# PEDIATRIC ENDOCRINOLOGY AND DIABETES

## 2023 UPDATE

Editors:

Iulian P. VELEA
Corina PAUL
Stuart J. BRINK

EDITURA MIRTON

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# PEDIATRIC ENDOCRINOLOGY AND DIABETES 2023 UPDATE

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2023

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# Preface

Respecting the goal of the "ENDOPED" society of involvement in the professional training of doctors who are in contact with small patients, we offer all participants of the 10th National Congress of Diabetes, Nutrition and Pediatric Endocrinology a new volume "Pediatric Endocrinology and Diabetes - Update 2023".

As in previous years, the materials contained in this year's volume, we hope, will arouse interest, sensitize the reader to the diversity and difficulty of endocrinology and pediatric diabetes problems that they must have faced or may face in current practice, becoming a provider more and more competent in medical services even if he is not specialized in endocrinology and pediatric diabetes.

With friendship,

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

# Contents

# NOONAN SYNDROME AND ENDOCRINE ISSUES

**Stuart J. Brink**

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Noonan Syndrome is a clinically heterogeneous condition affecting between 1:1000-1:2500 live births[1] and was originally described by Flavell "incorrectly" in 1943[2] as "male Turner's Syndrome."

Jacqueline Noonan, a pediatric cardiologist, first in 1963[3] with Ehmke and then in a more expanded fashion in 1968[4] described the classical male and female patients from her cardiac clinic and since shortly thereafter, her name has been associated with the syndrome.

Generally, but not exclusively an autosomal dominant disorder occurring in both males and females and with some striking similarities to clinical characteristics of females with Turner Syndrome: short stature, congenital heart disease, early feeding difficulties, characteristic facies including web neck as well as some nonspecific learning issues. Of importance to general physicians and pediatricians as well as pediatric endocrinologists is the rarity of early clinical identification of Noonan Syndrome, much like Turner Syndrome, despite what appear to be rather typical features but only recognized in hindsight. Short stature is present in approximately 80% of Noonan Syndrome patients[5,6,7] with congenital heart defects that usually predominantly affect the right rather than the left side of the heart (*see Table*) in approximately 60-70% of Noonan Syndrome patients[1], cryptorchidism in about 50-60% of the males, nuchal webbing with a low-set ears, broad forehead, low posterior hairline and pectus excavatum or carinatum.

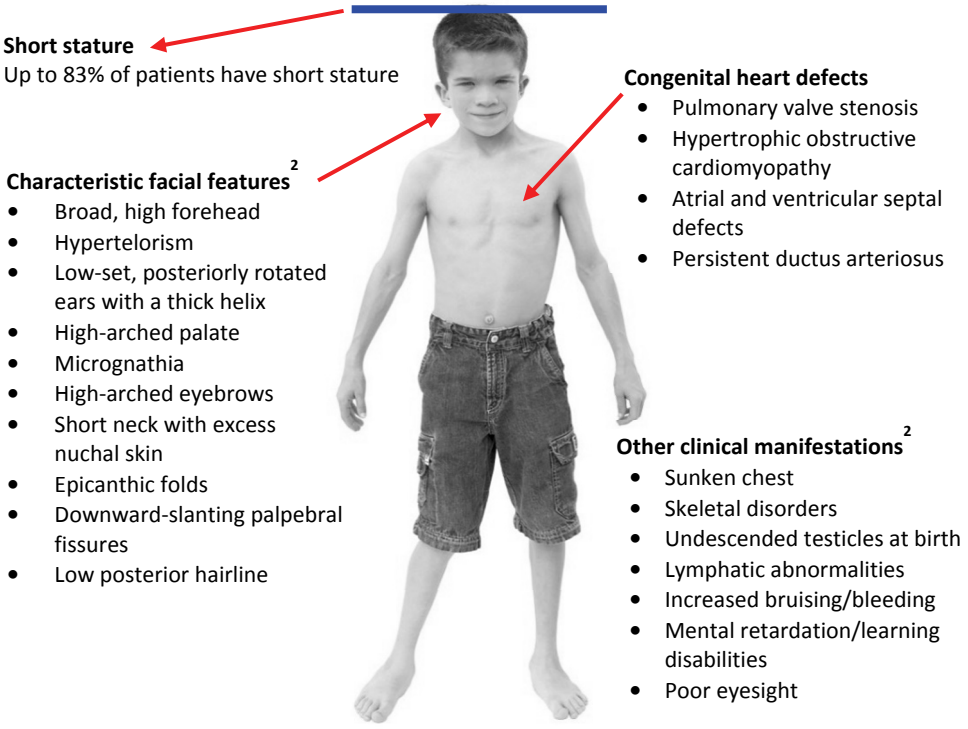



*Figure 1. - Noonan Syndrome. Clinical Features*

A subset of Noonan Syndrome patients also have bleeding tendencies especially problematic after tooth extraction or post-partum. Easy bruising associated with low platelet counts as well as blood clotting disorders can be present. These include Von Willebrand disease, prolonged activated partial thomboplastin time, partial deficiency of Factor VIII, XI and XII as well as combined coagulation deficiencies.[8] Characteristic clinical features are listed in *figure 1* but as with most genetic syndromes not all characteristics are present in every patient. Of importance to emphasize is the rather characteristic facial features that often provide the first clues to consideration of the diagnosis in a short child particularly one with the listed cardiac conditions in which the cardiac status does not correlate with such poor height parameters.

Four representative patient pictures are shown in *Figure 2*.

*Figure 2: Infant, two school-age girls and pre-adolescent*

**Noonan Syndrome Cardiac Problems**

Two thirds of Noonan Syndrome patients have heart defects often associated with heart murmurs on clinical examination.

When there is non-familial short stature with some of these other nonspecific physical and history findings, consideration for the diagnosis occur and it is not uncommon for cardiologists to make referral for available genetic testing as well as pediatric endocrinology consultation when such referrals could have been recognized many years earlier. Pediatric cardiology consultation may be very important with ultrasonography and more specialized testing helpful in making an exact diagnosis and informing treatment decisions.

- About 50% have pulmonary valvular stenosis. Typical pulmonary stenosis heart murmurs are often present.
- Atrial septal defects (ASDs) occur in about 10% of Noonan Syndrome patients but some also have ventral septal defects (VSDs) and less commonly - but associated with the RAF1 and SOS1 genetic mutations - is hypertrophic cardiomyopathy.
- Persistent patent ductus arteriosus (PDA) also can be associated with Noonan Syndrome.
- The common aortic (left-sided) lesions of Turner Syndrome are not so prevalent in Noonan Syndrome thus one of the distinguishing features between the two conditions involves evaluation of the cardiovascular system.

**Newborn and infant recognizable features and clinical conditions**

A comprehensive Noonan Syndrome "scoring system" has been proposed and may be helpful when considering the diagnosis.[9]

Typical facial features of Noonan Syndrome include hypertelorism in up to 95% as well as ptosis of one or both eyelids,

epicanthal folds and sometimes proptosis. Strabismus and nystagmus also occur. The nose can be somewhat bulbous and upturned. Ears are low set in over 90% with backward rotation and a thick helix. Later, chronic otitis media can be a problem. A deeply grooved philtrum may be present also with high arched palate and micrognathia all of which can be associated with articulation difficulties later in childhood. Webbed neck as well as extremity edema may be present in the nursery or the early infant period and may persist. High, broad forehead and low posterior hairline at the nape of the neck may also be present.

Neonatal cryptorchidism and micropenis also occur and may persist with delayed puberty as the adolescent years of those boys. Girls also often present with delayed puberty.

In later infancy and preschool years, short stature may become more evident sometimes, but not always, associated with hypotonia and developmental delay especially speech and language delay should be explored. Failure to thrive with poor feeding pattern, nonspecific digestive problems as well as swallowing abnormalities and regurgitation/vomiting may occur necessitating gastrointestinal specialty consultation. As the child grows, plotting on standard growth charts will likely document short stature as well as slowed annualized height velocity usually with weight and height proportionately deviating from age and sex matched normative curves.[10] Both pectus carinatum as well as pectus excavatum can occur. Cubitus valgus with abnormal turning-in at the elbow can occur and edema of the back of the hands and tops of the feet sometimes can occur not only in the nursery but also persist as lymphedema. As with Turner Syndrome, hyperkeratosis and keloid formation can occur as can increased pigmented nevi.

**Noonan Syndrome genetic mutations: PTPN11, KRAS, RAF1, SOS1**

Four different genetic mutations so far have been identified that, when taken together, identify approximately 80% of Noonan Syndrome patients when studied in several reports. Nevertheless, Noonan Syndrome features are similar enough to allow clinical diagnosis if suspicion is raised. Genetic testing is not mandatory but may be confirmatory if known abnormalities occur. Differential diagnosis should include fetal alcohol syndrome, neurofibromatosis, Leopard syndrome, cardiofaciocutaneous syndrome and, of course, females who may have Turner Syndrome.

The most common genetic mutation abnormality is called PTPN11. This protein tyrosine phosphatase (PTP) mutation occurs on the long arm of chromosome (12q24).[11,12] The PTPN11 is thought to explain about 50% of the patients with Noonan Syndrome and especially those with pulmonary valve stenosis, face dysmorphology and short stature with the PTPN11 mutations involved with growth hormone postreceptor signaling processes as well as cardiac developmental processes especially those involving the pulmonary valve and the cardiac septa.[13]

KRAS (Kirsten Rat sarcoma) mutations are thought to explain about 3-5% of Noonan Syndrome phenotypes with somewhat more extensive phenotypes compared to the PTPN11 subset.[14]

RAF1 (v-raf-1 murine leukemia viral oncogene homolog 1) mutations [15] add another 3-17% prevalence in some reported series especially focusing on hypertrophic cardiomyopathy subsets of Noonan Syndrome patients.

SOS1 (Son of Sevenless 1) mutations explain another 17% of the Noonan Syndrome cohort with less common growth disorders but more common facial dysmorphology and cardiac anomalies prevalent.

At present about 20% of patients with clinical features of Noonan Syndrome do not have any of these four types of genetic mutations and still fit the clinical characteristics sufficiently to warrant at least a tentative diagnosis on clinical grounds. This is particularly pertinent when seeking explanations for cryptorchidism and delayed puberty as well as persistent and otherwise unexplained short stature when associated with some of the other clinical features (ie. learning problems, ptosis, neck webbing, posterior hairline, typical facies, poor eyesight, low set ears). *Table 1* summarizes the current genetic mutation associations of Noonan Syndrome. Noonan Syndrome can be autosomal dominant or autosomal recessive according to several of the studies cited but with variable expression of clinical features.[16]

A high proportion of cases, however, seem to represent new, sporadic mutations in comparison to another subset of Noonan Syndrome patients where a clear apparent transmission (~20%) from parent to several children occurs.

*Table 1 – Genetic mutations and etiology of Noonan syndrome*

| Gene | Prevalence of Mutation in Noonan Syndrome | Effect of Genetic Change |
|---|---|---|
| **PTPN11** Mutation along the signaling pathway can lead to Noonan syndrome (Protein tyrosine phosphatase nonreceptor type 11) | 50% | • Pulmonary valve stenosis<br>• Short stature<br>• Face dysmorphology |
| **KRAS** | <5% | • Mutations caused more severe phenotype |
| **SOS1** | 17%* | • Typical face dysmorphology and cardiac anomalies observed in Noonan syndrome<br>• Less frequent growth disorders |
| **RAF1** | 3%-17% | • Hypertrophic cardiomyopathy |

**Noonan Syndrome, Growth Abnormalities and Growth Hormone Treatment**

Birth weight and length are typically normal but subsequent growth retardation affects infant, child and adolescent height but less commonly weight deficiency with significant short stature in untreated adult men averaging approximately 162.5 cm (63.9 inches) and 152.7 cm (60.1 inches) in untreated adult women.[7] Clinical growth charts for male and female infants as well as children and adolescents with Noonan Syndrome are now available (courtesy of Dr Susan Rose and NovoNordisk) which also provide comparisons with non-Noonan Syndrome children and adolescents of the same sex and ages. Typical adult heights in Noonan Syndrome are approximately 2 standard deviations below the normative data for the general population so that about 50% of untreated Noonan Syndrome patients will be significantly short as adults. A large multicentered study in France included 420 untreated Noonan Syndrome patients and confirmed remaining at about that same distribution but with some exceptions remaining unexplained with current medical and genetic testing. (*Figure 3* )[17]

*Figure 3: French Noonan Syndrome untreated birth, childhood, adolescent and adult height with wide variability but average approximately -2 standard deviations from norms without treatment.*

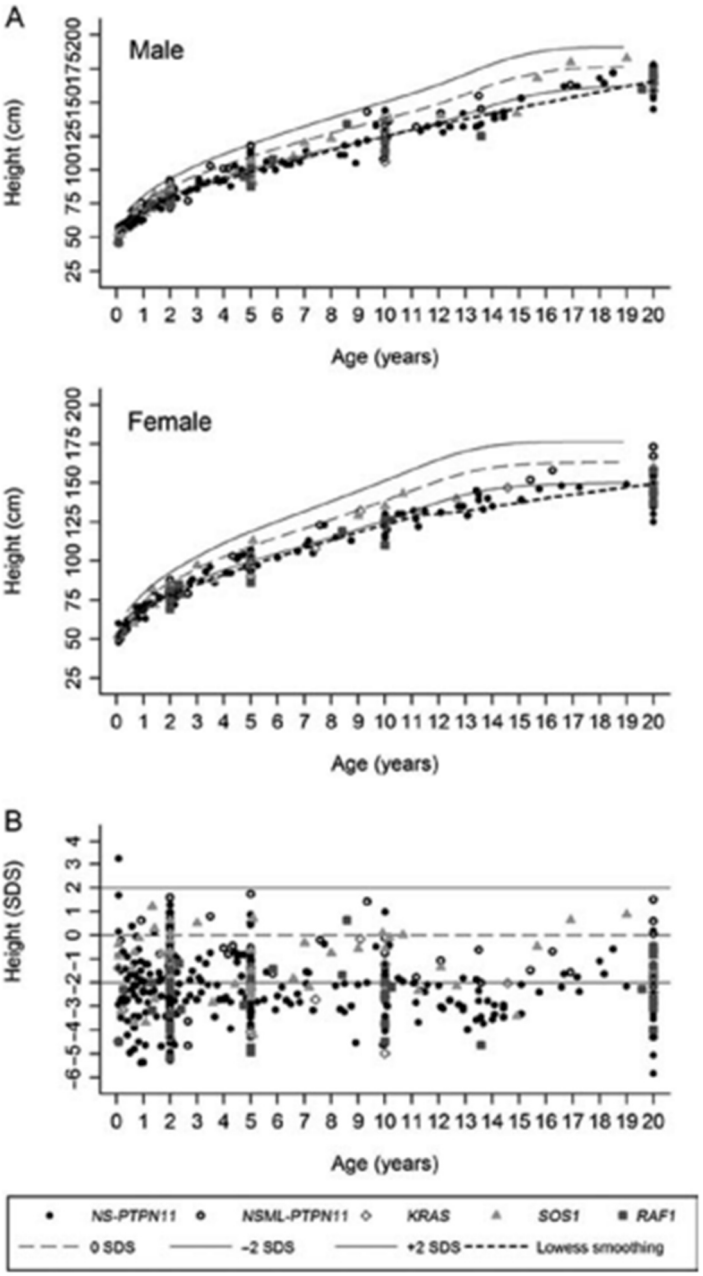
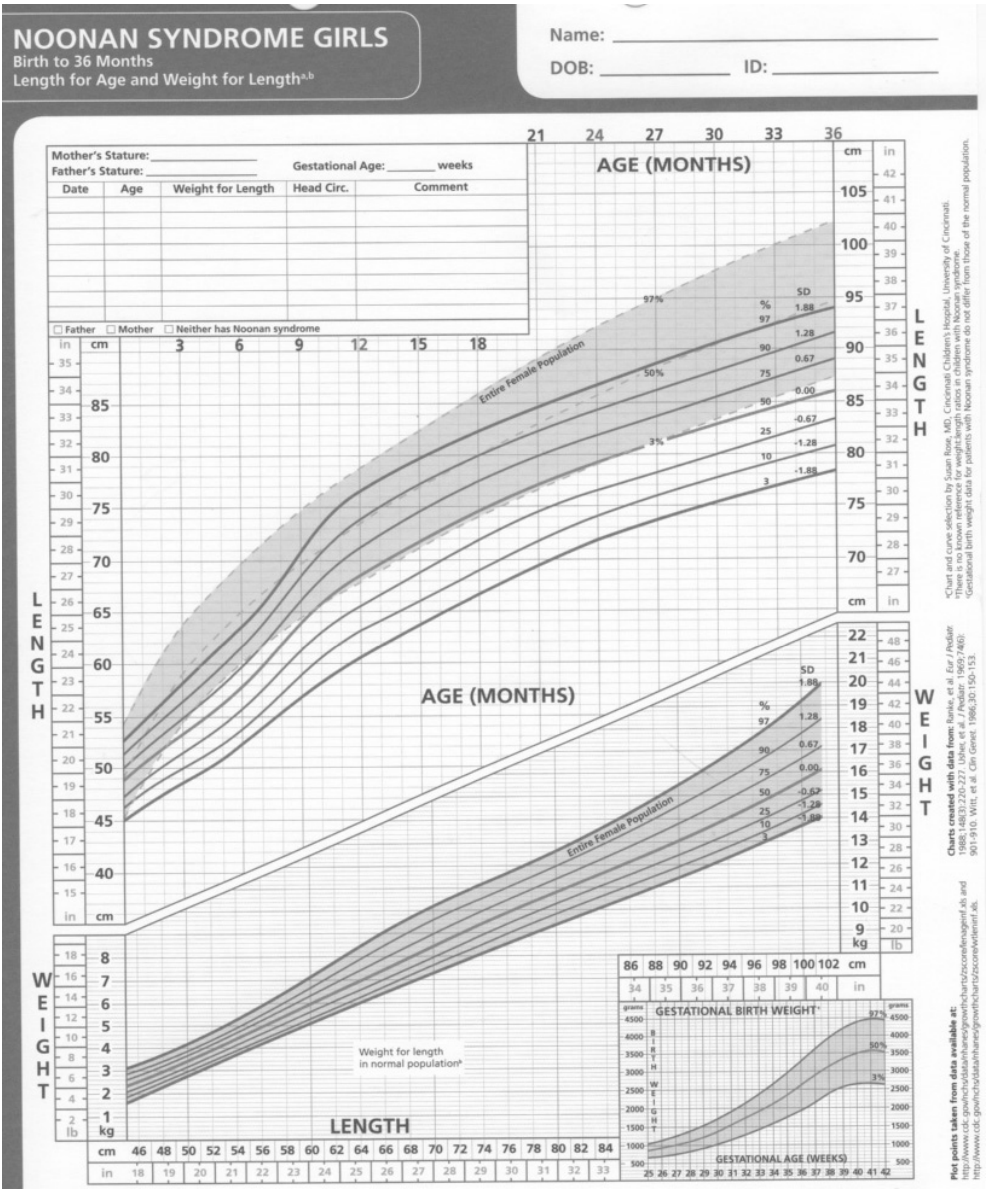
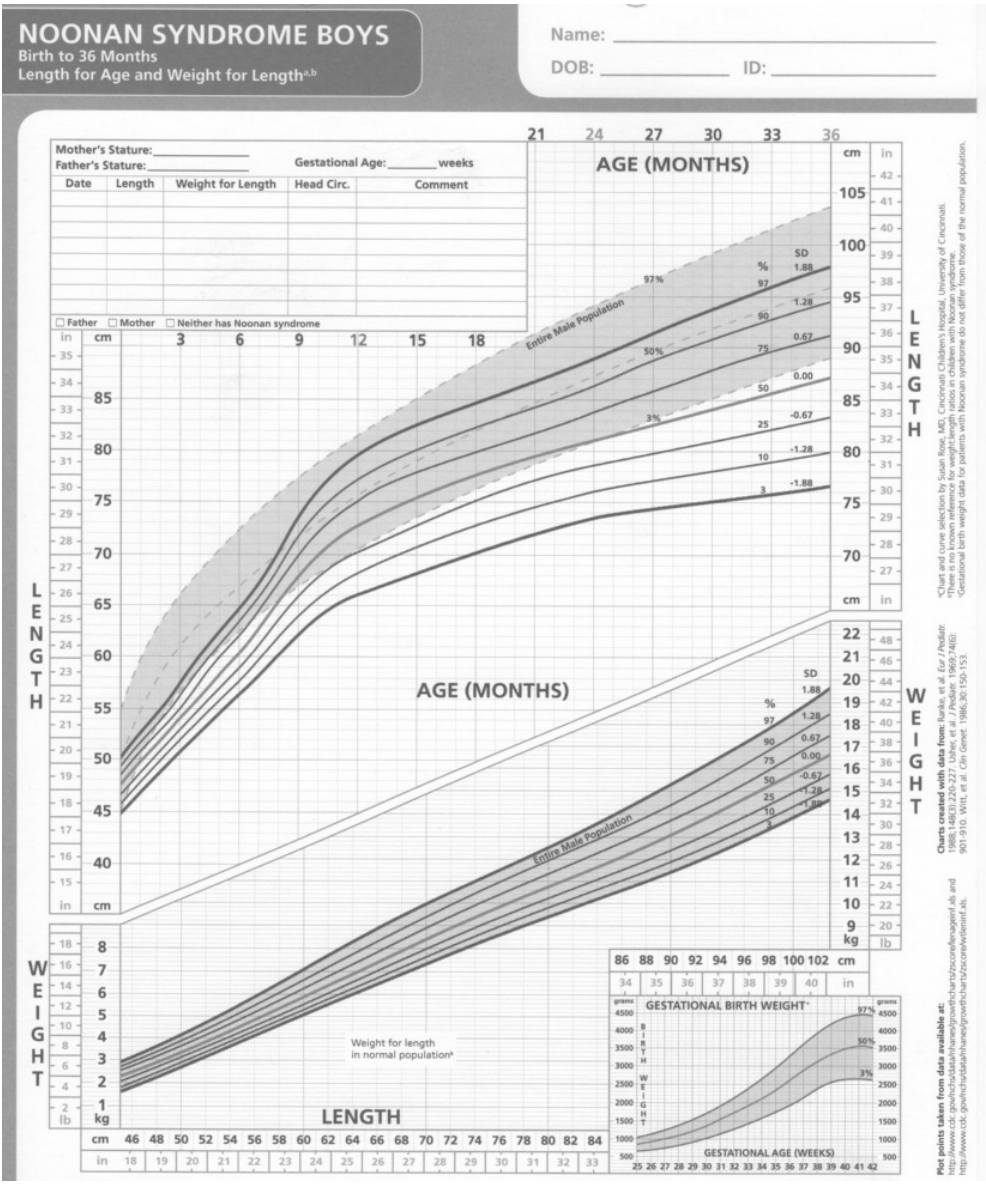


*Figure 3A-D: Noonan Syndrome female and male infant growth charts; Noonan Syndrome female and male childhood and adolescent growth charts*

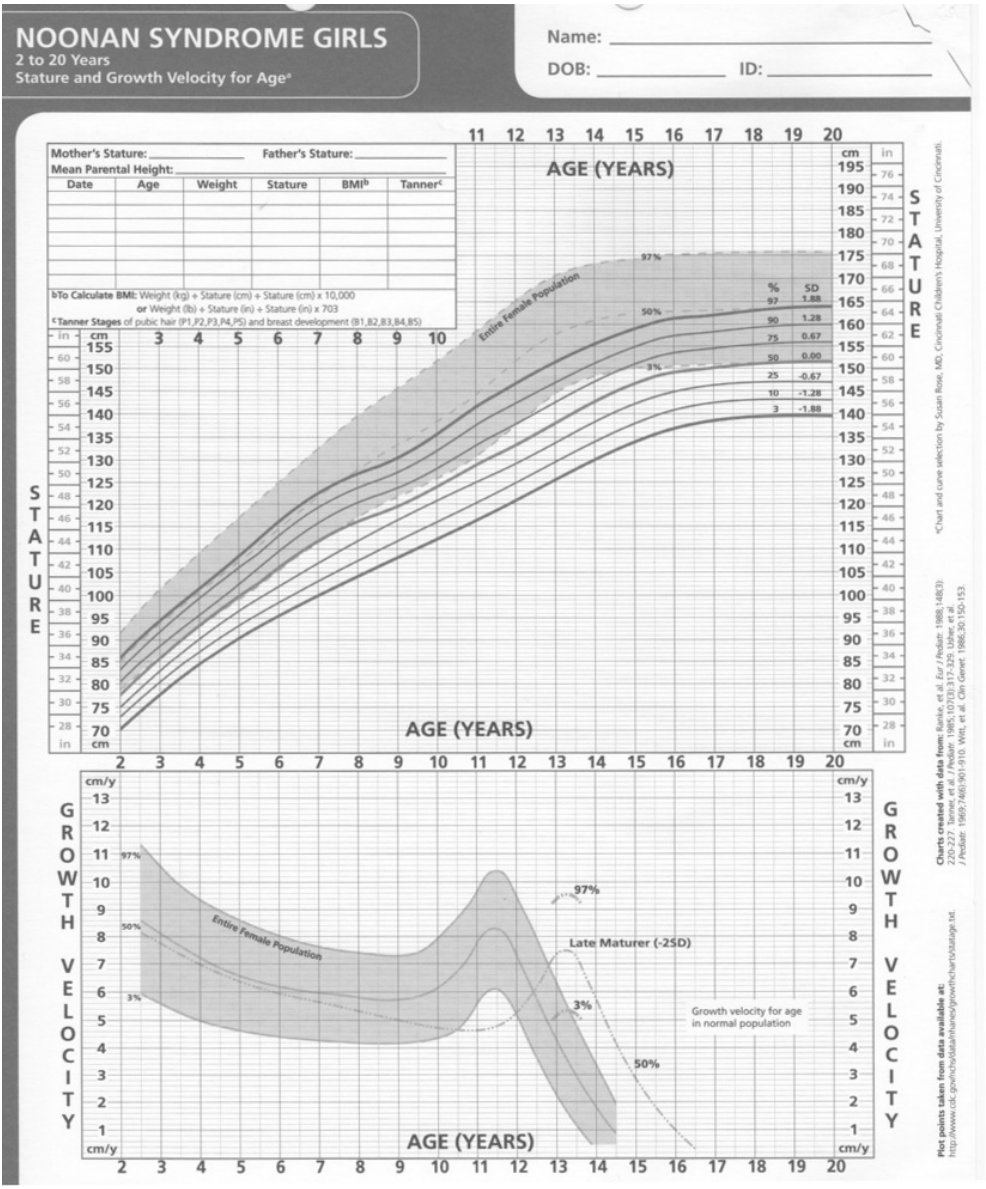
*3A: Noonan Syndrome girls length and weight chart birth to 36 months*



