Type 1 Diabetes Mellitus (Juvenile Diabetes) – A Review for the Pediatric Oral Health Provider

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Objective: *To describe the significance of type 1 diabetes mellitus (juvenile diabetes) to the pediatric oral health provider.* ***Relevance***: *The oral health provider must be aware of type 1 diabetes mellitus (T1DM) characteristics, influence of on oral health, each patient pre-operative diabetic management, symptoms and treatment of hypo and hyper-glycemia, and the clinical implications before, during and after treatment of children with T1DM.* ***Study design***: *A review of the scientific literature about the T1DM influence on dental development, caries prevalence, gingival and periodontal diseases, wound healing, salivary and taste dysfunction, oral infections, and the factors that must be taken in consideration before, during and after oral treatment of children with T1DM is presented.* ***Conclusion***: *The increasing prevalence of T1DB in children strongly emphasizes the need for oral health providers to be aware of the complicacy of the treatment aimed to obtain and maintain acceptable blood glucose levels in diabetic children, the effect of diabetes on the oral cavity, the possible serious complications due to hypo- or hyper glycemia before, during and after oral treatments, the effect of stress on blood glucose levels, and the special behavioral interaction between the diabetic child, his/her family and the oral health providers.*

Keywords: Diabetes, pediatric dentistry, management

INTRODUCTION

Diabetes mellitus (DM) is a group of chronic, metabolic diseases characterized by elevated levels of blood glucose as the result of defects in insulin secretion, insulin action or both.[1-6] The most common type of DM is type 2 (T2DM), it occurs mostly in adults when the body becomes resistant to insulin or doesn't make enough insulin; type 1 diabetes mellitus (T1DM) also known as juvenile diabetes or insulin-dependent diabetes, is the most common type of diabetes mellitus in children and adolescents, it is a chronic condition in which the pancreas produces little or no insulin by itself, and despite of being named juvenile diabetes, this disease may develop at any age.[1-4] The decrease of insulin production and consequent hyperglycemia in T1DM is caused by β-cell destruction, including two major forms based on the presence or absence of pseudo atrophic islets: Pattern A, with all or a subset of islets lacking all insulin secreting β-cells usually in a lobular pattern; Pattern B, with islets with decreased number of β-cells.[2] The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in year 2000, this prevalence is expected to increase to 4.4% in 2030, with an increase of 21% in the prevalence of T1DM in people under age 20 years in the United states between 2001 and 2009, T1DM constituting 5% to 10% of DM cases and its incidence rate increasing from birth peaking between the ages of 10–14 years[1, 7-11]

DM has a most significant influence on oral health, and on oral treatment and its outcome. Therefore, pediatric oral health providers

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must be aware of the different aspects of T1DM, which is the most common type of DM in children and adolescents.[1, 2, 4, 6] The purpose of the present manuscript is to present a review of T1DM, focused on its behavioral and procedural relevance to the pediatric oral health provider. For this purpose, a thorough review of scientific sources was performed, based on a search including the terms: juvenile diabetes, T1DM, oral health, patient care.

Type 1 diabetes mellitus (T1DM)

Approximately 75% of the T1DM cases are diagnosed during childhood, its incidence in <14-year-olds varies from 0.1/100, 000 to 37/100, 000 in various countries.[1, 10, 12] Type1 diabetes is the most prevalent in American white children; one out of 600 school-aged children has the disease, and it has been suggested that about 50% of them may dye of renal disease 25 years after having been diagnosed.[13] T1DM manifests itself in genetically predisposed individuals after interaction of genetic and environmental factors (both approximately to the same extent), with a strong correlation between the appearance of multiple islet autoantibodies and the risk of developing T1DM.[14, 15] Major environmental factors associated with an increased risk of autoimmune insulitis include enterovirus infections (*Coxsackie virus type B*),[16, 17] nutritional factors such as high exposure to cow's milk proteins, breastfeeding duration (exclusive breast-feeding may a protective effect against T1DB), the effect of nitrates and nitrites and vitamin D deficiency.[18] Diabetes may also appear as a component of syndromes such as Turner syndrome, Prader-Willi syndrome, Friedreich ataxia, Alström syndrome, Klinefelter syndrome, Bardet-Biedl syndrome, Berardinelli-Seip syndrome and Down syndrome.[19] Additional precipitating factors that may elicit the autoimmune reaction that leads to DM include the stress, trauma of war, surgery, glucocorticoids, thiazides, malnutrition, infections, excessive amounts of glucagon, epinephrine and growth hormone.[11, 20]

