Bacterial Infection in Diabetic Children

Research Project

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BY:

Nura Star HamadAli

Supervised by:

Prof. Dr.Khadija Khaled Mustafa Barzani

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Introduction:

Diabetes mellitus (DM) is a group of chronic metabolic disorders characterized by elevated glucose in blood (hyperglycemia) and urine (glycosuria) resulting either from partial orabsolute insulin deficiency due to autoimmune destruction of β cells (type 1 DM, T1DM) or from a significant reduction in the ability of cells to respond to insulin (insulin resistance) accompanied by a progressive loss of insulin secretion by β cells (type 2 DM, T2DM). Gestational DM (GDM) is marked by insulin resistance during the second or third trimester of pregnancy (Association AD,2019). The association between diabetes mellitus (DM) and infections is a topic of greatinterest and a reason for considerable discussion in the medical literature. Several studies have assessed this association, mostly in adults, but many have also assessed the impact and incidence of infections in children and adolescents with DM. It has been reported that, in addition to the usual community-acquired infections, some infections occur preferentially in patients with diabetes, and other common infections may be more aggressive in these patients. There is evidence that adequate glycemic control improves immune function and decreases morbidity and mortality associated with severe infections in patients with DM (Dunachie S et al ,2019). children with Diabetes Mellitus can develop various infections due to different factors, including immune disorders, gastric motility disorders, increased number of hospital visits and gastrointestinal complaints; it therefore appears that Helicobacter pylori (H. pylori) infection causes some gastrointestinal symptoms (Giannakiset al , 2008). Type 1 diabetes mellitus (T1DM), arising from a complex interaction between immune, genetic and environmental factors, results from autoimmune-mediated destruction of insulin-producing pancreatic b-cells in genetically predisposed individuals (DiMeglio et al ,2018) . Even if the causative mechanisms are not yet completely defined, T1DM incidence is

increasing worldwide (Lawrence et al , 2021). Several studies showed that genetic susceptibility alone does not explain the development of the disease and suggested that environmental factors play an important etiopathogenetic role (3). Among environmental factors, the most frequently studied include feeding, infections, gut microbiota, perinatal, and social factors (Xia et al , 2019). On the other hand, the impact of infectious diseases on pediatric patients with diabetes mellitus deserves attention. A US retrospective analysis performed on children and adolescents with DM requiring hospitalization for infectious diseases showed a dramatic increase in patients with T1DM (8%), with a longer length of admission (Korbel et al ,2018). There is a recent growing evidence that abnormalities in the microbiota composition can have a major role in the development of diabetes (Pascale et al, 2019) .

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Literature Review :

Diabetes mellitus , often known simply as diabetes, is a group of common endocrine diseases characterized by sustained high blood sugar levels.[11][12] Diabetes is due to either the pancreas not producing enough insulin, or the cells of the body becoming unresponsive to the hormone's effects.[13] Classic symptoms include thirst, polyuria, weight loss, and blurred vision. If left untreated, the disease can lead to various health complications, including disorders of the cardiovascular system, eye, kidney, and nerves.[3] Untreated or poorly treated diabetes accounts for approximately 1.5 million deaths every year.[11] The major types of diabetes are type 1 and type 2, though other forms also exist. The most common treatment for type 1 is insulin replacement therapy (insulin injections), while anti-diabetic medications (such as metformin and semaglutide) and lifestyle modifications can be used to manage type 2. Gestational diabetes, a form that arises during pregnancy in some women, normally resolves shortly after delivery. As of 2021, an estimated 537 million people had diabetes worldwide accounting for 10.5% of the adult population, with type 2 making up about 90% of all cases. It is estimated that by 2045, approximately 783 million adults, or 1 in 8, will be living with diabetes, representing a 46% increase from the current figures.[14] The prevalence of the disease continues to increase, most dramatically in low- and middle-income nations.[15] Rates are similar in women and men, with diabetes being the seventh leading cause of death globally.[16][17] The global expenditure on diabetes-related healthcare is an estimated US$760 billion a year.[18] Diabetes is classified by the World Health Organization into six categories: type 1 diabetes, type 2 diabetes, hybrid forms of diabetes (including include slowly evolving, immune-mediated diabetes of adults and ketosis-prone type 2 diabetes), hyperglycemia first detected during

pregnancy, "other specific types", and "unclassified diabetes".[41] Diabetes is a more variable disease than once thought, and individuals may have a combination of forms.[42]

Type 1 Diabet:

Type 1 accounts for 5 to 10% of diabetes cases and is the most common type diagnosed in patients under 20 years;[43] however, the older term "juvenile-onset diabetes" is no longer used as the disease not uncommonly has onset in adulthood.[29] The disease is characterized by loss of the insulin-producing beta cells of the pancreatic islets, leading to severe insulin deficiency, and can be further classified as immune-mediated or idiopathic (without known cause).[43] The majority of cases are immune-mediated, in which a T cell-mediated autoimmune attack causes loss of beta cells and thus insulin deficiency.[44] Patients often have irregular and unpredictable blood sugar levels due to very low insulin and an impaired counter-response to hypoglycaemia.[45]. Type 1 diabetes is partly inherited, with multiple genes, including certain HLA genotypes, known to influence the risk of diabetes. In genetically susceptible people, the onset of diabetes can be triggered by one or more environmental factors,[46] such as a viral infection or diet. Several viruses have been implicated, but to date there is no stringent evidence to support this hypothesis in humans.[46][47] Type 1 diabetes can occur at any age, and a significant proportion is diagnosed during adulthood. Latent autoimmune diabetes of adults (LADA) is the diagnostic term applied when type 1 diabetes develops in adults; it has a slower onset than the same condition in children. Given this difference, some use the unofficial term "type 1.5 diabetes" for this condition. Adults with LADA are frequently initially misdiagnosed as having type 2 diabetes, based on age rather than a cause.[48] LADA leaves adults with higher levels of insulin production than type 1 diabetes, but not enough insulin production for healthy blood sugar levels(49 50) .

Type 2 diabet :

Type 2 diabetes is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion.[13] The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. Diabetes mellitus cases due to a known defect are classified separately. Type 2 diabetes is the most common type of diabetes mellitus accounting for 95% of diabetes.[2] Many people with type 2 diabetes have evidence of prediabetes (impaired fasting glucose and/or impaired glucose tolerance) before meeting the criteria for type 2 diabetes.[51] The progression of prediabetes to overt type 2 diabetes can be slowed or reversed by lifestyle changes or medications that improve insulin sensitivity or reduce the liver's glucose production.[52] Type 2 diabetes is primarily due to lifestyle factors and genetics.[53] A number of lifestyle factors are known to be important to the development of type 2 diabetes, including obesity (defined by a body mass index of greater than 30), lack of physical activity, poor diet, stress, and urbanization.[33][54] Excess body fat is associated with 30% of cases in people of Chinese and Japanese descent, 60–80% of cases in those of European and African descent, and 100% of Pima Indians and Pacific Islanders.[13] Even those who are not obese may have a high waist–hip ratio.[13] Dietary factors such as sugar-sweetened drinks are associated with an increased risk.[55][56] The type of fats in the diet is also important, with saturated fat and trans fats increasing the risk and polyunsaturated and monounsaturated fat decreasing the risk.[53] Eating white rice excessively may increase the risk of diabetes, especially in Chinese and Japanese people.[57] Lack of physical activity may increase the risk of diabetes in some people.[58] Adverse childhood experiences, including abuse, neglect, and household difficulties, increase the likelihood of type 2 diabetes later in life by 32%, with neglect having the strongest

effect.[59] . Antipsychotic medication side effects (specifically metabolic abnormalities, dyslipidemia and weight gain) and unhealthy lifestyles (including poor diet and decreased physical activity), are potential risk factors.[60)

Comparison of type 1 and 2 diabetes[33]		
Feature	Type 1 diabetes	Type 2 diabetes
Onset	Sudden	Gradual
Age at onset	Mostly in children	Mostly in adults
Body size	Thin or normal[34]	Often obese
Ketoacidosis	Common	Rare
Autoantibodies	Usually present	Absent
ndogenous insulin	Low or absent	Normal, decreased or increased
Heritability	0.69 to 0.88[35][36][37]	0.47 to 0.77[38]
Prevalence age standardized)	<2 per 1,000[39]	~6% (men), ~5% (women)[40]

Gestational diabetes :

Gestational diabetes resembles type 2 diabetes in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2–10% of all pregnancies and may improve or disappear after delivery.[61] It is recommended that all pregnant women get tested starting around 24–28 weeks gestation.[62] It is most often diagnosed in the second or third trimester because of the increase in insulin-antagonist hormone levels that occurs at this time.[62] However, after pregnancy approximately 5–10% of women with gestational diabetes are found to have another form of diabetes, most commonly type 2.[61] Gestational diabetes is fully treatable, but requires careful medical supervision throughout the pregnancy.