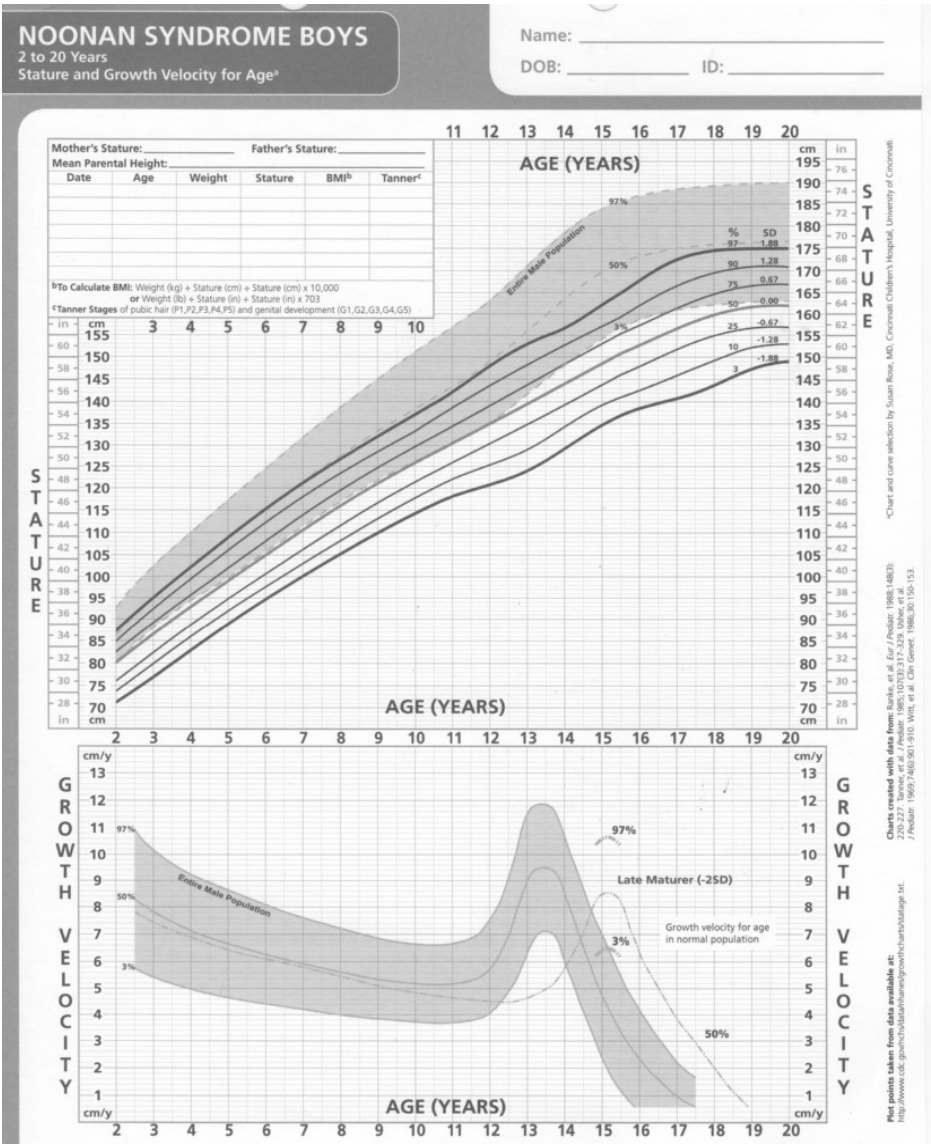
*3B: Noonan Syndrome boys length and weight chart birth to 36 months*



*3C: Noonan Syndrome girls height and weight chart 2-18 years*



*3D: Noonan Syndrome boys height and weight chart 2-18 years*




Research[18] suggests children with Noonan Syndrome are not classically growth hormone deficient. They do not have consistently low IGF-1 or associated binding protein levels nor do they have consistently low results following growth hormone stimulation

testing. Some studies, however, do show such results but there is no consensus among researchers or clinicians to date. Other studies suggest growth hormone insensitivity rather than a true growth hormone resistant state wherein higher than usual growth hormone doses may be required to produce the desired effect on actual height change. The PTPN11 mutation subset of Noonan Syndrome patients may be related to such mild growth hormone resistance by a post-receptor signaling defect.

Growth hormone treatment has been available based upon a combination of short term, small numbers of patients studied in prospective studies as well as several longer term prospective studies reported by several large international cooperative studies: Genentech's National Cooperative Growth Study (NCGS)[10,19], Pfizer's Kabi International Growth Study (KIGS)[20,21,22,23,24], Lilly's Genesis Study[25] and NovoNordisk's Answer Study[26].

Most of such industry sponsored studies were nonrandomized and descriptive but when analyzed together provide a substantive body of research and large enough numbers of patients in favor of nonspecific growth hormone abnormalities in Noonan Syndrome patients who respond favorably to therapeutic growth hormone treatment (much like Turner Syndrome counterparts). NovoNordisk's study provided a cross-over, randomized, prospective project lasting until final height and about 11 years treatment duration. A low and a higher dose of growth hormone was provided for the first two years after a one year run-in period; thereafter, dose was adjusted clinically for all patients in the study. As a result of such studies, several authoritative bodies such as those of the United States Food and Drug Administration in 2003 and comparable groups in the European Union, Australia, Japan and Canada accepted Noonan Syndrome as a diagnosis that is acceptable for use of growth hormone treatment to increase height even without classical growth hormone deficiency. Such conditions as Turner Syndrome, following small for gestational age infants who do not clinically "catch-up" and Prader Willi Syndrome are also similarly acceptable conditions for using growth hormone without classical growth hormone deficiency but in whom satisfactory growth acceleration occurs.

Height velocity pretreatment was normal although nonfamilial short stature was present and obvious in the patients enrolled in this prospective study and both groups were comparable during the first year prior to randomization. Thereafter, height velocity increased in both treatment arms of the study but more so in the Noonan

Syndrome patients who received the slightly higher dosage of daily growth hormone.

*Table 2: height velocity with GH treatment of Noonan Syndrome* [25]

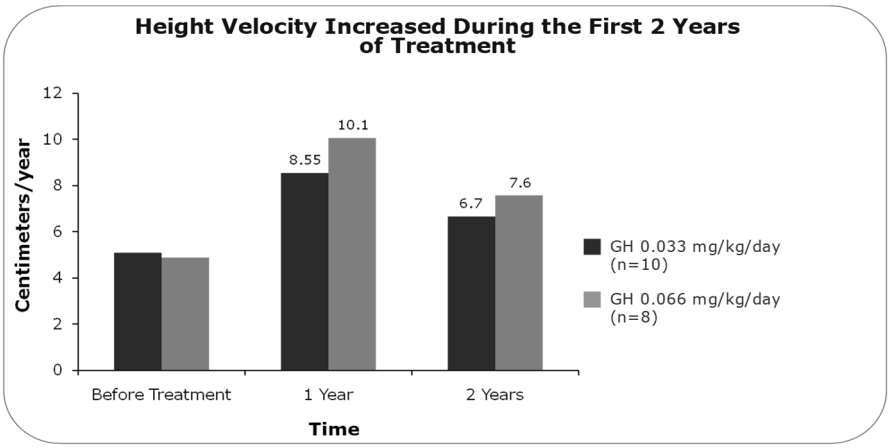
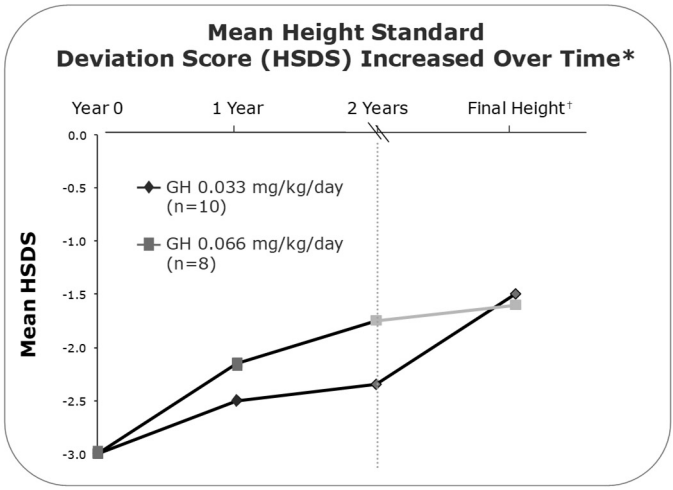



*Table 3: mean height gain with GH treatment* [25]




- Mean height gain from baseline of 1.5 HSDS
  - 9.9 cm for boys
  - 9.1 cm for girls
- At 2 years, dose was adjusted to 0.033 mg/kg/day or 0.066 mg/kg/day depending on clinical response

This was significantly different between the two groups and this effect continued for the second year of the study although with slightly slower height velocity as is typically seen with any growth hormone treatment for whatever diagnosis (classical and severe growth hormone deficiency, neurosecretory growth hormone

deficiency, Turner Syndrome, s/p SGA etc. and also in other Noonan Syndrome study populations reported). Mean height gain, as expressed by change in height score standard deviation (z-scores), was significantly different at the end of the two years of the prospective arm of the study and at final height since the study treatment dosage was then adjusted clinically according to height gain, IGF-1 levels and other standard criteria used by pediatric endocrinologists around the world, there was no final height difference at study termination.

At present, clinical practice is common to provide 0.05 mg/kg/day growth hormone at the time that growth hormone treatment is started and to titrate the growth hormone dosage according to clinical response and IGF-1 levels to optimize final height. Many pediatric endocrinologists, including this author, and especially those in the United States as compared to Europe, increase the dose further if there is documented growth hormone resistance (with low IGF-1 levels) at or around puberty with an aim of sustaining IGF-1 levels in the mid-range of therapeutic response and believe that this produces better results than giving a dose of growth hormone only based upon weight. This allows daily growth hormone doses up to 0.1 mg/kg/day in the peripubertal and pubertal child.

With significant hypogonadism, usually in males, then consideration for addition of androgen should be determined using common clinical criteria s/p cryptorchidism and based upon evaluation of pituitary LH and FSH as well as testosterone levels and clinical Tanner staging. Sequential bone age determinations are helpful in monitoring such growth hormone treatment and is not different than in other growth hormone treated patients. In none of the Noonan Syndrome growth hormone treatment studies to date anywhere in the world has there been a significant safety concern different than when growth hormone is used for treatment of other entities.[22] Specifically in response to concerns about cardiac disease and whether growth hormone treatment would exacerbate pre-existing cardiac conditions in Noonan Syndrome, no such results have been evident as well although larger numbers of treated Noonan Syndrome patients and longer duration of treatment and follow-up will be needed to answer this question definitively. Patients with cardiac hypertrophy who are treated with growth hormone need closer cardiac follow-up to ensure that growth hormone truly does not cause harm to their cardiac status and specifically should have, at a minimum, close cardiology consultation as well as sequential

echocardiography to monitor cardiac function until there are sufficient prospective longitudinal studies to provide more assurance than currently exists.[17]

Examples of several Noonan Syndrome patients' pretreatment and then ongoing treatment growth charts are presented in *Figures 5-7* which document the short stature present at diagnosis and evaluation by the author and then subsequent therapeutic response to growth hormone moving toward mid-parental height percentiles quite nicely.

*Figure 5: Brandon R.*

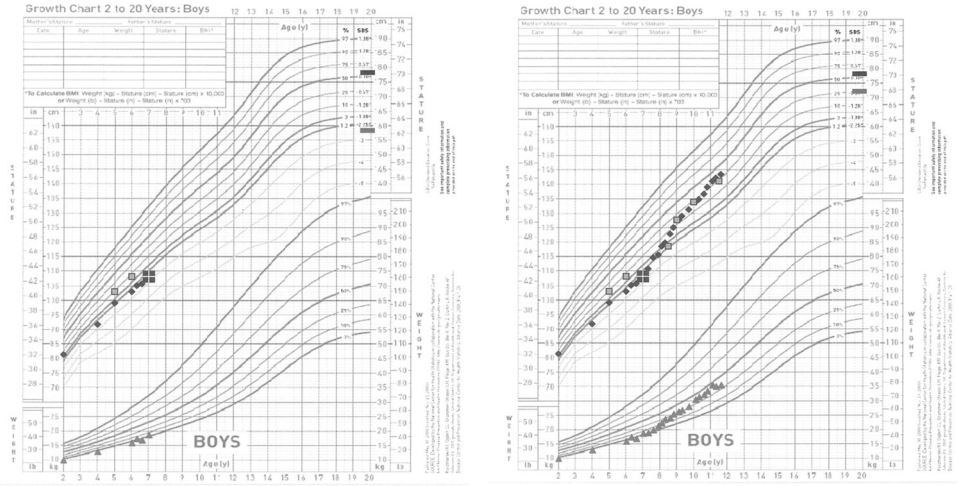



*Figure 6: Alexander A.*

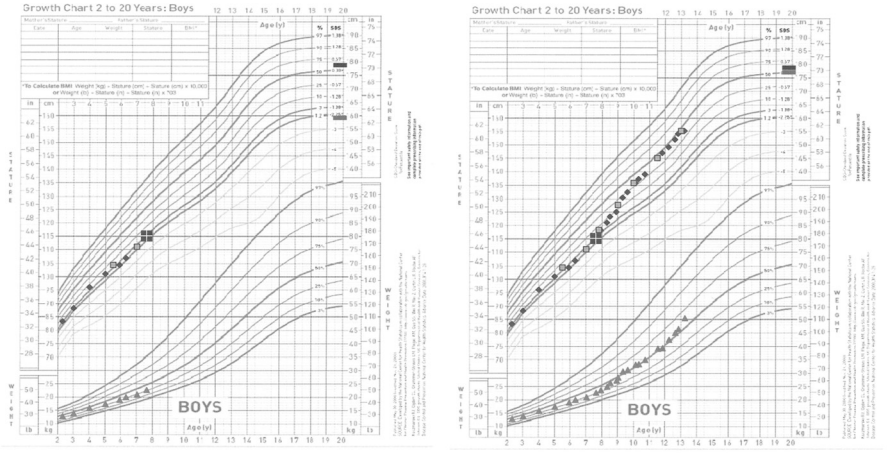
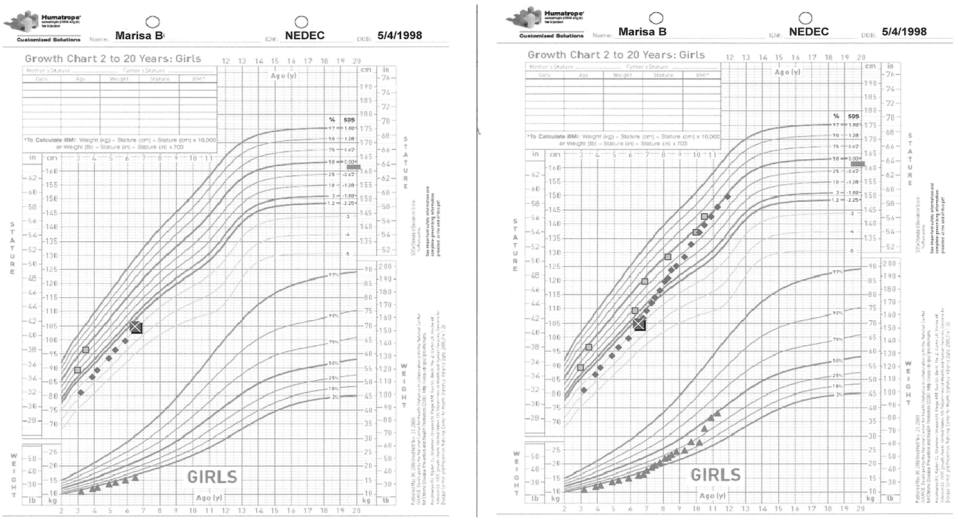


*Figure 7: Marisa B*




**Nonspecific learning problems as well as mental retardation**

Noonan Syndrome patients sometimes will have developmental delay and some will also be hypotonic. Estimates of 15-50% will have lower IQ or significant learning difficulties, some of which may be related to visual or hearing difficulties but exact cause is usually not determined. Other members of the family may also have such difficulties.[27] Special school assistance accommodations and/or attention deficit medication may be required but this should be determined individually and without discrimination for the patient with Noonan Syndrome who requires such assistance.

**Cryptorchidism and delayed puberty as well as microphallus**[1, 28]

In contrast to Turner Syndrome, ovarian function including fertility is normal in women with Noonan Syndrome. Boys with Noonan Syndrome often have delayed puberty. Cryptorchidism is not uncommon and perhaps should raise suspicion about diagnosis of Noonan Syndrome much earlier than is often the case. Hypoplastic testes and microphallus can persist even after surgical correction of cryptorchidism. Germ cell aplasia associated with such gonadal hypoplasia can occur especially if Noonan Syndrome is not diagnosed until adolescence or adulthood or if the cryptorchidism is not

corrected "early enough." Testosterone treatment may be needed to assist pubertal development and improve final adult height. Nevertheless, about 50% of Noonan Syndrome males have normal testicular function and fertility.

**Hypovitaminosis D, osteopenia, and osteoporosis**

As with so many other pediatric and adolescent short stature patients, dietary calcium and vitamin D insufficiency and deficiency and asymptomatic but is quite common and may be exacerbated if there is also concomitant gonadal delay in addition to abnormalities of the growth hormone axis itself. There are no definitive long term studies of vitamin D measurements in Noonan Syndrome patients nor are there definitive assessments of bone density and bone mineralization by DXA for Noonan Syndrome patients but this author's clinical experience is that Noonan Syndrome, like other patients who eventually will or should be treated with growth hormone, should have detailed dietary history of calcium and vitamin D status, consideration for measurements of blood vitamin D levels and baseline bone density determinations using DXA techniques now becoming more readily available around the world. If there is dietary insufficiency, then corrective supplements should be instituted if dietary correction is not feasible or likely. Similarly, baseline abnormalities identified on DXA should be followed through with sequential DXA assessments every 2-3 years to document treatment response and hopefully improvement of osteoporosis or osteopenia depending upon what is discovered from these initial assessments. Blood vitamin D levels are helpful in an effort to maximize those which are subnormal and aim for high-normal range values in an effort to correct any low levels, documented osteopenia or osteopenia and hopefully prevent future fracture problem as well as any associated long term cardiovascular ad lipid abnormalities also associated with lower mineral and vitamin provision.

**Conclusions**

Much research has taken place over the past twenty years concerning Noonan Syndrome, clinical characteristics and specific genetic mutations. Growth hormone treatment has been added to the armamentarium for clinicians to help promote accelerated growth and move patients with Noonan Syndrome close to population norms of height. Attention to neurologic and learning issues, cardiac concerns, bone mineralization and numerous other parts of the

syndrome should promote improved quality of life as we continue to learn to optimize our medical interventions. Applying our scientific knowledge helps to optimize our therapeutic approaches to remediate and improve the clinical conundrum [29] while we continue to explore new avenues to approach these problems in a multidisciplinary fashion. Paying particular attention to differentiating Turner from Noonan Syndrome clinically, biochemically and with appropriately more and more sophisticated genetic studies will help promote recognition and early diagnosis as summarized in *Table 4* but, most importantly awareness for the general practitioner, pediatrician, school nurses should be raised and consideration provided for earlier diagnosis and care for those with Noonan Syndrome.

*Table 4 - Turner Syndrome and Noonan Syndrome Differentiation*

| Clinical Feature | Noonan Syndrome[1] | Turner Syndrome[2] |
|---|---|---|
| Gender Specificity | Male & Female | ✓ (Females only) |
| Genetic Mutations/ Chromosomal | ✓ PTPN11, KRAS, SOS1, RAF1[3] | ✓ (Partial or complete missing second sex chromosome) |
| Congenital Heart Defects | ✓ **Right sided** | ✓ **Left sided** |
| Short Stature | ✓ | ✓ |
| Puberty | ✓ Delayed | ✓ Often absent |
| Reproductive Dysfunction | ✓ | ✓ |
| Men | Cryptorchidism; potential spermatogenesis failure | |
| Women | | Ovarian failure |

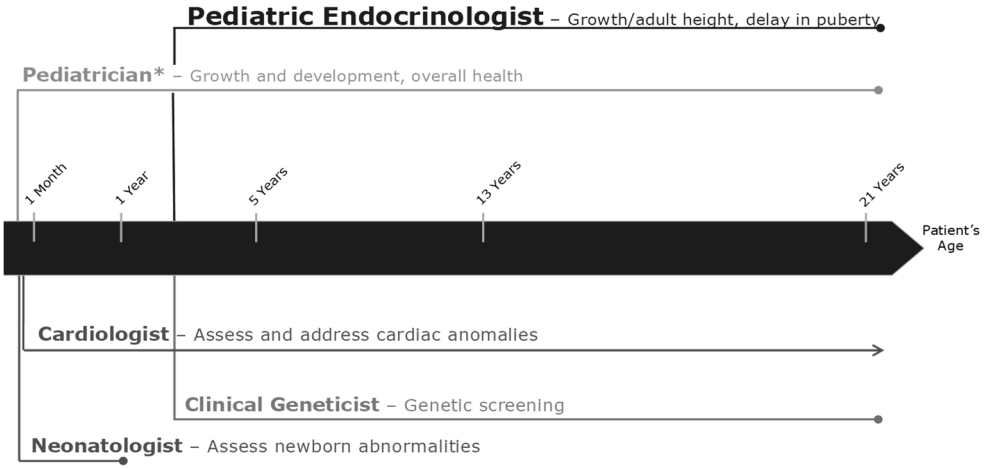



*Figure 8 – Multidisciplinary Approach in Noonan Syndrome: ongoing monitoring and care*

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# DELAYED PUBERTY IN GIRLS

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**Abstract**

The notion of delayed puberty refers to a condition in which the onset of puberty is prolonged. The absence of secondary sexual characteristics after the ages of 14 for boys and 13 for girls is a common definition of this condition, which can affect both genders. Multiple factors, including genetics, hormonal imbalances, chronic diseases, and malnutrition, can contribute to delayed puberty. Significant consequences can result from delayed puberty, including psychological distress, social isolation, and potential health risks. Additionally, delayed puberty can influence an individual's self-esteem and cause them to feel different from their peers. The signs of delayed puberty in girls may include absent or irregular periods, lack of breast development, and lack of pubic and underarm hair growth. Delayed puberty can cause emotional distress for some girls. With appropriate diagnosis and treatment, however, the majority of individuals with delayed puberty can achieve normal pubertal development. A comprehensive medical evaluation, including a physical examination, medical history, and laboratory tests, is required to diagnose delayed puberty. Depending on the underlying cause, treatment options for delayed puberty may include hormone replacement therapy, nutritional supplements, or changes in lifestyle.

*In conclusion*, delayed puberty can have significant physical and psychological consequences. To ensure normal pubertal development and prevent potential health risks, early diagnosis, and treatment are crucial. To promote the physical and emotional health

of delayed puberty patients, healthcare providers must be vigilant in identifying and treating them.
*Keywords: puberty, delayed puberty, sexual characteristics*

**Introduction**

In utero and during the first postnatal months, the hypothalamic-pituitary-gonadal (HPG) axis has a period of activity as a physiological development. The HPG axis becomes inactive by the age of 6 months and does not become active again until puberty. The hypothalamic-releasing factor gonadotropin-releasing hormone (GnRH) has a pulsatile secretion witch induces the pituitary gonadotropins: luteinizing hormone (LH) and follicle-stimulating hormone (FSH) to have also a pulsatile secretion. High levels of LH stimulate the production of sex steroids, while increasing FSH determine the development of ovarian follicles involved in oocyte production. The majority of girls enter puberty between the ages of 9 and 12 years old, with breast development being the first noticeable sign. This is followed by height growth and menarche, which typically occurs at an average age of 12.5 years. If there is no sign of breast development by the age of 13, puberty is considered delayed[1]. Pubic and axillary hair growth and odor are caused by increases in adrenal androgen production that are unrelated to HPG axis activation. Therefore, a pubertal delay may exist if pubic hair growth has begun but breast development has not occurred. Constitutional delayed puberty (CDP) is less common in females than in boys, but can be detected in healthy 13- to 15-year-old girls with a family record of pubertal delay in any of their parents. Functional gonadotropin deficiency is a frequent diagnosis among girls with delayed puberty and low body weight. The doctor should consider the diagnosis of anorexia nervosa if the patient has a history of inadequate caloric intake and irrational anxiety about gaining weight. Also at risk for pubertal delay or very slow progression through puberty, with delayed menarche, are girls who exercise intensely without consuming enough calories to maintain a normal weight. Reduced body fat results in lower leptin concentrations and a reversible gonadotropin deficiency; the same explanation is probable for girls who are extremely thin due to chronic diseases. Persistently low estrogen concentrations might affect bone formation, resulting in lower bone density and a higher risk of fractures. The diagnosis of Turner syndrome must always be considered in short girls with delayed puberty. This condition affects approximately 1 in 2,500 girls

and is typically diagnosed in childhood based on short stature and typical physical findings, including the webbed neck (present in 40%), high-arched palate and cubitus valgus. Girls who are not diagnosed until they are in their teenage years typically have fewer physical findings and are more likely to have chromosomal mosaicism (for example, 45,X/46,XX) rather than the more frequent 45,X karyotype. Due to gonadal dysgenesis, estrogen production is low or absent, but pubic hair growth typically occurs because adrenal androgen secretion is unaffected. [2]

Hypergonadotropic hypogonadism is characterized by appropriate activation of the hypothalamic-pituitary component, but incapacity to produce gonadal sex steroids. In the opposite case, hypogonadotropic hypogonadism (HH) is caused by the hypothalamic/pituitary portion of the HPG axis failing to develop normally or developing too slowly. Except for CDGP and complete androgen insensitivity syndrome (CAIS), the classification of pubertal delay can proceed along these lines.