The warning symptoms of T1DM include polyuria, polydipsia, polyphagia, weight loss, blurred vision, decreased level of consciousness, difficulty in concentration, moderate to severe dehydration, abdominal pain, weight loss due to fluid loss, hyperventilation, hypotension, genital yeast infections in girls and shock, laboratory findings include hyperglycemia, glycosuria and ketonuria. [1, 3, 21] Interesting is the fact that difficulty in concentration may be one of the warning symptoms of DM since this symptom is also one of the several symptoms of attention deficit hyperactivity disorder (ADHD).[22-26] Therefore, parents, educators and health care providers should take in consideration that learning difficulties may not just be a mental problem but also related to a systemic factors such as diabetes, atopic diseases and allergic disorders; furthermore, diabetic ketoacidosis (DKA) related to T1DM may result in morphologic and functional brain changes.[27]

The diagnosis of diabetes is based on a fasting blood glucose concentration above 7.0 mmol/L (126 mg/dL), a random blood glucose concentration above 11.1 mmol/L (200 mg/dL) or an abnormal result from an oral glucose tolerance test in children with diabetic symptoms, and in the absence of symptoms, abnormal glycemia must be present on two different occasions.[28] The diagnosis of diabetes can also be made on the basis of a glycated haemoglobin (HbA1c) concentration above 48 mmol/mol. However, since abnormal glycemia progression can be rapid in patients with type 1 diabetes, HbA1c is less sensitive for diagnosis than fasting or stimulated blood glucose measurements.[28]

The treatment of DM is focused on achieving sugar blood levels that are normal or at least that allow the patient to function properly and prevent diabetes related deleterious effects, however, this is a most challenging task since insulin dosage calculations are related to constantly changing parameters such as diet, physical activity, mental condition and life style; therefore, hyperglycemia or hypoglycemia may suddenly develop in children with T1DM and they should rapidly be recognized to prevent systemic and mental complications.[3, 29]

Oral health and treatment considerations

a. Basic concepts

Oral health providers must keep in mind that in children and adolescents with T1DM may suddenly develop hypo-glycemia or hyper-glycemia due to the challenge involved in blood glucose management (BGM). The first step must be to obtain from the child, its parents and the pediatric endocrinologist a comprehensive systemic health history, knowledge of the individual BGM, triggers and odds for the development of hypo or hyper-glycemia, and their management, all this information leading to an individually tailored oral health treatment plan.

b. Oral implications of T1DM.

Risk for dental caries

Since dental caries is a multifactorial disease, salivary counts of *Streptococcus mutans* (*S. mutans*) and *Lactobacilli* are higher in patients with active caries whether being diabetic or not, and while some factors in T1DM may increase the risk of dental caries others may reduce it, there is no consistency about the caries prevalence and cariogenic bacteria levels between children with or without diabetes.[30-36] Cariogenic bacteria, particularly *S. mutans* and *Lactobacillus casei* (*L. Casei*) may be higher in diabetic patients, especially in those with poor diabetic control, than in non-diabetic children.[32, 33] Yet, another study described no difference in the counts for *S. mutans* and *L. casei* or caries prevalence between the diabetic and nondiabetic children, but a positive correlation between caries and salivary glucose levels.[34] Furthermore, while a lower prevalence of dental caries in deciduous teeth of diabetic children compared to the healthy controls has been reported, a higher prevalence of dental caries in permanent teeth of children with poorly controlled diabetes has also been reported.[35-36]

These inconsistent and possibly conflicting results may be due to several factors:[3, 34, 37-39] 1) a relationship between a shift in the oral microflora and the dietary habits; 2) reduced unstimulated and stimulated salivary secretion in children with diabetes; 3) higher buffering capacity and pH of the saliva in diabetic children; 4) higher viscosity of the saliva; 5) higher levels of carbohydrates, glucose, and total protein in the saliva of diabetic children; 6) higher levels of IgA and IgG antibodies and lower levels of antimicrobial proteins such as lactoferrin and lysozyme in diabetic patients.