Management may include dietary changes, blood glucose monitoring, and in some cases, insulin may be required.[63] Though it may be transient, untreated gestational diabetes can damage the health of the fetus or mother. Risks to the baby include macrosomia (high birth weight), congenital heart and central nervous system abnormalities, and skeletal muscle malformations. Increased levels of insulin in a fetus's blood may inhibit fetal surfactant production and cause infant respiratory distress syndrome. A high blood bilirubin level may result from red blood cell destruction. In severe cases, perinatal death may occur, most commonly as a result of poor placental perfusion due to vascular impairment. Labor induction may be indicated with decreased placental function. A caesarean section may be performed if there is marked fetal distress[64] or an increased risk of injury associated with macrosomia, such as shoulder dystocia [65].

Other types :

Maturity onset diabetes of the young (MODY) is a rare autosomal dominant inherited form of diabetes, due to one of several single-gene mutations causing defects in insulin production.[66] It is significantly less common than the three main types, constituting 1–2% of all cases. The name of this disease refers to early hypotheses as to its nature. Being due to a defective gene, this disease varies in age at presentation and in severity according to the specific gene defect; thus, there are at least 13 subtypes of MODY. People with MODY often can control it without using insulin.[67] Some cases of diabetes are caused by the body's tissue receptors not responding to insulin (even when insulin levels are normal, which is what separates it from type 2 diabetes); this form is very uncommon. Genetic mutations (autosomal or mitochondrial) can lead to defects in beta cell function. Abnormal insulin action may also have been genetically determined in some cases. Any disease that causes extensive damage to the pancreas may lead to diabetes (for example, chronic

pancreatitis and cystic fibrosis). Diseases associated with excessive secretion of insulin-antagonistic hormones can cause diabetes (which is typically resolved once the hormone excess is removed). Many drugs impair insulin secretion and some toxins damage pancreatic beta cells, whereas others increase insulin resistance (especially glucocorticoids which can provoke "steroid diabetes"). The ICD-10 (1992) diagnostic entity, malnutrition-related diabetes mellitus (ICD-10 code E12), was deprecated by the World Health Organization (WHO) when the current taxonomy was introduced in 1999.[68] Yet another form of diabetes that people may develop is double diabetes. This is when a type 1 diabetic becomes insulin resistant, the hallmark for type 2 diabetes or has a family history for type 2 diabetes.[69] It was first discovered in 1990 or 1991 .

Type 1 diabetes mellitus (T1DM) is a chronic disease characterized by hyperglycaemia owing to insulin deficiency as a consequence of pancreatic β-cell loss. The most common type of T1DM — autoimmune T1DM — is marked by immune-mediated β-cell loss.T1DM is the most common cause of diabetes in children, with >500,000 children currently living with this condition globally — making it one of the most common endocrine and metabolic conditions in childhood. Incidence peaks around 12–14 years of age, although children are increasingly being diagnosed at younger ages. The number of new patients of <5 years of age is expected to increase between 2005 and 2020 (Marshall,2017) . The association between diabetes mellitus and infections is very common. These infections, even when mild, interfere with blood glucose control. T1D is caused by an autoimmune process directed against pancreatic beta cells, responsible for the production and secretion of insulin, leading to their destruction, with consequent insulin deficiency and hyperglycemia. It Is the most common type in children and adolescents in Brazil, and it is mainly associated with microvascular

complications (retinopathy, nephropathy, and neuropathy) (American Diabetes Association, 2019). It is unquestionable that infections, even typical childhood diseases, significantly interfere with glycemic control. There is an increase in counter-regulatory hormones, cortisol, epinephrine, and growth hormone (GH) caused by the infectious process, leading to increased neoglycogenesis, glycogenolysis, and increased insulin resistance. This increase in insulin resistance requires adjustments in the patient's usual insulin dose, both basal and bolus. There is usually a period of hours or days before this need is perceived and the increase in the dose may take time to be performed, which can result in hyperglycemia during this period. Sustained hyperglycemia may lead to increased production of ketone bodies. The evolution of this condition may reach diabetic ketoacidosis (DKA), the main cause of death in young T1D patients (wolfsdorf et al , 2018).

Most common infections in children and adolescents with diabetes :

children with Diabetes Mellitus can develop various infections due to different factors, including immune disorders, gastric motility disorders, increased number of hospital visits and gastrointestinal complaints; it therefore appears that Helicobacter pylori (H. pylori) infection causes some gastrointestinal symptoms (Giannakis et al , 2020).

H. pylori which inhabits various areas of the stomach and duodenum, is a Gram-negative helix-shaped bacterium. H. pylori infection leading to chronic gastritis is asymptomatic in the majority of carriers, but is considered a major risk factor for the development of gastric and duodenal ulcers and gastric malignancies (Kusters et al , 2020) . t he prevalence of H. pylori infection is associated with age. The overall prevalence of H. pylori infection is less than 10% in children from developed countries. H. pylori infection is more common in the

developing world, and more than 80% of the population are infected before puberty (Kadhim et al , 2015) .

