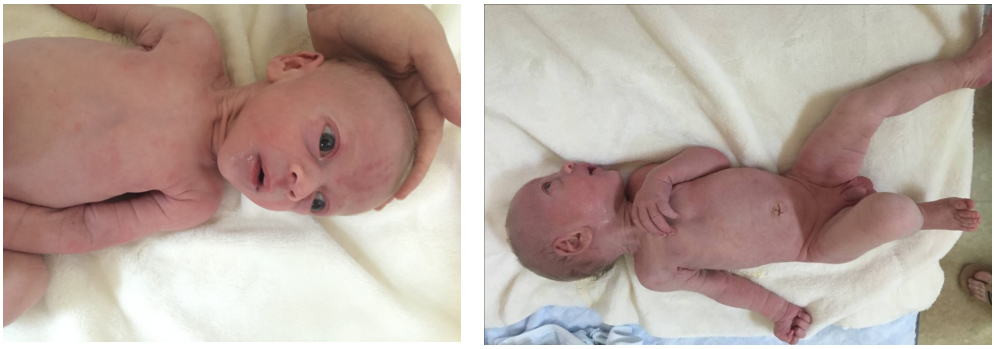


Fig. 5.2. - Clinical features of GD in the newborn
(Collection Corina Paul)

The newborn also presents prolonged jaundice, good apetite but poor weight gain, false diarrhea (frequent stools), vomiting, hepatosplenomegaly, tachycardia, arrhytmias, systemic and pulmonary hypertension (even cardiac failure), restless and poor sleep, hyperactivity, difuse goiter, persistent acrocyanosis, hyperviscosity syndrome/ thrombocytopenia.[17,18]

In most cases of neonatal GD, the diagnosis is suspected because of the maternal history of GD.

Laboratory investigations and imaging in GD

Laboratory investigations in GD will show increased serum free thyroxine (FT4) and free triiodothyronine (FT3), suppressed serum TSH (almost undetectable TSH in the serum).

However, there are patients showing normal FT4 and high serum FT3 (condition known as *T3 toxicosis*) which is possible at the onset of GD or during relapses that occure in the course of the disease.[2]

The thyroid stimulating hormone receptor antibodies (TRAbs) are present in the serum of most of the GD patients, being specific for Graves` disease.

There is a positive correlation between serum TRAbs and serum FT4 levels.[2] In young children (under 5 years of age) serum TRAbs levels are significantly higher than in older children (> 5 years) with GD. Also in patients with severe initial clinical presentation, serum TRAbs are higher than in those with a milder clinical onset.[2,19]

A positive titre of both ATPO (antithyroxinperoxidaze antibodies) and antiTg (anti-thyroglobulin antibodies) is usefull to confirm the diagnosis of autoimmune thyroid disease (ATD). [2]

Thyroid echography is the main imaging procedure used in GD, to evaluate both the volume and the morphologic and vascular modifications (Doppler). The thyroid volume is increased in most GD patients (still, 10 % of the patient present normal thyroid volume), with normal echogenicity (rare) or hypoechogenic aspect (similar to the appearance of thyroiditis) and hypervascularity (specific aspect of "thyroid inferno") (*Figure 5.3*).

Other imaging procedures (scintygraphy, MRI, CT are not needed for the diagnosis of GD.

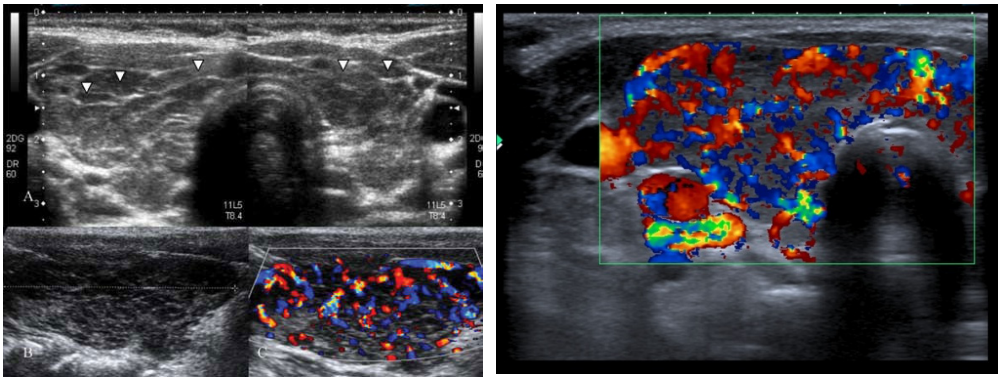


Fig. 5.3. – Thyroid echography -"thyroid inferno"
(Collection Corina Paul)

Diagnosis of GD

Diagnosis of GD is based on family history (of thyroid or other autoimmune disease), clinical features, thyroid echography and laboratory investigations (with significant TRAb titre).

Management of pediatric GD

GD treatment aims to decrease serum thyroid hormone levels and the symptoms determined by the hormonal excess. Yet, there is no general consensus regarding the management of GD in children and adolescents, so there is large variation between the therapeutic approach of the disease in different countries, depending on severity of the disease, the age of the patient, the presence of goiter etc.[10]

Three main possibilities are available for treatment of GD in children:

1) antithyrois drugs (ATD) associated, when needed, with adjuvant drugs (beta-blockers, glucocorticoids etc)

2) surgery (total/near-total/subtotal surgical removal of the thyroid gland) and

3) radioactive iodine (RAI; I^{131}).

It is common practice to start therapy of GD in children, with ATD. However, this approach may be associated with poor compliance or high relapse rate, or, sometimes, with treatment-related toxicity.[4]

Antithyroid drugs

Antithyroid drugs (ATDs) are the therapy of choice in children with GD. The benefits of ATDs include no risk of radioactive iodine exposure, no hospitalization nor surgical procedure. The drawbacks include a lower remission rate in children compared to adults, longer duration of the treatment and higher frequency of adverse drug reactions.[20]

The most commonly used ATDs are: carbimazole (CMZ), its active metabolite methimazole (MMI)/ thiamazole (TMZ) and propylthiouracil (PTU). CMZ is a precursor of MMI and rapidly converted to MMI in serum: 10 mg of CMZ is metabolized to yield aproximately 6 mg of MMI.[2]

ATDs inhibit thyroid hormone synthesis by interfering wih the thyroid peroxidase–mediated iodination of the thyrosine residues of thyroglobulin.

Side effects of ATDs are encountered in 5-25 % of patient and are, usually, minor (rash, urticaria, arthralgia, gastrointestinal problems). Agranulocytosis, the most severe side-effect, is quite rare in children (0,2 - 0,5% for both MMI/CMZ and PTU).[2] Other rare side effects, observed mostly in patients treated with PTU, are drug-induced hepatitis and hepatic failure, that is why, the drug should be avoided in children.

Side effects of ATDs may be dose-related, are rarely encountered with low doses of MMI/CMZ (MMI ≤10 mg/day), usually occuring within the first 6 months of ATD treatment.[2,4,10]

In pediatric GD, PTU should only be used in special circumstances, for short periods and with close monitoring, in patients experiencing a toxic reaction to MMI/CMZ where ATD therapy is necessary.

The starting dose of MMI/CMZ is 0,2 - 1 mg/kg/day, with a maximal dose of 30 mg/day for MMI and 40 mg/day for CMZ, divided, usually, in 2 - 3 equal daily doses for CMZ and 2-3/once daily for MMI which has a longer half – life. [2,4,21.]

After 2 – 4 weeks of drug therapy, when the thyroid hormone secretion is effectively blocked and thyroid hormone levels have normalized, the initial dose of CMZ/MMI should be reduced gradually by 30% - 50 %.

ATD treatment should be closely monitored, every 3- 6 weeks initially, every 3 months later, checking for serum FT4, FT3, TSH (because hypothyroidism may occur if the TAD doses are not reduced properly as serum FT4 normalize) but, also blood count and hepatic function, to avoid unexpected side-effects.

If needed, additional treatment with beta-blockers might be used, to control cardiac symptoms like palpitations, tachycardia, hypertension (Propranolol p.o/inj, 0,5-2 mg/kg/day, divided in 2 daily doses.

ATD therapy aims to restore normal thyroid function rather than reduce autoimmunity. Hypertiroidism itself has been shown to worsen the autoimmune process, leading to generation of more TRAbs, while the euthyroid state obtained with ATD treatment, will have a benifical effect on TRAb production and the remission of GD.[2,19]

The second therapy regimen known as "block and replace therapy" (BR) involves the use of high doses of ATD with the addition of L-thyroxine, showed no real benefits in children. More than that, high-doses of ATD may be harmful for the young patients, so, recently, the American Thyroid Association guidelines suggested that BR regimen should be avoided in children.[22]

ATD therapy improves the metabolic rates, growth velocity and body weight within 3 months. Serum thyroid levels normalize after one month, but TSH becomes detectable in serum only after 3-4 months of therapy. In a small percent of patients FT3 is still increased after normalization of FT4. These patients present an increased FT3/FT4 ratio and low/undetectable TSH, associate higher TRAbs and larger thyroid gland and, sometimes, need higher doses of ATDs for longer periods.[2,23,24]

Only 20-30 % of the children treated with ATD for 2 years achieve remission, compared with ATD treated adults who achieve remission in 40-60 %. [20,26]

The rate of relapse is increased after a first course of treatment, potentially reaching 80 %, (about 75 % in the first 6 months after completing therapy and only 10 %, after 18 months of ATD therapy). According to literature data, remission is lower and relapses are frequently encountered in younger children (age below 12 years), non-caucasian, with large goiter (increased thyroid volume > 2,5x normal size for age) who present high TRAb titre and FT4 levels (> 4 ng/dl or > 50 pmol/l) at the onset of GD. [19,21,25]

Treatment of GD in foetuses, neonates and infants

Foetal hyperthyroidism can be prevented by administrating ATDs to the mother with GD. Both PTU and MMI/CMZ are crossing the placenta and are equally effective for treating hyperthyroidism in pregnancy. PTU is most widely used during pregnancy. The foetus benefits directly from the ingestion of the drug, which crosses the placenta and acts on the foetal thyroid gland. However these drugs may also expose the foetus to the risk of hypothyroidism, therefore, small doses of ATDs are recommended during the second half of gestation (100-150 mg/day for PTU, 10-15 mg/day for MMI/CMZ).

Neonatal hyperthyroidism is, usually, a transient disease, lasting 2- 3 months, until the clearance of maternal TRAbs from the bloodstream of the infant is complete (2,5). Hyperthyroidism may develop in neonates within two to five days of life, if TRAbs persist

after the clearance of transplacentally transmitted ATDs from the mother.