The most important causes of delayed puberty are listed below.[3] *(see Table 1).*

**Diagnostic**

People with delayed puberty must give a full medical history, including height and weight charts, nutritional state, medicines, history and/or signs of chronic disease, and psychosocial performance. A comprehensive history should also include evidence of anorexia and the intensity of the patient's athletic training. A history of chronic conditions such as celiac disease and inflammatory bowel disease may indicate a transient or secondary delay in puberty. A full family history is needed, including growth patterns as a kid, the age when both parents and siblings started puberty, and any history of infertility, anosmia, and midline abnormalities in parents and siblings, as a positive family history is common. The physical examination must include an assessment of pubertal stages. Assessment of Tanner stages can help to identify previously unrecognized early indicators of puberty. Children with a low weight-to-height ratio are more likely to have an underlying condition that delays HPG axis activation.[4,5]

In a healthy child experiencing pubertal delay for whom a chronic illness was excluded, it is preferable, to begin with a limited number of tests instead of ordering a large number of investigations with limited diagnostic value.

*Table 1. Causes of delayed puberty*

| Causes | Examples |
|---|---|
| Constitutional delay in growth and puberty | |
| Functional delayed onset of HPG-axis activity | **Physical conditions:** isolated growth hormone deficiency, hypothyroidism, asthma, coeliac disease, inflammatory bowel disease, chronic renal failure, cystic fibrosis |
| | **Malnutrition:** anorexia nervosa, poverty and starvation |
| | **Overtraining:** athletes, gymnastics |
| Hypogonadotrophic hypogonadism | **Idiopathic Hypogonadotrophic Hypogonadism** |
| | **Intracranial disorders:** tumours, other acquired disorders, congenital disorders |
| | **Congenital gonadotrophic deficiency:** Monogenetic mutation for isolated gonadotrophin deficiency (GnRH1, GnRH Receptor, Kiss1R, Kiss1, TAC3 neurokinin B, TACR3); Kallmann syndrome (KAL1, FGF8, FGR1, PROK2, PROKR2) DAX1 mutations (adrenal hypoplasia congenita) |
| | Multiple pituitary hormone deficiencies associated with **mutations of transcription factors**: HESX1, PROP1, SOX2, SOX3, LHX3, LHX4 |
| | Part of a **genetic syndrome**: Prader–Willi, Laurence–Moon or Bardet–Biedl syndromes |
| | Permanent damage secondary to **chronic disease**: iron deposition from transfusion-dependent haemoglobinopathies |
| Hypergonadotrophic hypogonadism | Abnormal sex chromosomes: Turner syndrome |
| | Damage to gonads: trauma, torsion, mumps orchitis, radiotherapy, chemotherapy, galactosaemia, iron deposition, cystic fibrosis Anorchia or cryptorchidism |
| | Disorder of sexual development, Eg, gonadal dysgenesis, androgen insensitivity syndrome |
| Unclassified | |

The most important tests are an evaluation of LH and FSH, as well as the measurement of total testosterone in males and

estradiol in girls. LH levels below 0.3 mIU/mL (0.3 IU/L) and estradiol levels higher than 20 pg/mL (73.4 pmol/L) generally are proof of the onset of puberty in females.

By 10 to 12 years of age, any child with primary gonadal failure will have elevated LH and FSH values due to the inability of gonadal steroids and a gonadal protein called inhibin to exert negative feedback on the HPG axis. If the concentrations of LH and FSH are not elevated, the child has CDP or permanent or functional gonadotropin deficiency. Although extremely low LH and FSH values (0.3 mIU/L) are suggestive of gonadotropin deficiency, there is an overlap between basal LH and FSH in CDP and IGD.

Sometimes, endocrinologists measure LH and FSH after GnRH stimulation.

A karyotype is required to rule out Turner syndrome in a girl with elevated LH and FSH levels, unless there is another explanation, such as a history of ovarian radiation exposure.[6] If ovarian failure is idiopathic, an autoimmune cause should be considered, but testing with antiovarian antibodies is not a reliable way to diagnose this condition. Thyroid testing (i.e., free thyroxine [T4] and thyroid-stimulating hormone [TSH] can also be necessary for healthy children with delayed puberty.

If short stature is severe enough to cause hypopituitarism, monitoring insulin-like growth factor 1 (IGF-1) may help. Additionally, the free T4 concentration may be insufficient, while the TSH concentration is normal.[7]

Because the bone age is typically delayed by at least 2 years in children with CDP, a radiography of the hand and wrist is commonly acquired to determine the age of the bones in short children experiencing delayed puberty. Even when the child's height is below the third percentile, the endocrinologist may be able to predict a low-normal adult height, which is encouraging for the child and parents.

A computed tomography or magnetic resonance imaging scan of the head is unnecessary unless the endocrinologist detects evidence of hypopituitarism, such as a very low IGF-1 concentration, low GH values after provocative testing, a low free T4 concentration, or diabetes insipidus.

Thus, the initial evaluation of a girl with signs of delayed puberty includes LH, FSH, estradiol dosage, and radiography for bone age evaluation.[8]

**Management**

Exogenous estrogen is able to induce pubertal development in girls. There are two forms of oral estrogen: synthetic ethinyl oestradiol and natural 17- oestradiol. 17-Oestradiol is more expensive, but more physiological and safer, with a lower risk of thromboembolism and hypertension.

The variable bioavailability of oral oestrogen due to hepatic first-pass metabolism limits the effectiveness of oral oestrogens. This is not an issue with transdermal preparations, which come in the form of patches or gel and require reduced equivalent concentrations. As there is no paediatric preparation currently available, dose titration necessitates cutting adult matrix patches. A few small randomised controlled trials and observational studies have demonstrated that transdermal oestrogen preparations induce pubertal development in girls with hypogonadism more effectively than oral oestrogen preparations. This is demonstrated by quicker spinal bone accumulation, increased uterine growth, and more effective breast development.[9,10]

Short-term therapies are less effective in females, and treatment for both CDGP and hypogonadism is typically continued until the end of puberty. The majority of protocols begin with a modest dose of oestrogen that is gradually increased to the adult dose over three to four years, followed by the addition of cyclical progesterone. A rapid increase in oestrogen levels leads to poor breast development and a prominent areola, so slow titration is essential.

After discussing the advantages and negative aspects, hypogonadal girls choose when to start oestrogen replacement to keep growth in line with peers. Particularly with Turner syndrome, there may be different goals. Pubertal induction delayed till 14 years improves ultimate height in growth hormone-treated children. However, more recent research demonstrated better results, such as improved bone mineral density, memory, and cognitive development, and enhanced growth in patients initiated on very-low-dose oestrogen at a significantly younger age to replicate peripubertal oestradiol levels prior to breast development.[11]

*Examples of treatment protocols for pubertal induction*

1. *Ethinyl estradiol (EE)*
   - Year 1: EE 2 μg daily
   - Year 2: EE 4 μg daily
   - Year 2½: EE 6 μg daily
   - Year 3: EE 8 μg daily
   - Year 3½: EE 10 μg daily
   - Adult dose: EE 20–30 μg daily

In patients with a uterus, add in oral cyclical progesterone (e.g. norethisterone 5 mg or medroxyprogesterone acetate 5 mg) day 14–21 of cycle, or change to a combined oral hormone replacement therapy (HRT) which included cyclical progesterone at the onset of menstruation or when adult dose is reached even without onset of menstruation*

2. *17 ß-estradiol*
   - Initial dose 5 μg/kg daily

Increased every 6–12 months to 10 μg/kg daily, then 15 μg/kg daily then 20 μg/kg daily

   - Adult dose: 1–2 mg daily

In patients with a uterus, add in oral cyclical progesterone (e.g. norethisterone 5 mg or medroxyprogesterone acetate 5 mg) day 14–21 of cycle, or change to a combined oral HRT which included cyclical progesterone at the onset of menstruation or when adult dose is reached even without onset of menstruation*

3. *Transdermal* (Evorel 25 patches = 25 μg/24h; Evorel 50 patches = 50 μg/24 h)
   - Year 1: Evorel 25 ¼ patch twice a week
   - Year 2: Evorel 25 ½ patch twice a week
   - Year 2½: Evorel 25 alternate ½ and whole patch twice a week
   - Year 3: Evorel 25 whole patch twice a week
   - Adult dose: Evorel 50 whole patch twice a week

In patients with a uterus, add in oral cyclical progesterone or change to a combined HRT patch which included cyclical progesterone (eg, Evorel 50 Sequi) at the onset of menstruation or when adult dose is reached even without onset of menstruation*.[3]
*(* transabdominal pelvic ultrasound scans may be used to guide the introduction of progesterone*)

Understanding the mechanisms underlying pubertal initiation and establishing the signaling pathways involved in the control of puberty have been the focus of recent research.

There are effective treatments available, such as pulsatile GnRH or gonadotropin therapy (hCG alone or in combination with FSH), not only for promoting virilization or estrogenization, but also for successful reproductive development.

Kisspeptin, a puberty-regulating neuropeptide, has emerged as a critical element in controlling GnRH release; research is underway to determine if kisspeptin substitution may be useful in the treatment of HH.[12] Other studies are looking at whether environmental endocrine disruptors can interfere with pubertal timing. As plausible causes of delayed puberty in girls, substances including dioxin and dioxin-like compounds, lead, and polybrominated biphenyls have been identified.[13]

As a result of the necessity to properly titrate the dose and mode of administration to clinical, radiologic, and biochemical effects, sex steroid replacement must be carried out under the supervision of an endocrinologist.[14]

Understanding best practices in pharmacological pubertal initiation and management, with an emphasis on fertility preservation and discussion of reproductive options for children and families, is also a continuing area of research. Understanding whether delayed pubertal development is associated with long-term health or psychosocial risk factors will also be essential.

**Conclusion**

In conclusion, in girls, delayed puberty is frequently caused by a functional gonadotropin deficiency along with excessive thinness or by primary ovarian failure, especially Turner syndrome. LH, FSH,

and estradiol should be measured to begin laboratory testing. Gonadotropin levels that are elevated are a reliable indicator of primary gonadal failure. Even with laboratory tests, constitutional delay, and isolated gonadotropin deficiency are frequently difficult to distinguish. Current evidence suggests that oral or transdermal estrogens are equally effective and safe in treating pubertal delay in females.

Recent advances in our understanding of the endocrine, genetic, and environmental controls of puberty have enhanced our knowledge of the pathophysiology of delayed puberty. There is ongoing investigation into the causes and treatments for delayed puberty. Careful clinical evaluation and an understanding of normal pubertal physiology continue to be essential in the management of patients with delayed puberty.

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# TREATMENT OF TYPE 1 DIABETES (T1D) IN CHILDREN YOUNGER THAN 3 YEARS

**John W. Gregory**

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The management of preschool-aged children aged under three years, may prove difficult and because of their age, small size, neurodevelopmental considerations and insulin sensitivity, may require different approaches to those used in older children. This review will consider the diagnostic and therapeutic challenges that may arise when providing care for such young children.

**Diagnosis.**

The diagnosis of diabetes in very young children is often delayed as the characteristic symptoms of polyuria (heavy, wet diapers) & polydipsia may be less obvious. Symptoms such as vomiting, abdominal pain, increased appetite especially for carbohydrate-containing foods, weight loss, growth failure, fatigue, listlessness or intercurrent infection, suggestive of other conditions, may predominate. As a result, the diagnosis is often overlooked by parents and primary care physicians and there is a greater likelihood that these young children will present in potentially life-threatening diabetic ketoacidosis (DKA). Furthermore, studies suggest that these young children experience a more vigorous autoimmune process with higher titres of islet-cell and insulin autoantibodies and a greater likelihood of HLA-defined disease susceptibility, leading to a shorter prodrome, lower C-peptide and a greater likelihood of DKA at diagnosis. Thereafter, a shorter honeymoon period with little evidence for recovery of endogenous insulin secretion than that seen in older children is observed [*Komulainen, 1999*].

When diabetes presents in the very young child, the possibility of parenteral glucose, stress, sepsis or steroid treatment as possible causes need to be considered. The presence of a strong family history,

congenital abnormalities or presentation under 6 months of age in particular, raise the possibility of monogenic forms of neonatal diabetes which should be investigated by genetic testing (see for example http://diabetesgenes.org). The latter is important, in the 30-58% of cases which are caused by heterozygous mutations of genes that encode the Kir6.2 subunit of the ATP-sensitive subunit of the potassium channel which cause severe hyperglycaemia and ketosis. Studies from the Exeter group have shown that 90% of these cases can be successfully weaned off insulin following sulfonylurea therapy, usually with better glycaemic control than that see on insulin alone, due most likely to the effect of sulfonylureas closing the mutant potassium channel [*Pearson, 2006*].

**Challenges.**

T1D in preschool age children presents particular therapeutic challenges due to their small size, daily variability in insulin requirements, activity & food intake, marked insulin sensitivity, frequent illnesses & concerns for the carers about hypoglycaemia. Studies of the variability of closed-loop pump insulin requirements through the day & night in four multinational randomised controlled trials show that young children aged less than six years demonstrate a significantly greater coefficient of variation in both diurnal & to a greater degree, nocturnal insulin requirements when compared to adolescents & adults [*Dovc, 2019*]. The authors concluded that part of the explanation for this variability included day to day differences in activity levels & nutritional intake & that these challenges merit an early adoption of hybrid closed-loop systems in very young children. An additional therapeutic challenge arises from the greater sensitivity to insulin that which has been reported in preschool aged children, approximately four times that seen in older teenagers [*Snider, 2018*].

Hypoglycaemia is a particular cause for concern to parents & clinicians caring for very young children with T1D. Several studies have demonstrated adverse neurodevelopmental findings on longer term follow up of young people with T1D but there is debate over whether these can be attributed to the cumulative adverse effects of recurrent hypoglycaemia [*Cacciatore, 2022*]. In particular, cognition is said to be reduced through childhood & some have reported adverse effects on intelligence, memory, learning & verbal fluency [*Blasetti, 2011*]. Hypoglycaemia is thought to cause brain cell damage through a glutamate-mediated cytotoxic process [Auer, 1988].

Furthermore, brain imaging studies show reduced grey & white matter volumes, suggestive of white matter axonal & cortical neuronal injuries [*Perantie, 2007*], though the link with previous recurrent hypoglycaemia remains uncertain. Unsurprisingly, parents experience great anxiety about hypoglycaemia in very young children due to their variability in physical activity & eating & the challenges of identifying hypoglycaemia when the child is too young to communicate the presence of symptoms. This anxiety is greatest whilst the child is asleep & seems higher in those parents of children using pumps & continuous glucose monitoring though directionality of the association is unclear [*Van Name, 2018*]. Previous clinical observations using continuous glucose monitoring suggest that these children may experience prolonged periods of asymptomatic hypoglycaemia lasting several hours, particularly during sleep, which may not be evident to their carers [*Deiss, 2001*]. More recent studies using blinded continuous glucose monitoring suggest that only 32% of hypoglycaemic events are detected by young children & their carers despite blood glucose testing 10 times daily, and that 90% of hypoglycaemic events overall are asymptomatic (98% of nocturnal episodes) [*Sundberg, 2014*]. In light of these observations, international societies have in the past suggested higher HbA1c targets for the very young, although this more relaxed view is now being reconsidered in many parts of the world [*Redondo, 2021*].

Given parental concerns such as those discussed above, it is unsurprising that the parents of preschool-aged children often struggle hugely with the diagnosis of T1D in their offspring. Phenomenological studies have suggested that parents experience three distinct phases of coming to terms with the diagnosis [*Hatton, 1995*]. Parents initially report feeling a heavy burden, isolated & exhausted following the diagnosis, with grief, guilt & anger being commonly felt. Adjusting to care at home is described as a 'survival' stage, before longer term adaptation kicks in, with parents starting to trust others with the care of their child & to build support systems.

**Therapeutic options.**

Given these concerns, there has been an increasing interest in pump therapy, even though early small-scale randomized controlled studies [*DiMeglio, 2004; Wilson, 2005*] failed to show significant improvements in glycaemic control, despite systems proving safe & feasible. However, with increased experience, recent large-scale registry studies show a dramatic increase between 2004-17 in pump

usage, with up to 92% of preschool aged children in the German-Austrian Diabetes Prospective Follow-up (DPV) Database now using pumps [*van den Boom, 2019*].

Analyses of pump data have shown that insulin requirements vary significantly by age with basal insulin requirements typically 0.25U/kg/d in preschoolers, compared to 0.43U/kg/d in teenagers [*Bachran, 2012*]. Reviews of data from pump trials & registries, have produced inconsistent findings in preschool aged children. Earlier studies showed improved parental quality of life despite little sustained effect on HbA1c values [*Opipari-Arrigan, 2007; Berghaueser, 2008; Nabhan, 2009*], whereas more recent studies show improved HbA1c values without evidence for a deterioration in hypoglycaemia [*Blackman, 2014; Szypowska, 2016*].

Relatively recent studies on parents of young children treated with insulin pumps [Nevo-Shenker, 2020] suggest that they experience greater satisfaction & improved family life with less fear of hypoglycaemia. They particularly appreciate the lack of need for painful injections & the easier control of meals & snacks that pumps provide & most continue to use pumps after the study they have taken part in has finished. However, parents emphasise the importance of adequate clinical support & education to optimise outcomes using insulin pumps.

In addition to insulin pumps, continuous glucose monitoring (CGM) has attracted interest in those managing T1D in very young children who cannot communicate the symptoms of or respond appropriately to hypoglycaemia. Over 10 years ago, it was shown that CGM was feasible in very young children, leading to greater parental satisfaction at that time, despite no impact on HbA1c [*Tsalikian, 2012*]. With increased experience, more recent studies are now showing that CGM leads to greater time of blood glucose values in range [*Dovc 2022*]. However, there are challenges, such as parents reporting being overwhelmed with information & not using the data to make changes to insulin therapy between clinic appointments. CGM sensors seem less accurate when blood glucose values are low & may cause skin irritation. Finally, there are practical challenges maintaining the sensor in situ in very young children [*Nevo-Shenker, 2020*]. Nationwide data-sets show a rapid uptake in this technology in very young children in recent years [*van den Boom, 2019*]. Flash Glucose Monitoring in which subcutaneous glucose data are stored on an external reader has increased the appeal of CGM.

Further technological advances now allow CGM & insulin pumps to work in synergy with features such as automated predictive low glucose suspend or as part of hybrid closed loop system. These sensor-augmented pump systems are producing less time in hypoglycaemia & greater time in range [Alotaibi, 2020], despite the greater variability in insulin requirements of younger children [*Dovc 2019*] & now merit more extensive evaluation in very young children.

Caring for a very young child with T1D is an enormous challenge for their families. Clinical teams need to provide extra support & guidance to parents to help them deal with their fears about how to recognise, treat & prevent hypoglycaemia, manage food refusal or variable food intake & the effects of intercurrent illness on diabetes care. In particular, these families need help to build support systems they can trust, which allow them to share caring responsibilities with others, to give the parents a well-earnt rest [*Lowes, 2005; Whittemore, 2012*].

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# DIABETES SCHOOL ISSUES

**Stuart J. Brink**

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Societal trends around the world show increasing childhood, adolescent and young adult diabetes increasing and, since so much of childhood and adolescence is spent at school, living with diabetes necessitates that some of the care[1,2] that is required of such youngsters must take place away from the family unit … and at either day-care for the pre-school age children or at elementary, middle, high school and college … but away from parents and other caregivers who might share in the care and many decisions of managing daily diabetes care.[3] Management of diabetes[4,5] necessitates incorporation of more intensified treatment options but also acknowledging that school personnel must take a more active role in providing such care including not only teachers but also school nurses (if they are present) and school administrative staff (principals and vice-principals), lunch aides, bus drivers and athletic staff where the PWD (person with diabetes) spends some of their school or after-school hours. Education about diabetes for everyone involved is often woefully absent or out-of-date in many schools even though such care should be an individual's right as part of school attendance and any issues about diabetes care should be accommodated routinely. This may place the PWD in a position to fend for themselves unsupervised and un-reminded of what needs to be done, especially if assistance for hypoglycemic episodes is needed, so that the trials and tribulations of following a meal plan, adjusting and administering insulin before lunch or afternoon snack, minimizing or preventing hypoglycemia with insulin peaks or unbalanced activities as well as hyperglycemia episodes from excess snacking or meals interfere with meeting treatment objectives.

An important part of any action plan is negotiating with school officials. Some may be extremely valuable allies while others may be evasive worried about liability issues or difficult to engage positively.

Expecting both kinds and being able to offer ways to work together should be one of the goals of parents and caretakers as well as the local diabetes medical team. Being aware of such potential problems and discussing them in a straight-forward and rationale fashion often eases some of these difficulties and allows appropriate information and empowers positive outcomes enlisting the help of the local school board, local officials and other parents courteously to motivate potential change and closer working relationships.[6]

With the incidence of diabetes increasing in children around the world, it is likely that school staff will need to provide care for a child with diabetes (CWD) at some point. Unfortunately, studies show that the average schoolteacher generally knows something about type 2 diabetes and relatively little about type 1 diabetes.[7,8] Parents and youngsters with diabetes usually have reported a lack of confidence in the teacher's ability to manage diabetes effectively.[9] Many CWD are now routinely testing blood glucose levels, following a meal plan, and administering insulin during school hours on the advice of their diabetes medical care team but the team does not routinely/always provide proactive information with specific advice to the PWD or parents/caretakers about interactions with teachers and other school staff.[4,10] Technological advances have also grown in support of the rigorous care demands with insulin pumps as well as glucose sensors prescribed or with multiple daily doses of insulin all designed to better reproduce physiologic-non-diabetes insulin delivery[4,10] as well as improve quality of life.[11,12,13] CWD as well as young adults, middle-aged adults and the elderly are now using improved blood glucose meters, more rapid-acting insulins, pen devices to ease self-injection as well as updated insulin pumps and sensors during the school day and in after-school activities but all this new technology can be confusing and frightening to untrained school personnel although perhaps easier than learning how to use the older vials and needle systems. School nursing shortages often create situations where there is no school nurse present or one school nurse may be covering several schools and may not always be available for direct supervision or even feel comfortable providing needed medical/nursing advice.

As numbers of children with conditions that require medical attention during school hours grows, so do the numbers of teachers, and sometimes also school nurses, who express their inadequacy in understanding such conditions and how they should respond, professionally and responsibly, during the school day because they

have not received updated and appropriate education and support. Learning about asthma and allergic problems, celiac disease and other gastrointestinal problems, seizures or diabetes as well as increasing recognition of eating disorders/bulimia, anxiety, depression or attention deficit and learning disorders all require such annual updates to ensure school safety for the student. Diabetes is different than most of these other chronic conditions because of more than 125 daily tasks and decisions that must be made either by the parent and caregivers or the CWD/PWD themselves. Although teachers have observed an increase in their CWD's self-efficacy in managing their diabetes,[14] teachers also report an inability to cope on their part because they often do not understand details of medical conditions such as diabetes nor are they necessarily up-to-date with the latest guidelines for treatment goals as well as the latest technology being utilized; they also worry and feel unprepared to handle emergencies or to provide proper advice about adjusting insulin, food or activities.

Nevertheless, excellent teaching tools are available not only for the PWD and family members but these can also be utilized by school staff (see websites of the children with diabetes, American Diabetes Association, British Diabetes Association, Australian Diabetes Association, Eli Lilly & Company, NovoNordisk, Sanofi, childrenwithdiabetes (CWD), Life for a Child (LFAC) and Changing Diabetes in Children (CDIC) as well as many other diabetes societies to help them learn more about the day-to-day management issues. More work for such school staff but worthwhile to ease their concerns and provide up-to-date information. Learning to Live Well with Diabetes[15], Type 1 Diabetes: A Guide for Children, Adolescents, Young Adults and Their Caregivers[16], Diabetes for Dummies[17], Understanding Diabetes, A Handbook for People who are Living with Diabetes[18], A Guide for Parents of Children and Youth with Diabetes[19] as well as Diabetes in Children and Adolescents. Basic Training Manual for Healthcare Professionals in Developing Countries[20] are just some of the available excellent books, often with multiple translations into different languages. (Hanas' excellent book[16] and the Brink et al training manual[20] are also available in multiple translations and for free downloading.) Specific information about insulin pumps and continuous glucose monitoring systems is also available (such as the Yale Children's Diabetes Program Guide to Continuous Glucose Monitoring) and from Medtronic Minimed®, Insulet®, Tandem®, DexCom®, Abbott® websites and other pump

and sensor manufacturers to help with teacher and school staff education.[21] The Australian approach to such difficulties has been innovative and extremely helpful with the 2019 T1D Learning Center pamphlet, A Parent Guide. International best practice Type 1 diabetes care in Australian schools an excellent tool for both parents and school personnel.[22]

Teachers express concern not only about their own liability for getting involved but also in their ability to know what they really could or should be doing under different circumstances. In certain circumstances, some teachers' unions have refused to "allow" teachers or class-aides to provide any medical care and insist that such care only be provided by a school nurse – even when sometimes no school nurse is always available! Principals, assistant principals, administrative staff have often needed to be the "supervisor" when there is no other alternative and are frequently less than ideally educated about what they need to do – but all such staff can be educated and helpful if trained.

