Complications of type 1 diabetes mellitus during childhood and adolescence

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Abstract. Type 1 diabetes mellitus (T1DM) is a multifactorial autoimmune pathology associated with the complete inability to produce insulin, as a result of the destruction of insulin-producing β-cells on the pancreas islets of Langerhans. The disease is the most common chronic metabolic illness during childhood and adolescence, being directly affected by factors such as genetics, environment, diet and exercise, which can lead to more predisposition to develop this condition. A cure for T1DM is not available and patients depend on strict life-long treatments and medical monitoring, which is a difficulty since those most affected have young age and, consequently, have more obstacles on adapting appropriately to the therapy, being more prone to develop complications. The main worsenings of this disease are cardiovascular involvement, ketoacidosis, nephropathy, retinopathy and neuropathy that can be developed in the long and short term after diagnosis, decreasing life-quality and life expectancy of individuals with T1DM. Thus, it is crucial to have a high knowledge about these pathology complications, in order to identify decompensations, avoiding irreversible injuries and sequels on patients that can lead to high morbimortality.

Keywords. Type 1 diabetes mellitus, complications, insulin and decompensations.

1. Introduction

Type 1 diabetes mellitus (T1DM) is a multifactorial chronic autoimmune pathology associated with the complete inability to produce insulin, an essential anabolic hormone directly associated with the glucose metabolism and homeostasis. The pathophysiologic of this condition is not completely understood, although it is thought to be associated with the mediated destruction of insulin-producing β-cells on the pancreas islets of Langerhans by T-cells, correlated to the production of autoantibodies that target insulin and proteins related to secretory granules in β-cells. [1], [3]

T1DM is the most common chronic metabolic disease during childhood and adolescence, being referred to as “juvenile diabetes”. However, currently it is known that it can be diagnosed at any age and that factors such as genetics, environment, diet and exercise can lead to more predisposition to develop this condition. [3], [4]

This pathology can be diagnosed through clinical and laboratory exams, such as fasting glucose measurement, glucose tolerance test, glycated haemoglobin and characteristic symptoms. However, due to neglect in the diagnosis of children and adolescents, many cases are identified during peaks of hyperglycemia or due to complications, the most common being ketoacidosis [4].

Furthermore, the main characteristic of this disease is hyperglycemia, due to the modifications on the metabolism of carbohydrates, proteins and lipids, as a consequence of the low insulin seric levels. Moreover, the most prevalent symptoms are polydipsia, polyuria and polyphagia, which can lead to homeostasis dysfunctions and severe complications if not correctly managed and monitored. The main worsening of this disease affects the cardiovascular system, acid-base balance and renal system, which can lead to irreversible injuries that compromise the patient's prognosis. [2], [3],[5]

A cure is not available for this pathology and patients depend on life-long insulin treatments, such as injections, insulin pumps and continuous glucose

monitoring. Thus, the addiction to specific treatment is crucial to improve life-quality and avoid T1DM complications, which can lead to high morbimortality. [3], [4]

2. Methods

This research carried out a bibliographic survey in the online databases of the electronic platforms SciELO and Pubmed. The selected articles were published between 2001-2023. The search execution involved original and relevant articles to the objective of this work, without language restrictions. For the search execution, articles with a higher level of evidence were prioritised, as they expose applicability that is more coherent with current medical practice. Furthermore, systematic reviews, clinical trials and consensus or guidelines from medical societies were used for the development of the project. The search strategy used the following descriptors: type 1 diabetes mellitus; T1DM complications; ketoacidosis; diabetic nephropathy; cardiovascular complications; ocular complications on T1DM.

3. Discussion

The incidence of Type 1 diabetes mellitus has been increasing about 3% a year in children and adolescents. Despite the high number of cases, a cure for this pathology is not available, which requires the patients an intensive and challenging self-managing regimen to achieve a good prognosis. The treatment includes daily insulin intake, regular exercise, balanced diet, blood glucose tests and behaviour changes. However, due to social demands, knowledge deficiency, less autonomy and family dynamics, younger people have more difficulties in adapting efficiently to the treatment. Furthermore, they have more chances of developing social, psychological and self-acceptance problems, which contributes to less effective medical monitoring. [1],[3],[4]

Consequently, children and adolescents are more susceptible to develop T1DM complications, which can affect metabolism, hemodynamic and body systems. Therefore, it is crucial to increase knowledge about these decompensations, in order to guarantee a better prognosis and life-quality to these patients.