Neonates from mothers testing negative for TRAbs during the second half of gestation (with negative test on cord blood) can be discharges and require no further follow–up.[26-27] Neonates born to mothers with very low TRAb levels (less than 2-3 times the upper limit of normal range) may have serum FT4 levels at about the 95th percentile, on day 2-5 of life, with these levels subsequently decreasing to the normal range, during the second week of life.[28]

When TRABs are detectable in high levels (more than 3 times the upper limit of normal range; generally > 5 UI/l) in cord blood and serum FT4, FT3 are high in the first 2-4 days after delivery, autoimmune hyperthyroidism (neonatal GD) should strongly be suspected and lead to initiation of ATD therapy in the neonate, shortly after birth.

Newborns with symptomatic hyperthyroidism should be admitted and their heart rate monitored. ATD treatment should be started immediately after diagnosis, with MMI/CMZ 0,5-1 mg/day in divided doses at 8 hours interval. Beta-blockers (Propranolol) iodine (Lugol or saturated KI solutions) and, sometimes glucocorticoids, digitalization or sedatives may be needed for treatment.

Propranolol (orally or intravenous) is used to control cardiovascular symptoms (0,5-2 mg/kg/day) divided in 3-4 daily doses.

Iodine is useful as it rapidly inhibits the hormone release (Lugol solution 126 mg iodine/ml, 8 mg/drop), one drop every 8 hours) or SSKI (saturated solution of KI 1g/ml, 1-2 drops/daily). If a satisfactory response is not obtained within 24-36 hours, with MMI and iodine treatment, the doses can be increased by 50%.[5]

Glucocorticoids, in high doses, (Prednison or Prednisolone 2 mg/kg/day) diminish the thyroid hormone secretion and T4 to T3 conversion, and may, therefore, be helpful in severe cases.[10]

As the clinical and biochemical features of thyrotoxicosis improves, treatment should be adjusted, by reducing the MMI/CMZ doses gradually (from 0,5 to 0,3 and 0,1 mg/kg/day) and, finally, discontinuing ATD treatment. This period lasts for about 3 months, but sometimes may be continued for 6 months or even longer.

While treated with ATDs, mothers may breastfeed the newborn/ infant, with no adverse effects on the thyroid status of

the infant (the daily dose accepted for a safe breastfeeding should not exceed 40 mg/day MMI/CMZ or 400 mg for PTU).[29]

Radioactive iodine treatment

Radioactive iodine (RAI) is used to treat hyperthyroidism due to GD also in children and most patients can be successfully treated with a single oral dose. In several units, this therapy has become the preffered treatment, with excellent long term outcome and low risk of remission.[30]

^{131}I therapy should even be considered in children who do not respond at all to drug therapy, cannot receive drug therapy because of an adverse reaction and/or refuse to have surgical treatment. The usefulness of ^{131}I therapy for pediatric patients has been reported in several studies. [20, 31-34] Also, a remission rate exceeding 95% in RAI treated children has been reported.[21]

The goal of ^{131}I therapy is to induce hypothyroidism. ^{131}I doses are calculated to deliver the desired amount of radiation, based on gland size and RAI uptake. To achieve thyroid ablation or hypothyroidism, doses higher than150 μCi of ^{131}I per estimated gram thyroid are needed. Even higher doses (200-300 μCi of ^{131}I per gram) should be used in larger thyroid glands (30-80g).[21]

Higher doses of ^{131}I are preferred over lower doses, as the later are associated with a higher relapse rate.[2]

Patients should be preferably rendered euthyroid with ATD treatment before proceeding with RAI therapy.[2]

Prior to ^{131}I therapy, iodine intake should be restricted for more than one week and the antithyroid drug discontinued for more than 3 days. To confirm that iodine is restricted, the RAIU (RAI uptake) should be measured.[20]

Practices vary from one country to another, according to local or regional guidelines.

ATA guidelines[22] state that ^{131}I therapy should be avoided in children younger than 5 yr of age. ^{131}I therapy is acceptable in children aged 5–10 yr if less than 10 mCi of ^{131}I is administered, while in patients 10 yr or older, ^{131}I therapy is acceptable if the dose exceeds 150 μCi/g of thyroid tissue.[35-37]

In Brazil, the national guidelines state that ^{131}I therapy is acceptable in patients 10 yr or older if the dose exceeds 160 μCi/g of thyroid tissue. For patients with a smaller goiter, ^{131}I therapy is useful at a ^{131}I dose between 10 and 15 mCi. ^{131}I dose exceeding 150

μCi/g of thyroid tissue induced hypothyroidism in 95% of patients.[38-40]

Other autors suggested that the ^{131}I dose should be between 220 and 275 μCi/g of thyroid tissue.[41]

If hyperthyroidism persists 3-6 months after treatment, a second therapeutic cure with ^{131}I is indicated.

In large goiters (>80 g), RAI therapy usually fails to succeed (>80 g), so, for theese cases, surgery should be the treatment of choice.[21]

Secondary effects of RAI

Very few children complain of mild tenderness over the thyroid in the first week after therapy, which can be treated effectively with acetaminophen or nonsteroidal anitinflamatory agents.

Hypothyroidism occurs after RAI therapy thus, Lthyroxine should be administered throughout the patients` life span.[2,4]

Previous reported data raised concerns about potential thyroid malignancy, hyperparathyroidism and increased mortality rates in patients treated by RAI, but the later studies showed that the increased cancer risk is due to hyperthyroidism and shared risk factors and not to therapy.[2,20]

Still, most guidelines recommend that in children younger than 5 y, RAI therapy should be avoided because of an increased potential risk of neoplasia.[20,22]

Surgical treatment

Thyroid surgery is the radical treatment choice recommended in children and adolescents with hyperthyroidism with large goiters or ophtalmopathy.

Total (or near-total) thyroidectomy is preffered to subtotal (or partial) thyroidectomy in order to avoid the risk of relapse (reccurent hyperthyroidism).

Prior to surgery, ATD treatment should be administered (for about one month). The vascularity of the gland should be decreased by iodine treatment (Lugol solution 5-10 drops daily).

Following surgery, the replacement therapy with Lthyroxine should be initiated and continued life-long, with appropriate long-term monitoring.

Complications following thyroid surgery – hypoparathyroidism, vocal cords palsy due to reccurent laryngeal nerve injury and keloid formation, are rare, if experienced surgeons, with extensive experience, perform the operation (15 %).[42]

In the case of reccurent hyperthyroidism after surgery, RAI therapy is recommneded.[2]

Long term outcome. Conclusions

Unlike the adult in whom the ATD treatment results in long-term remission in 40-60 % of patients, *in children,* less than 30 % of the treated children (for a mean of 2 years) achieve remission, lasting for at least 2 years. About 75 % of patients relapse within 6 months of the end of drug treatment, whereas only 10 % relapse after 18 months. [2,4,21]

Recent studies are showing that the risk of relapse after a course of about 2 years ATD therapy was higher in very young patients and in children of non-caucasian origin; also in children with severe hyperthyroidism at diagnosis (high TRAbs, high FT4). Conversely, the longer the duration of first course ATD therapy, the lower the risk of relapse, meaning that a longer course of primary ATD therapy seems to reduce thyroid autoimmunity and the reccurence of the disease in children.[2,43]

The optimal treatment of GD in children remains still a matter of debate. ATD is still the primary treatment option for children. The major advantage of ATD therapy is that the normal homeostasis of the hypothalamic-pituitary-thyroidal axis may be restored with medical treatment. However, this may take a long time and may not be achieved in a significant proportion of children.

RAI and surgical therapy are the second-line therapeutic option in children and the decision for one of them should be made carefully, keeping in mind the consequences – the permanent hypothyroidism - and, also, the possible undesirable effects.

References

1. Abraham Nordling M, Bystrom K, Torring O et al. Incidence of hyperthyroidism in Sweden. Eur J Endocrinol 2011; 165:899-905.
2. Leger J . Graves` disease in children in Szinnai G (ed) Pediatric Thyroidology . Basel Karger, 2014, vol 26, pp 171-182

3. Williamson S, Greene SA : Incidence of thyrotoxicosis in childhood : a national population based study in the UK and Ireland. Clin Endocrinol (Oxf) 2010; 72: 358-363.
4. Radetti G, Baronio F Hyperthyroidism in Bona G, DE Luca F, Monzani A - Thyroid diseases in childhood ,Springer ed, 2015: 203-217.
5. Fisher DA - Disorders of the Thyroid in the Newborn and Infant in Mark Sperling - Pediatric Endocrinology; 2002;161-209.
6. De Luca F, Corrias A, Salerno M, Wasniewska M, Gastaldi R, CAssio A, Mussa A, Aversa T, Radetti G, Arrigo T: Peculiarities of Graves` disease in children and adolescents with Down Syndrome. Eur J Endocrinol 2010;162:591-595
7. Wasniewska M, Corrias A Messina MF, Crisafulli G et al: Graves` disease prevalence in young population with Turner syndrome. J Endocrinol Invest 2010; 33: 69-70.
8. Michels AW, Eisenbarth GS : Immunologic endocrine disorders. J Allergy Clin Immunol 2010; 125: S226-S237.
9. BrixTH, KyvikKO, Christensen K, Hegedus L: Evidence for a major role of heredity in Graves` disease: a population based study of two Danish twin cohorts. J Clin Endocrinol Metab 2001;86:930-934.
10. Paul C, Stoian D,Velea PI Hipertiroidismul la copil in Velea PI, Paul C (ed).Patologia tiroidei la copil, ed Mirton Timisoara 2016, 115-137
11. Wang Z, Zhang Q, Lu j, Jiang F, Zhang H, GAo L, Zhao J: Identification of outer membrane porin F protein of Yersinia enterocolitica recognized by antithryotropin receptor antibodies in Graves disease and determination of its epitope using mass spectrometry and bioinformatics tools. J Clin Endocrinol Metab 2010; 95: 4012-4020.
12. Hargreaves CE, Grasso M, HAmpe CS, Stenkova A Atkinson S, Joshua GV, Wren BW, Buckle AM, Dunn-Ealters D, Banga P:Yersinia Enterocolitica provides the link between thyroid-stimulating antibodies and their gerline counterparts in Graves disease. J Immunol 2013;190:5373-5381.
13. Wiersinga WM. Thyroid autoimmunity in Szinnai G (ed) Pediatric Thyroidology . Basel Karger, 2014, vol 26, pp 139-157
14. Gogakos AI, Boboridis K, Krassas GE, Pediatric aspects in Graves`orbitopathy. Pediatr Endocrinol Rev 2010; 234-244.
15. Lucidarme N, Ruiz JC, Czernikow P et al. Reduced bone mineral density at diagnosis and bone mineral recovery during treatment in children with Graves` disease. J pediatr 2000.137:56-62.
16. Leblicq C, Duval M, Carmant L, Van Vliet G, Alos N, Rising serum thyroxine level and chorea in Graves` disease. Pediatrics 2013; 131:e616-e619
17. Ogilvy Stuart AL Neonatal thyroid disorders. Arch Dis Child Fetal Neonatal Ed 2002, 87:F165-F171.
18. Polak M. Legac I.Vuillard E et al. Congenital hyperthyroidism: the fetus as a patient. Horm Res 2011;65: 235-242.
19. Kaguelidou F, Alberti C, Castanet M, Guitteny MA, Czernikow P, Leger J. Predictors of autoimmune hyperthyroidism relapse in children after discontinuation of antithyroid drug treatment. J Clin Endocrinol Metab 2008;93:3817-3826