Recommendations for parents[23] to specifically talk to and meet with teachers just before each school term begins, to discuss the diabetes treatment plan being utilized as well as the rationale for the specific type of plan (the older method of two injections of insulin daily with more hyperglycemia as well as more hypoglycemia episodes being replaced by a more intensified approach utilizing three or four insulin boluses daily better designed to try to match meal and snack as well as planned activity throughout the day and night, more blood glucose monitoring to allow more adjustment of insulin and/or food during the day, more use of insulin pumps to allow better physiologic basal/background insulin delivery than injectable basal doses as well as better meal-time bolusing decisions, continuous sensor glucose monitoring … all towards lowering A1c levels while minimizing both time when hyperglycemic as well as avoiding, identifying and better treatment of hypoglycemic episodes.[24]

Parents can recommend that school nurses, teachers and other school staff make contact with their diabetes healthcare team members and even share some of the tools that they as a family have found helpful with the school staff, recommend that the diabetes health care team invite their school staff to periodic education sessions specifically for school nurses and teachers (in person or on-line) as well as other school staff and administrators to facilitate overcoming some of these hurdles.[25]

As children, pre-adolescents and adolescents spend about more time away from home, comprehensive education for all potential caregivers needs to be planned. Diabetes health care professionals must take it upon themselves to bring up such topics with parents and the PWD, help plan an approach that is non-intrusive but also focus on safety issues and the PWD interests and level of self-care.[26]

Individual Education Plans (called IEPs) can also be developed if needed for the CWD as well as specific written instructions (sometimes called DMMPs: Diabetes Medical Management Plans).[23] Formal DMMPs (an example is provided in Table 1 for hypoglycemia) annually should be provided by the diabetes health care team with appropriate review and discussion with parents and caregivers as well as understanding of school hours, testing and insulin administration needed, school schedules of gym and after-school activities, planned school excursions/trips,[27] school lunch options, snack options, potential bullying[28] or peer pressure etc.[14,23] At the same time, such planning should take into account the age and maturity as well as self-care level of the PWD, how the parent(s) will be involved and when they should be contacted, how, when the diabetes health care team can assist/be available for any school staff especially if an emergency situation occurs and also the specific education and support needs and interests of the teaching, administrative and school nursing staff.[16,29]

Some teachers and school nurses are very sophisticated and interested in participating while many are overwhelmed and frightened not only at their lack of knowledge and training but also their ability to appropriately assume such responsibility in addition to their day-to-day education responsibilities. Some worry about legal liabilities since they are non-medical professionals especially when full-time nurses are not always available at their facilities. Nevertheless, teachers and school nurses as well as school administrators and coaches/gym teachers need to attain knowledge about diabetes in order to feel comfortable with management and provide a safe environment. In the USA and in many countries, federal and local state as well as city laws mandate such responsibility under anti-discrimination regulations (called 504 plans) and these legal requirements have been useful when litigation was necessary to ensure safety for the CWD.[30,31,32]

School personnel have also identified the need to train principals and vice-principals as well as administrative staff and ancillary staff including gym teachers and after-school coaches, bus

drivers, classroom aides and parent volunteers since such other adults often help provide supervision and care.[33,34] Providing diabetes care, particularly intensive therapy, for the CWD creates special challenges that are very different than providing medication for acute infections or asthma, epilepsy or learning/attention deficit problems. School personnel also must be aware of the constant changing treatment venue for youngsters with diabetes because of the likelihood of new technologic advances as well as normal growth and development issues that impact diabetes care decisions, autonomy and needs. Involved teachers and school staff can support adherence issues, help mitigate peer pressure, and teachers who have creatively incorporated discussions about diabetes and the care that is required into health and science lectures and invitations of the CWD to speak and demonstrate what it's all about have been extremely helpful and welcoming if the CWD is willing to do so.[35,36]

Since the release in 1993 of results of the Diabetes Control and Complications Trial (DCCT)[37] there has been a trend for children with type 1 diabetes to intensify therapy even though the trial did not include children <13 years and only a small portion of the study participants were teenagers 14-18 years old.[4]

The pediatric, adolescent and young adult diabetes health care community worldwide has adopted more vigorous goals because this approach is more likely to improve chances of better growth and reduce long term complications associated with diabetes as confirmed by many reports since then[2,38]. This is true in LRC (low resource countries) as well as MRC (middle resource countries) and HRC (high resource countries) but in most LRC and many MRC, older less-physiologic types of insulin are preferred once or twice-a-day in an effort to reduce costs; sufficient glucose monitoring is unavailable because of lack of supplies in addition to added costs and in many parts of the world, lack of trained diabetes health care professionals adds to these difficulties.[39]

As a result of current treatment recommendations promulgated by organizations such as the American Diabetes Association (ADA) and its Council on Diabetes and Youth (CODY), the International Society for Pediatric and Adolescent Diabetes (ISPAD) and the International Diabetes Federation (IDF) as well as Non-Governmental Organizations (NGOs) such as Life for a Child (LFAC) and Changing Diabetes in Children (CDIC) there have been increased attention providing education and staff recruitment as well as training, encouraging diabetes team care with coordinated and

consistent messaging and support for the PWD and their family, providing free medical supplies including insulin, meters and test strips, education supplies and advice. This has occurred around the world over the past twenty years so that LRC and MRC difficulties can often be overcome while recruiting and assisting active participation of local medical teams as well as hospitals, clinics, medical and nursing schools and official government cooperation.[40]

ISPAD has been a critically important partner with CDIC and LFAC endeavors in cooperation with funding by many biopharmaceutical and technology international companies donating needed medication and supplies. Many shared multi-language information sources are listed on the LFAC and CDIC websites so they also would be an excellent source of information for school staff education and support.

The aim of modern treatment is near-normoglycemia while minimizing time above range (TAR; hyperglycemia) and time below range (TBR; hypoglycemia).[1,2] Coupled with such tighter glycemic control goals is a trend utilizing multidose insulin programs (basal-bolus insulin instead of once-a-day or twice-a-day mixed insulin doses) as well as insulin pumps attached to more frequent daily monitoring or continuous glucose monitoring sensors (CSGM) so that more time is required to supervise and allow such monitoring to occur prior to meals and snacks and often before and after activities as well. In the past decade, CGMS[41,42,43,44] have provided every 5 minute glucose measurements automatically (but at significant added expense) while cost-effective studies have documented improvements in quality of life as well as better glycemic outcomes. Nevertheless, the burden of needing devoted time to review what is occurring, identify patterns, if they exist, and figure out strategies to minimize wide glycemic excursions as well as the extremes of both hyperglycemia and hypoglycemia accordingly add to the demands on the PWD, their family and potentially the school nurse or classroom teacher.[11]

Teachers and other staff may be resentful of such added chores but, in fact, the ability of a CWD to function in school is dependent upon their medical needs being met at the same time that their emotional and educational needs are addressed.[45,46] In older children, adolescents and young adults, as they mature emotionally and cognitively, they usually – but not always – assume such responsibilities but still sometimes need prompts or

assistance/discussion support as they make such decisions. This too should be individualized for the PWD circumstances.

A potential complication of trying to achieve tighter blood glucose control is an increase in episodes of hypoglycemia. This was reported in the multicentered North American DCCT[47] and confirmed in the multinational Hvidore study[48] but not reported from published studies in Belgium by Dorchy[49] and in Sweden by Ludvigsson [50] as well as this author in the USA.[3,4] Nevertheless, there are numerous reports on the deleterious effects of symptomatic and asymptomatic hypoglycemia on cognitive functioning in the child.[51] Clearly, there is a relationship between cognitive, motor functioning and hypoglycemia but each such episode idiosyncratic effects. As stated previously, the aim of treatment, therefore, is to achieve the best metabolic control possible without causing severe or excessive hypoglycemia. Hypoglycemia prevention becomes a key part of the education, re-education and treatment plan requiring not only monitoring but also intervention on the part of the CWD and appropriate adults at home, at school and at afternoon, vacation or weekend activities with scouts and sports events. The younger the child, the more likely the need for direct adult assistance and involvement with treatment especially since hypoglycemia is not totally avoidable with current treatment modalities. If there is already a pre-existing history of severe hypoglycemic episodes (seizures or loss of consciousness) or moderate hypoglycemia (needing assistance of others), this too should be documented in the treatment plan provided to the school staff by the diabetes health care team and specific requirements for availability as well as designated nasal or injectable glucagon administration must be enforced.[16,24] Hypoglycemic episodes that occur at school can be disruptive, take time away from other teaching tasks and may be embarrassing for the student in front of peers. Recognizing and treating hypoglycemia should be a priority for parents and health care providers as well as an important task for school staff.

**Diabetes Medical Management Plan (DMMP)**

Both parents and the health care team should work together to provide school systems and day care providers as well as after-school and weekend programs with the information necessary to allow CWD to participate fully and safely.[52] Efforts to exclude youngster with diabetes from all such activities should be actively discouraged and protected by laws and regulations as appropriate for

the situation. In meeting treatment goals and providing a safe environment, it is the responsibility of the parent and school personnel to work cooperatively in developing a care plan for the PWD.

A written plan of care (DMMP) is most effective since it provides a formal document upon which the school may rely.[23,24,53] This is especially important to acknowledge how many diabetes management tasks occur during school hours. For the very young child in a day care setting or the older child in school, an individualized plan of care that addresses needs related to all of the diabetes care components is essential. Including in such a plan must also be a plan for recognizing and treating acute emergencies such as hypoglycemic episodes and also sick days and ketoacidosis. Hyperglycemic events will occur but usually these are easily managed and not as physically or symptomatically disruptive compared to hypoglycemia but this also needs to be discussed and individually assessed to fit each PWDs needs and situation. An official request for an Individual Education Plan (IEP) or a 504 Plan adds some legal backup in the United States and similar civil rights may also be available in other countries. A free downloadable PDF format DMMP updated in 2022 is available (in English) from the American Diabetes Association's website (then search for Safe at Schools or DMMP) to move to the appropriate form that can be used as a template and translated into local languages and adapted as needed.

It has been reported that parents of newly diagnosed and younger children usually are very responsible in providing information to the school. However, parents and teachers have reported a reduction in care plan development as the PWD moves toward more independence and self-care with adolescence[54] when appropriate responsibility for care is often being or has been transitioned to the PWD. Nevertheless, other studies have repeatedly demonstrated the need for adult interaction and supervision in helping the pre-adolescent and teenager with such diabetes care.[55] This too should be individualized since there are some who still need such direct prompting and supervision while others readily accept such self-care responsibility and carry it out without problems. This message also needs to be translated to adults in contact with the adolescent during school as part of the PWD DMMP, IEP and 504 planning.[53-57] Parental diligence sometimes also wanes as parents get more comfortable living with diabetes but forget that the new

teachers each year do not have the same knowledge base, experience or comfort level so open discussions are key.

The diabetes care plan should address the specific needs of the PWD, delineate responsibilities and provide specific instructions for each of the specific areas of diabetes care. In addressing all relevant elements, questions of why, when, where, who and how should be documented with responsibilities specified for teachers as well as nursing staff in addition to those responsibilities of the parents and age-appropriate responsibilities of the CWD and who is the backup person when a school nurse or teacher is not immediately available or present.

**Blood Glucose Monitoring in School**

Blood glucose testing (self-blood glucose management, SBGM)[16,18,21] is the cornerstone of modern self-management replacing previous urinary glucose testing. However, such testing is expensive, not always covered by health insurance or government health programs sufficiently depending on local circumstances and laws as well as the diabetes care providers in those local regions.[2,20] Although SBGM provides helpful information for the student, parent and teachers, it can also be nuisance for the student during a busy school day. For some, it is embarrassing and emphasizes the difference that the PWD has from peers; for others, it is sometimes an occasion to actually explain what they are doing and why they are doing the SBGM. It is important for health care providers to explain why there is a need for a BG test during school since not all teachers or administration will fully understand the necessity. Some teachers and schools will readily allow in-classroom SBGM while others will insist that this only can be done in the nursing office; if the nurse is not always present, then the principal or another designated school staff person has to assume such supervisory responsibility, and this too should be discussed and agreed-upon through the DMMP and IEP/IDEA.[53-57]

Letters from parents and/or the diabetes team may be required to help school nursing and teaching personnel as well as school administrator understand that this is a legal and moral right of the CWD and part of their unique medical needs.[56,57] Issues involving hypoglycemia are the most difficult since they may be erratic in their occurrence and difficult to ascertain and also more likely to interrupt classroom situations especially if they escalate but BG confirmation (strip, meter or continuous glucose monitor) helps

in such decisions. A key benefit of school staff knowing how to actually perform capillary blood glucose testing (or check a continuous glucose monitor result) is their ability to then use this skill to actual ascertain hypoglycemia in real-time rather than merely rely upon more subtle symptom recognition alone or patient self-reporting. If some of the PWD's peers actually have become aware of what diabetes is all about sometimes they can also assist with needed reminders, treatment or even BG testing - if agreed upon in advance by the patient and family.

Parents, in turn, need to translate this partnership message to school personnel and provide parameters for blood glucose results so that algorithms can be developed for action by school staff as part of the DMMP. For example, parents need to communicate to the school their CWD's actual "target" blood glucose ranges and when parents should be notified, when and how to reach diabetes medical staff if parents are unavailable, what to do when hyperglycemia occurs (ie. booster insulin dosage) and how to respond to different levels of hypoglycemia (see below, mild, moderate and severe hypo's). School staff also needs to be reassured that blood glucose results outside of the recommended target range are not unusual nor cause for panic since lots of glycemic variability is usually the case. With more modern insulin pumps communicating with continuous glucose sensors [58] there is some evidence that computerized algorithms the past few years have significantly decreased glycemic variability, almost completely been able to alert the PWD (or family members) of impending hypoglycemia (using hybrid closed loop systems) and automatically reduce insulin provided to mitigate or avoid the hypo episodes. Some teachers and school nurses have also been able to access this BG information on their own mobile phones, as has become possible for parental review, for help with their own assistance using the same blue tooth wireless communication options. More recently, updated systems are also sending audible alerts when trends of hyperglycemia exist and then the automatic systems are able to respond by increasing basal dose and mitigating hyperglycemia as well - but this is not yet fully available while more and more hypoglycemia automatic response (hybrid closed loop, HCL, systems) has increasingly been adopted in keeping with FDA requirements for such HCLs.

Cost concerns are another barrier but these are steadily being overcome with documented published studies providing cost-efficacy, improved outcomes and health care costs[59] decreased as a result of

these technologies.[60,61,62,63,64,65] If concerns arise from teachers or any other school personnel, they should be able to consult with the school nurse and/or principal. Facilitation for communication with the CWD and parents should be encouraged and agreed upon as part of the written DMMP whenever such questions arise.

When blood glucose testing is done is highly individualized and should be agreed upon by the PWD, parents and health care team with specific written inclusion in the DMMP. Although most CWD monitor routinely before the mid-day meal, others may only test when documenting hypoglycemia or specific symptoms. CGMS makes this easier to accomplish and less disruptive for the PWD than finger-stick testing. The care plan should outline the routine times for testing e.g. before lunch or exercise, and always if the CWD is experiencing symptoms of hypoglycemia. New meters that test for blood ketones may require specific usage rules (or guidelines for urine ketone measurements) when blood glucose readings are elevated (see hyperglycemia/DKA section below).

Where testing occurs can also be a controversial issue. Although most health care providers and parents agree that testing should be available to the CWD at all times, some school officials fear problems with bloodletting devices outside the nurse's office. A designated space for routine testing is usually best and this should be discussed directly. Asking the PWD their preference for where such testing could be done, allows them some self-input, some discussions of peer pressure or need for privacy etc. For example, if the CWD tests before the midday meal, stopping at the nurses or school office may be the safest place and also affords the opportunity for school personnel to be involved in the process. This is especially important for younger children who may need assistance but some prepubertal and pubertal CWD also may need supervision. However, access to testing equipment is critical in documenting hypoglycemia and options for minimizing travel time to the nurse or principal's office compared to doing what needs to be done quietly and safely in the classroom without taking away time from lunch or gym periods. Ideally, the PWD should be permitted to test in their classroom, in the lunchroom or play yard and gymnasium (if necessary) so that there is no delay in getting to a school nurse or administrator's office.

As discussed, with hypoglycemia, it is best for a CWD to obtain a blood glucose level and for safety reasons shouldn't be sent to another room alone. This allows needed response to the results as quickly and conveniently as possible right in the classroom so not

having to move from classroom to nursing office, not always knowing if a nurse is present and available is avoided by allowing classroom self-care. This is important to avoid medical problems being worsened by a delay in testing/treatment and to minimize educational problems caused by possible mental confusion during a hypoglycemic episode in the classroom. As some students desire privacy during testing, this preference should also be accommodated.

Although the testing process has become much simpler with the "user friendly" blood glucose meters, smaller and quicker sampling (5 seconds with some systems), there has been some concern about safety issues and potential blood contamination or risks for infections by accidentally touching a needle or lancet or test strip. School personnel supporting the CWD need to be aware of proper safe storage and disposal of lancets and syringes as well as used glucose test strips but this is rarely a problem if openly discussed and sharps containers provided (in classroom, nurse or principal office). Fears of blood-borne pathogen contamination often are exaggerated and not based upon current medical knowledge of the extremely minimal risks for nearly all youngsters with diabetes or those around them in school. The health care team should discuss this directly with parents and older patients as well as serve as a resource with the school personnel involved to alleviate such fears and this too should be included in the written DMMP.

The situation and the age of the child will determine who actually should be in-charge of the SBGM. Meters made today are quite simple to use and very young children frequently perform their own blood glucose test with some adult oversight. Even though the child may be able to accurately perform self-testing, supervision and support should be available and a system for recording and communicating actual results should be established. Memory meters facilitate such communication since they can be viewed later in the day by parents at home and even downloaded and merged with other meter files to assess patterns of glycemic control.

**Insulin Administration**

As discussed, in the past, traditional insulin injections were given before and after the school day once or twice-a-day. With attempts to achieve euglycemia and the introduction of new delivery devices and improved insulins, CWD now frequently give injections or boluses of insulin many times each day usually pre-meals with adjustments of dosage downward for planned activity and upward for

increased food intake. Temporarily decreasing insulin doses in association with planned activities also helps better improve glucose results as well and much emphasis is lately paid to such adaptations with home and self-management planning.[1,2,3,4] Some use an insulin pump; others use smaller and finer needle tips with less scary-looking insulin syringes, semi-automatic jet injectors, insulin pens or syringe aids which have eased some of the burdens of daily management for many. The reasons for a particular insulin regimen should be explained to the school staff in a way that helps them understand the short and long term treatment goals. This probably needs repetition at the beginning of each school year initially by parents, and then, when the PWD is able and willing, directly with schoolteachers and other school staff. Written algorithms are extremely helpful for providing guidelines for dose adjustments and what to do under different circumstances for the younger CWDs as well as some general guidelines for all PWD as part of the written annual DMMP.[53-57] Parents should be allowed to adjust insulin doses with written "certification" that they are capable of making such decisions and, if the school insists, written authorization from the medical team can be provided. Older children should also have this option without the necessity of daily telephone communications with the diabetes care team if they are willing and able to make such dose decisions. Most schools find it useful to have a formal document with predetermined, approved algorithms for the CWD to rely on for direction included (and updated, as needed) in the DMMP. This prevents any dispute regarding the amount of insulin to be delivered. Extra syringes and insulin (refrigeration needed if an extra insulin vial is kept at school but no refrigeration needed if the PWD is bringing these supplies back and forth to school each day) as well as test equipment should be stored appropriately by school personnel in case these are forgotten at home or if preferred by the family. A safe, convenient place should be established for insulin administration as well as safe disposal of used equipment usually in the nursing office as discussed previously but sometimes also in the principal's office. If these tasks are done in the classroom itself, then similar accommodation should be provided.

Although most school-aged children should be able to administer their own insulin, exactly when such tasks are mastered and reliably performed needs individualized assessment and agreement. The school nurse may want to offer assistance in checking the dose and double-checking/confirming proper technique

and dose with younger PWD. Arrangements for giving insulin to very young children attending preschools or day care centers need to be made and this is equally important for the younger elementary school CWD. Most schools are willing to provide this assistance. There are more legal ramifications of refusing such medically needed care than in allowing appropriate medication administration by trained personnel. The PWD's diabetes health care teams should be ready and make themselves available for any emergencies or for routine questions to assist in teaching school staff; school staff should be willing to learn what is required to provide for this safe medical environment for all students and, at a minimum, annually before the school year begins, such discussions should be provided during outpatient ambulatory sessions by the diabetes team.[66] Lawsuits in the USA co-sponsored by the American Diabetes Association have guaranteed such student rights in recent years and similar circumstances may or may not exist around the world.

Continuous subcutaneous insulin infusion (CSII) is becoming increasingly popular in the management of CWD with more and more PWD using insulin pumps showing statistically improved quality of life as well as statistically significant glycemic improvements (SBGM, CSII).[61-65] School staff needs to be informed about the basic tenets of CSII and aware of potential problems for any CWD using insulin pump therapy. For example, staff needs to appreciate a student's request to be excused from the classroom for blood glucose monitoring, insulin administration, a site change or a urine ketone test without delay or penalty even if in the midst of an exam. Designated areas for privacy in performing these insulin pump therapy tasks should be predetermined and specifically written in the DMMP. As with all other aspects of diabetes care, circumstances to contact parents and/or diabetes health care team members should also be established and written in the DMMP. School staff should always feel free to communicate problems that they perceive with their students either with parents and/or with diabetes health care team members and this, too, should be specifically acknowledged and written in the CWD DMMP.[53-57]

**Meals and Snacks**

Nutrition therapy plays a key role in achieving metabolic control along with promoting optimum growth and development. The overall goal of nutritional management is to enable the CWD to attain blood glucose levels as near to normal as possible by integrating

exogenous insulin into the usual eating and activity patterns and daily changes that affect everyone with and without diabetes.[1-4,16,24]

The importance of nutrition and an update on current nutrition practices needs to be presented to school personnel. Community myths about food and the place of food in a diabetes treatment program may not be based upon current scientific knowledge or may mix up type 2 vs type 1 diabetes knowledge. School personnel are often unaware of the increased flexibility in current meal planning approaches and often base their responses to knowledge of dietary restrictions for what they know about adults or family members with type 2 diabetes. Rigid rules should be avoided and food must not become a source of frustration and argumentation while acknowledging that many school snack machines and lunch options are “less than optimal” (not only for those with diabetes but also for everyone else because of high sugar and perhaps also high fat and calorie content). Flexibility is essential associated with either carbohydrate counting, meal-planning and appropriate adjustments with activity and insulin as well as food as taught by the diabetes health care team. Rigidity often leads to protest and conflict, especially with younger children and, even more so, with many adolescents. Unless the school personnel are updated on current diabetes nutrition practices, the student's eating habits could be a source of contention. Carbohydrate counting has produced a great deal of flexibility for the child and adolescent in recent years but may not be understood by school lunch monitors, school nurses or teachers unless explained by parents and confirmed by the health care team in the DMMP.[53-57]

School staff should be made aware of the importance of timing in relationship to exercise and the actions and peaks in insulin, especially when insulin injections or boluses are given during school. Teachers must be made aware of the need for a readily available meal when rapid acting insulin or boluses via a pump are delivered so there is no delay of food when insulin has already been administered. Newer, faster insulins in recent years have helped decrease the wait time from insulin bolus administration to actual food intake so this is becoming less of an issue with this more rapid fast acting boluses.[1-4,16,24]

It is just as important for the school to provide information to the parents regarding availability of foods, timing, and known changes in schedules. Publishing school lunch menus or notifying parents of an upcoming party where snacks will be served is useful

in the total management scheme. Many CWD find it much more convenient and easier to manage when they bring home-prepared snacks and/or lunches rather than rely on what is available from the school so this too is an easier solution for many to consider and discuss.

**Exercise/Activity**

The benefits and risks related to activity need to be communicated to all school staff since they apply to people with and without diabetes. CWD should be encouraged to exercise and participate in sports while ensuring safety issues. No child or adolescent with diabetes should be excluded from school or after-school sports since diabetes management should allow accommodation for such activities provided that BG monitoring is adequate, supplemented appropriately for the timing and extent of the activities in an effort to allow modification of insulin and/or food accordingly. Education for the PWD is important with activity as with all other conditions that might have an impact on glycemic response. Having the diabetes medical team purposefully discuss what is to be expected with school-related gym or after-school sports with the CWD and family is an important concept that helps to minimize such problems, allows the team to provide new information as appropriate for the changing self-care and maturity of the CWD through elementary, middle and high school and college years. In most cases checking blood glucose levels prior to rigorous, unplanned activities is best and sometimes some more testing in the midst and/or after activity helps to provide a good learning experience for all involved and allows learning how to adjust better in days ahead. Teachers and students need to be reminded to reduce insulin dosage and/or add an extra snack if activity is prolonged and aerobic in style. Guidelines individually developed for each student should be shared with school personnel and included in the individualized written yearly DMMP.[53-57] Sometimes mid-exercise or post-exercise blood glucose testing should be accommodated in the classroom, gym, on the field or wherever needed.

Of course, the greatest risk associated with extra activity is exercise-induced hypoglycemia and all school personnel, especially gym teachers and coaching staff, need to be trained to recognizing subtle and common symptoms of hypoglycemia and how to respond (eg. changes in usual performance, not paying attention or following instructions). An individual diabetes-specific written DMMP should

include parameters for blood glucose ranges in which exercise is permissible to proceed or should be delayed pending correction of already present hypoglycemia or near-hypoglycemia. Lower and upper limits of blood glucose ranges should be documented for teachers, coaches and athletic supervisors to make sound decisions that keep students participating in sports with peers and also provide for student safety. This allows decisions for not only insulin adjustment but also potentially extra food or fast-acting sugars to allow activity participation safely.

**Hypoglycemia** (see *Table 1*)

Low blood glucose (hypoglycemia; sometimes called hypos or reactions) is the most common immediate health problem for students with diabetes.[67,68,69,70]

The plan of care[71] should clearly outline symptoms (confusion or inattentiveness, moodiness, irascibility, inability to perform known tasks) signs (pallor, shakiness, crying, inexplicable anger or inability to follow instructions, dizzyness, inability to walk or maintain posture, falling asleep at the desk, falling to the floor, loss of consciousness or seizures) and specific treatment parameters (who can do what, where the testing and treatment will be stored etc.). For most mild and moderate episodes, oral glucose or sucrose in the form of juice, sugar-containing liquids such as non-sugar-free soda, glucose tablets or gels; glucagon for severe episodes. Recently released nasal glucagon[73] or prefilled glucagon pen or syringe injection for severe episodes must be available at school with several appropriate school staff besides only the school nurse (who may not always be present) for the most severe hypoglycemic episodes although most hypo events will be mild or moderate and not severe enough to require glucagon.[1,2,3,4,16,24]

Parents of very youngest children need to be especially clear and explain even the subtlest signs of low blood glucose but the DMMP[53-57] should include the usual symptoms for the CWD as understood by all PWD as well as their family members as proposed in *Table 1*.