Gingivitis and high risk of periodontal disease

Diabetes increases the risk of periodontal tissue destruction in children as early as in the sixth year of life with the destruction depending on the duration of the disease: a study on 270 diabetic children and 320 non-diabetic controls (6- 14 years old) revealed that diabetic children had more gingival inflammation, earlier dental eruption and higher incidence of gingival bleeding in the primary and permanent teeth than the non-diabetic counterparts.[40] An additional study on 187 cases of children with type 1 diabetes and 178 non-diabetic controls (6 to 18 years old), indicated that diabetic children had more dental plaque accumulation, gingival inflammation, and periodontal tissue destruction than the controls, and that diabetic children had 2.8 times more risk of being in the initial stage of gingival or periodontal disease than the controls.[41] Consistent with these findings, a research performed on Brazilian diabetic children (mean age: 13 ± 3.5 years) reported gingivitis and periodontitis in 21% and 6% of the diabetes and control subjects respectively.[42] In addition, despite similar oral hygiene habits, children with T1DM are more prone to gingivitis and calculus accumulation.[44-46] It is interesting that despite of these findings, no significant statistical differences have been found between type 1 diabetic and healthy children in the prevalence of *Porphyromonas. gingivalis*, *Treponema denticola*, and *Aggregatibacter actinomycetemcomitans*.[44, 45]

Periodontitis does not belong to clinical manifestations of any specific type of diabetes mellitus and it is still being labeled as "the sixth chronic complication of diabetes" since it has been confirmed that in individuals with diabetes, there is about a three times higher risk of periodontitis; therefore, diabetes is considered to be a predisposing factor for periodontitis.[47] with the severity of the periodontal destruction being associated with the degree of glycemic control as measured by levels of HbA1c.[35]

Hyperglycemia increases glucose level of saliva and gingival crevicular fluid and glucose in the environment of oral cavity increases proliferation of periodontopathic and cariogenic bacteria increasing oral inflammation; elevated levels of pro-inflammatory mediators in the gingival crevicular fluid of periodontal pockets of poorly controlled diabetics, compared to nondiabetics or well-controlled diabetics, results in significant more severe periodontal destruction despite an equivalent bacterial challenge.[48] Diabetic hyperglycemia can also lead to microangiopathy: endothelial cells lining blood vessels use more glucose than usually and form more glycoproteins on their surface, the basement membrane grows thicker and weaker and therefore, blood vessels bleed easily and leak proteins; these vascular changes decrease chemotaxis, adherence, phagocytosis, migration antigens elimination by polymorphonuclear cells and leading to progression of periodontitis.[49] Hyperglycemia also increases the formation of advanced glycation end-products resulting in the alteration of structures and functions, these glycosylated products can create complex molecules, reduce collagen solubility and increase levels of proinflammatory mediators responsible for the degradation of non-mineralized connective tissue and mineralized bone.[49, 50] The interaction of advanced glycation end-products with target cells, such as macrophages, via cell-surface polypeptide receptors stimulates the production of cytokines and matrix metalloproteinases, including collagenases and other connective tissue-degrading enzymes.[50] Monocytes from diabetics overexpress proinflammatory mediators such as interleukin-1β, tumor necrosis factor-α, and prostaglandin E2.[51] It is possible that periodontal diseases may serve as accelerators of insulin resistance and aggravate glycemic control, and that periodontal treatment may improve glycemic control in patients with type 2 diabetes.[52]

Accelerated tooth eruption

In diabetic children, accelerated dental development may take place in those younger than 11.5 years, while a delay in dental development may take place in in older children.[53] These findings being consistent with a "biphasic" effect of the diabetic state on dental development,[54] but inconsistent with another report of a small and non-significant influence of diabetes on dental development.[55] An accelerated tooth eruption with increasing age in diabetic children suggests that there is a dual complement of mechanisms influencing the intra- and extra-alveolar phases of eruption; whereas the intra-alveolar phase of eruption is shown to be primarily governed by molecular signals generated by the dental follicle proper, extra-alveolar eruption seems to depend more on root development and bone apposition in the apical region of the erupting tooth;[56] despite that the exact mechanisms responsible for tooth eruption remains unclear, recent findings in murine models demonstrated enhanced tooth eruption by colony-stimulating factor-1, which upregulates the immunoreactivity of bone marrow mononuclear cells to growth hormone receptor and insulin-like growth factor-I.[57] Gingival inflammation and expedited eruption have been found to have a statistically not significant correlation,; however, it is possible that an exaggerated inflammatory response to bacterial plaque in hyperglycemia associated periodontal disease may lead to diminished quality and quantity of surrounding bone, resulting in the premature exfoliation of primary teeth that has been reported for diabetic children.[58]

Impaired or delayed wound healing

Poor soft tissue regeneration and delayed osseous healing in patients with diabetes are known complications during oral surgery, this may be attributed to a delayed vascularization, reduction in blood flow, decline in innate immunity, decreases in growth factor production, and psychological stresses may be involved in the protracted wound healing of the oral mucosa in diabetic patients.[59]