3.1 Cardiovascular system

Cardiovascular disease is associated with 50 to 80% of mortality in type diabetic mellitus population, which mainly involves coronary disease, cerebrovascular accident (CVA) and peripheral arterial disease. The main risk factors to these conditions are sedentarism, age, diet, obesity, smoking, hypertension and dyslipidemia. [13]

T1DM can induce micro and macrovascular modifications. The microvascular is associated with the thickening of the capillary basement membrane of small vessels, capillaries and arterioles affecting the systemic vascular system. The macrovascular involves large vessels, triggering an accelerated form of atherosclerosis, being responsible for the high incidence of cardiovascular diseases. [13]

The physiopathology of these complications is mainly associated with hyperglycemia, which induces endothelial dysfunction and accelerated atherosclerosis. Furthermore, high levels of glucose increase circulating fatty acid levels, modify lipoproteins, produce derivatives of glycation and oxidation which can damage the vascular endothelium, leading to endothelial dysfunction with proinflammatory and prothrombotic changes. The potential mechanisms that might lead to these phenomena are associated with oxidative stress, activation of protein kinase C and increased expression of adhesion molecules.[13],[15]

Furthermore, heart diseases induced by T1DM are associated to diabetic nephropathy because of proteinuria, which increases mortality, mainly due to cardiac causes. The prevention and treatment of diabetic nephropathy and associated cardiovascular disease is the solution of aggressive risk factors that both present in common, such as hyperglycemia, arterial hypertension and dyslipidemia. [13]

3.2 Ketoacidosis

Diabetic ketoacidosis (DKA) is defined by presence of metabolic acidosis, ketosis (arterial pH <7.3 or venous <7.25 and/or HCO3 <15 mEq/L), hyperglycemia (>200 mg/dL) and varying degrees of dehydration on patients with type 1 diabetes mellitus. DKA is the most frequent admission to emergency and pediatric ICU, constituting the main cause of death in children and adolescents with T1DM. [6]

The pathophysiology of DKA is associated with continuous insulin deficiency resulting in intracellular starvation of insulin-dependent tissues (muscle, liver and adipose), stimulating the release of counterregulatory hormones, such as catecholamines, glucagon, cortisol and somatotropin. Consequently, the body achieves a catabolic state, with increased production of glucose via glycogenolysis and gluconeogenesis, associated with a decreased use of glucose by peripheral tissues. As a result, a stage of hyperglycemia, hyperosmolarity, increased lipolysis and ketogenesis is developed, which causes ketonemia and metabolic acidosis. [6], [7]

DKA is characterised by polyuria, polydipsia and weight loss, which evolves with dehydration, nausea,

vomiting, hyperventilation (Kussmaul breathing) and breath keto. Abdominal pain, progressive anorexia, lethargy, altered consciousness can also be observed. The most serious complications of DKA, due to the high mortality, are cerebral edema, hyper or hypokalemia, hypoglycemia, thrombosis, sepsis, infections and aspiration pneumonia. Thus, it is crucial to have an efficient therapy involving replacement of fluid, electrolyte, insuline, potassium, phosphate and constant monitoring of the affected patient [6],[7].

As DKA is the most frequent worsening of T1DM [6], it is indispensable to achieve an efficient care outpatient for DM1 patients in order to avoid irreversible sequels. Furthermore, to prevent these decompensations and guarantee a better prognosis, the patient and his family can learn to recognize early signs of decompensation, so they can take the necessary measures on time.

3.3 Renal System

Diabetic nephropathy occurs due to interactions between multiple factors including increased systemic and intraglomerular pressure, activation of the renin-angiotensin aldosterone system, activation of vascular endothelial growth factor, and from hyperglycemia due to oxidative stress, renal polyol formation and accumulation of advanced glycation end products [10]. Approximately 30 to 40% of the cases of T1DM develop diabetic nephropathy, which can evolve with kidney involvement both in the acute setting presenting with acute kidney injury (AKI), as well as tubular damage and in the chronic can be associated with diabetic kidney disease (DKD). [8]

Diabetic nephropathy is characterised by microvascular dysfunction which leads to renal function loss, proteinuria, followed by hypertension and renal insufficiency [8], [9]. The main cause of this pathology is hyperglycemia, which generates a renal overload generating increased filtration glomerular, developing important substances to be lost. Furthermore, the stages of diabetic nephropathy progress from renal hypertrophy, albuminuria, proteinuria, impairment of glomerular filtration rate and end-stage kidney disease [10]. The diabetic nephropathy is also associated to progressive dyslipidemia, decreased glomerular filtration rate and five times higher mortality risk. This condition can be associated with risk factors such as inadequate glycemic and blood pressure control, smoking, diabetic retinopathy, hypercholesterolemia and glomerular hyperfiltration. [9]

The main pathophysiological mechanism is associated with osmotic polyuria, which leads to dehydration, hypovolemia, and kidney hypoperfusion, triggering tubular damage. The kidney failure is strongly linked to hyperglycemia due to modifications on the glucose metabolism [11]. Moreover, the main consequence of continuous hyperglycemia is non-enzymatic glycation, which glucose binds to the amino group of proteins and generates short and long term complexes (AGEs) that cause endothelial damage and, consequently, a disruption of the glomerular basement membrane, reducing glomerular filtration. The products of the glycation are deposited on the vessel walls, bind to macrophages that produce cytokines and growth factors, leading to reactions that contribute to increase the production of collagen and extracellular matrix, occasion in glomerular occlusion due to fibrosis. [8], [9]