*Table 1. Recognition and Treatment of Hypoglycemia*
(low blood sugar or insulin reaction; sometimes called “hypo’s”)[72]

Hypoglycemia is the most common medical emergency you may encounter in the school in a CWD. IT REQUIRES PROMPT

RECOGNITION AND IMMEDIATE TEATMENT. The most likely times to suspect low blood sugar would be close to or before a usual meal or snack as well as following physical activity such as recess, gym, band marching etc.

**RECOGNITION**

A. Early Warning Signs (adrenalin response to try to correct the low sugar)
   1. Shakiness and tremors
   2. Pale appearance
   3. Rapid, strong pulse
   4. Unusual sweating
   5. Unusual hunger
   6. Not paying attention or being able to follow instructions

B. Central Nervous Systems Signs (caused by lack of sugar to the brain)
   1. Sudden mood swings or inappropriate behavior
   2. Tiredness, fatigue or sleepiness
   3. Inability to concentrate or pay attention
   4. Headache
   5. Confusion or garbled speech
   6. Yawning

C. **Mild Hypoglycemia**: able to recognize hypoglycemia and self-treat

D. **Moderate Hypoglycemia**: able to recognize hypoglycemia but needs assistance in treatment

E. **Severe Hypoglycemia**: unable to recognize hypoglycemia and unable to self-treat: must be treated with ***emergency injectable or nasal glucagon*** (or in ambulance, emergency room or hospital with intravenous glucose)
   1. Loss of consciousness
   2. Convulsions/seizures

**Treatment**

Treat as soon as you recognize symptoms (ie. early warning signs). Initial treatment should be done in the classroom, without disruption when possible. If a blood glucose strip or meter is available, this will answer the question with values <70 confirmatory. Severe hypoglycemia with loss of consciousness or convulsions/seizures must be treated with intravenous glucose or with nasal or injectable glucagon. Attempting to get someone unconscious or convulsing with something to drink or to eat, is too dangerous because of risks of aspiration or asphyxiation.

For those fully awake but needing assistance (moderate hypo) or those self-treating (mild hypo), treatment with one of the following three fast-acting sugary recommendations is usually what will be required. If in doubt as to whether the symptoms indicate low blood sugar and/or no testing is possible, it is always best to treat with one of the following to avoid exacerbation/worsening of the hypoglycemia by further delay:

1. 4-6 ounces of any type of fruit juice or sugar-containing soda (not diet soda)
2. One tablespoon or honey or sugar or one sugar packet
3. Commercially prepared items such as glucose tablets, Insta-glucose if this has been provided and available

If symptoms do not subside within 10 minutes, repeat the treatment. Document a blood glucose level if available and consider whether or not a second glucose determination is needed about 15 minutes after treatment. If there is worsening symptoms or no response, call for emergency help from the principal, administrative staff, school nurse or call 911. Notify parents, school nurse and administrative staff as time permits. Moderate hypoglycemia can be treated in the same fashion as well as with nasal glucagon (or injectable glucagon) if this is available. Severe hypo's will not only by definition need assistance by someone other than the PWD but also will be required to have emergency nasal or injectable glucagon (or emergency intravenous glucose) immediately provided because choking may occur if not fully awake and able to swallow without aspiration.

*Other Recommendations*

1. If a meal or snack is not scheduled after the above treatment within the next 15 minutes, follow initial treatment with a protein and carbohydrate combination snack such as milk, cheese or peanut butter and crackers,
2. NEVER leave a PWD alone during the low blood sugar reaction and keep them supine laying on their side to decrease the chances of vomiting and choking/lung aspiration
3. You cannot harm a CWD by giving sugar if the blood sugar is not low since all such treatment will only increase the blood sugar level for a short period of time
4. If the CWD is unable to swallow liquids or food, is unconscious or having a seizure, glucagon by nasal spray or by injection, depending upon what has been provided,

may be administered by anyone on staff who has been trained to do so (ie. school nurse, principal, administrative staff, teachers, aides, coaches etc.) Recently available nasal glucagon emergency plastic spray devices cause only minimal nasal irritation so are replacing previously available injected glucagon kids. Glucagon causes some headaches and sometimes nausea and vomiting by either nasal spray or injection and both ways of providing glucagon work equally well to rapidly raise low blood sugar levels within minutes

5. Follow DMMP for notifications to parents
6. Discuss with school staff and consider notifying parents as well as CWD, if sufficiently mature, of concerns about repetitive hypo events

If possible, it is useful for mild and moderate hypoglycemia to be validated with a blood glucose test (or sensor check) but under emergency conditions of loss of consciousness and/or convulsions (severe hypoglycemia), treatment with nasal or injectable glucagon should be available and provided immediately. No delay for getting meters, lancets, BG strips or waiting for results should occur with glucagon administration for severe hypo's … but with a blood glucose test taken immediately afterwards and perhaps 15 minutes or so after whatever treatment is provided to document improved increase in blood glucose level and/or need for further food or sugar (see *Table 1*). It should be acknowledged by all involved that glucagon is a safe emergency drug with minor stomach upset and headaches as usual side effects but lifesaving when there is a moderate or severe hypoglycemic event and urgently provided and always available. This is not only important for young CWD who often cannot verbally express symptoms, but older CWD have been known to mistaken nervousness or anxiety for a low blood glucose. Teachers should also be made aware that validation of hypoglycemic symptoms might be particularly helpful for them to be able to recognize in a CWD who has hypoglycemia unawareness or is frequently experiencing too frequent low blood glucose symptoms. Such less common difficulties may be a signal to be concerned about compliance issues or other emotional/psychosocial concerns in the PWD.

CWD, especially teens, have been known to feign problems ("I'm having a reaction") in an effort avoid class or gain some added attention; documenting actual BG levels can be very important in figuring out repetitive issues. Recent availability of nasal glucagon

with easy, plastic nasal devices[73] are likely going to replace vial and syringe glucagon as well as prefilled glucagon pens because they work, they are not scary (small, nonintrusive plastic disposable devices that instantly mix glucagon powder in a liquid that is sprayed not the nasal area) and they do the same job without any added side effects except for some minor nasal irritation compared to injectable formats. *Table 1* can be provided for all school personnel for review and kept with the glucagon supplies provided at the beginning of each year as part of the DMMP with a copy kept at the teacher's desk as well as school nurse's desk for quick reference needs.

The necessity of educating all school personnel about how to recognize and treat hypoglycemia cannot be overemphasized. Multiple school personnel working with CWD of all ages should be trained in each school on the basic steps of blood glucose testing in the event that a PWD is confused and unable to test independently (by definition, a moderate or severe hypo event). In addition, CWD may require a reminder (prompt) to eat or drink during any hypoglycemia instance and should not be left unsupervised until such treatment has taken place and observed … and the blood glucose value has been documented and returned to the normal range defined in the DMMP.

Studies have shown that it may take up to one hour for the brain fully to recover completely from glucose depravation so a period of followup observation by school staff is also wise. Students should not be expected to take exams, give presentations, drive or participate in an athletic activity until they are fully recovered. Make-up tests or assignments should be easily arranged without fuss and all of this should be reviewed with the CWD, parents, school nursing staff and teachers as well as included in writing in the DMMP. If there is disagreement or lack of appropriate followup, having such discussions written, discussed and co-signed by all parties minimizes future conflicts.

In achieving tighter glycemic goals, the risk of hypoglycemia generally increases [35] unless the PWD is using a hybrid closed loop pump with connected sensor to alert and/or self-adjust insulin provision. Many parents today request and agree that school personnel be trained on glucagon administration. This is quite reasonable for the safety of the PWD and can be confirmed by the diabetes medical team working with the PWD and family. Although the need for a glucagon is rare, many schools have been reluctant to assume this responsibility for its administration in such emergency

situations. As a result this issue has led to great debate and sometimes attorneys have been involved to force the school to have appropriate nursing or designated staff correctly trained since legally the CWD has the right to attend and participate in school even if they have diabetes. Regulations and laws differ from district to district, state to state and country to country. The safety and well-being of the CWD must be regarded as the highest priority and efforts to advocate for this are paramount including getting politicians involved to create appropriate laws and enforcement options for all. Transitioning to treatment with nasal glucagon instead of injectable glucagon[74] in recent years has eased some of these concerns because of the non-scary nature of using small, disposable, plastic nose-spray devices compared to glucagon pens or glucagon vial and syringe systems. The devices themselves look like the ones that most people have seen or used for allergy or viral colds and learning how to use them takes less than five minutes. When moderate of severe hypo's take place, any delay or hesitation in obtaining and administering glucagon, can allow worsening of symptoms and signs of the hypo event. It is not medically appropriate to insist that ONLY nursing staff provide such testing or treatment but, rather, that available staff be they teachers, classroom aides, coaches, gym teachers, principals and assistant principals and counselors can ALL safely and legally learn how to do such glucose testing and emergency assistance in a manner which gives them the education and skills to carry this out appropriately since school nurses are not always present or available. The PWD's life may be at stake if this is not set up appropriately. Information and assistance well as education tools are available from the American Diabetes Association and most national diabetes associations around the world from their websites or after telephone consultation. (ie. www.diabetes.org for the ADA). Similarly, your health care team will likely have such information also available if requested and may also be able to directly be in communication with the schoolteachers, coaches, administration and nursing staff. Many teams have free community education programs annually to up-date information for interested staff and this has been incredibly valuable to consider if your team is not doing so at present. Children with Diabetes (www.chldrenwithdiabetes.com), Juvenile Diabetes Research Foundation (www.JDRF.org), www.LearningDiabetes.com (nurse educator Jean Betschart Roemer's website) and (www.ndep.nih.gov/diabetes/youth/youth.htm) at the National Diabetes Education Program all have available information,

guidelines and pamphlets and booklets available for parents, PWD, school nurses, teachers and other school staff interested and involved. More specific information in numerous excellent diabetes teaching manuals; these are available in multiple translations for the PWD and family education and also for school staff as well. All health care insurance coverage, whether provided by government, employer or self-paid should cover all prescribed glucagon preparations with minimal or no deductible or self-payment costs because of their emergency need for the PWD. Hopefully, the easier and less scary nasal glucagon preparation will also be available around the world shortly for all the reasons already mentioned. The original glucagon vial and syringe preparations which are more difficult to teach, more scary to contemplate using a syringe for someone not used to using syringes and require the extra step of mixing the diluting fluid with the powdered glucagon before injection so adds further delay. This has been overcome by alternative prefilled glucagon syringes as well as auto-injectable glucagon format but the nasal version seems to provide the same benefits the same rapid increase in blood glucose levels for emergency situations, and aside from some mild nasal irritation, the same headaches and stomach upset as comparable older glucagon preparations in numerous safety and efficacy studies to date. Parents, family members and family friends as well as non-medical staff at schools have easily and quickly learned to use both the autoinjectors as well as the nasal glucagon in the past few years of their availability so should receive strong recommendations for obtaining these products, gaining more international approvals and more NGO supplying around the world.

**Hyperglycemia**

Ordinarily, hyperglycemia should not present a problem for the school staff. Education for school personnel should include the causes and signs of hyperglycemia but treatment during the school day should not be the focus of care plans except for allowing slightly higher dose adjustments when hyperglycemia presents itself per agreed-upon guidance. Unless there is an acute illness or chronic adherence issues, diabetic ketoacidosis (DKA) would be highly unlikely to arise as an issue although periodic hyperglycemic glucose results at times of acute stress or anxiety, illness or peaks after overeating could always occur and are actually quite common with type 1 diabetes.[1-4,16,24] Under most circumstances, intermittent hyperglycemia can be treated with appropriate insulin correction

algorithms (dose boosters) or with temporary adjustments/changes in the snack or meal at school as agreed upon in the written DMMP.[53-57] If school staff are worried about repetitive, symptomatic hyperglycemia or positive urine or blood ketone test results, part of the written medical plan for the child or teenagers should include when and how to contact parents or direct communication with the CWD's medical team. Guidelines for urine or blood ketone testing should be followed and results communicated to parents as agreed upon in the written DMMP. This is particularly important when someone is being treated with an insulin pump since early recognition of pump failure or occlusion/site disconnection problems involves recognizing unexpected hyperglycemia, ketonuria and/or ketonuria especially if significantly higher than usually experienced.

Symptoms of hyperglycemia can be disruptive to the school day and affect the child's learning capability. Tiredness, frequent trips to the restroom and drinking fountain remove the CWD from classroom time and limit opportunities in instruction and may play a part in peer pressure or bullying. Frequent or prolonged hyperglycemia may eventually effect cognition although in a manner different from hypoglycemia. If reports and symptoms of hyperglycemia are chronic during the school day, teachers should alert the parent. Omitted insulin (diabulimia) and/or overeating, sneaking sugary foods or snacks or psychosocial problems such bulimia, anxiety or depression may be the cause. If management techniques planned at home don't resolve the problem, telephone communication and sometimes a face-to-face group conference with health care providers, parents and school staff may be necessary.

**Responsibility for Care**

Children and youth should be able to implement prescribed diabetes care at school to the extent that is appropriate for the student's development, ability and his or her experience with diabetes. The extent of the student's ability to participate in diabetes care should be agreed upon by the school personnel, the parent/guardian, and the health care team, and individualized for the PWD's situation. All PWD of any age should always wear medic-alert identification either as bracelet or a necklace, if these are available. This should be discussed with parents and the CWD including the rationale for such emergency identification. Discussing what may be expected and specifics with the CWD themselves is also to be encouraged since some may prefer to discuss their diabetes and

some may want this less public. Some will prefer going to the nurse or principal's office for such tasks while others would refer staying in the classroom and listening to what is going on instead of being absent for some of the time. Often teachers can incorporate a health or science lecture about tasks or living with diabetes and "star" the CWD,[75] if they are willing and able to explain why they are testing their blood sugar levels, how might someone help them re: hypoglycemia events etc. Over many years, many patients of mine when they have agreed to openly discuss their diabetes, find that there is much interest, many questions and often this opens up positive discussions with their peers in ways that they wouldn't have supposed possible. Such care decisions may change with increasing maturity and self-care responsibilities, too. The ages at which children are able to perform self-care tasks also are very individual and variable, and a CWD's capabilities and willingness to provide self-care should be respected with open discussions at home as well as with their medical team.

Children develop the psychomotor and cognitive skills to handle diabetes care tasks at different chronological ages and varying rates. Most CWD, however, have characteristics at specific developmental stages that can serve as a guide in assessing the CWD's need for assistance and/or supervision.

1. *Infants, toddlers and preschoolers in day care.*[76] The very young child is usually unable to perform diabetes tasks independently. Food choices and intake need to be monitored by an adult. Usually by 4 years of age, most children may be expected to generally cooperate in diabetes tasks. Baby-sitters and other caregivers such as older siblings or relatives need to be alert to signs of hypoglycemia and trained on treatment especially focusing on subtle hypoglycemia, treatment guidelines and the emergency administration of glucagon.
2. *Elementary school.* The CWD should be expected to cooperate in all diabetes tasks at school. By age 8 years, most children are able to perform their own blood glucose tests initially with supervision and they are beginning to learn about appropriate food choices. By age 10, most children - but not all - can administer insulin with supervision – but continue to need such adult supervision and oversight especially double checking dosage, leakage and techniques.
3. *Middle school or junior high school.* The student should be able to administer insulin with supervision, make food choices and

perform self-monitoring of blood glucose under usual circumstances when not experiencing a low blood glucose level or have some other cognitive issue (ie. Down Syndrome). Parental supervision as well as family support gradually lessens with increasing maturity and self-care responsibilities but all this is highly individualized. Discussions with the diabetes health care team should include such advice and guidance.

4. *High school.* The student should be able to perform self-monitoring of blood glucose under usual circumstances when not experiencing low blood glucose levels. In high school, adolescents should be able to administer insulin without supervision and follow their own meal plan. The adolescent should be aware of how to determine appropriate food choices, make insulin adjustments (by injection or pump) based upon blood glucose readings, recognize problems with hyperglycemia and sick days (with increased monitoring if not using CGMS as well as ketone testing) as well as self-treat mild episodes of hypoglycemia. Moderate or severe episodes of hypoglycemia, by definition, require the assistance of others and this falls upon the school staff and personnel although peers in school, on athletic teams or in other group settings like scouts) may be taught to help as well. Care during intermittent illness usually can be self-provided but sometimes with such illnesses, assistance from parents or other family members is available and welcome. This unfortunately is also a time period when such independence can run amok and under such circumstances, eating disorders, alcohol and marijuana use as well as nicotine use can have big impacts on diabetes management. This can be conflated if there are concomitant other medical problems with cognitive difficulties, omitting insulin to avoid weight gain (diabulimia) or gain parental attention by always needing to be seen in the emergency room etc.
5. *University college student.*[77] The adolescent and young adult preparing to go to university should be expected to be fully independent in diabetes care but this also varies with each individual circumstance. Responsible parents and health care providers are wise to provide a review in helping the student make such transition with appropriate assistance by relationships with members of the diabetes health care team.

Students preparing for university need to be reminded to train roommates about hypoglycemia, wear medic-alert identification, maintain health care and visits and about special situations like use of alcohol, marijuana, contraception and dating. Sleeping late when away from home poses special problems with severe hypoglycemia the most obvious acute risk but deterioration in overall glycemic control also possible depending upon erratic schedules, school exam stress, sports activities coupled with often living away from home so without parental or family support. This is frequently a time when followup medical team appointment are cancelled or missed because of distance or other concerns so awareness can help mitigate such issues.

**After-school care**

When both parents are working and no extended family or friends are available, especially with younger CWD, babysitting arrangements obviously need to include the adults involved with providing such care and observation as well as instructions about snacks. CWD after school often participate in after-school sports or extended school programs and so the adults in charge need education and hypoglycemia symptoms as well as treatment options discussed. This should be encouraged and appropriate staff educated as already mentioned. Personnel for such program should be aware of the diagnosis of diabetes and aware of all the same issues as all school staff. The association of extra activity with hypoglycemia is particularly likely in the later afternoon, early evening especially if dinnertime will be delayed as well as on weekends and vacation time if adjustment of food and/or insulin is not routine.

**School sports**

Gym coaches or activity supervisors during school hours, during intramural or extramural sports, must be aware of the diagnosis of diabetes and must be aware of the subtle and overt symptoms and signs as well as the risks of hypoglycemia and how these can be prevented or mitigated. Sometimes practice sessions are more intense than actual sports games and hypoglycemia risks may be increased accordingly. Allowing blood glucose testing before, during or after such activities should be encouraged and school personnel responsible for such activities should be trained in the individual needs of the student with diabetes who is also

participating. Summer camping activities often will involve more concentrated exercise and so diabetes issues must be addressed by PWD participating accordingly. Specific diabetes camping activities have been around for many decades and have successfully provided not only disease-specific peer contact and support but also demonstrated the manner in which increased activity can be safely and successfully managed.[78]

**Type 2 diabetes**

Although type 2 diabetes has been considered rare in the pediatric population, there has been an increased incidence reported throughout the world especially in the pre-pubertal and adolescent as well as young adult age groups[79,80]. The common denominator in most of the younger PWD adolescents is their weight excess, usually not unknown to them individually or their family, as well as positive family history not only of overweight but also type 2 diabetes, hypertension and cardiovascular medical diagnoses. So environmental and family interaction as well as genetic risks all combine to see the rise in HRC as well as LRC and MRC regions. Known risk factors for the PWD with type 2 diabetes include acanthosis nigricans, hypertension, hyperandrogenism, menstrual problems, being overweight, high caloric intake and low physical activity. Schools, of course, contribute to such problems because of poorly designed school lunch programs, frequent candy and soda machines on school grounds and decreased physical activity sessions. Therefore, the increasing incidence of type 2 diabetes among pre-teens and adolescents as well as young adults appears to be a consequence of the well-documented increase in obesity combined with a decrease in exercise leading to an earlier presentation in genetically susceptible patients. The pathophysiology of this epidemic involves insulin resistance at a much earlier age than was present in the past. This is especially true in descendents of the non-Caucasian populations not only in the USA but also around the world: African Black people as well as African Americans, Asian and Arab populations as well as Asian-Americans, Latinos and those living in Latin America and indigenous populations such as the Australian aborigines, American Indians and Inuit. Asian ethnic groups tend to have significantly less adiposity compared to the other groups, presumably from genetic but as yet not specifically identified reasons.

Reduction in total body fat and improvement in exercise tolerance are the most effective means of overcoming insulin resistance and insulin resistance is the hallmark of early or frank type 2 diabetes mellitus[81]. It is important for school personnel to be aware of this growing epidemic, its prevention and treatment. Were more school staff aware of the details of this epidemic, then nutrition and physical activity at school might change in an easier fashion. Education should include a list of the signs of type 2 diabetes in youth: obesity, acanthosis nigricans, hirsutism and acne as well as its association with obvious problems like hypertension, hyperlipidemia, and polycystic ovarian problems. Teachers and school nurses can often be a resource in helping with earlier detection (eg. visible acanthosis which prompts not only BP determination but also discussion) and promotion of healthier eating, appropriate snack and lunch options as well as improved activity behaviors in the prevention and treatment of this disease. Monitoring is less rigorous than with typical type 1 diabetes but, more recently, studies involving sensor use and these results providing more and better feedback with CGMS have shown promising results[82] despite less glycemic variability in younger PWD with type 2 diabetes than those with type 1 diabetes on any typical SMBG or CGMS review.

**Summary**

With proper planning and the education and training of school personnel, children and youth with diabetes can fully participate in the school experience. Videotapes and written instructions are available to be shared with school personnel to aid in this task.[83,84] Many local physicians involved with diabetes care for children, adolescents and young adults will be interested in providing such training sessions once-a-year for teachers and school nurses as well as any other interested school and after-school staff if not already doing so. The childenwithdiabetes.com web, Life for a Child (LFAC) website (www.lifeforachild.org), Changing Diabetes in Children (CDIC) website (www.ispad.org/changing) as well as the Juvenile Diabetes Research Federation (www.jdrf.org) and the American Diabetes Association (www.diabetes.org) web sites have information in numerous languages and translations that will be helpful for educating school staff as well as PWD and family/friends – and can be shared - as do more and more local/national diabetes associations and diabetes biopharmaceutical and equipment providers. To this end, the family, the health care team, and the school should work

together to optimize creating and maintaining a safe learning environment, to minimize any subtle or direct discrimination in the school and to ensure that students with diabetes are fully integrated and receive the best education possible while in school.

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# THE USE OF CGMS IN CHILDREN WITH DIABETES MELLITUS TYPE 1: BETWEEN CHALLENGES AND BENEFITS

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## Introduction

It is unanimously recognized that the clinical onset of type 1 DM represents the end of metabolic alterations. In these conditions, the treatment aims at an insulin substitution that is desired to be as close as possible to the physiological secretion of insulin in order to prevent the occurrence of hyperglycemia and / or hypoglycemia responsible for the installation of complications.

Of equal importance to insulin therapy are: specific nutrition, physical exercise and specific medical education.

Euglycemia is the main goal of DM treatment.

The use of self-glycemic control by determining blood glucose from capillary blood, used intensively in the last 30 years, has proven over time to be a method of monitoring glycemic balance with inherent limits induced by the technique of obtaining the drop, the small number of glycemic determinations / day and especially the impossibility of predicting the evolution of glycemic excursions.

The main idea that emerges from the onset of diabetes is that diabetes is an ambivalent disease, both acute (each patient's day is fragmented by determining blood sugar, determining the dose of insulin and administering it, calculating carbohydrates, etc.) and chronic (the patients' life having the imprint of the risk of installing chronic complications).

In the category of classical means of evaluating long-term glycemic balance, HbA1c was considered, according to the DCCT study, the "gold standard". Time has proven that HbA1c does not reflect the fluctuations (glycemic excursions) that can lead to acute

events (especially postprandial hypo-/hyperglycemia), so it does not give a 100% guarantee of clinical recommendations for a specific and effective adjustment of insulin treatment in patients with DZ type 1.

From the beginning, the medical team's efforts are mainly aimed at hyperglycemia (secondary prevention) in order to remove the risk of chronic complications as much as possible over time.

The results of the DDCT study showed that the reduction of the HbA1c value is directly proportional to the reduction of the percentage of patients who develop chronic degenerative complications. Thus, lowering the HbA1c value by 1% reduces the risk of vascular complications by 37%.[1]

In this sense, the current therapeutic guidelines recommend for children with type 1 DM as a therapeutic target an HbA1c below 7% with the maintenance of blood glucose values, regardless of the time of day (pre-, postprandial, bedtime and nighttime), below the renal elimination threshold but without reach hypoglycemic values.

Despite all the efforts of the companies (obtaining new insulin molecules, new injection devices, modern methods of self-glycemic control) studies show that the recommended therapeutic targets (HbA1c < 7%) can be reached in the pediatric age group only in a small number of patients (below 25%) regardless of whether we are talking about preschool, school or adolescent children. On the other hand, numerous studies have shown that adolescents, around the age of 17, have the highest HbA1c value (9%) among all age groups of type 1 DM patients.[2]

Given that more and more cases of DM type 1 are diagnosed in children at younger and younger ages, the risk of developing chronic complications increases due to the duration of exposure to the disease during the period with the greatest neuro-endocrine vulnerability (determined by periods of growth and puberty).

Ample evidence shows that in both children and adults with DM there is mild brain dysfunction and even structural brain changes as a consequence of diabetes.[3]

The brain is a complex target organ among the complications of diabetes; in childhood and adolescence, the brain has a significantly increased risk for damage to the white matter (with impact on myelination) but also to the gray matter. Glucose uptake in the brain is known to reach adult rates by age 2 and double by age 5, followed by a gradual decline to adult levels over the next decade.[4]

The brain does not store glycogen but relies on a continuous supply of glucose from the blood. During hypoglycemia, cerebral

blood flow increases very little in children, so this mechanism alone is unlikely to explain the maintenance of glucose utilization. For this reason, severe episodes of hypoglycemia in childhood can cause deterioration of neurocognitive functions.