Salivary and taste dysfunction

Taste alteration have been associated with diabetes.[60, 61] Children with T1DM have lower salivary flow rates and pH, and buffer capacity, but a higher glucose content in comparison to healthy children.[62-64] Forty to 80% of T2DM patients who do not have a well-controlled glucose blood level have diminished parotid flow rates.[65, 66] Significantly higher urea and glucose levels are present in 80% of DM patients and 10% of healthy subjects.[67] These findings suggest that DM may be related to xerostomia and that there is a significant correlation between the degree of xerostomia and glucose levels in saliva. However, while one study indicated no definitive association between diabetes and reduced salivary flow in the pediatric population,[68] another study indicated that about 50% of diabetic children had hyposalivation (<0.7ml / min), mainly in those with HbA1c values greater than 8.[69]

Oral candidiasis

A higher incidence of *Candida* species is found in the saliva of diabetic patients than in non-diabetic controls with *Candida albicans* (the most prominent specie) being found in 43.1% of diabetic patients and 27% in non-diabetic controls.[70-74] The factors that may predispose diabetic patients to oral candidiasis include high levels of salivary glucose, low secretion of saliva, impaired chemotaxis, and defect of phagocytosis due to polymorphonuclear leukocyte deficiency and reduction of tissue resistance against infection.[72, 75]

Bacterial infections

Patients with diabetes have an impaired defense mechanism hence considered to be immuno-compromised, moreover, those with poor metabolic control are more prone to spreading and recurrent bacterial infection and therefore, several studies have reported that patients with diabetes are more prone to deep neck bacterial infection compared to patient without diabetes.[76] A four year prospective study by Rao *et al.* (2010) investigated the severity of maxillofacial space infection of odontogenic origin, the type of micro-organism, the sensitivity of the micro-organisms to antibiotics and the length of hospital stay of patients with diabetes compared to patient without diabetes; they concluded that the spread of the bacterial infection to the submandibular space was more common in patients and controls and that the second commonest area was the buccal space, with *Streptococcus* species being more commonly isolated in both groups, and patients with diabetes were found to stay longer in hospital due to more severe infection and required more time to control their blood glucose levels.[77]

GENERAL CONSIDERATIONS BEFORE TREATMENT

Health history

Child diabetes-management regimens necessitate a family-endocrinologist teamwork effort.[78, 79] Therefore, it is imperative for the oral health provider to communicate with the child's parents and pediatric endocrinologist to obtain a detailed description of the child's diabetes status, control and recommendations for the dental treatment, including the child's diabetic status and individual blood glucose management (BGM), e. g.: the most significant independent predictor for poor BGM in children and adolescents is poor compliance with a healthy lifestyle, but with an excessive intake of sweets (particularly DKA rather than hyperglycemia).[80] Moreover, individual protocols are required for the correlation of fasting periods related to pre- or post-treatment indications, glucose monitoring, diet and insulin dosage.[81]

Parents and children quality of life and concerns

Child care providers should be aware of the fact that families with children with special needs in general have a reduced quality of life, this being most relevant with parents of children with T1DM who had experienced T1DB unconsciousness or seizures and therefore, have serious concerns about their children functioning and wellbeing, and the children may have fears elicited by their parents anxiety.[82, 83]

Hypoglycemia

Hypoglycemia predictable triggers include skipped meals, exercise, insulin over dosage, as well as defective counter regulation, a component of hypoglycemia-associated autonomic failure. While hypoglycemia is often easily recognized by clinicians and patients with longstanding diabetes, its presence can be substantiated by three key findings known as Whipple's triad: 1) signs and symptoms consistent with low blood glucose; 2) a low blood glucose concentration; and 3) resolution of the signs and symptoms of hypoglycemia when the blood glucose concentration is increased.[84]

Hypoglycemia may manifest with hunger, pallor, shakiness, tiredness, anxiety, tremors, increased sweating, slurred speech altered consciousness, poor concentration, poor judgement, confusion, lethargy, tachycardia, blurred or double vision, disturbed color vision, difficulty in hearing, dizziness, nausea, loss of consciousness and seizures, irritability, erratic behavior, agitation, inconsolable crying, headache, unsteady gait, nightmares and blood glucose levels <60 ml/dl or 70 ml/dl (3.9 mmol/L).[1, 3, 84, 85] Hypoglycemia is a serious clinical concern in children and adolescents with type 1 diabetes and their parents, followed by a negative impact on the diabetes management, metabolic control and subsequent health outcome.[3, 83-85] Episodes of severe hypoglycemia require to actively administer carbohydrate, glucagon, or other resuscitative actions.[83, 84] Therefore, oral health providers should plan in advance a protocol for the diagnosis and treatment of hypoglycemia during or after treatment.