20. Kanshi Minamitani, Hirokazu Sato, Hidemi Ohye, Shohei Harada, and Osamu Arisaka The Committee on Pharmaceutical Affairs, Japanese Society for Pediatric Endocrinology, and the Pediatric Thyroid Disease Committee, Japan Thyroid Association (Taskforce for the Revision of the Guidelines for the Treatment of Childhood-Onset Graves' Disease) Guidelines for the treatment of childhood-onset Graves' disease in Japan, 2016 Clin Pediatr Endocrinol 2017; 26(2), 29–62
21. Rivkees SA Pediatric Graves disease Controversies in management Horm Res Pediatr 2010;74:305-311.
22. Bahn Chair RS, Burch HB, Cooper DS et al Hyperthyroidism and other causes of thyrotoxicosis : management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Thyroid 21:593-646. Erratum in : Thyroid 2011,21 (10) 1169.Thyroid 2012, 22 (11):1195
23. Chen JJ, Landenson PW Discordant hypothyroxinemia and hypertriiodothyroninemia in treated patients with hyperthyroid Graves' disease. J Clin Endocrinol Metab 1986; 63:102-106
24. Matsumoto C, Ito M, Yamada H, Yamakawa N, Yoshida H, Date Aet al Genes that characterize T3 predominant Grave thyroid tissues. Eur J Endocrinol 2013; 168:137-144.
25. Glaser NS, Styne DM: Predicting the likelihood of remission in children with Graves' disease: a prospective multicentre study. Pediatrics 2008;121: e481-488.
26. Besancon A, Beltrand J, Le Gac I., Luton D, Polak M: Management of neonates born to women with Graves' Disease. A cohort study. Eur J Endocrinol 2014; 170:855-962
27. Van der Kaay DC, Wassermann JD, Palmert MR: Management of neonates born to mothers with Graves' Disease. Pediatrics 2016; 137.
28. Levy- Shraga Y, Tamir- Hostovsky L, Boyko V, Lerner – Geva L, Pinhas-Hamiel O: Follow-up of newborns of mothers with Graves' disease.Thyroid 2014; 24:1032-1039.
29. Brown RS , Huang S. The thyroid and its disorders in Brooks CGD(ed) Clinical Pediatric Endocrinology Blackwell (ed) 2006,218-253.
30. De Beaufort C Hyperthyroidism in children and adolescent in Velea PI, Paul C, Brink SJ (ed).Pediatric Endocrinology Clinical Update ed Mirton Timisoara 2011, 43-52.
31. Rivkees SA, Sklar C, Freemark M. Clinical review 99: The management of Graves' disease in children, with special emphasis on radioiodine treatment. J Clin Endocrinol Metab 1998;83: 3767–76.
32. Kraiem Z, Newfield RS. Graves' disease in childhood. J Pediatr Endocrinol Metab 2001;14: 229–43.
33. Ma C, Kuang A, Xie J, Liu G. Radioiodine treatment for pediatric Graves' disease. Cochrane Database Syst Rev 2008; CD006294. [PubMed
34. Rivkees SA, Dinauer C. An optimal treatment for pediatric Grave's disease is radioiodine. J Clin Endocrinol Metab 2007;92: 797–800.

35. Levy WJ, Schumacher OP, Gupta M. Treatment of childhood Graves' disease. A review with emphasis on radioiodine treatment. Cleve Clin J Med 1988;55: 373–82. doi: 10.3949/ccjm.55.4.373
36. Freitas JE, Swanson DP, Gross MD, Sisson JC. Iodine-131: optimal therapy for hyperthyroidism in children and adolescents? J Nucl Med 1979;20: 847–50.
37. Kalinyak JE, McDougall IR. How should the dose of iodine-131 be determined in the treatment of Graves' hyperthyroidism? J Clin Endocrinol Metab 2003;88: 975–7. doi: 10.1210/jc.2002-021801 [PubMed] [Cross Ref]
38. Maia AL, Scheffel RS, Meyer EL, Mazeto GM, Carvalho GA, Graf H, et al. Brazilian Society of Endocrinology and Metabolism. The Brazilian consensus for the diagnosis and treatment of hyperthyroidism: recommendations by the Thyroid Department of the Brazilian Society of Endocrinology and Metabolism. Arq Bras Endocrinol Metabol 2013;57: 205–32.
39. Zantut-Wittmann DE, Ramos CD, Santos AO, Lima MM, Panzan AD, Facuri FV, et al. High pre-therapy [99mTc]pertechnetate thyroid uptake, thyroid size and thyrostatic drugs: predictive factors of failure in [^{131}I]iodide therapy in Graves' disease. Nucl Med Commun 2005;26: 957–63. doi: 10.1097/01.mnm.0000183795.59097.42 [PubMed] [Cross Ref]
40. Nebesio TD, Siddiqui AR, Pescovitz OH, Eugster EA.Time course to hypothyroidism after fixed-dose radioablation therapy of Graves' disease in children.J Pediatr. 2002 Jul; 141(1):99-103. [PubMed] [Ref list]
41. Kaguelidou F, Carel JC, Léger J. Graves' disease in childhood: advances in management with antithyroid drug therapy. Horm Res 2009;71: 310–7. doi: 10.1159/000223414 [PubMed] [Cross Ref]
42. Sosa JA, Tuggle CT, Wang TS, Thomas DC, Boudourakis L, Rivkees S, Roman SA.Clinical and economical outcomes of thyroid and parathyroid surgery in children. J Clin Endocrinol Metab 2008;93:3058-3065.
43. Leger J, Gelvane G, KAguelidou F et al.Positive impact of long-term antithyroid drug treatment on the outcome of children with Graves' disease: national long-term cohort study. J Clin Endocrinol Metab 2012; 97:110-119.

Corina Paul MD, PhD
Lecturer, "Victor Babes" University of Medicine and Pharmacy Timişoara,
Senior Pediatrician, Clinic II Pediatrics, "Pius Branzeu" Clinical County Hospital, Timişoara, Romania.
Address: 1 - 3, Evlia Celebi str, 300226, Timişoara, Romania
E-mail: paulcorina@yahoo.com

March 2018

PRECOCIOUS PUBERTY OVERVIEW AND THERAPEUTIC CONSIDERATIONS

Maia Mincheva Konstantinova

Introduction

Puberty is a pocess of physical maturation manifestated by an increase of growth velocity and appearance of secondary sexual characteristics.

Precocious puberty (PP) is defined as earlier than expected initiation of pubertal development.

In the majority of cases PP is due to early activation of the hormonal changes occuring during the normal puberty: pulsatile activity of the hypothalamic-pituitary – gonadal axis (HPG) with a pulsatile secretion of gonadotropin- releasing hormone (GnRH), which enters the hypothalamic-pituitary portal circulation and stimulates the anterior pituitary to secrete luteinizing hormone (LH) and to a lesser extent - follicle-stimulating hormone (FSH). LH and FSH enter the systemic circulation and stimulate the ovaries and testes to produce sex steroids. This type of PP is defined as central precocious puberty (CPP).[1,2]

CPP has to be differentiated from peripheral precocious puberty (PPP), which is gonadotropin-independent and is also called precocious pseudopuberty. PPP may be due to an autonomous production of sex steroids by the gonads or by the adrenal glands; due to pharmacological or environmental exposure to sex steroids or due to human Chorionic Gonadotropin (hCG) production by tumors.[3,4]

The exquisite sensitivity of the growth plate to the effects of estrogens, premature fusion of the growth plates may result in adult

short stature - one of the concerns for early diagnosis and initiation of treatment of PP. [1]

What is the expected/normal age for the start of puberty?

The timing of pubertal onset is dependent on both genetic and environmental factors. It is estimated that 50% to 80% of the variations of pubertal timing is determined by genetic factors. [5] On average black girls enter puberty earlier than the girls of other racial background, followed by Mexican –American and then white girls.[6]

Pubertal timing is also influenced by environmental factors such as nutrition, illustrated by the association of obesity and earlier pubertal onset in girls.[7] Environmental industrial compounds can also cause earlier breast development by influencing the hypothalamo-pituitary axis (HPA).[8]

From the 60-th years of the 20th century it is perceived that the cut-off age for the start of puberty is 9.0 years for boys and 8 years for girls.[1,2,9,10] This is the prevailing opinion for the pediatric endocrinlogists in Europe and for the American Academy of Pediatrics (AAP). However, the results from an observational study including over 17 000 girls from the Pediatric Research in Office Settings (PROS) network caused a change in the recommendations of the Executive Committee of Lawson Wilkins Pediatric Endocrine Society (LWPES) to a lower age of the cut-off to younger than 7 years for white girls and younger than 6 years for black girls.[14,15] According LWPES recomendations pubertal onset occuring between 7 and 8 years for white girls and 6 and 8 years for black girls should be evaluated if:

1. there is an unusually rapid pubertal progression resulting in bone age advancement by more than 2 years and a predicted height that is less than 150 cm or 2 SDs below the genetic target height;
2. Symptoms of a central nervous system lesion and
3. behavior - based factors suggesting adverse effect on a child's emotional state by early puberty.[3, 11,12,13]

In a recent study, FM Biro et al. using a sample of 1239 white, black, and Hispanic girls in New York City, Cincinnati, and San Francisco, examined breast development by palpation, allaying the concern that lipomastia might have been confused with early breast development (one of the problems with the PROS study).[14] They

reported that in the sample of 7- to 8-year-old girls, 23% of black, 15% of Hispanic, and 10% of white girls had breast development. The above mentioned studies, as well as others, have highlighted the ethnic/racial differences in the timing of pubertal onset as well as the observation that overweight children appear to undergo earlier breast and pubic hair development and somewhat earlier menarche than do girls of normal weight. [14,15,16]
Thus, the evaluation of girls with signs of early puberty, increased BMI and ethnicity have to be taken into account. [17]

VARIATIONS OF NORMAL PUBERTAL DEVELOPMENT

Premature Adrenarche

Adrenarche refers to the maturation of the adrenal cortex that leads to increased production of androgens responsible for some secondary sexual characteristics such as pubic hair, body odor, and acne. Adrenarche is independant of the HPG axis.[18] Most often adrenarche precedes the onset of central puberty, typically around the age of 8 years. As the physical signs of premature adrenarche may be caused by underlined disorder of puberty, children with earlier onset of adrenalchal characteristics have to be evaluated for either central or peripheral PP.