On the other hand, studies have shown that there are significant inter-individual differences in vulnerability to hypoglycemia. [5]

Children and young people with DM have an increased risk of developing neurocognitive disorders, with information processing difficulties, learning difficulties, especially those with an early onset of the disease or with recurrent severe hypoglycemia. Although it is not clear why, these disorders are more common in boys than in girls.

Adaptive responses to hypoglycemia may vary depending on the degree and frequency of previous hypoglycemia and the presence of structural brain changes induced by chronic hyperglycemia. High frequency and early exposure to severe hypoglycemia during brain development negatively affects long-term spatial memory performance.[6]

As a consequence, academic performance in children who have low metabolic control is lower.

It should be noted that the full recovery of cognitive function is not simultaneous with the restoration of euglycemia, a fact proven in tests that require quick reactions and decision-making (choice of reaction time). The very high degree of intersubject variability suggests that, in addition to plasma glucose values, a number of other unknown physiological variables are responsible for triggering cognitive impairment in school-aged children with diabetes during an episode of hypoglycemia even and light.[7]

Imaging studies (MRI scan) showed that severe hypoglycemia slowed the normal increase in white matter volume in the occipital/parietal region, possibly by interfering with normal myelination or directly damaging the white matter.[8]

As a conclusion: hypo- and hyperglycemia have qualitatively different effects on cognitive function in T1DM, which depend in part on the timing of exposure during development, independent of the age of onset.[9]

This information extends the known benefits of avoiding both chronic hypoglycemia and hyperglycemia during childhood to preserve specific cognitive abilities.

The child's cognitive development includes all the processes that lead to the maturation of their mental activity.

According to Jean Piaget's biological concept, cognitive development takes place in stages that go through a certain order. So:

a. the "sensorimotor" stage that takes place from birth to 2 years is the stage in which the child uses his senses and activity to explore the environment;
b. the "pre-operational" stage takes place from 2 to 7 years and is the period when the child thinks intuitively, symbolically without logic, which is why he does not have the ability to perceive himself separately from others in his microclimate;
c. the "concrete - operational" stage runs from 7 to 11 years old and is characterized by the child's ability to think logically and in an organized way. At the end of this stage, the capacity for abstract thinking develops.

The socio-cultural scheme of cognitive development (Leon-Vygotsky) states that after the age of 2, cognitive maturation consists in the acquisition of skills that will in turn shape their mental representations.

The third model of cognitive development is the "computer-like" model. According to it, the child uses stereotypes that help him to: process information from the environment in which he lives, encode information within a mental system of symbols and record information.

It is known that prolonged hyperglycemia causes apoptosis. Studies have shown that apoptosis (cell death) was triggered to an even greater degree when cells were exposed to glycemic variability (*Risso et all*), variability that significantly increases oxidative stress (*Ceriello et all*), and triggers inflammation (*Piconi et all*) promoting the binding of monocytes to the intima of vessels to a much greater extent than in euglycemic conditions (Azuma et all & Watada et all)

Based on these records, it is the duty of all care teams for children with type 1 DM to make efforts to generalize the recommendations that support: replacing meal planning with carbohydrate calculation, using continuous glycemic monitoring systems and intensifying insulin therapy by switching to pumps of insulin.

**Arguments.**

***Limits of traditional methods of assessing glycemic control.***

Time has shown that self-monitoring of blood glucose by determination of blood glucose (SMBG) has inherent limitations that can affect its usefulness.

- the need to prick a finger to obtain a blood sample may negatively influence patient adherence to prescribed regimens,
- is not feasible (or desired) at work or school,
- is susceptible to errors due to faulty testing technique (inadequate blood sample, presence of contaminants on fingers etc.[10]
- not all commercially available devices comply with the recommended standards,
- measures glucose only at a single "moment in time" and does not provide information about direction or rate of change, cannot predict impending hypoglycaemia.[11]
- does not provide hypoglycemia alerts.

Use of SMBG data in isolation may lead to incorrect therapeutic decisions. [11,12]

On the other hand HbA1c:

- only provides an average of blood sugars over the last 6-8 weeks,
- does not reflect daily glucose fluctuations, glycemic excursions from one day to another that can lead to acute events (postprandial hypo- / hyperglycemia), variability or time spent in the optimal range,
- it is an unreliable measure in patients with certain types of anemia[13], hemoglobinopathies[14] and iron deficiency[15], as well as during pregnancy[16],
- correlation with mean glucose differs significantly between races. [17]
- it is therefore an incomplete marker that can mislead patients because it does not provide a reliable basis for correct clinical recommendations for the specific adjustment of insulin treatment regimens in patients with Type 1 DM.

Given these inconveniences, "we have to look beyond the Hba1c value". HbA1c does not provide information on: TIR, frequency/duration/severity of hyperglycemia, frequency/duration/ severity of hypoglycemia, glycemic variability. All of this information is patient-centered short-term information that can only be obtained using CGMS.

Recently, continuous glycemic monitoring (CGM) systems have made their place in the management of type 1 DM, providing more information to both the medical team and the patient. The analysis of the data obtained in real time as well as the retrospective reports downloaded from the application, at desired time intervals 14, 30

days), achieves, for each individual patient, a much more complete picture of glycemic patterns (day, night, degree of glycemic variability, etc.).

**Material and method**

The studied group was represented by 84 children with DM type 1 who were fitted with CGMS in the regional center of the II Pediatric Clinic of the Timişoara County Emergency Clinic Spit. The patients came from the 6 counties in the west of the country methodologically arrondissement of the regional center.

At the beginning, the child and at least 1 parent benefited from the same training program, the follow-up of the patient then returning to the attending physician.

Patients in the study group benefited, free of charge through the national diabetes program, from the same real-time CGMS (rtCGM) Guardian Senzor 3. This CGMS consists of an implantable sensor, transmitter and a receiver represented by a smartphone on which the application has been downloaded Guardian Connect.

The sensor is a minimally invasive electrochemical sensor that measures interstitial glucose concentration via a small transcutaneous electrode placed under the skin of the abdomen or arm. Oxidation of glucose near the sensor generates a current signal, which is then converted into a glucose concentration profile.[18]

The sensor measures interstitial glucose concentrations in the subcutaneous tissue almost continuously and provides an average of the determined values every 5 minutes (so 288 determinations/day) for 7 days. [19]

In order to verify the results obtained, sensor calibration was practiced by introducing the glucose value obtained from the capillary blood into the application at least 2 times/day (morning and evening at 12 hours interval before the meal and before the insulin injection).

The application downloaded on the smartphone provides access to a series of information: the current blood glucose value, the rate (speed of decrease / increase of blood glucose), event markers (insulin, physical exercise performed, mass), the trend line of the sensor.

In all patients, somatometric indices (weight, height), insulin requirement (I.U./kg body weight), HbA1c, parameters of lipid metabolism (Total cholesterol, HDLc, LDLc, Triglycerides), renal function (urea, creatinine, eGFR) were determined quarterly. , vitamin D.

At the same time intervals, the changes in glycemic parameters were analyzed by analyzing the reports obtained by the sensor: time in range (TR), i.e. the percentage of time in which the patient's glycemic level is between 70 - 180 mg/dl (3.9 - 10.0 mmol/L), time above range (TAR) with the two levels of hyperglycemia (level 1 = 180 – 250 mg/dl, level 2: blood glucose = 251 – 400 mg/dl), time below range (TBR) with the two hypoglycemia levels (level 1 = 54 – 69 mg/dl and level 2 < 54 mg/dl), the glucose management indicator (GMI) and the coefficient of variation (CV).

According to the ISPAD Guide, the therapeutic targets must reach the following values (20)

- >70% between 3.9 and 10 mmol/L (70–180 mg/dl)
- <4%: <3.9 mmol/L (70 mg/dl)
- <1%: <3.0 mmol/L (54 mg/dl)
- <25%: >10 mmol/L (180 mg/dl)
- <5%: >13.9 mmol/L (250 mg/dl)
- Glycemic variability (coefficient of variation, [%CV]) target ≤36%

**Results**

A sample of 84 children with type 1 diabetes, aged between 4 and 18 years, average 11.20 (±4.13) years, were included in the study. Table 1 shows the anthropometric and clinical characteristics of the sample at the beginning of the study. The diabetes duration ranged between less than a year and 13 years, median 4 (2-6.5) years. The children presented a median HbA1c level of 7.45% (6.9-8.02). Besides DM, 15 children presented chronic autoimmune thyroiditis, and other comorbidities, such as overweight, obesity, ponderal hypotrophy, or dyslipidemia were present to half of the children included in the study. The daily required insulin ranged between 4 UI and 107 UI, median 35.5 UI (18.75-64.8).

*Table 1. Baseline clinical characteristics of the study population.*

| Parameters | Children with type 1 diabetes (N=84) |
|---|---|
| Age (years) | 11.20 (±4.13) |
| Sex M (%) | 49 (58.33%) |
| DM duration (years) | 4 (2 - 6.5) |
| Weight (kg) | 41.5 (27 - 59.25) |
| HbA1c (%) | 7.45 (6.9 - 8.02) |
| eGFR (mg/dL) | 108.75 (96.76 - 125) |
| Insulin/kg (Ul) | 0.88 (0.71 - 1.03) |

*Table 2. Includes the change of glucose parameters measured during the three periods analyzed.*

| Parameters | Time 1 | Time 2 | Time 3 | *p* |
|---|---|---|---|---|
| GMI (%) | 7.00 (6.62-7.30) | 6.90 (6.50-7.10) | 6.75 (6.40-7.20) | 0.002 |
| CV (%) | 36.35 (33.47-39.40) | 35.45 (32.40-40.15) | 37.00 (33.05-41.48) | 0.202 |
| TIR [70-180 mg/dL] (%) | 65.50 (56.25-73.00) | 68.00 (59.00-73.75) | 68.50 (58.50-73.75) | 0.347 |
| TAR level 1 [181-250 mg/dL] (%) | 23.00 (17.75-29.00) | 22.00 (15.00-26.75) | 21.00 (14.25-26.00) | 0.103 |
| TAR level 2 [251-400 mg/dL] (%) | 6.00 (3.00-12.00) | 5.00 (3.00-9.00) | 5.00 (2.00-9.75) | 0.016 |
| TBR level 1 [54-69 mg/dL] (%) | 3.00 (2.00-6.00) | 3.00 (1.25-6.00) | 4.00 (2.00-6.00) | 0.115 |
| TBR level 2 [<54 mg/dL] (%) | 1.00 (0.00-2.00) | 1.00 (0.00-2.00) | 1.00 (0.00-3.00) | 0.002 |

GMI slightly worsen between Time 1 [median (IQR), 7.00% (6.62-7.30)] vs. Time 2 [median (IQR), 6.90% (6.50-7.10)] ($p$ = 0.020), but it did not significantly change between Time 2 [median (IQR), 6.90% (6.50-7.10)] vs. Time 3 [median (IQR), 6.75% (6.40-7.20)] ($p$ = 0.056).

TIR did not change significantly over time when comparing the three periods, Time 1 [median (IQR), 65.50 (56.25-73.00)] vs Time 2 [median (IQR), 68.00 (59.00-73.75)] ($p$ = 0.058). Also, it did not change when comparing Time 2 [median (IQR), 68.00 (59.00-73.75)] vs Time 3 [median (IQR), 68.50 (58.50-73.75)] ($p$ = 0.695).

TAR level 1 significantly decreased at Time 2 [median (IQR), 22.00 (15.00-26.75)] when comparing to Time 1 [median (IQR), 23.00 (17.75-29.00)] ($p$ = 0.021), whereas it did not change between Time 2 [median (IQR), 22.00 (15.00-26.75)] and Time 3 [median (IQR), 21.00 (14.25-26.00)] ($p$ = 0.386).

TAR level 2 significantly decreased at Time 2 [median (IQR), 5.00 (3.00-9.00)] when comparing to Time 1 [median (IQR), 6.00 (3.00-12.00)] (p = 0.042), but it did not change when comparing Time 2 to Time 3 ($p$ = 0.540).

TBR level 1 did not change at Time 2 when comparing to Time 1 ($p$ = 0.432), and it did not change when comparing Time 2 to Time 3 ($p$ = 0.129).

TBR level 2 did not change at Time 2 when comparing to Time 1 ($p$ = 0.685), but it significantly increased when comparing Time 2 to Time 3 ($p$ = 0.010).

When analyzing the correlations between GMI after 3 months and the different glucose metrics, we observed that GMI positively significantly correlated with both TAR level 1 (rho = 0.898, p < 0.001) and TAR level 2 (rho = 0.916, p < 0.001), and it negatively significantly correlated with TIR (rho = -0.883, p < 0.001) and both TBR level 1 (rho = -0.492, p < 0.001) and TBR level 2 (rho = -0.294, p < 0.001). Similarly, GMI after 6 months and 9 months positively significantly correlated with both TAR level 1, TAR level 2, and it negatively significantly correlated with TIR and both TBR level 1 and TBR level 2.

Similarly, we observed that average GMI positively significantly correlated with both TAR level 1 and TAR level 2, and it negatively significantly correlated with TIR, and both TBR level 1 and TBR level 2 (Table 3).

*Table 3. Correlations between GMI and glucose parameters.*

| | *rho* | *p* |
|---|---|---|
| TIR | -0.711 | <0.001 |
| TAR level 2 | 0.693 | <0.001 |
| TBR level 2 | -0.379 | <0.001 |
| CV | 0.078 | 0.479 |

*Discussions*

In our study, GMI was positively correlated with TAR value both at time 1 and at time T2 and T3, respectively. This correlation confirms why BMI can be considered an estimated HbA1c. On the other hand, GMI in the studied lot does not correlate with TIR or TBR. This negative correlation supports the results of other studies showing the limits of HbA1c in terms of lack of information about acute glycemic excursions and acute complications of hyper- and hypoglycemia, respectively. HbA1C also fails to identify the magnitude and frequency of glucose variation during the same day and between different days. [21,22]

Despite these limitations, HbA1C is the only prospective tool for assessing the risk of type 1 DM complications, and its importance in clinical decision-making should not be underestimated. [23]

At the beginning of the study, the average HbA1c was 7.45%, a value that could satisfy us considering that it would approach the targets proposed by the therapeutic guidelines. After 3 months of wearing the sensor and isolation at home due to the COVID-19 pandemic, the average GMI in the studied group was 7%, reaching 6.75% after 9 months of wearing the sensor.

This evolution correlates positively with the decreasing evolution of TAR both level 1 and level 2. (*table 2*). The result of the decrease of GMI and TAR is, however, followed by the increase of level 1 TBR under the conditions of keeping level 2 TBR at the same average of 1% and with the increase of TIR which, 9 months after the installation of the sensor, reaches an unsatisfactory average (68.50%). Current recommendations indicate that TIR should exceed 75%.

If we were to analyze these correlations and the evolution of glycemic parameters, we could say that the evolution is satisfactory. The primary goal for effective and safe glucose control is to increase TIR while reducing TBR. [24]

The first priority is to reduce TBR to target levels and then address TIR or TAR targets. [24]

No significant correlation has been found between GMI and the change in CV.

CV, an indicator brought more and more into discussion as being involved in the appearance of chronic complications, did not have the expected evolution. If at 6 months it approached the recommendations of the current guidelines with an average value of 35.45%, at 9 months the average was 37%.

With these findings we can say that the utility of HbA1c can be further improved when supplemented with glycemic records through CGMS [24] and especially with the intensification of specific medical education through the analysis of CGMS reports at time intervals (monthly, quarterly) adapted to each individual depending on the results.

**Factors involved in glycemic variability**

Ongoing psychoeducation and training of CGM recipients is required to optimally use this technology.

This education must aim at the analysis of all the factors involved in glycemic variability: dietary factors (the amount and type of carbohydrates from the respective meal, the intake of lipids, proteins, the personal microbiome, meal times, the degree of hydration, alcohol consumption), physical activity (type of exercises practiced: light, moderate or severe, the time of day they are practiced), biological factors (sleep duration, recent hypoglycemia, dawn phenomenon, existence of lipodystrophy, allergies, puberty, celiac disease, smoking).

**Food factors**

***a.1. The amount and type of carbohydrates in that meal***

Current nutritional recommendations for children with type 1 DM are based on a rational, balanced, age- and sex-appropriate diet just like that of a healthy child.

Food planning will be done in correlation with the type of insulins and the insulin therapy scheme, respecting the schedule of meals and snacks from one day to the next to prevent large variations in blood sugar (hypo-, hyperglycemia);

The need for carbohydrates is determined individually, depending on: age, sex, physical activity and possibly the caloric intake prior to the onset. After the onset, the caloric requirement will adapt according to the evolution of the somatometric indices (height and weight) compared to the "growth corridor" of each individual case (the percentile it must follow). Current data show that carbohydrate intake is between 40%-50% of daily energy requirements, and optimal glycemic targets (including postprandial 1-hour postprandial targets) can be achieved with an adequate insulin-to-carbohydrate ratio.

The number and composition of the meals (the amount of carbohydrates calculated for the meal at the same time) must be constant from one day to the next. Failure to comply with this principle will lead to the impossibility of correct adaptation of insulin doses and finally to the installation or worsening of glycemic variability with repercussions on the risk of installation of chronic complications.

From the beginning, in children with DM type 1, it is mandatory to calculate carbohydrates for each meal, as no meal (or snacks) can be composed of only one type of food.

Healthy food sources of carbohydrates are recommended, such as breads and whole grains, legumes (peas, beans, lentils), fruits, vegetables, and low-fat dairy products (full fat is recommended for children under 2) that will minimize glycemic excursions and will implicitly improve the quality of the diet. [25]

The inequality of the glycemic response produced by equivalent amounts of carbohydrates from different foods was intensively studied by Jenkins et al. who launched and developed the concept of "glycemic index".

The long-term benefits of the glycemic index concept and especially the use of diets with an average glycemic index have been highlighted by numerous studies in patients with type 1 DM.

Despite all the encouraging results of numerous studies, there are still unanswered questions:

- what is the value of the glycemic index of the food when it is part of a mixed meal;
- what is the role of the individual factor.

It is also proven that if the glycemic index varies very little in the same individual, there can be important variations between different individuals, the glycemic index alone not fully explaining the glycemic variations. [26]

Numerous other factors influence the value of the glycemic response: hydration status, particle size (in the case of starch or other polysaccharides), food presentation form, preparation technique, amount and type of associated dietary fiber, presence of phytates or natural enzyme inhibitors, amount of lipids and proteins from the mixed lunch, the state of insulinization, the insulin therapy scheme used. [27]

Foods and liquids containing sucrose are not recommended. They can be consumed in the context of a healthy diet and possibly at the end of mixed meals. Consuming sucrose-containing foods can lead to nutrient-dense replacement and decreased diet quality.[28]

*Sucrose* can provide a maximum of 10% of the total daily energy intake. Apart from the fact that it is associated with weight gain[29] sugary drinks produce hyperglycemia that cannot be handled by circulating insulin. For this reason, the consumption of sweetened drinks, soft drinks are prohibited both for the child with DM type 1 and for the family.

Children with DM type 1 do not need a higher protein requirement compared to non-diabetics. The ISPAD guide recommends that proteins represent 15-25% of caloric needs. Protein intake declines during childhood and adolescence from about 2 g/kg/day in preschool to 1 g/kg/day in toddlers and prepubert and to 0.8–0.9 g/kg/day in adolescence. [30]

*Proteins* contribute to growth only when the energy intake is sufficient.

In DM type 1 under conditions of subinsulinization, the conversion of proteins to glucose sets in quickly, influencing the glycemic balance over time, when glycemic control is good, protein intake does not produce significant changes in glycemia.[31]

Regarding lipid intake, for a child with type 1 DM, the recommendations are the same as for a healthy child, i.e. 30 - 40% of the daily caloric requirement. [32]

In a healthy person or a patient with DM type 1 properly insulinized, insulin prevents the mobilization of lipids from deposits through two mechanisms: it dephosphorylates the hormone-sensitive lipase, preventing lipolysis, and on the other hand, it favors the re-esterification of glycerol-3-phosphate with FA. In this way it is understood why the lack of insulin in DM favors lipolysis and the melting of adipose tissue. [33]

Unsatisfactory glycemic control (result of underinsulinization, or in the conditions of non-compliance with the quantity of carbohydrates per meal) associated with an excessive intake of saturated fatty acids and cholesterol in the diet, aggravates dyslipidemia. Restoring glycemic and metabolic balance through correct insulinization associated with compliance with nutritional recommendations can influence the relationship between DM and hyperlipidemia. As a result, the diet must also aim to maintain the lipid fractions (LDLc, HDLc, VLDLc) at a level as close as possible to the normal for age and sex in order to prevent the onset of dyslipidemic syndrome. [34]

Simple measures such as: replacing butter with margarine, using vegetable oils instead of animal oils, fish meat instead of fatty meat or ham, limiting the number of eggs consumed reduce cholesterol intake and implicitly the serum level of LDL-cholesterol, one of the predisposing factors for atherosclerotic diseases. [35]

**The degree of hydration**

Normally, the water consumption of children and adolescents with DM type 1 is the same as that of non-diabetics.

The need for water relative to body weight decreases with age. Thus, if in infants the daily requirement is 170-200 ml / kg body (without exceeding 1000 ml / day), at 18 years this requirement is only 30-50 ml / kg body. So, the total amount of fluids that a child should receive during 24 hours differs according to age.

- 1 year = 1100 – 1300 ml / day;
- 2 years = 1300 – 1500 ml / day;
- 4 years = 1600 – 1800 ml / day;
- 6 years = 1800 – 2000 ml / day;
- 10 years = 2000 – 2500 ml / day;
- after 14 years = 2200 - = 2700 ml / day

Fluids come from drinking water and food, most foods containing water in varying amounts. Drinks allowed to be freely consumed in DZ type 1 are: water, mineral water, herbal tea, lemon juice. Fruit

juices and nectars are allowed only at the main meals, taking into account the carbohydrate content, which will be deducted from the carbohydrate requirement of the respective meal (preferably at lunch).
Depending on the concentration in water, some foods are rich (milk, juices, fresh fruits and vegetables), while others are dry (dried fruits and vegetables, flour, cereals, etc.).

The **gut microbiome**, a collection of bacteria that lives primarily in our large intestine, shapes health in many ways, including the prevention, development, and progression of several chronic diseases, including diabetes.

Research on the role of the gut microbiome in patients with type 1 diabetes has focused in particular on the pathogenesis of the disease.

It is widely accepted that hyperglycemia is an important risk factor in the development of several diabetes-related complications.[36]

Recently, there are studies that show that the HbA1c value would explain the variations in the composition of the intestinal microbiome of patients with type 1 DM, with a significant positive association between HbA1c and D. formicigenerans. This species has previously been linked to the presence of glycoside hydrolases involved in mucin degradation and may therefore affect intestinal permeability. [37]

The positive association between HbA1c and D. formicigenerans may affect intestinal permeability in patients with poor glycemic control, and the resulting increased intestinal permeability may lead to a greater systemic inflammatory state. [38]
So, poor glycemic control could lead to changes in the composition of the gut microbiome that can affect glycemic control and subsequently lead to the development of systemic inflammation and an increased risk of complications.

The strongest associations were found between microvascular complications and the gut microbiome, particularly with nephropathy, which were mainly with the family Clostridioforme (C. bolteae and C. clostridioforme) and Bacteroides, known opportunistic pathogens.[39, 40]

Some studies, found that the presence of complications was associated with increased levels of Clostridia, Dialister and Anaerotruncus and decreased butyrate producers from the genera Roseburia and Alistipes, which are very important for colon health

through their role in mucin production and anti-inflammatory properties. [41,42]

As a conclusion, it can be stated that the intestinal microbiome is not only important in the context of the development of type 1 diabetes (as previous studies have shown), but can also be involved in the development of complications associated with diabetes.

**Physical exercises**

According to the ISAPD guide, children between the ages of 6 and 18 should practice physical activity daily for 60 minutes/day in the form of at least moderate aerobic activity. Despite these recommendations, both the duration and the intensity of physical activity are difficult to achieve in children with DM type 1 due to the parents' anxiety generated by the fear of hypoglycemia.

Practicing physical exercises in children with type 1 DM is recommended to be performed as much as possible in the euglycemic range, exercises being contraindicated or postponed if the blood glucose determined before exercise is below 80 mg/dl or above 250 mg/dl.

Most school children are more active in the morning (at school) or in the afternoon after school hours. With them, caution is necessary in achieving a hyperinsulinemic state during these periods of the day, especially since there may be days when the child is less mobile (he does not have sports class, the weather does not allow him to exercise during the breaks between classes, etc).

Exceptions to the rule are preschool children who have an uncontrolled, explosive and especially difficult to control physical activity and for whom the recommendations cannot be generalized from one child to another.

Blood glucose monitoring is key to maintaining glycemic balance in the active child with type 1 DM so that trends in glycemic responses can be identified.

**Sleep in patients with DM type 1**

There are studies that report a poorer quality of sleep in patients with DM type 1 compared to healthy subjects.
Polysomnography has shown that children with type 1 DM spend more time in stage 2 (lighter) sleep and less time in stage 3 (deep sleep) compared to healthy children.[43]

On the other hand, changes in growth hormone and epinephrine levels have been reported to be more elevated throughout the night, while adrenocortotropic hormone levels were found to be higher during the first 4 hours of the night in young adults with diabetes. of type 1. [44]

*The impact of hypoglycemia on sleep*

Unfortunately, there is no type 1 DM patient (regardless of age) who does not develop nocturnal hypoglycemia. Research has shown that patients with type 1 DM have a decreased awakening response to hypoglycemia during sleep[45] which could be the result of decreased counterregulatory response. [46]

Polysomnography recordings in children with type 1 DM showed that episodes of rapid glucose dips (≥25 mg/dL per hour) were associated with increased awakenings from sleep.[47]

*Hyperglycemia and sleep*

There are more and more authors showing that there is a strong link between disturbed sleep and poorer glycemic control; thus it was found that sleep restriction in people with type 1 diabetes led to impaired insulin sensitivity the next day, which would disrupt glycemic control.[48]

Sleep may also be disturbed by symptoms of hyperglycemia. Hyperglycemia leads to osmotic diuresis, leading to the need to urinate more frequently, which can lead to sleep disruptions.