The diagnosis of nephropathy is made by the increasing level of albumin and creatinine and decreasing levels of TGF on urine, which cause frequent injuries to the kidneys that can lead to irreversible and chronic damage to kidney cells and tissues [9]. Consequently, patients with this condition are more prone to develop critical conditions and depend on life-long treatments such as hemodialyse. Thus, it is crucial to monitor T1DM evolution on children and adolescents in order to avoid decompensations, specially hyperglycemia, that can evolve to irreversible complications. [8], [10]

3.4 Retinopathy

Retinopathy is the most common microvascular complication of diabetes, resulting in blindness for over 10,000 people with diabetes per year [13]. The incidence of this complication increases between 5 and 15 years after the diagnosis and affects all tissues of the eyes, being the main cause of loss of vision on T1DM. [14]

The pathophysiology of this complication is associated with several biochemical pathways, such as polyol accumulation, formation of advanced glycation end products (AGEs), oxidative stress, and activation of protein kinase C (PKC). These processes are thought to modulate the disease process affecting cellular metabolism, signaling, and growth factors [13]. Consequently, diabetic retinopathy develops vascular endothelial cell apoptosis, thickening of the capillary basement membranes and loss of pericytes, increasing the permeability across the blood vessel walls while leading to closure of the most affected capillaries [14]. The increased oxidative stress causes precocious vascular endothelial cell damage, breakdown of the blood-retinal barrier, which can evolve to microaneurysms and haemorrhage focus. Furthermore, retinopathy develops exudation from the retinal vasculature into the interstitial space leading to macular edema, worsening the condition.[14]

Diabetic retinopathy progression can be reduced by controlling hyperglycemia in patients with T1DM. The studies show that for every 1% reduction in glycated hemoglobin (A1c) there is a decrease in the risk of retinopathy by 35%, and of progression by

39% in individuals with T1DM. Moreover, to prevent this complication, adolescents should have an early monitoring by fundoscopy exam with pupil dilation after diabetes diagnosis [15].

The main form of treatment for DR is laser photocoagulation, using factors of growth of vascular endothelium and VEGF antagonists in order to inhibit vascular leakage of diabetic macular edema [15].

3.5 Neuropathy

Diabetic neuropathy (NeD) is the most common late complication of diabetes and can be evident in T1DM usually appearing five years or more after the diagnosis, being rare in childhood. However, it must be considered in adolescents with long-term diabetes [15].

The pathogenesis of NeD is not yet fully understood, the studied mechanisms include microvascular insufficiency with reduction in flow
neural blood, resulting in ischemia of the endoneurial and epineural vessels, which leads to thickening of the basement membrane, reducing the blood flow and permeability vascular changes. As a result, there is damage to microvascular perfusion, insufficient flow and, consequently, neural injury [15].

This complication can present different forms and diffuse sensorimotor polyneuropathy peripheral symmetry is the most common. The symptoms of this condition are paresthesia, pain in legs and feet, hyperesthesia, decrease or loss of tactile sensitivity, thermal or painful, loss of reflexes, weakness and foot ulcers [15].

Furthermore, the symptoms and the gravity of the neuropathy depends on the fibers that are committed. The small demyelinated type C fibers are responsible for thermal sensation, pain and function autonomic, consequently, in the initial stages of lesion to these fibers, the patient suffers from burning pain with hyperalgesia and allodynia. On the other hand, the involvement of large fibers induce the sensation of deep and unbearable pain. [16]

This complication can have sympathetic involvement, affecting the regulation of sweat glands and arteriovenous shunts in the feet, which develop modifications that are favorable for the growth and penetration of bacterias. Moreover, the patients develop dry skin that leads to the appearance of small cracks, which act as a gateway to microorganisms, all associated with a decrease in blood perfusion and, consequently, decrease of defense mechanisms. The complete disappearance of pain is an important symptom, as it could represent the definitive loss of local nerve endings, which can induce foot depletion of C fibers, ulcers, progression to gangrene and amputation [16].

4. Conclusion

Type 1 diabetes mellitus is a serious chronic pathology which requires a life-long strict treatment and medical monitoring. Thus, it is crucial to emphasise the importance of a proper and well adapted therapy in order to avoid decompensations of this pathology that can lead to high morbimortality risks. Furthermore, it is essential to increase the knowledge about these complications, so that their signs and symptoms can be early identified and appropriately controlled, reducing the risks of developing sequels in children and adolescents.

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6. References

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