Benign premature adrenarche can be distinguished from pathologic forms of PP by lack of significant bone age advancement (usually <2 years advanced or equivalent to the height age), lack of linear growth acceleration, absence of breast development in girls or testicular enlargement in boys. The concentrations of the adrenal androgens dehydroepiandrosterone (DHEA), DHEA-S or androstenedione are moderately increased, usually consistent with Tanner stage of pubic hair development. Such children should be monitored clinically to ensure that the speed of the pubertal maturation is normal. [2]

Premature adrenarche usually occurs with increasing frequency between the ages of 3 and 8 years, but it may present as early as the age of 1 year. The ratio between girls and boys is 10:1. Although considered a benign variation of maturation, girls with premature adrenarche have increased risk for devoloping insulin resistance and polycystic ovary syndrome.[19]

Premature Thelarche (PT)

Premature thelarche refers to the isolated development of breast tissue in girls within the first 2 years of life. It is usually self-limited and is most often characterized by Tanner stage of 2 or 3 development.

Unlike PP there is no accompanying linear growth acceleration or bone age advancement. The reasons for premature thelarche are still unclear, but the levels of estradiol are increased in these girls and they may also have FSH-driven follicular maturation.

A recent Swedish study from Martin Österbrand et al. defined the upper limit for 17β-Estradiol (17- βE2) in benign PT to be 31 pmol/L.[20] From the examined 128 girls aged 9 – 48 months, 124 had benign breast development with a mean level of 17β-E2 15.2 pmol/L and a mean +2SDs of 31pmol/L, which is regarded as the upper limit for benign PT. LH level was below the detection limit of 0.1IU/L. From the 4 girls who showed 17β-E2 above 46 pmol/L, two were diagnosed with hamartomas, and 1 – with McCune-Albright syndrome. One of the girls with higher level initially was found to be with benigh PT as during the follow up the level of 17β-E2 decreased spontaneously to 21 pmol/L.[20]

A subset of the girls with PT may have mutation in the Gs protein representing nonclassic form of McCune-Albright syndrome, as also evidenced from the sample of girls examined by M. Österbrand.

No therapy is required in cases of premature thelarche, but close clinical follow up is recommended.

Rarely premature telarche may progress to true central precocious puberty.

Central Precocious Puberty (CPP)

CPP results from the premature reactivation of HPG axis and mimics that of normal puberty. [21] The approximate incidence is 1:5000 – to 1:10 000 and is 10 times more common in girls than in boys.[22]

Central PP can be caused by a demonstrable central nervous system (CNS) lesion – *organic CPP*, or may be *idiopathic CPP* (no lesion is found).

Idiopathic CPP (iCPP) is a diagnosis of exclusion.

Despite the efforts to establish the genetic background for the normal pubertal timing and the idiopathic central precocious puberty, it is still largely unknown.

Kisspeptin protein (gene KISS1) modulates GnRH neuronal excitability, function, and expression and thereby influences the hypothalamic–pituitary–gonadal axis and the onset of puberty. It is also called „the gatekeeper" of puberty. Kisspeptin is the natural ligand of KISS1R (a G-protein R).[23, 24]

For the first time MG Teles et al. in 2008 described a molecular defect, a dominant KISS1R (previously named GPR54) activating mutation, resulting in iCPP in a girl.[25] Later another mutation was found in KISS1 – gain-of-function mutation, causing precocious puberty.[26] So far no other mutations in KISS1 or KISS1R have been reported connected to CPP and thus it is thought that the mutations in KISS1 or KISS1R are rather rare.[27]

Another gene involved in iCPP is makorin ring finger protein 3 gene (MKRN3) which loss-of–function mutations have been identified either in familial and sporadic Icpp.[28] MKRN3 gene is located in 15q11.2 in the crucial region for Prader-Willi syndrome. The maternal allele is imprinted (silenced) and therefore the mutations are paternally inherited. Males whose mother is the carrier of the mutation do not develop CPP, but there are also data about males with paternaly inherited mutation in the gene, who are asymptomatic. [29] There are above 25 mutations in the MKRN3 gene for now and their number increases. The usual age of pubertal onset is 5.0 – 7.0 years, bone advancement – with 2.4 years.

Organic CPP

About 20% of the boys with CPP have an underlying CNS lesion (organic CPP), compared to the girls – about 5%.

The risk factors for CNS etiology include young age and male gender. The most common CNS lesions associated to CPP is the hypothalamic hamartoma – a congenital, nonneoplastic, heterotopic collection of neural tissue located at the floor of the third ventricle. Hamartomas contain neurosecretory neurons composed of LH-releasing hormone (LHRH) or tumor necrosis factor-α (a stimulus for LHRH release), which likely function as an ectopic GnRH-pulse generator and are responsible for the premature release of pulsatile gonadotropins.[30] Other CNS suprasellar or pineal tumors may cause CPP including optic gliomas, astrocytomas and epidendimomas.

Congenital and acquired malformations and conditians like empty sella syndrome, Arnold-Chiari malformation, subarachnoidal cyst, neurofibromatosis type 1, hydrocephalus, cranial irradiation, head trauma and meningitis or encephalitis may predispose to CPP. [8,31,32]

Clinical presentation of CPP

Children with CPP present with isosexual pubertal development at an early age.

In girls breast development and estrogenization of the vaginal mucosa precede the development of pubic and axillary hair. Onset of menstruation follows if untreated.

In boys testicular enlargement is followed by penile enlargement, development of pubic hair, increase muscle mass and deepening of the voice.

Penile or breast development may be signs of both central and peripheral onset of puberty; however ovarian follicle maturation/or menarche and testicular enlargement are usually result from central activation of HPG axis.

Boys and girls exhibit an increased growth velocity typical for the pubertal growth spurt.

Bone age is significantly advanced compared to the chronological age.

Headaches, seizures or other neurologic signs and symptoms have to raise suspicion for an underlying CNS lesion (tumor). Patients with hypothalamic hamartoma have early PP, usually before the 4th year, and sometimes even before the 2nd year of life. About 50% of the girls with hypothalamic hamartoma undergo menarche by the age of 4 year. [33] Gelastic seizures manifested with laughing spells are characteristic of hypothalamic hamartomas.[34]

Peripheral Precocious Puberty (PPP)

PPP, or gonadotropin independent precocious puberty, refers to the development of secondary sex characteristics without activation of HPG axis.[2]

Pubertal development may be virilizing or feminizing depending on the underlying disorder. Excess sex steroids may originate from the adrenal glands, gonads or exogenous sources. The differential diagnosis for PPP is broad: McCune-Albright syndrome (MAS), familial or sporadic male-limited PP (MLPP), gonadal tumors, congenital adrenal hyperplasia (CAH), adrenal

tumors, β-chorionic gonadotropin (hCG) – secreting tumors, hypothyroidism, ovarian cysts and exogenous exposure to sex-steroids/questions about contraceptive pills or transdermal estrogen or testosterone gells; environmental exposure to chemicals like phthalates or polychlorinated biphenyls or aromatic oils – lavender and tea tree oil have estrogenic activity.[13]

MAS and male-limited PP (MLPP) are unique category of gonadotropin independent PP in which genetic mutations cause autonomous production of sex steroids by the gonads in absence of pubertal gonadotropin stimulation.[2]

Mc Cune-Albright syndrome (MAS) is characterized by cafè au-lait skin lesions, precocious puberty and polyostotic fibrous displasia of bones.

Females are affected more often than males. The disease is considered non-classic if two of the three classical symptoms are present. PPP may start as early as 1 year of age.

Estradiol production from an autonomously functioning ovarian cyst can lead to rapid breast development and/or menstruation. Onset of menses may precede breast development. Pubertal hair is seen less frequently. Progression of pubertal signs may slow and regression of secondary sex characteristics is common.

PP in males occurs later, between 4 – 9 years and is characterized by testicular enlargement, androgenization of the external genitalia and less often – pubic hair.

Cafè au-lait macules are pigmented skin lesions well demarcated with irregular borders, occuring in more than 90% of the patients with MAS. They are usually present at birth and do not typically increase in size or number with age.

Polyostotic fibrous dysplasia occurs in above 60% of the patients and most often involves the long bones and the base of the skull. It causes pain, pathological fractures and deformity of the bones. Cranial fibrous dysplasia may cause facial asymmetry and compression of the optic or auditory nerves leading to visual or hearing imparement.[2,35]

Male-limited precocious puberty (also known as familial testotoxicosis) is an autosomal dominand disorder with greater than 90% penetrance. It is caused by an activating mutation of the LH receptor in the Leydig cells and results in an autonomous testosterone production in the absence of gonadotropin

stimulation.[36] The expression of the mutation is gender limited as females are asymtomatic carriers.[37]

DIAGNOSIS

Laboratoty/hormonal examinations

Once PP is established clinically, the next step is to determine whether the process is GnRH-dependend (CPP) or GnRH – independent (PPP).

The diagnosis is based on the assesment of gonadotropins, mainly LH, basal or/and after exogeneous GnRH or GnRH agonists stimulation.

The development of more sensitive third-generation assays for LH, which can detect levels as low as 0.1 IU/L or lower, makes a random LH examination the best screening test for central precocious puberty (CPP).

The immunochemiluminometric (ICMA) method for LH is found very specific and LH level of less than 0.1 IU/L is generally prepubertal; one study suggested an upper reference range limit for LH measured by an ICMA of <0.2 IU/L in both boys and girls, with no overlap between prepubertal and pubertal levels in boys and a 10% overlap in girls.[38]

A study from CP Houk et al. found that a basal LH level measured by 2 different ICMA assays was sufficient to document central precocious puberty in 90% of girls, with levels of more than 0.83 IU/L in all but one patient; 29 of 34 prepubertal girls had undetectable values (< 0.15 IU/L to < 0.2 IU/L).[39]

The ratio of basal or stimulated LH/FSH above 1.0 may be sufficient for the diagnosis of CPP without GnRH stimulation.[37]

A definitive diagnosis of central precocious puberty may be confirmed by measuring LH and FSH levels 30-60 minutes after stimulation with gonadotropin-releasing hormone (GnRH) at 100 mcg or with a GnRH analogue. Because native GnRH is no longer available, most centers are using the analogue leuprolide (aquous form) at a dose of 20 mcg/kg, up to a maximum of 500 mcg.

Basal levels of LH above 0.3 IU/L and stimulated levels of LH above 5 IU/L is diagnostic for CPP.[13,40] An increase in FSH levels much greater than the increase in LH levels suggests that the child is prepubertal. Elevation of serum testosterone in boys and estradiol in girls are also typical for CPP.[13]

The stages of puberty as indicated by serum testosterone levels are as follows:

Testosterone level less than 30 ng/dL is generally prepubertal; level of 30-100 ng/dL – early pubertal; level of 100-300 ng/dL – mid-to-late pubertal and more than 300 ng/dL – adult.