*Glycemic variability*

Glycemic oscillations were associated with increased awakenings from sleep in children with type 1 diabetes. This finding raises the suspicion that glycemic variability may affect sleep architecture.[47]

It can be stated that both adults and children with type 1 DM are very likely to have changes in sleep architecture and therefore reduced sleep quality compared to non-diabetics.

Changes in sleep architecture can be generated by both behavioral problems and diabetes management difficulties/ problems.

There are data that show that the patient with DM type 1 has a 25% higher insulin requirement in the days following a night with less than 7 hours of sleep, and the blood sugar has a 21% higher variability. The result of sleep deprivation therefore consists in increased blood sugar, insulin resistance, weight gain and even increased food intake.

Recently, the American Academy of Sleep Medicine has updated age-appropriate sleep recommendations for children (including afternoon naps).

- Babies 4-12 months: 12-16 hours of sleep
- Children aged 1-2 years: 11-14 hours of sleep
- Children 3-5 years: 10-13 hours of sleep
- Children 6-12 years: 9-12 hours sleep
- Teenagers 13-18 years: 8-10 hours of sleep per night

**Conclusion**

All this information must be discussed when analyzing CGMS reports, especially in adolescents who have problems with reaching therapeutic targets (TIR, CV, fasting hyperglycemia, etc.) and promoted to improve glycemic balance and implicitly to increase the quality of life of patients with diabetes.

Analysis of glycemic monitoring reports must be performed at least every 3 months in the doctor's office.

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# OXIDATIVE STRESS IN CHILDREN WITH TYPE 1 DIABETES: IMPLICATIONS FOR VASCULAR AND OTHER COMPLICATIONS

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## Introduction

Type 1 diabetes (T1D) is a medical condition typified by the autoimmune destruction of pancreatic β-cells that are responsible for producing insulin. This phenomenon results in a notable decrease in insulin production and metabolic dysregulation, which ultimately contributes to the clinical manifestations associated with T1D[1].

The impact of endothelial dysfunction and oxidative stress on the well-being and metabolic regulation of individuals with type 1 diabetes is evident.

Numerous indicators of oxidative stress exist that may be effectively utilized for the prediction of vascular dysfunction, including advances oxidation protein products (AOPP), prooxidant-antioxidant balance (PAB), and superoxide dismutase (SOD) activity[2].

The assessment of nutritional status using measures such as body mass index (BMI), waist and hip circumference, alongside the evaluation of lipid metabolism, including LDL cholesterol, HDL cholesterol, and triglyceride levels, constitutes an essential aspect of monitoring patients with type 1 diabetes. In addition, the monitoring of metabolic control factors, such as glucose levels and HbA1c, as well as renal marker factors, such as urinary albumin excretion rate, are critical in the timely identification of potential micro- and macrovascular complications. These measures are particularly salient for both initial screenings and symptom-based monitoring of type 1 diabetes patients[3,4].

## Definition

Diabetes mellitus is an imperative chance calculate for atherosclerosis and both the frequency and mortality of cardiovascular illness are expanded in diabetic patients[5]. Among the different pathophysiological components interceding the atherosclerotic handle, both oxidative push (OS) and endothelial brokenness happen at an early arrange in creature models of diabetes[6].

Oxidative stress (OS) is characterized as the alter within the pro-oxidant/antioxidant adjust in favor of the previous, possibly driving to biologic harm to macromolecules and cell brokenness[7]. As a result of hyperglycemia, over the top pro-oxidants (free radicals and responsive oxygen species) are shaped by means of auto-oxidation of glucose, nonenzymatic glycation and arrangement of progressed glycation conclusion items, expanded flux through the polyol and hexosamine pathways, and actuation of protein kinase C. These forms too lead to diminished antioxidant guards. Brownlee has connected all these anomalies to the over the top generation of superoxide by the mitochondria[8].

In children with type 1 diabetes mellitus (T1DM), expanded OS has been detailed to be display indeed in the blink of an eye after determination[9]. Other reports appeared the parallelism between OS and unusual markers of endothelial cell work (such as E-Selectin and ICAM-1) in youthful T1DM patients, proposing a interface between these two variations from the norm[10]. Ultrasound testing of skin microcirculation and of brachial course flow-mediated dilatation (FMD) have illustrated early endothelial brokenness in diabetic children and youths[11].

## Oxidative stress (OS)

In later decades, OS has ended up a center of intrigued in most biomedical disciplines and numerous sorts of clinical investigate. Expanding prove appears that oxidative stretch is related with the pathogenesis of diabetes, corpulence, cancer, maturing, irritation, neurodegenerative disarranges, hypertension, apoptosis, cardiovascular illnesses, and heart disappointment. Based on these thinks about, an developing concept is that oxidative stretch is the “final common pathway” through which the hazard variables for a

few illnesses apply their pernicious impacts. Oxidative push causes a complex dysregulation of cell digestion system and cell–cell homeostasis; in specific, oxidative push plays a key part within the pathogenesis of affront resistance and β-cell brokenness. These are the two most significant components within the pathophysiology of sort 2 diabetes and its vascular complications, the driving cause of passing in diabetic patients.[12]

OS with resulting glucotoxicity and lipotoxicity are diabetes-related wonders that have been included within the pathogenesis of β-cell brokenness[13]. In this way, hyperglycemia and hyperlipidemia that take after the essential pathogenic handle of diabetes may apply extra harmful impacts on β-cells. Prove coming about from in vitro and in vivo thinks about proposes that both glucose and lipids are undoubtedly destructive for the β-cells. Interests, a few considers have detailed that lipotoxicity as it were happens within the nearness of concomitantly hoisted glucose levels[14,15].

Subsequently, hyperglycemia may be a prerequisite for the negative impacts of lipotoxicity, consequently the term glucolipotoxicity may be favored to lipotoxicity to way better depict the destructive relationship between lipids and β-cell work. A few creators have illustrated that affront quality expression, affront substance, and glucose-induced affront emission are continuously and radically compromised over time when β-cell lines (HIT-T15 cells) are uncovered to tall glucose concentrations.[15]

**Oxidative stress and insulin resistance**

Insulin resistance constitutes a prevailing issue of pandemic proportions that exhibits no inclination for discrimination based on demographic variables, such as ethnicity or socioeconomic status[16.] Insulin resistance-mediated Type 2 diabetes mellitus is a metabolic disorder that has been reported to have a high global prevalence, as per the most recent World Health Organization statistics.

Insulin resistance is typified by a reduction in cellular reactivity towards insulin stimulation, specifically in peripheral tissues. Therefore, it is imperative to examine the underlying mechanisms of the peripheral insulin response to comprehensively comprehend the pathogenesis of subsequent metabolic complications.[17]

Recent research has acknowledged oxidative stress as a crucial mechanism in the development of insulin resistance. The notion of oxidative stress is characterized by an overabundance of endogenous oxidative species that lead to the deterioration of cellular organisms and alteration of signal pathways[18].

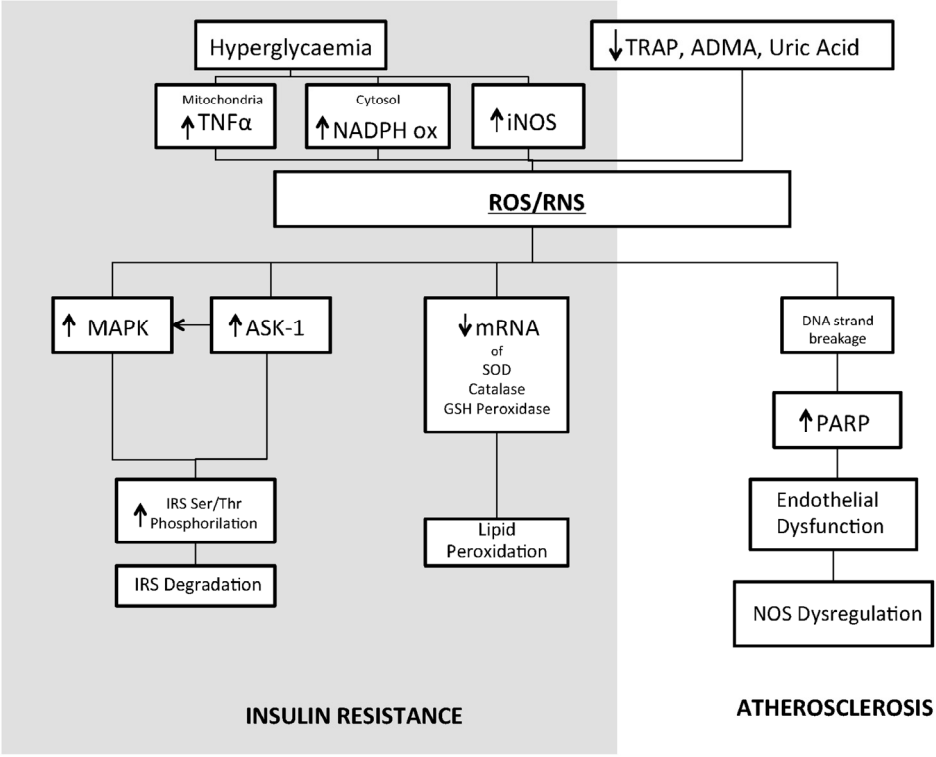


*Figure 1 - Proposed mechanisms by which increased oxidative stress in diabetes may lead to insulin resistance and atherosclerosis. All abbreviations are spelled out in the text. ↑ indicates increased levels; ↓ indicates decreased levels.*[17]

Reactive species, specifically reactive oxygen species (ROS), such as superoxide, hydrogen peroxide, and hydroxyl radical ions, have been implicated as the causative agents of oxidative stress. They are generated at relatively low levels within the mitochondria and peroxisomes under physiological conditions. Reactive oxygen species (ROS) are endogenously synthesized and hold physiological relevance

when present at lower concentrations, particularly in signaling pathways[19].

However, the precise mechanisms underlying such effects remain largely indeterminate owing to the dual role of ROS, which perform both as signaling molecules and damaging agents[20]. Several signaling roles that have been identified include transcriptional control[21] and regulation of the cell cycle. Interactions occur between endogenous mitochondrial reactive oxygen species and redox enzymes, encompassing a diverse range of factors such as NADPH oxidases and angiotensin I/II receptors[22].

Reactive oxygen species (ROS) refer to a class of molecular oxygen derivatives that exhibit high reactivity. The properties of certain species can be attributed to the presence of an unpaired electron on their valence shell, as has been established in the literature[23]. Nonetheless, it should be noted that the impact of reactive oxygen species (ROS) extends beyond its conventional role as a catalyst for cellular damage[23,24]. It has been demonstrated that trace quantities of these compounds participate in various physiological mechanisms within the human body[24,25]. The functions of ROS extend to the regulation of various signaling pathways implicated in fundamental cellular processes ranging from proliferation and survival, which involve the mitogen-activated protein kinase (MAPK), to apoptosis and ageing, which involve p66 Src homology/collagen (Shc)[25]. This phenomenon arises from the intricate interplay between ROS and other cellular components, thereby highlighting the complex nature of ROS-mediated signaling as it shows in *figure 2.*

## Macrovascular and microvascular complication in type 1 diabetes

Hyperglycemia driving to expanded oxidative push is embroiled within the expanded chance for the improvement of macrovascular and microvascular complications in patients with sort 1 diabetes mellitus.

The ISPAD Guidelines 2022 for screening of the macrovascular and microvascular complications are shown in Figure 3

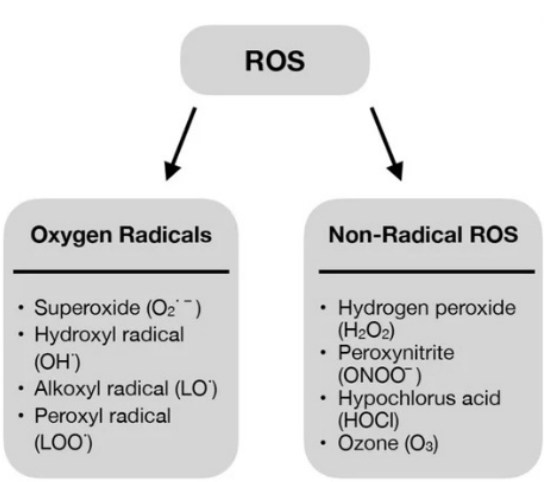


*Figure 2 - Oxygen Radicals and Non-Radical Reactive Oxygen Species*[26]

| | When to commence screening? | Screening methods |
|---|---|---|
| Nephropathy | **T1D:** at puberty or age 11 years with 2–5 years diabetes duration<br>**T2D:** at diagnosis | Urinary ACR<br>Confirm with 1st morning urine sample<br>Frequency: annually |
| Retinopathy | **T1D:** 11 years with 2–5 years diabetes duration<br>**T2D:** at diagnosis | Fundus photography or mydriatic ophthalmoscopy<br>Frequency: every 2–3 years |
| Neuropathy | **T1D:** 11 years with 2–5 years diabetes duration<br>**T2D:** at diagnosis | History<br>Physical examination<br>Clinical tests<br>Frequency: annually |
| Macrovascular disease | **T1D:** 11 years with 2–5 years diabetes duration<br>**T2D:** at diagnosis | Lipid panel every 3 years<br>BP at least annually; ideally at every clinic visit |

*Figure 3 - Screening recommendations for vascular complications*[27]

Diabetes-associated morbidity is a result of the co-occurrence of macrovascular disease, namely atherosclerosis, and microvascular disease, encompassing retinopathy, nephropathy, and neuropathy. The significance of pursuing intensive glycemic control to provide safeguards against microvascular and macrovascular disease in diabetes has been proven through the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study conducted on type 1 diabetes patients.

**Diabetic neuropathy**, also known as diabetic sensorimotor polyneuropathy, is the most prevalent form of the disorder. However, it is worth noting that this condition can affect other areas of the somatic and autonomic nervous networks as well. Peripheral neuropathy is characterized by a sequential impairment of the sensory function followed by motor function. According to prior literature[28], patients may experience initial feelings of numbness that may subsequently escalate to sensations of pain.

Autonomic neuropathy has the potential to impact numerous physiological systems, such as cardiovascular, urogenital, or gastrointestinal.[29,30] The susceptibility to severe hypoglycaemia may be heightened as a result of impaired hypoglycaemia awareness caused by cardiovascular autonomic neuropathy-induced loss of heart rate variability, as evidenced by extant research[31]. The cardiovascular symptoms may suggest an increased activity of the sympathetic nervous system and a decline in parasympathetic function.

**Diabetic nephropathy** is characterized by persistent proteinuria exceeding 500 mg/24 hours or albuminuria exceeding 300 mg/24 hours and frequently co-occurs with hypertension and a gradual decrease in the glomerular filtration rate (GFR)[32]. The onset of end-stage renal failure is often characterized by its chronicity and may manifest after a protracted period of time, necessitating intervention via dialysis or kidney transplantation. Diabetic nephropathy represents a significant factor contributing to morbidity and mortality in the population of young adults diagnosed with type 1 diabetes[33].

The timely identification and management of diabetic nephropathy, coupled with appropriate control of blood pressure, play a critical role in mitigating the risk of end-stage renal failure in both young individuals and adults living with diabetes.[34]

**Hypertension** has been identified as a significant risk factor for microvascular complications, such as diabetic nephropathy and retinopathy. Therefore, regular screening is essential and should occur at least once annually, and preferably during each visit, as recommended by literature sources. In children, hypertension is defined as having a blood pressure of 95th centile or above concerning age, sex, and height, below the age of 13 years, and systolic blood pressure of 130 mmHg or diastolic blood pressure of 80 mmHg or above in those aged 13 years and above. Additionally, elevated blood pressure, formerly known as prehypertension, in children is defined as a blood pressure measurement at the 90-95th centiles and ⩾120-129/80 mmHg in adolescents. To confirm hypertension, elevated measurements must be observed on three separate days, and further confirmation may necessitate 24-hour ambulatory monitoring.

Compared to adult patients with diabetes, adolescents possess a greater susceptibility to the progression of vision-threatening **retinopathy,** as evidenced by previous research[35]. The pace of progression may prove expedited, particularly among individuals exhibiting inadequate glycaemic management[36]. Therefore, during the period of adolescence, it is imperative to focus on screening for initial indicators of diabetic retinopathy and assess modifiable risk elements. The phenomenon of retinopathy regression has been demonstrated in previous studies[35,36,37].

According to research findings, diabetes has emerged as the prevailing cause of fresh instances of visual impairment among individuals falling within the age bracket of 18 to 64 years[38]. Diabetic eye disease comprises a combination of ocular disorders, which primarily includes diabetic retinopathy, macular edema, cataract, and glaucoma.[39]

Diabetic retinopathy, a microvascular complication that arises as a result of diabetes, is categorized into three classes: mild-to-

moderate non-proliferative, severe non-proliferative, and proliferative. The affliction of severe non-proliferative and proliferative disease is a grave threat to one's vision, as per the research evidence provided[40].

Severe non-proliferative retinopathy is characterized by the presence of a vascular obstruction, accompanied by a significant increase in the number of retinal hemorrhages and microaneurysms, as well as marked venous abnormalities. Proliferative retinopathy is distinguished by the manifestation of neovascularization within either the retina or the posterior vitreous cavity.[40]

## Conclusions

A substantial body of empirical evidence indicates that oxidative stress plays a pivotal role in the pathophysiology of diabetes and its associated complications. The pathogenesis of type 1 diabetes involves two pivotal factors--insulin resistance and β-cell dysfunction--which have been shown to be associated with an imbalance of redox status. Concurrently, the involvement of oxidative stress in the etiology of vascular impairments linked to diabetes has been postulated.

The contribution of oxidative stress to endothelial and smooth muscle dysfunction is a significant factor in diabetic vascular disease. This phenomenon largely stems from an incongruity in the operation of endogenous pro-oxidative enzymes (including NADPH oxidase, xanthine oxidase, and the mitochondrial respiratory chain) and antioxidative enzymes (such as superoxide dismutase, glutathione peroxidase, heme oxygenase, and catalase), which leads to an overproduction of reactive oxygen species (ROS) that surpasses the existing antioxidant defense mechanisms.

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# OBESITY, A BURDEN FOR THE EYE

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Obesity represents an international problem due to its complications on the human body, as well as the high costs for patient care.

The World Health Organization (WHO) reported in March 2022 that more than 1 billion people worldwide are obese. From this one billion, more than a half are adults, 340 million adolescents and 39 million children[1].

The prevalence of obesity is continuously increasing, with an estimated rate of approximately 167 million people by the year 2025.

Obesity is defined by WHO as a body mass index (BMI) of 30 kg/m or greater, and overweight for BMI between 25 kg/m and 29.9 kg/m.[2]. For the Asian population and for children, different classifications are used. A BMI of 25 kg/m or greater defines obesity for the Asians, as for children BMI is classified according to percentiles for age and sex[3]. In a young population a BMI greater than 95th percentiles for age and sex defines an overweight status.[4]

The effect of obesity on human body are well known, affecting organs such as heart, liver, kidneys, joints, and reproductive system. Obesity leads to cardiovascular disease, hypertension, stroke, type 2 diabetes, mental health issues (depression, low self-esteem), dyslipidemia, osteoarthritis, sleep apnea and different types of cancer.[5]

The effect of obesity on the ocular structure is mentioned by some studies, affecting both the anterior and posterior pole. Most of the studies reported an association between obesity and cataract, age related maculopathy, diabetic retinopathy, retinal occlusion, myopia, glaucoma and entropion.

**Obesity and cataract**

Cataract is the most common eye condition that occurs with aging. The association of obesity with cataract has been reported by different studies in adult populations.

A randomized trial including 22071 healthy male American physicians aged 40–84 years, evaluated BMI, abdominal adiposity, measured as waist-to-hip ratio (WHR) and the prevalence of cataract. Obesity was reported as an independent risk factors for cataract with 12% increase risk for 2-unit higher level of.[6]

A particular type of cataract was reported by different studies. Posterior subcapsular cataract (PSC) was mentioned in obese patients by the Health Professionals Follow-up Study[7], (*Fig.1*). The Framingham Eye Study observed an independent association between PSC and cortical cataract and greater BMI.[8]

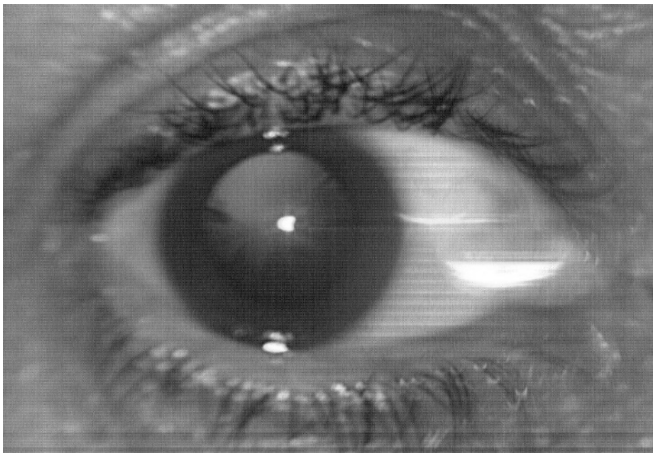

*Figure 1- Posterior subcapsular cataract*

The Blue Mountain Eye Study that included white Australians reported a half and twofold increase risk for PSC and cortical cataract in patients with BMI of 30 kg/m or greater.[9] An important study entitled the Age-Related Eye Disease Study (AREDS), suggested that a higher BMI is associated with moderate cortical cataract.[2]

For the young population, consistent data are not available. A study conducted in Zhongshan Ophthalmic Center, Republic of China, including 595 children, aged ≤14 years with congenital cataract found no association with high BMI. The patients were evaluated for height, weight, and BMI according to the WHO Child Growth Reference. The results revealed normal ranges for the height,

weight, and BMI. In girls aged 5-14 years, congenital cataract was associated with shorter height, lower body weight and lower BMI.[10]

Different pathophysiological mechanisms were proposed to explain the association between obesity and cataract. One of the mechanism makes reference to leptin, a hormone produced by the adipocytes. In obese patients, hyperleptinemia and leptin resistance were reported.[11] Leptin increases the accumulation of reactive oxygen mentioned to have an important pathogenic role in lens opacities formation.[2] Cataract may also be explained by the inflammatory status observed in obese patients. High levels of plasma fibrinogen and C-reactive protein are reported in obesity and have been linked to cataract.[12] (*Fig.2*).

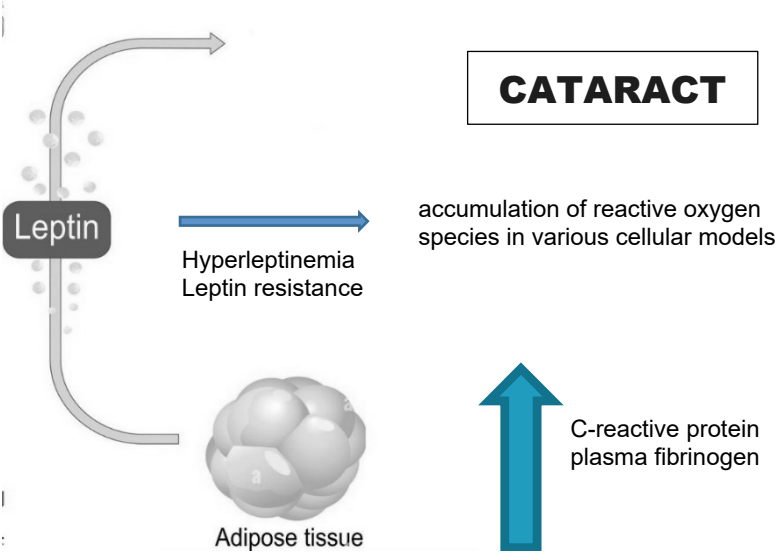


*Figure 2- The pathophysiological mechanism of cataract in obesity*

Obesity is often associated with diabetes, hyperlipidemia, glucose intolerance, insulin resistance, all of which play a role in the formation of lens opacities.[9]

**Obesity and glaucoma**

Obesity was linked to intraocular pressure and glaucomatous optic neuropathy (*Fig.3*).

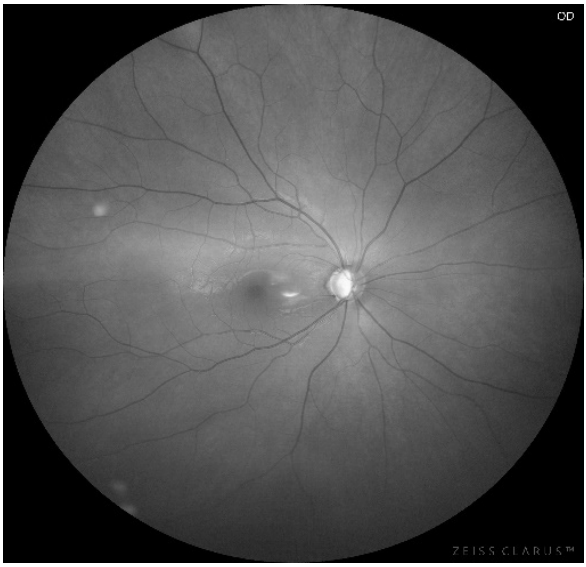


*Figure 3- Glaucomatous optic neuropathy*

A study on a large population of 25,216 Japanese aged 14–94 years reported an association between obesity and high ocular pressure in cross-sectional and longitudinal analysis after adjusting for gender, age and blood pressure.[13] Similar results were obtained in a Korean large population-based study.[2] The Beaver Dam Eye Study linked higher values of intraocular pressure to a BMI of 30 or greater, independent of age and sex.[14]

Similar results were obtained in obese children. A study that included 72 obese children (body mass index in the 95th percentile or greater) and 72 age-matched and sex-matched controls reported higher diurnal variation of intraocular pressure in the first mentioned group, after adjusting for systolic and diastolic blood pressure.[15]

In a random Italian population, aged 8 years old, that included five hundred and seventy-six subjects of which 42.4% were overweight or obese, increased intraocular pressure was associated with high BMI.[16]

The pathophysiological mechanism related to higher intraocular pressure in obese patients consists in two theories: mechanical and vascular. Obesity is associated with increased intraorbital adipose tissue, excessive blood viscosity, increased episcleral venous pressure, and deficiency of aqueous outflow. In most cases obesity is associated with systemic hypertension that increases the filtration fraction of the aqueous humor through a

raised ciliary artery pressure.[17] The vascular theory approaches the low blood supply to the optic nerve and its predisposition to intraocular pressure variations. Hyperleptinemia observed in obesity, increases oxidative stress that has been linked to glaucomatous optic neuropathy on the molecular level. A trabecular meshwork degeneration was reported in obese patients with increased oxidative DNA damage.[18]

**Obesity and retinal alterations**

Obesity was reported to be involved in different retinochoroidal microvascular changes, retinal diseases such as: age-related maculopathy, diabetic retinopathy retinal vasculopathy.