Respiratory infections :

Respiratory infections are the leading cause of infection in children, including diabetic patients. The main etiological agents of lower respiratory tract infections are Streptococcus pneumoniae and respiratory viruses, including influenza viruses. Although the prevalence of Streptococcus pneumoniae in the nasopharynx of children with diabetes is not increased in relation to healthy children or those with other chronic diseases(Pekzu et al, 2019). some studies have shown that diabetic patients are more susceptible to pneumococcal infections and also at higher risk of bacteremia, worse prognosis, and higher mortality in the presence of these infections (Semingo et al, 2013) There are few data in the literature on children, but overall, diabetic patients are more likely to be hospitalized and to develop complications than non-diabetic patients during the influenza season (Miller et al ,2019) .

Candida spp. infections

Diabetes is a well-known risk factor for candidiasis. The most common location is the vulvovaginal area, and the risk is higher depending on the type of DM, severity, and degree of glycemic control. Type 1 DM patients with elevated glycated hemoglobin and inadequate glycemic control are more likely to have Candidaspp colonization. The hyperglycemia impairs neutrophil function, including phagocytosis, while acting as a nutrient for Candida. Patients with poorlycontrolled DM have higher acid proteinase activity, which are enzymes that facilitate the adhesion of the fungus to the epithelial cells (Rodrigues et al ,2019 ; Atabek et al , 2019). Several studies show a higher prevalence of asymptomatic vaginal colonization and symptomatic infection by Candida spp. in diabetic women. Vaginal colonization in prepubertal diabetic girls is uncommon, at around 12.5%,

as the low estrogen levels result in rich anaerobic flora, which inhibit the growth of Candida. Colonization increases with age, reaching 55%. The most commonly found species is Candida albicans, followed by Candida glabrata (Rodrigues et al ,2019 ; Atabek et al , 2019). The clinical diagnosis in patients with vulvovaginal candidiasis is based on typical clinical signs such as thick, whitish vaginal discharge, itching, pain, burning, erythema, and edema. Diabetic patients may have recurrent conditions, with up to four episodes per year. When recurrence occurs, vaginal secretion culture should be performed to identify the Candida species (Pappas et al , 2016). Treatment may be topical with clotrimazole or ketoconazole, or systemic with a single dose of fluconazole. In cases of recurrent candidiasis, the treatment should be directed to the isolated species; it may be topical with clotrimazole cream or systemic with fluconazole for ten to 14 days. In these cases, a maintenance schedule with fluconazole is recommended once a week for at least six months(Pappas et al , 2016).

Periodontal infections

Children and adolescents with T1D, especially poorly controlled patients, have a two- to three-fold higher prevalence of periodontal infection. The predisposing factor is the alteration of gingival vascularization, in addition to immune impairment.15 Periodontitis can lead to ligament loss, tooth mobility, and need for extraction. Dental abscesses and bacteremia may occur(Dakovic et al ,2019) .

Urinary tract infections

Urinary tract infections (UTIs) are more prevalent in individuals with DM, and severe complications and manifestations may occur (Chita et al , 2016) . Some factors contribute to a higher risk of UTI: compromised host immune response, incomplete bladder emptying due to autonomic neuropathy (in T2D), and altered metabolic control, as elevated urine

glucose also favors colonization by pathogenic microorganisms. The most common agents are the same as those in the general population: Escherichia coli and other enterobacteria (Chita et al , 2016). The most common infections are asymptomatic bacteriuria, lower UTI (cystitis), upper UTI (pyelonephritis), and urosepsis. Complications may also occur, such as renal papillary necrosis, emphysematous cystitis, and renal abscess.16 Much is discussed about asymptomatic bacteriuria in patients with diabetes. Although more prevalent (Renko et al , 2019) a randomized controlled trial of antimicrobial treatment in asymptomatic bacteriuria showed no difference in UTI development, time until symptom onset, risk of pyelonephritis, or need for hospitalization (Hrding et al , 2019) . Therefore, although controversial, there seems to be no need for screening or treatment of asymptomatic bacteriuria in these patients.

Skin and soft tissue infections

Skin and soft tissue infections are common in individuals with diabetes, particularly when glycemic control is inadequate. Candidiasis, bacterial infections, dermatomycosis, and onychomycosis may occur. In bacterial infections (furunculosis, cellulitis) the main agents are the Streptococcus pyogenes and Staphylococcus aureus. Deep soft tissue infections also occur more frequently in diabetic individuals, such as pyomyositis, necrotizing fasciitis, and Fournier's gangrene (Casqueirq et al , 2019).

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