For girls**,** *estradiol* measurements are less reliable indicators of the stage of puberty. Many commercial assays are not sufficiently specific or sensitive enough to demonstrate an increase during early puberty. Levels that exceed 20 pg/mL usually indicate puberty, but some girls who are clearly pubertal may have levels of less than 20 pg/mL. In addition, estradiol levels may fluctuate from week to week. Girls who have ovarian tumors or cysts often have estradiol levels that exceed 100 pg/mL.[13]

PPP is characterized *by low (prepubertal) basal and/or stimulated levels of gonadotropins,* and at the same time – *pubertal levels of sex steroids.* For the differentiation of the cause for PPP the following examinations would be relevant:

Levels of *adrenal androgens* (eg, dehydroepiandrosterone [DHEA], dehydroepiandrosterone sulfate [DHEAS]) are usually elevated in boys and girls with premature pubarche. DHEA-S, the storage form of DHEA, is the preferred steroid to measure because its levels are much higher and vary much less during the day. In most children with premature pubarche, DHEA-S levels are 20-100 mcg/dL, whereas in rare patients with virilizing adrenal tumors, levels may exceed 500 mcg/dL.[13]

Examination of *17-OH serum progesterone* is needed if mild or nonclassic congenital adrenal hyperplasia is suspected. A recent study from Paris found that if a basal level is below 200 ng/dL, the diagnosis of nonclassic congenital adrenal hyperplasia can be excluded; however, if the random 17-OH progesterone level is elevated, a corticotropin (ie, Cortrosyn) – stimulation test provides the greatest diagnostic accuracy, with a post corticotropin 17-hydroxyprogesterone of greater than 1000 ng/dL being diagnostic.[41]

Urinary 17-ketosteroids in 24-hour urine collection: It is markedly elevated in patients with tumors of the adrenal glands.

Human chorionic gonadotropin (HCG) is elevated in HCG-secreting tumors.

Thyroid function test: High level of TSH and low level of free tyroxin in patients with sexual precocity secondary the severe primary hypothyroidism.

IMAGING STUDIES

Bone age

Radiography of the left hand and wrist used to determine bone age is a quick and helpful means to estimate the likelihood of precocious puberty and its speed of progression. If bone age is advanced by 2 years or more, puberty likely has been present for a year or more or is progressing more rapidly.

Head MRI

Once the hormonal studies indicate a disgnosis of central precocious puberty head imagings may be indicated (MRI).

For healthy girls aged 6-8 years with no signs or symptoms of CNS disease, the likelihood of finding a tumor or hamartoma is only about 2%; therefore, this test may be unnecessary depending on the clinical situation.

The younger the child with central precocious puberty, the greater the chance of finding CNS pathology (among children younger than 6 y).

For boys younger than 9 years, the incidence of CNS findings is much higher than in girls, and MRI should be part of the evaluation.

Pelvic ultrasonography

Pelvic ultrasonography is essential when precocious pseudopuberty is suspected in girls because an ovarian tumor or cyst may be detected.

Ultrasonography is not necessary for girls with a definite diagnosis of central precocious puberty. If performed, however, ultrasonography usually reveals bilaterally enlarged ovaries, often with multiple small follicular cysts, and an enlarged uterus with an endometrial stripe.

ultrasonography may detect Leydig cell tumors that are not palpable on testicular examination.

HISTOLOGIC FINDINGS

If central precocious puberty is caused by a tumor in the hypothalamic-pituitary area, the histology of the tumor can be important to the patient's prognosis.

Gliomas tend to grow more rapidly than astrocytomas, whereas hamartomas are benign. Treatment of precocious puberty associated with a hamartoma suppresses gonadotropin production by the pituitary without effect on the hamartoma itself.

GENETIC EXAMINATIONS

As mentioned earlier, patients with iCPP – either familial or sporadic have to be screened for mutations in MKRN3 as they are the most frequent genetic cause for iCPP.[25,27] It would also be relevant for the younger siblings of the proband of a possible MKRN3 mutation to be screened in order to be followed and treated properly on time.

Genetic testing can be used to confirm the diagnosis and provide genetic counseling for different types of CAH, including the most common 21-hydroxilase deficiency.

For the patients with McCune–Albright syndrome it is also possible to identify the mutation in the GNAS1 gene. But individuals with MAS may be mosaic for the GNAS1 mutation, analysis of peripheral blood leucocytes is often negative for the mutation.[2]

Boys suspected for familial male-limited precocious puberty (FMPP), a gain-of-function mutation of the LHCGR gene encoding the luteinizing hormone/choriongonadotropin receptor may confirm the diagnosis.[13]

TREATMENT

Central Precocious Puberty

Gonadotropin-releasing hormone agonists (GnRH agonists)

Treatment with GnRH agonists is generally indicated in cases of *idiopathic CPP* in girls younger than 6 years of age and in boys younger than 9 years of age. The decision whether to treat iCPP is more difficult in girls 6 – 8 years old. Most common indications for therapy include:

- bone age advancement greater than 2 years beyond the chronological age
- predicted adult height greater than 2 SDs below the target height or less than 150 cm
- rapid advancement of pubertal development
- psychological or behavioral concerns

Continuous administration of GnRH agonists provides negative feedback and results in decreased levels of LH and FSH 2-4 weeks after initiating treatment. In the past, the 1-month formulation of leuprolide, called Lupron-Depot, was the mainstay of therapy. In 2011, 3-month formulations of Lupron-Depot 11.25 mg and 30 mg, were approved for children with precocious puberty. A study comparing the 1-month 7.5 mg leuprolide with the 11.25-mg 3-month leuprolide found that both preparations resulted in prompt and effective suppression of puberty, but LH and FSH levels were slightly higher with the 3-month dosing, which has the advantage of being more convenient for the family.[42] Metaanalysis of pediatric patients with central precocious puberty treated with intramuscular triptorelin 11.25 mg 3 month prolonged-release showed its efficacy in suppressing LH peak (<3.0IU/L) and other gonadal hormones as well.[43]

Nafarelin (Synarel) is analogue of GnRH with 200 greater potency compared to the natural endogenous GnRH. It is administered intranasally by a nasal spray 200 mcg/spray twice daily. It is considered a second line agent if leuprotide is difficult to administer.

Histrelin (Supprelin LA) – is an implant injected subcutaneously once a year, which releases 50 – 65 mcg/day of the LHRH analogue.

Progestins

Progestins were mostly used before GnRH agonists were available. They provide feed-back suppression of pituitary gonadotropin secretion and lack significant androgenic or estrogenic activity. They are less expensive and are considered when leuprolide cost is a factor and when adult height prediction is close to the reference range or is not a major concern.[13]

Medroxyprogesterone (Depo-Provera) is adminisered once in 3 months and is effective in slowing breast growth and preventing or stopping menstruation, although breakthrough bleeding may occur. [13]

Combination of GnRHa and rhGH

Some authors indicate that in girls with idiopathic central precocious puberty, treatment with a combination of GnRH analogue and growth hormone leads to better height results than does therapy with GnRH analogue alone, with no severe adverse

effects.[46] A literature review by M Wang et al. found that the addition of recombinant human growth hormone to GnRH agonist therapy resulted in significant height increase, as well as increases in predicted adult height and height standard deviation for bone age, in children with central precocious puberty. Efficacy was greater in patients whose initial treatment began prior to age 10 years or whose therapy lasted more than 12 months.[13, 44,45]

When central precocious puberty is caused by a CNS tumor other than a hamartoma, a resection should be attempted to the extent possible without impinging on vital structures such as the optic nerves. Radiation therapy is often indicated if surgical resection is incomplete. Unfortunately, removal of the tumor rarely causes regression of precocious puberty.

Peripheral Precocious Puberty

Treatment of ***CAH*** with near-physiologic replacement dose of hydrocortisone is used to suppress adrenal androgen production.

Treatment of ***MAS*** is necessary if puberty is rapidly progressive or adult height can be severely compromised.

Drugs used are cyproterone acetate (CPA, androcur) - an antiandrogen with inherent progestine and antiestrogen activity, or medroxyprogesterone acetate (MPA) – a progesterone with antiestrogen effects. Both drugs decrease breast development and menstrual bleeding, but have little effect on adult height.

Aromatase inhibitors like Letrozole, Testolactone and Tamoxifen have also been used in MAS.[13]

Treatment of **testotoxicosis** is difficult but treatment options include CPA, MPA, ketoconazole, spironolactone, testolactone, anastrozole, letrozole and bicalutamid.

Surgical care

For patients with a tumor that is causing PP, surgical consultation is indicated.

Follow up of patients with precocious puberty treated with gonadotropin-releasing hormone (GnRH) agonists:

Follow up every 4-6 months to ensure that progression of puberty has been arrested. Favorable signs include normalization of accelerated growth, reduction (or at least no increase) in size of

breasts, and suppression of gonadotropin levels after a challenge of GnRH.

A suggested timeline for girls is to obtain a GnRH test about 4 months after starting the drug to confirm suppression and then no more often than yearly, as long as clinical indicators suggest that the drug is working as intended.

Some clinicians advocate dispensing with formal GnRH testing as long as growth has slowed and breasts have decreased in size.[13]

In boys, a decrease in the size of the testes and a fall in serum testosterone level to less than 20 ng/dL are good indications of efficacy.

Monitor bone age yearly to confirm that the rapid advancement seen in the untreated state has slowed, typically to a half year of bone age per year or less.[13]

Patients not treated with GnRH agonists

In many cases, the physician may elect to observe the child with central precocious puberty (CPP), either because the age is borderline (ie, 7-8 y) and the child and family are coping well or because the progression of puberty is not rapid and the bone age is only mildly advanced (ie, ≤ 1 y), so that predicted adult height falls well within the reference range. In these cases, follow-up at 6-month intervals is appropriate.

Testing and treatment may be initiated if the tempo of puberty begins to accelerate and predicted adult height deteriorates.