In older patients' obesity was associated with age-related maculopathy, a major blinding condition. Several studies have investigated the association between obesity and age-related maculopathy (*Fig.4*).

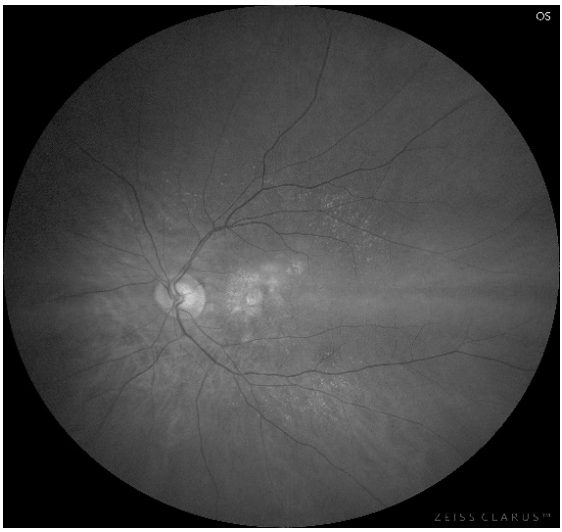


*Figure 4 - Age-related maculopathy*

The Physicians' Health Study, a prospective study, reported higher incidence for visually significant dry age-related maculopathy in obese men and lower in cases with normal BMI. No significant association was found between neovascular age-related maculopathy and obesity.[19] An important study that included fundus photographs, the AREDS, observed an association between advanced cases of age-related maculopathy and higher BMI.[20] Similar results were reported

by a study from 2005, where geographic atrophy and advanced age-related maculopathy were associated with higher BMI after age, gender controlling.[21]The pathophysiological mechanisms of age-related maculopathy are unclear. Multiple factors are involved in the pathogenesis of age-related maculopathy, of which obesity. Several studies reported higher leptin levels in patient with increased BMI. Hyperleptinemia induces oxidative stress affecting the lipids of Bruch membrane. Secondary, the retinal pigment epithelium cells detach, migrate and produce vascular endothelial growth factor.[22] Obesity is also known to be associated with higher levels of inflammation markers such as C-reactive protein, plasma fibrinogen and complications like hyperlipidemia, hypertension. All of these are risk factors for age-related maculopathy.[23]

A study that included 111 children (54 obese children and 57 healthy subjects), aged 8-17 years old, reported in obese patients an increase of the vascular density measurements in the superior retinal capillary plexuses with no visual impairment and normal fundoscopic examination. No significant association was found in the macular and peripapillary region. The study highlighted the importance of optical coherence tomography angiography (OCT-A), a non-invasive method, in the ocular examination of obese children. The HOORN study observed that higher levels of blood pressure, hyperglycaemia, obesity and hyperlipidemia are risk factors for retinopathy.[24]

A study performed on 39 obese children without hypertension and diabetes and 26 children with normal BMI found in OCT-A imaging no significant alterations in superficial and deep capillary plexus vascular densities and foveal avascular zone area in both groups. In the obese patients, the subfoveal choroid was thicker than in the control group ($325.89 \pm 52.77$ μm vs. $304.52 \pm 21.76$ μm, $p = 0.04$). The study analysed also the retrobulbar ocular blood flow parameters by using Colour Doppler Imaging: peak systolic velocity, end-diastolic velocity and resistivity index from ophthalmic, central retinal and posterior ciliary arteries. Lower values were obtained in peak systolic and end-diastolic velocities in the obese patients and no significant changes in the resistivity index. The study concluded that early ocular macrovascular alterations are present in childhood obesity rather than on retinal microvascular system.[25]

A study conducted at the First Afiliated Hospital of the Nanjing Medical University on forty obese children and 40 age- and sex-matched controls revealed at the angiography scans lower vessel

density in the nasal, inferior parafovea and temporal perifovea of deep vascular complex and smaller foveal avascular zone in the obese group. When compared to controls, higher vessel density was found in the fovea of superficial and deep vascular complex. No significant results were obtained when analysing the differences of the retinal quadrants and the subfoveal thickness.[26]

A study with 10 years' follow-up on 582 diabetic patients, aged 15–34, reported that higher BMI was associated with earlier retinopathy changes. at earlier stag.[27] The EURODIAB Prospective Complications Study that included 764 type 1 diabetes patients with a follow-up of more than 7 years observed that waist-to-hip ratio is an independent risk factor for diabetic retinopathy.[28] (*Fig.5*).

The pathophysiological mechanisms of diabetic retinopathy include different theories such as: oxidative stress, vasoproliferative factors, aldose reductase activity and platelet function. Hyperlipemia, high levels of inflammatory markers induce oxidative stress and production of the vasoproliferative factors.

In patients with proliferative diabetic retinopathy, higher levels of vascular endothelial growth factor were obtained from the vitreous.[29]

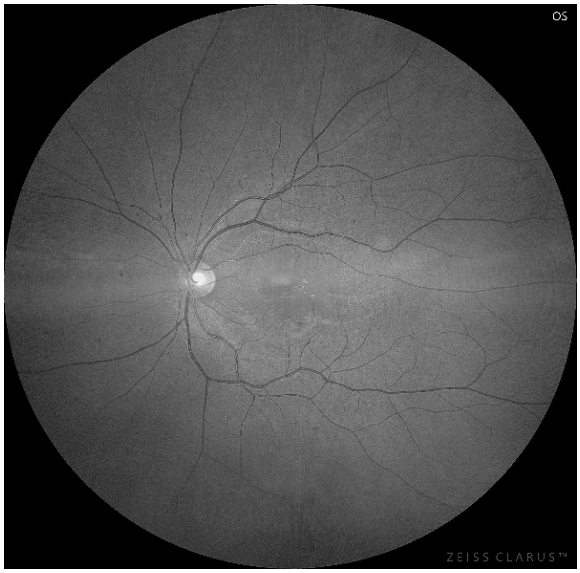


*Figure 5- Diabetic retinopathy*

Bilateral central retinal vein occlusion was diagnosed in patients with obesity–hypoventilation syndrome (pickwick syndrome). Hypoxia and hypercapnia increase the secretion of vascular endothelial growth factor on a nonischemic pathway.[30]

Papilledema and sixth nerve palsy are present in pseudotumor cerebri or idiopathic intracranial hypertension (*Fig. 6*).

According to the Centers for Disease Control and Prevention, 19% of children with this pathology (aged 6 to 11 years) and 17% of adolescents, aged 12 to 19 are overweight.[31] Central obesity increases the intra-abdominal, pleural and intracranial pressure with secondary increase of cardiac filling pressure and deficient brain venous return.[2]

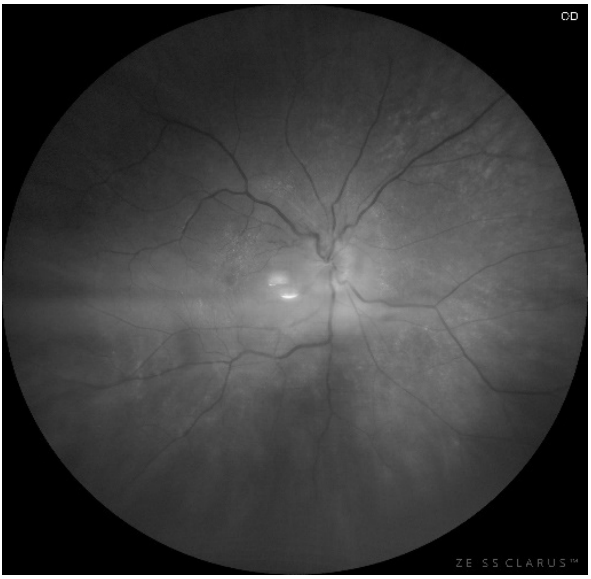


*Figure 6- Papilledema*

**Obesity and refractive errors**

Myopia is a multifactorial disease with genetic and environmental risk factors.

Several studies mentioned that insulin resistance in obese patients induces the secretion of Insulin-like growth factor 1 (IGF-1) with secondary increase of the ocular axial length.[32]

A study that included 1114 children, aged 5–18 years, reported an odds ratio 3.77 times higher in developing high myopia

in when compared to normal weight subjects.[33] Similar results were reported by a Danish study, on a 6 years old population.[34]

According to different studies, the obesity increases the risk of developing myopia in a paediatric population from 1.03 to 2.7 times.[35,36]

**Obesity and eyelids**

Entropion may be observed in obese patient. The medical literature presents the case of a 10 years old boy with recurrent entropion. The cause of entropion was the deposits of additional fatty and edematous tissue in the cheeks and lower eyelids. After surgery, with the increase of the BMI, the entropion reappeared with corneal complications.[37]

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# CACHEXIA - A CLINICAL SIGNATURE OF DIENCEPHALIC-LIKE SYNDROME IN CHILDREN

**Bianca Simionescu, Alexandru Pîrvan, Otilia Fufezan, Ştefan Florian, Rodica Elena Cornean**

## Abstract

*Background:* The diencephalic syndrome (DS) is a rare condition including emaciation associated with nystagmus, secondary to an intracranial tumour in the hypothalamic region. The patient develops cachexia despite a quite normal food intake. The linear growth is usually preserved.

A diencephalic-like syndrome can be produced by a tumour localized in another brain region.

*Aims:* This case report describes the struggle facing the symptoms caused by a tumour localized on the floor of the IV ventricle in a child.

*Material and methods:* A 2 year and 11 months old boy was hospitalized presenting: food refusal, irritability, failure to thrive, asthenia, vomiting, headache, agitation.

Because of early feeding difficulties, he had a slow ascending weight curve and, in evolution, he progressively lost weight. Consequently, the diagnostic algorithm was mainly oriented towards a digestive disease. The patient presented a slight hypotonia and diminution of the lower limb reflexes.

There were no elements as inflammation or nutrient deficiencies. The thyroid function was normal.

The endoscopy identified a mild esophagitis.

Some features looked unrelated to a digestive disease: irritability, anxiety and mood shifts, headache. The appearance of the child suggested a consumptive disease.

*Result:* The brain IRM identified a tumour localized on the floor of the IV ventricle

The brain surgery was successful, with total macroscopical removal of an astrocytoma.

After a rapid post operatory recovery, he was infected with COVID -19 and died because a respiratory failure.

*Conclusion:* The diencephalic syndrome should be considered as differential diagnosis in any child with malnutrition despite adequate caloric intake.

*Keywords: cachexia, child, diencephalic syndrome*

**Background**

The diencephalic syndrome is a rare condition including severe emaciation associated with nystagmus, secondary to an intracranial tumour situated in the hypothalamic region. The patient develops cachexia despite a normal or slightly reduced food intake. The linear growth is usually preserved.

Besides this classical localization, a diencephalic-like syndrome can be produced by a tumour localized in another region of the brain.

**Aims:**

This case report describes the delay and struggle facing the symptoms caused by a tumour localized on the floor of the IV ventricle in a young boy. The classical neurologic signs reported in the diencephalic syndrome were absent; however, poor weight gain was present. He associated atypical general and digestive symptoms.

**Material and methods:** A 2 year and 11 months old boy was sent in our service for a second opinion for the following symptoms: food refusal, irritability, failure to thrive, lack of energy, vomiting, frequent regurgitations, bilateral parietal headache accompanied by extreme agitation.

Starting from the age of 4 months up to 2 years, the child presented a permanent noisy breathing; the ENT consultation did not establish an etiological diagnosis of the stridor, which remitted without treatment.

Despite a normal pregnancy and perinatal period, he presented eating disorders from birth, accepting only small meals, vomiting post alimentation. He accepted with great difficulty the solid meals.

He was exclusively breastfed until the age of 1 month, then the mother decided to change several brands of standard milk formulas, because of the feeding difficulties.

At 3 months, the patient presented an allergic rash, interpreted as cow milk protein allergy. In consequence, an extensive hydrolysed milk formula was indicated. The introduction of complementary feeding started at 6 months. At 10 months, facing a poor weight gain, his mother decided to replace the special formula with plain goat milk, then with donkey milk.

The psychosomatic development was normal until around the age of 1 year and a half.
During all this time, the patient weight -for-age curve was slowly ascending. The birth weight was 3300 grams, and he attended the maximum weight of 8800 g at 1 year and 6 months. Afterwards his weight stagnated up to 2 years, when the child began to lose weight. (*Figure 1*)

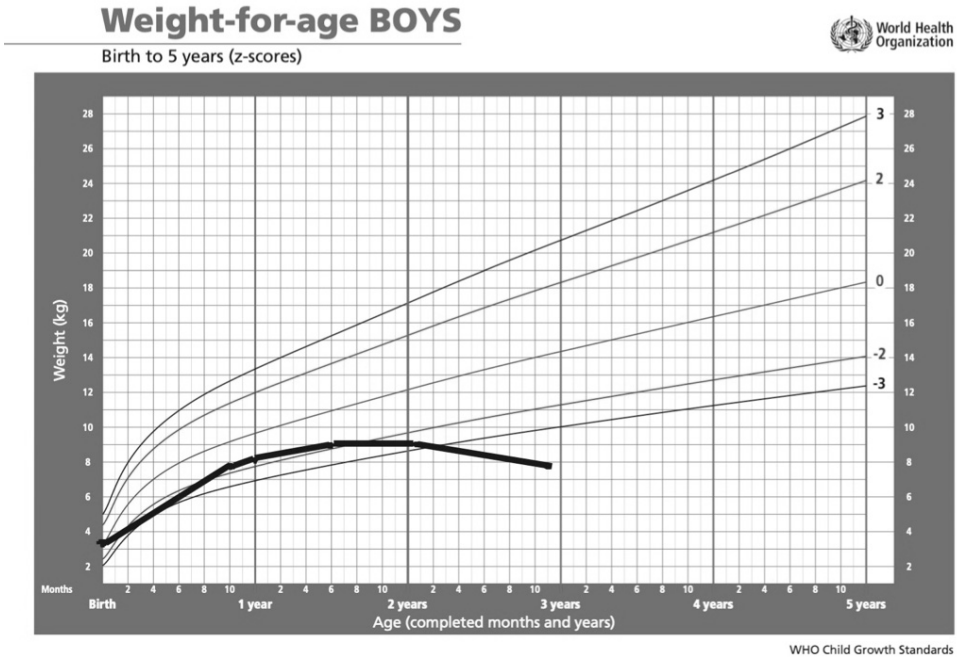


*FIGURE 1 Patient's weight for age Z score*

At the age of 2 years and 6 months he was hospitalized in another paediatric service.

The patient accused post alimentary pain, burns, which he could not locate, so, the diagnostic algorithm was mainly oriented towards a digestive disease. A neurological exam and electroencephalogram were performed. The only pathological elements were a slight hypotonia and diminution of the lower limb reflexes.

The final diagnosis was severe protein caloric malnutrition, chronic gastritis and duodenitis, gastroesophageal reflux disease with reflux esophagitis, Sandifer's syndrome, emotional disorders

and eating behaviour disorder, pavor nocturnus. The prescribed treatment with prokinetics and proton pump inhibitors was unsuccessful.

At 2 years and 8 months the family consulted another gastroenterologist who maintained the diagnosis of reflux disease and indicated the continuation of proton pump inhibitors.

Affirmatively, in the last 3 months preceding the hospitalization in our clinic, the patient had a general condition in progressive degradation, with lack of energy (he wanted to just lie in bed), capricious appetite, food refusal, weight loss, episodes of reflux and multiple vomiting.

In our clinic he weighted 7600 grams.

The initial workup was normal: no inflammation, no anaemia or hypoalbuminemia. Fasting blood sugar levels were normal. We ruled out a celiac disease. The total and specific IgE's for the main food proteins: cow milk, egg, wheat, peanuts, soy were negative. Thyroid hormone levels were normal.

The upper digestive endoscopy identified a mild esophagitis.

We observed during the 12 days of hospitalization the child's behaviour, and we considered that the following elements were unexplained and seemingly unrelated to a digestive disease: the irritability, the anxiety and the mood shifts, the headache, unusually described by a young child, the marked asthenia despite a present appetite. The appearance of the child compared to the photographs from the infant period suggested a consumptive disease. *Figure 2*

We supposed a diencephalic syndrome as the real cause of the cachexia and general regress.

Result: The brain IRM identified a tumour localized on the floor of the IV ventricle with an important mass effect on the brainstem, important ventriculomegaly and protrusion by foramen ovale. *Figure 2*

The brain surgery was successful, with total macroscopical removal of the tumour, an astrocytoma.

After a rapid post operatory recovery, the child was infected with COVID -19 and died because a respiratory failure.

*Conclusion:* The diencephalic syndrome should be considered as differential diagnosis in any child with malnutrition despite an adequate caloric intake

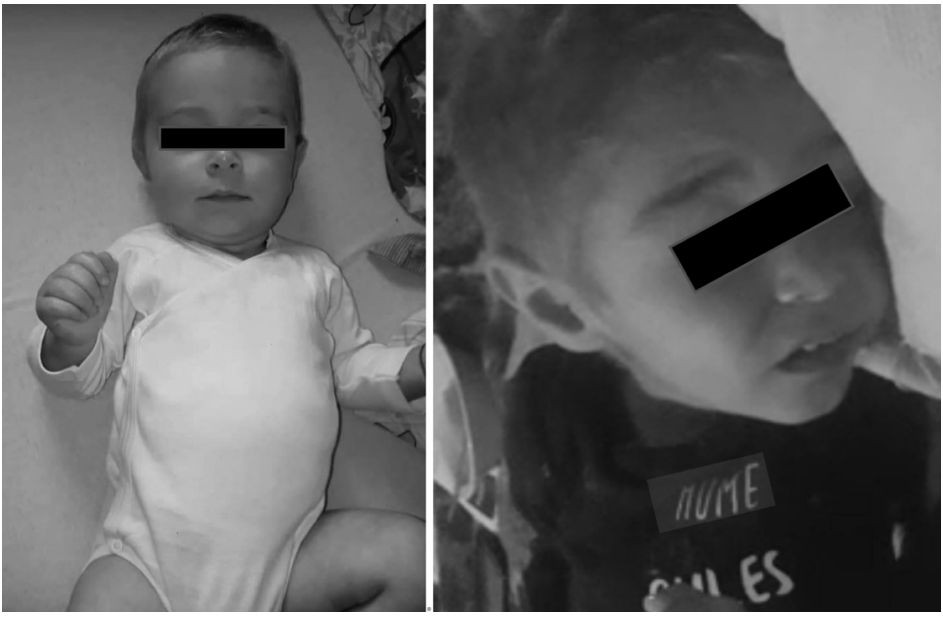

*Figure 2 - Comparison of the patient general appearance at the age of 6 months and at 2 years and 11 months*

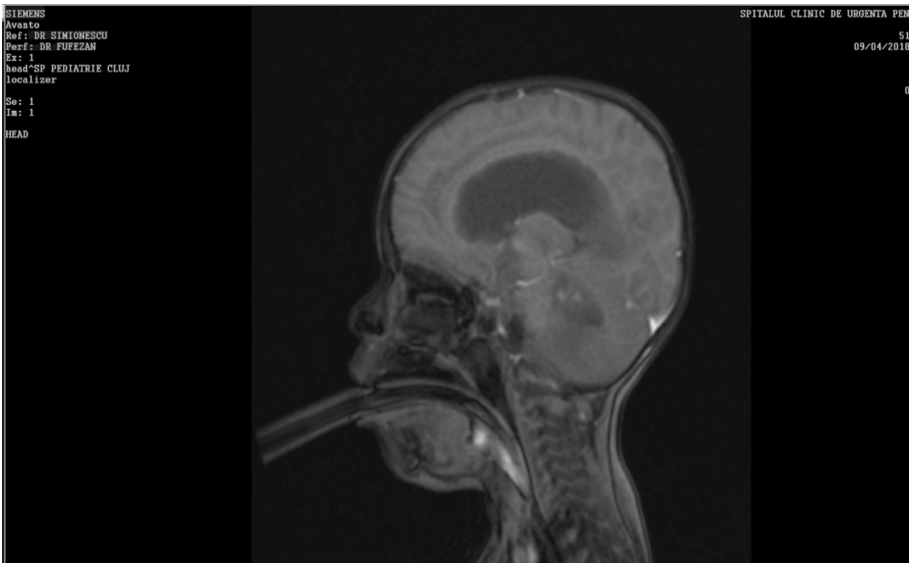


*Figure 3 - Brain IRM sagital incidence*

**Discussion**

In this patient, the progressive weight loss suggested the diagnosis of malabsorption, but the final diagnosis was a diencephalic -like syndrome secondary to a fourth ventricle astrocytoma.

Diencephalic syndrome (DS) is a rare but potentially lethal cause of failure to thrive (FTT) in young children, not explained by digestive loss, poor caloric intake, or other gastrointestinal causes. The classical diencephalic syndrome is the consequence of a diencephalic tumour (localized around the thalamus/hypothalamus and optic chiasm).[1,2]

In 9% of cases presenting the features of the diencephalic syndrome the tumour is positioned in another region of the brain, including the posterior fossa.[3]

The first description was made by Russel in 1951.[2] Although, since than there are hundreds of scientific papers published regarding this pathological condition in children, there are still a lot of diagnostic confusions and delay because the late occurrence of the neurological features in the evolution of the disease.

The clinical characteristics of DS can be classified in major and minor manifestations. The major features include failure to thrive evolving to cachexia, despite an adequate or slightly decreased caloric intake, hyperactivity, and euphoria, while minor features comprise pallor without anaemia, hypoglycaemia and hypotension.[4,5] Neurological symptoms, including nystagmus and strabismus, classically develop later.

In terms of frequency, the most frequent brain tumours in children are astrocytoma (45%), medulloblastoma (20%), ependymoma (10%), central primitive neuroectodermal tumour (5%), oligodendroglioma (4%) and germinoma (4%).[6]

The signs and symptoms linked to a brain tumour are variable, depending on the part of the brain affected, the developmental stage of the child, and whether there is an intracranial high pressure associated or not. In preschool children this could be a short list of red flags suggesting the presence of a brain tumour: recurrent vomiting, abnormal head position such as head tilt, persistent stiff neck, progressively increasing head circumference, problems with equilibrium, coordination, or walking, abnormal eye movements, behavioural change (irritability, lethargy), seizures. Subtle symptoms in preschool children are especially

problematic. In older children, they could also have complaints as: double vision, blurred vision, recurrent headache.

Headache is a very common complaint at all ages, with up to 20% of children presenting headache at some time.[4,7]
Facing a child with persistent or recurrent headache resistant to treatment, the paediatrician must exclude a brain tumour, especially if there are other symptoms such as behavioural or neurological changes.

It must be known that the modifications in the mood and cognition are occurring more frequently in the last 3 to 6 months preceding the diagnosis. The specific symptoms suggesting a high intracranial pressure become prominent only one month prior to diagnosis.[8]

In a child with severe malnutrition, the diencephalic syndrome must be considered, and the imaging should be performed, even if there are no obvious neurological symptoms.[9]
The tumours associated with diencephalic syndrome in children are mainly the optic and hypothalamic astrocytomas, but, as in our patient, other localizations as the fourth ventricle tumours are possible.[9,10]

Our patient did not present the classical signs of the DS: hypotension, hypoglycaemia, hyperactivity, or euphoria.[2] The neurological signs were very subtle.

Other features linked to the DS in children are include hyper alertness, hyperkinesia, euphoria, nystagmus, hydrocephalus, visual field defects, optic pallor, emesis, and vomiting.[11] Besides the severe failure to thrive, our patient presented only headache, irritability, and digestive symptoms. The last ones generated a prolonged wrong clinical orientation.

The mechanism of failure to thrive in the DS in children are poorly understood.[11]

One of the hypothesis postulate that the elevated growth hormone (GH) level generates a contradictory response to the rise of the blood sugar level. A GH associated resistance and an excessive β-lipotropin (a lipolytic peptide) secretion could be another mechanism.[12] Because the increased lipolysis, there is a progressive weight loss.[13]

The role of the ghrelin and leptin in the DS was also suggested.

The leptin (an adipose tissue hormone) stimulates the thermogenesis and reduces appetite. Its plasma levels are related to BMI (Body Mass Index).

The ghrelin is a gastric hormone which falls when the body mass index increases and directly stimulate the GH secretion.

In a series of 11patients diagnosed with DS syndrome there were found changes in the leptin and ghrelin levels.

In all cases, leptin was low and ghrelin was high at diagnosis.[15]

Before proposing the tumour surgery, it is indispensable to treat the severe nutritional deficit, given the negative impact of malnutrition on the peri and post operative outcome.[16]

Treatment of the brain astrocytoma includes surgical resection, radiation therapy and chemotherapy. Because of the localization of the tumour, the complete surgical resection of an astrocytoma is rarely possible.[11]

The diagnostic delay is common in the cases of the tumours causing a diencephalic syndrome in children.[17,18]

In the medical literature, the diagnostic delay for the diencephalic syndrome as an aetiology for severe malnutrition has a mean duration of 12.5 months.[13]

This delay in diagnosis is explained because of the rarity of the DS and because of his atypical symptoms, which may have a demoralizing outcome.[19]

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