With a conscious patient, the administration of 15 mg of simple carbohydrates, test glucose level in 15 minutes; if glucose level > 60 mg/dl patient should be asked to eat or drink. If glucose level is still < 60 ml/dl repeat ingestion of 15 g of simple carbohydrates and glucose level examination. With an unconscious patient, intra-venous administration of 25 grams of 50% dextrose is indicated; if no IV available, apply glucose gel inside the mouth or 1mg of glucagon intramuscularly or subcutaneously.[1]

Hyper-glycemia

Is considered when the sugar blood levels is >120 in people aged 59 and younger, it may manifest with thirst, frequent urination, stomach pain, blurry vision, increased hunger, drowsiness, exhaustion, impaired concentration, nausea, fruity or sweet-smelling breath and sweating. Diabetic ketoacidosis (DKA) happens when the body starts to burn fat and body tissue for energy, this release toxic acids called ketones that build up in the blood and urine and can lead to diabetic coma. When the patient's sensor indicates hyperglycemia, immediate insulin is the treatment of choice in order to prevent ketoacidosis which requires emergency hospital treatment.[86, 87]

Behavioral aspects

With stress the body prepares to act, hormone levels increase the availability of glucose and fat to cells and if insulin is not available the BGL increases drastically.[20, 86] Therefore, adequate behavior child and parents' guidance, which is always important, has crucial relevance in the case of oral treatment of children and adolescents with T1DB.

The oral health provider should take in consideration that: a) morning appointments are better since endogenous cortisol levels are generally higher; b) diet and insulin dosages that assure (as much as possible) an adequate blood glucose level should be confirmed; c) means for treatment of hypoglycemia and hyperglycemia are available (among other, insulin, sweet drinks, emergency glucose personal syringe). When sedation is required, at least 3 factors that

must be taken in consideration the: a) the fasting period before the sedation; b) use of sweet sedation syrups; c) use of sweeteners to modify the taste of sedative agents that have a bad taste; d) side effects of sedative agents that may affect the blood glucose levels.

A study by Amitai et al.[88] evaluated the safety of topical lidocaine anesthesia in children undergoing bronchoscopy and concluded that lidocaine up to 8.5 mg/kg proved safe and resulted in therapeutic serum lidocaine concentration. These findings suggest that the use of lidocaine use in children with T1DB is safe,

Practical issues

Children with T1DM may have an insulin pump and a blood glucose sensor attached to their body and the oral health providers should be aware not to accidentally displace them while positioning the child in the dental chair of if restrain is required. Regarding the use of dental materials, our search of the literature did not indicate any possible effect of dental materials on the BGL. In any case the oral health provider should be aware of any sweetener that may be included in materials such as topical anesthetic, fluoride varnish, etc.

Post-treatment considerations

While drinking may restart immediately after the treatment, solid food is not allowed for several hours due to sedation considerations and to prevent the child from biting the numbed area. The amount and sugar content of the liquid should be in accordance to the child's diet instructions, and taking in consideration the child's blood sugar level

Increased risk for post-treatment infections.

While diabetic patients are prone to infection because of the altered function of their polymorphonuclear leucocytes, the risk of infection after extractions and the use of prophylactic antibiotics remain controversial. Nevertheless, it appears that most dentists and researchers assume a higher risk for postoperative infections in subjects with diabetes specially if their BGL are not well controlled, whereas well controlled diabetic patients do not require antibiotic coverage in situations in which a nondiabetic patient would not. If antibiotics are recommended, the oral health provider should take in consideration that in juvenile onset diabetes the glomerular filtration rate is elevated and the serum half-lives of penicillin and carbenicillin are inversely related to the glomerular filtration rate and therefore, in order to maintain the same serum levels of these antibiotics diabetic patients need about one and one-half times the usual dose.[89] Since most of the oral microorganisms in diabetic patients are gram positive and gram negative organisms, Studies conducted to identify the empirical antimicrobial therapy for odontogenic infections have stated the use of amoxicillin with metronidazole as one of the most effective regimens.[77, 89]

CONCLUSION

The increasing prevalence of type 1 diabetes mellitus in children (juvenile diabetes) strongly emphasizes the need for oral health providers to be aware of the complicacy of the treatment aimed to obtain and maintain acceptable blood glucose levels in diabetic children, the effect of diabetes on the oral cavity, the possible serious complications due to hypo- or hyper glycemia before, during and after oral treatments, the distinct effect of stress on glucose levels in diabetic children, and the special behavioral interaction between the diabetic child, his/her family and the oral health provider.

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