In line with this is the recent publication from M Faienza et al. (2017), who present the data for 94 girls with iCPP, who were at least 2 years after menarche and had already attained adult height at the time of the study. 56 were previously treated with depot triptorelin 3.4 ± 0.6 years and 38 were untreated. The study showed that GnRHa therapy is helpful in improvement of the final height in girls with iCPP and is not associated with either increased risk for obesity, nor with lipid profile abnormalities. However the authors found a correlation between the treatment with GnRHa and HOMA-IR and development of other endocrine abnormalities like PCOS. It was also found that GnRHa may promote hyperandrogenemia and hyperandrogenism after withdrawal of the therapy for CPP.[47]

References

1. Carel JC, Lahlou N, Roger M, Chaussain JL. Precocious puberty and statural growth. Human Reproduction Update2004; 10:135-147.
2. Bellin M, Sarafoglou K, Nathan B. Pediatric endocrinology and inborn errors of metabolism. 2009 Ed. K. Sarafoglou The McGraw-Hill Company Inc. Precocious puberty: 495 -512.
3. Wendt S, Shelso L, Wright K, Furman W. Neoplastic causes of abnormal puberty. Pediatr Blood Cancer. 2014;61(4):664-671.
4. Leka-Emiri S, Chrousos GP, Kanaka-Gantenbein C. The mystery of puberty initiation: genetics and epigenetics of idiopathic central precocious puberty. J Endorinol Invest. 2017; 40 (8): 789-802.
5. Parent AS, Teilmann G, Yuul A et al. The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends and changes after migration. Endocr Rev. 2003; 24:668-693.
6. Wu T, Mendola P, Buck GM. Ethnic differences in the presence of secondary sex characteristics and menarche among US girls: Third NHNES 1988-1994. Pedatrics 2002; 110:752-757.
7. Kaplowitz PB, Slora EJ, Wasserman RC, etal. Earlier onset of puberty in girls: relation to increase BMI and race. Pediatrics 2001;108:347-353.
8. Parent AS, Rasier G, Gerard A, et al. Early onset of puberty: tracking genetic and environmental factors. Horm Res. 2005; 64 Suppl.2:41-47.
9. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in girls. Arch Dis Child. 1969;44:291-303.
10. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child. 1970;45:13-23.
11. Kaplowitz PB, Oberfield SE. Reexamination of the age limit for defining when puberty is precocious in girls in US: Implications for evaluation and treatment. Drug and Therapeutics and Executive Committees of LWPES. Pediatrics 1999;104:3059-3067.
12. Kaplowitz PB, Clifford B. Evaluation and referral of children with signs of early puberty. Pediatrics. 2016;137(1):e20153732
13. Kaplowitz BP. Precocious puberty. 2017 https://emedicine.medscape.com/article/924002
14. Herman-Giddens ME, Slora EJ, Wasserman RC, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. Pediatrics. 1997;99(4):505-12.
15. Biro FM, Galvez MP, Greenspan LC, et al. Pubertal assessment method and baseline characteristics in a mixed longitudinal study of girls. Pediatrics. 2010;126(3).
16. Biro FM, Greenspan LC and Galves MO. Puberty in girls of the 21st century. J Pediatr Adolesc Gynecol. 2012; 25(5):289-294.
17. Rosenfield RL, Lipton RB, Drum ML. Thelarche, pubarche, and menarche attainment in children with normal and elevated body mass index. Pediatrics. 2009;123(1):84–88
18. Palmert MR, Hayden DL, Mansfield MJ et al. The longitudinal study of adrenal maturation during gonadal suppression: evidence that adrenarche is a gradual process. J Clin Endocrinol Metab. 2001;86:4536-4542.
19. Ibanez L, Dimartino-Nardi, Potau N, et al. Premature adrenarche – normal variant or forerunner of adult disease? Endocr Rev. 2000;21:671-696.

20. Österbrand M., Fors H., Allvin K, Norjavaara E. 17β-Estradiol and Gonadotropin levels for the diagnosis of the benigh form of breast development in girls aged up to 4 years in real-life practice. Horm Res Paediatr 2017;87:315-323.
21. Lee PA. Central precocious puberty. An overview of diagnosis, treatment and outcome. Endocrinol Metab Clin North Am. 1999;28:901-918
22. Partsch CJ, Heger S, Sippell WC. Management and outcome of central precocious puberty. Clin Endocrinol /Oxf/. 2002; 56: 129-148.
23. Seminara SB, Messager S, Chatzidaki EE, et al. The GPR54 gene as aregulator of puberty. NEJM 2003;349:1614-1627.
24. Kaiser UB, Kuohung W. KiSS-1 and GPR54 as new players in gonadotropin regulation and puberty. .Endocrine. 2005 Apr; 26(3):277-84.
25. Teles MG, Bianco SD, Brito VN, et al. AGPR54-activating mutation in a patient with central precocious puberty. NEJM 2008;358:709-715.
26. Silveira LG, Noel SD, Silveira-Neto AP, et al. Mutations of the KISS1 gene in disorders of puberty. J Clin Endocrinol Metab 2010; 95:2276-2280.
27. Simsek E, Demira M, Ceylaner S, Kirel B. Two frameshift mutations in MKRN3 in Turkish patients with familial central precocious puberty. Horm Res Paediatr 2017;87:405-411.
28. Macedo DB, Abreu AP, Reis AC et al. Central precocious puberty that appears to be sporadic caused by paternally inherited mutations in the imprinted gene makorin ring finger 3. J Clin Endocrinol Metab 2014;99:E1097-E1103.
29. Dimitrova-Mladenova M, Stefanova E, Glushkova M et al. Males with paternally inherited MKRN3 mutation may be asymptomatic. J Pediatrics 2016;179:263-265.
30. Judge DM, Kulin HE, Page R, et al. Hypothalamic hamartoma: a source of LH –releasing factor in precocious piberty. NEJM 1977;296:7-10.
31. Lee PA. Central precocious puberty. An overview of diagnosis, treatment, and outcome. Endocrinol Metab Clin North Am. 1999;28:901-918.
32. Rivarola MA, Mendilaharzu H, et al. Precocious puberty in children with tumors of the suprasellarand pineal areas: organic central precocious puberty. Acta Pediatri. 2001;90: 751-756.
33. Cassio A, Cacciari E, Zucchini S, et al. Central precocious puberty: clinical and imaging aspects. J Pediatr Endocrinol Metab. 2000;13 Suppl 1:703-708.
34. Jung H, Neumaier PE, Hauffa BP, et al. Association of morphological characteristics with precocious puberty and/or gelastic seizures in hypothalamic hamartoma. J Clin Endocrinol Metab. 2003;88:4590-4595.
35. Lee PA, Van Drop C, Migeon CJ. McCune-Albright syndrome. Long-term follow-up. JAMA 1986;256:2980-2984.
36. Shenker A, Laue L, Kosugi S, et al. A constitutively activating mutation of the LH receptor in familial male precocious puberty. Nature 1993;365:652-654.
37. Egli CA, Rosental SM, Grumbach MM, et al. J Pediatr. 1985;106:33-40.
38. Resende EA, Lara BH, Reis JD, Ferreira BP, Pereira GA, Borges MF. of basal and gonadotropin-releasing hormone-stimulated gonadotropins by immunochemiluminometric and immunofluorometric assays in normal children. *J Clin Endocrinol Metab*. 2007;92(4):1424-1429.

39. Houk CP, Kunselman AR, Lee PA. Adequacy of a single unstimulated luteinizing hormone level to diagnose central precocious puberty in girls. Pediatrics. *2009* Jun. 123(6):e1059-1063.
40. Sathasivam A, Garibaldi L, Shapiro S, Godbold J, Rapaport R. Leuprolide Stimulation Testing for the Evaluation of Early Female Sexual Maturation. Clin Endocrinol (Oxf). 2010; 73(3):375-381.
41. Armengaud JB, Charkaluk ML, Trivin C, Tardy V, Bréart G, Brauner R. Precocious pubarche: distinguishing late-onset congenital adrenal hyperplasia from premature adrenarche. *J Clin Endocrinol Metab*. 2009; 94(8):2835-2840
42. Fuld K, Chi C, Neely EK. A randomized trial of 1- and 3-month depot leuprotide doses in the treatment of central precocious puberty. J Pediatr 2011;159(6):982-987.
43. Durand A, Tauber M, Patel B, Dutailly P. Metaanalysis of paediatric patients with central precocious puberty treated with intramuscular triptorelin 11.25 mg 3 month prolonged-release formulation. Horm Res Paediatr 2017;87:224-232.
44. Sinha SK. Precocious pseudopuberty treatment and management. 2017: https://emedicine.medscape.com/article/923876-treatment
45. Wang M, Zhang Y, Lan D, Hill JW. The efficacy of GnRHa alone or in combination with rhGH for the treatment of central precocious puberty. Sci Rep 2016;6:24259.
46. Liu S, Liu Q, Cheng X et al. Effects and safety of combination therapy with GnRH analogue and growth hormone in girls with idiopathic central precocious puberty: a meta-analysis. J Endocrinol Invest. 2016; 39(10): 1167 – 1178.
47. Faienza MF, Brunetti G,Acquafredda A, et al. Metabolic outcomes, bone health, and risk of PCOS in girls with iCPP treated with GnRH analogues. Horm Res Paediatr 2017;87:162-176.

Maia Konstantinova, MD, PhD
Professor, Leader of the Diabetic department in the University Pediatric Hospital – Sofia (Bulgaria)
President of the Bulgarian National Society of Pediatric Endocrinology
Sofia, Bulgaria, 1606, 11, „Academic Ivan Geshov"
E-mail: maiakonstantinova@gmail.com

February 2018

CRANIOPHARYNGIOMA – CLINICAL, THERAPEUTIC AND IMAGING OUTCOME DATA IN A MIXED COHORT OF ADULT AND PEDIATRICS CASES

Anda Dumitrașcu, Cristina Căpățînă, Mădălina Vintilă, Iuliana Gherlan, Andra Caragheorgheopol, Camelia Procopiuc, Vasilie Ciubotaru, Cătălina Poiană

Introduction

Craniopharyngiomas (CRF) are rare tumors, with an estimated incidence of less than 0.5/100000 in the general population[1] but represent around 10% of intracranian tumors in children.[2]

These tumors originate from Rathke's pouch remnants and despite their benign histological character, frequently have an evolution marked by complications and suboptimal therapeutic outcome. They are usually large and frequently have areas of fibrosis and calcifications; all these characteristics make total surgical removal a challenge. The recurrence rate is very high in cases incompletely resected but is also present in tumors apparently cured by initial surgery. Adjuvant radiotherapy is useful to decrease the recurrence or remnant growth rate but there are no precise guidelines regarding the timing and specific type of radiotherapy.[3]

Deficient function of the anterior pituitary is very frequent at diagnosis as well as central diabetes insipidus. Many cases present with growth arrest, delayed puberty, visual defect or intracranial hypertension-all caused by the compression exerted by the large tumor mass. [3]

Craniopharyngiomas (CPH) account for 2,1-4-6% off all brain tumors and they are more frequently found in children (17-21%, and 7% of all cases of brain tumors in children), 4% of all supratentorial tumors and up to 56% of all tumours of the chiasmal-sellar region. The distribution of CPH according to age is characterized by two peaks between 5 and 10 years and, the smaller group, on the sixth decade of life. (Carmel et al. 1982; Hoffman et al. 1992; Van Effenterre 2002).

The origin of CPH is the cells of the embryonic epithelium located along the pharyngeal-pituitary passage, from the bottom of the third ventricle up to the walls of pharynx. There are two types: distinguished intrasuprasellar "stalk" (infundibular) intraventricular and giant (intra-extraventricular).

CPH are a biologically heterogeneous group of tumors are represented by two main histological variant, adamantinomatous and papillomatous types. Which are not only pathologically, but also clinical different.

Neuroimaging findings depend on the type and anatomic variant of a tumor. X-ray craniography reveals typical signs of CPH such as changes in shape, size of the sella turcica, and calcifications in the chiasmal-sellar region. Calcifications are found in 75-95% of cases. The shape and size of calcifications vary, from small, crumb-like and poorly distintinguishable to large, lump-like and vivid coral-like ones. Laminar calcifications are frequent, which are usually situated in the tumor capsule.

Intrasuprasellar CPH cause change of the sella turcica: increase the size, deepening of the bottom, widening of the entry and deformity (thinning, lifting, shortening) of the anterior clinoid processes. Calcifications are usually found within the cavity of sella and about it.

Intraventricular CPH do not usually cause severe changes of the sella turcica: its size remains almost intact. However, in the majority of cases the dorsum sella turcica shortens. Beeing situated close to the CSF circulation pathways, CPH cause changes in the ventricular system and increase of intracranial pressure, which is observed on X-ray craniogram by way of "fingerprints" on the cranial vault bones, widening of cranial suture and change in the sella turcica elements. Calcifications of CPH may be found in the third and lateral ventricules. Calcifications are usually located in the chiasmal and adiacent region.

The navicular shape of the sella turcica, which is sometimes combined with shortening of its dorsum, is typical for stalk CPH cause hydrocephalus and rise of intracranial pressure, which can be seen on X-ray craniograms.

CT and MRI identify the precise size of a tumour, the ratio between the cystic and the solid part of a tumor, and their size and location and the condition of the ventricular system (the extent of concomitant hydrocephalus and in most cases, the level of occlusion of the CSF pathway) and spatial relation of the tumour to the third ventricle cavity; the extent of expansion beyoud the ventricular system is seen.

On coronal CT scans with or without reformation, the upward displacement of the third ventricle is detected clearly. In intrasuprasellar CPH, the size of the sella turcica is usually large. The intrasellar part of the tumors usually nodular with calcifications. Growing upwards, the tumors fills the region of chiasmal cisterns (partially or completely), with upward displacement of the bottom of the third ventricle. The suprasellar part of the tumor is usually cystic, but may be solid. Cysts may be located on the base of the anterior cranial fossa, in the paraventricular region (giant CPH), and be identified in the depth of the nodular part.

On CT a tumor is well delineated from the adjacent brain tissue. The density of certain components of CPH is different. The nodular part is almost isodensive to brain tissue, calcifications are found on CT in 95% of cases (in the tumour, stroma, capsule or walls of the cyst).

If cysts are situated in the cavity of the third ventricle, than they usually completely fill itsanterior portion. Sometimes cystic tumors are represented by a system of cysts, which is hardly differentiated and may be distinguished only on axial images. It should be emphasized again that all of three anatomic variants of CPH may be giant. Many calcifications are typical for adamantinomatous CPH in the solid area as well as in the walls of the cysts. In papillomatous CPH calcifications are rarely found.

On T1-weighted imaging, the nodular part of the tumor is isointensive, the signal of cysts may be hypo- or hyperintensive(this depends on the protein content, cholesterol and blood decay products within).

The cystic CPH located only in the sella turcica cavity (hypointensive on T1-weighted and hyperintensive on T2-weighted

images) should be differentiated from the mucocele of the sphenoidal sinus, the signal of which may be similar to the CPH.

On cerebral angiography, the vasculat net of a tumor is not usually detected, only displacement of vessels may be seen – the arteries of the circle of Willis and the anterior and middle cerebral arteries, which depends on tumor location. At present, direct angiography is almost never performed as a method of identificating the location of vessels in cases of CPH. The information presented by CT and MRI is sufficient for presurgical planning.

In the early postsurgical period, remnants of tumor, blood clots in the tumor bed, or CSF in the subdural space may be found on CT. In the late postsurgical period, CT may detect the absence or the presence of a tumor relaps and progression or reduction of hydrocephalus.

Control MRI early in the first days after surgery does not usually reveal any additional changes compared with CT. Later after surgery, MRI reveals presence or absence of cysts (the signal of cysts may differ, to compare with preoperative findings) and the solid section of tumor, changes of the ventricular system, residual accumulation of the CSF, or blood in the subdural space.

Objective

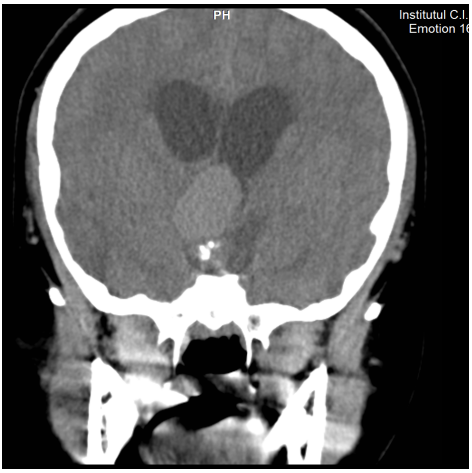
To study the clinical presentation of craniopharyngioma as well the outcome of management of craniopharyngioma in children in a cohort of pediatric patients with craniopharyngioma (CRF).

Methods

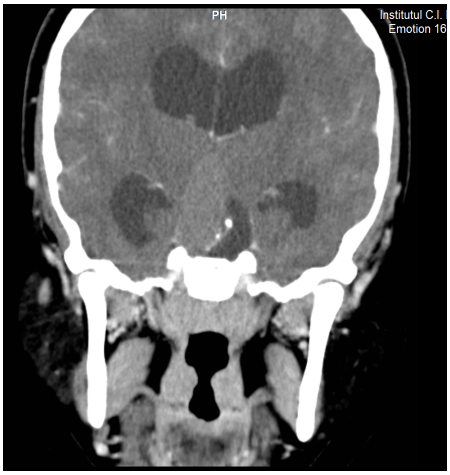
We retrospectively analysed 35 CRF cases (histologically confirmed) evaluated and followed up in two departments of the "C.I.Parhon" National Institute of Endocrinology in Bucharest.

We studied the presenting symptoms, complications at diagnosis, type of treatment, surgical complications, rate of tumor resection, endocrinological and visual outcome.

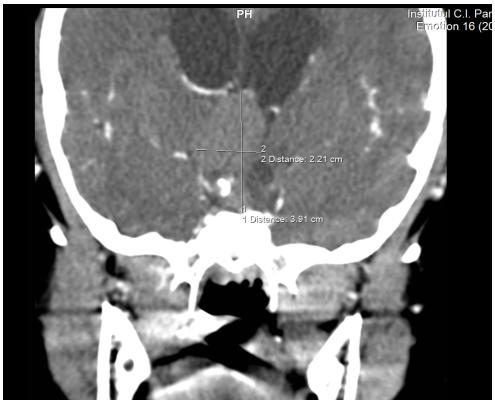
We assessed each case at 6-12 weeks postoperatively and yearly thereafter (or biannually in cases with more aggressive tumors) by clinical examination, assessment of visual function, evaluation of the pituitary function [4], imaging (MRI or CT scanning of the sellar region).



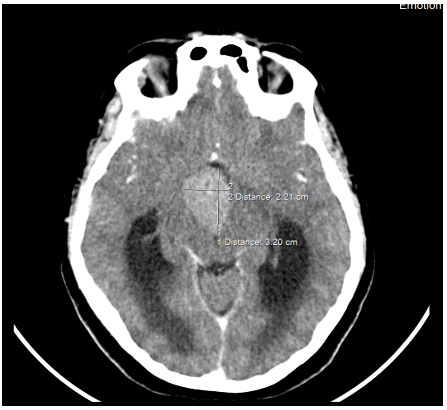
Craniopharingioma - computed tomography – coronal acquisition



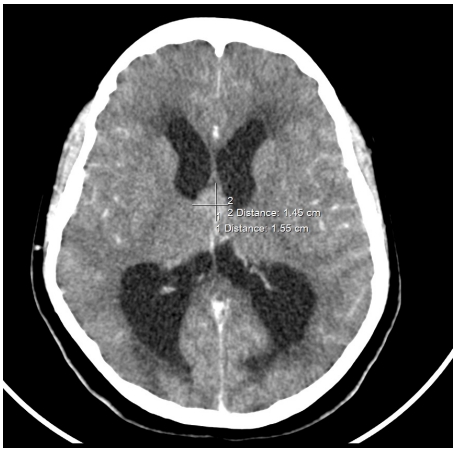
Craniopharingioma - computed tomography – coronal acquisition



Craniopharingioma - computed tomography – coronal acquisition



Craniopharingioma - computed tomography – axial acquisition



Craniopharingioma - computed tomography – axial acquisition

Statistical analysis. The data analyses were performed with SPSS for Windows version 19 software. Descriptive statistics are shown as mean ± standard deviation or median (minimum-maximum) for numerical variables.

Results

We retrospectively analysed 35 CRF cases in children (18 females, 17 males aged between 4 and 18 years-old, mean age 11.72). The mean and median follow-up duration were 6.08 and 4.32 years, respectively.

The most frequent symptoms leading to diagnosis were headache (91% of cases), nausea and vomiting (even in cases with normal adrenal function-48% of cases), neurological symptoms (eg convulsions, problems with memory, concentration, attention, sleep rhythm disturbances, confusion): 44%, visual problems (42% of cases, especially visual field defect) (*see figure 7.1*).

The tumor size was in all cases larger than 1 cm (range 1-4.8 cm, mean 2,83 cm, median 2,55 cm). Massive suprasellar extension reaching the third ventricle was frequently present.

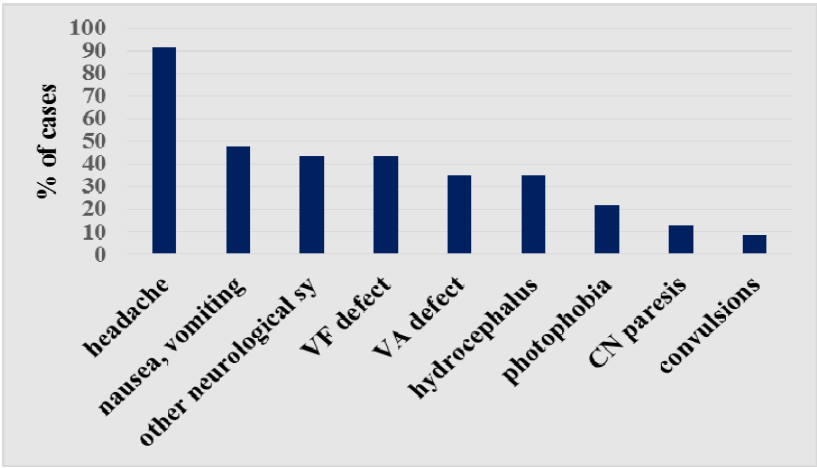


Fig. 7.1. - Clinical manifestations at diagnosis

The pituitary function was frequently already affected at diagnosis. GH and gonadotropin deficiency as well as central diabetes insipidus were most frequently encountered (in 90%, 84% and 30% of cases, respectively).

Visual acuity (VA) was impaired in 43% of cases (6% complete blindness) while visual field (VF) defect was present in 51% of cases (*see figure 7.2*).

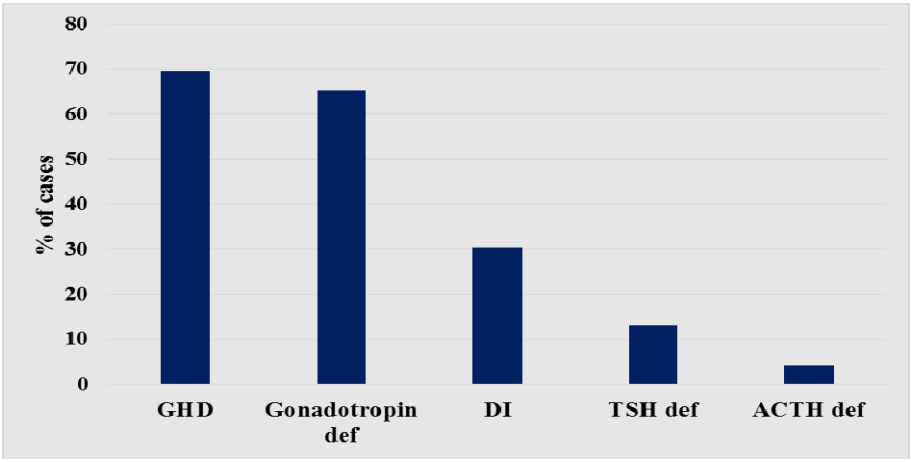


Fig. 7.2. - Pituitary function at diagnosis

Initial treatment was neurosurgical in all cases, especially by transfrontal route (76% of cases). Ventriculoperitoneal shunt was inserted in 2 cases preoperatively. Total tumor resection was

obtained in only 31,25% of cases at the first surgery, the rest had incomplete resection (various degrees).

During follow-up 7% of the cases with gross tumor resection recurred while in the cases with incomplete resection in 55% of cases the remnant was stable (in the other cases remnant growth was noted).

During follow-up 18 cases had only one intervention, 10 cases suffered 2 surgical interventions. In 2 cases multiple surgeries were necessary. Adjuvant radiotherapy was used in 5 cases. After complex treatments at the end of the time interval studied 40% of cases were considered cured.

The main postoperative complication was central diabetes insipidus (permanent in 24 cases, transient in 4). Anterior pituitary function remained impaired in a significant number of cases: GH deficiency in 74% of cases, gonadotropin deficiency in 60%, ACTH deficiency in 82%, TSH deficiency in 86% of cases (*see figure 7.3*).

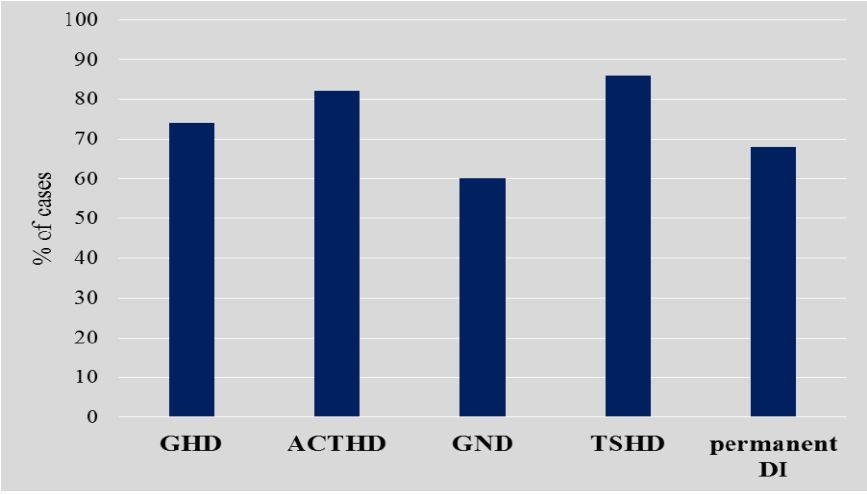


Fig. 7.3. - The anterior pituitary function after surgery

After surgery in most cases the visual deficit (both VA and VF) remained stable or even worsened (*see figure 7.4*).

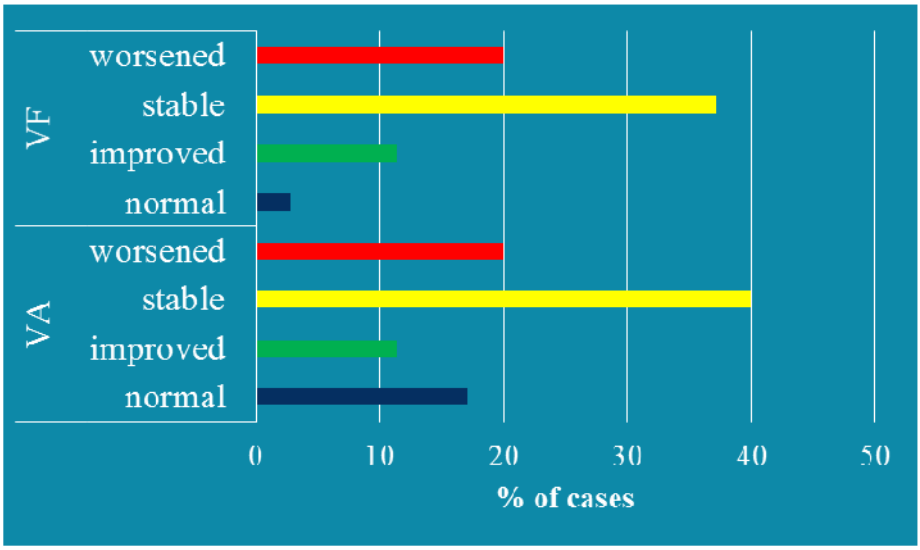


Fig. 7.4. - The evolution of the visual function after surgery

The most striking complication after treatment was weight gain (15 cases) and dyslipidemia (20 children)

Discussion

CRF are usually large tumors at the time of diagnosis and produce symptoms because of compression on the neighbouring structures.[5] The most frequent onset symptoms are headache, visual problems, endocrine dysfunction (especially GH and gonadotropin deficiency), nausea and vomiting.

The frequency of anterior pituitary deficiency at diagnosis was very high in our cohort, as in the studies previously published. In a large analysis of published data GH deficiency was present in 35–95% of the cases, gonadotropin deficiency in 38–82%, ACTH deficiency in 21–62%, TSH deficiency in 21–42%.[4]

Neurosurgical intervention is the first recommended treatment but the large tumor dimensions and adherent structure make total resection a challenge for the surgeon.

Gross tumor resection rate is extremely heterogeneous varying from 17 to 89%.[6, 7] Cases with subtotal resection (STR), are usually managed by adjuvant postoperative radiotherapy[6], an approach that reduces the recurrence rate. [6]

In our cohort the use of radiotherapy was lower than in other published series despite its proved beneficial effect. The most

plausible explanation is the large tumor remnant in cases with incomplete surgical resection.

The visual results after surgery were poor compared to other reported results. For instance in a large series 85.7% experienced visual improvement.[8] The pituitary function also worsened after surgery in our cohort, similar to other data reported. [9]

Obesity caused by hypothalamic damage is a major problem in patients with CRF, especially in larger tumors. Further studies are needed to improve our understanding of the pathophysiology and to design efficient intervention measures.

Conclusions

Craniopharyngiomas are benign intracranian tumors associated with significant morbidity. Hypopituitarism is frequent at diagnosis and, in contrast to anterior pituitary tumors, improvement of the pituitary function after surgery is absent or uncommon.

References

1. Olsson DS, Andersson E, Bryngelsson IL, Nilsson AG, Johannsson G. Excess mortality and morbidity in patients with craniopharyngioma, especially in patients with childhood onset: a population-based study in Sweden. J Clin Endocrinol Metab. 2015;100:467-74.
2. Bunin GR, Surawicz TS, Witman PA, Preston-Martin S, Davis F, Bruner JM. The descriptive epidemiology of craniopharyngioma. Neurosurg Focus. 1997;3:e1.
3. Karavitaki N, Cudlip S, Adams CB, Wass JA. Craniopharyngiomas. Endocr Rev. 2006;27:371-97.
4. Karavitaki N, Brufani C, Warner JT, Adams CB, Richards P, Ansorge O, et al. Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. Clin Endocrinol (Oxf). 2005;62:397-409.
5. Van Effenterre R, Boch AL. [Craniopharyngiomas]. Ann Endocrinol (Paris). 2007;68:412-21.
6. Varlotto J CD, Clemens Grassberger, Matthew Tangel, Heath Mackley, Matt Pavelic, Charles Specht, Steven Sogge, Dan Nguyen, Michael Glantz, Cheng Saw, Urvashi Upadhyay, Richard Moser, Shakeeb Yunus, Paul Rava, Thomas Fitzgerald, Jonathan Glanzman, Jonas Sheehan Multi-modality management of craniopharyngioma: a review of various treatments and their outcomes. Neuro-oncology practice. 2015;3:173-87.
7. Elwatidy SM, Jamjoom ZA, Jamjoom AB, Yakoub AO. Craniopharyngioma. Analysis of factors that affect the outcome. Saudi Med J. 2002;23:34-8.
8. Campbell PG, McGettigan B, Luginbuhl A, Yadla S, Rosen M, Evans JJ. Endocrinological and ophthalmological consequences of an initial

endonasal endoscopic approach for resection of craniopharyngiomas. Neurosurg Focus. 2010;28:E8.
9. Lopez-Serna R, Gomez-Amador JL, Barges-Coll J, Nathal-Vera E, Revuelta-Gutierrez R, Alonso-Vanegas M, et al. Treatment of craniopharyngioma in adults: systematic analysis of a 25-year experience. Arch Med Res. 2012;43:347-55.

Anda Dumitrașcu, MD, PhD
Assistant Professor, Department of Imagery & Radiology, C.I. Parhon National Institute of Endocrinology, Bucharest, Romania.
Bd. Aviatorilor 34-36, 011863 Bucharest, Romania
E-mail: anda.dumitrascu@gmail.com

February 2018

Tiparul executat la

IMPRIMERIA MIRTON
RO-Timişoara, str. Samuil Micu nr. 7
Tel.: 0256-225684, 272926; Fax: 0256-208924;
e-mail: mirton@mirton.ro; www.mirton.ro

ISBN 978-973-52-1799-0