v. 3, n. 68, 2023

International Journal of Health Science

TYPE 1 DIABETES MELLITUS AS AN EXTRA INTESTINAL MANIFESTATION OF CELIAC DISEASE: THE IMPORTANCE OF SCREENING AND EARLY TREATMENT

Bárbara Belloni Perez Couto
Faculdade Medical Sciences - Minas Gerais (FCMMG)

Izabella Pereira Chaves
Faculdade Medical Sciences - Minas Gerais (FCMMG)

Lucas Pinheiro Costa
Faculdade Medical Sciences - Minas Gerais (FCMMG)

Abstract: Introduction: Celiac disease (CD) is an autoimmune disease that has a specific serological and histological profile that occurs after gluten ingestion by genetically predisposed patients. The disease has a wide spectrum of symptoms and multifactorial causes. In addition, the disease is characterized by being difficult to diagnose, in part due to the wide range of clinical manifestations that can misdirect and prevent diagnosis. Type 1 Diabetes Mellitus (DM1) is a chronic autoimmune disease that leads to complete or partial destruction of pancreatic beta cells, thus resulting in a progressive inability to produce insulin. DM1 causes several lesions in different organs, due to micro and macrovascular alterations, which generate dysfunctions and insufficiencies in the body. It is known that there is an intimate relationship between these two pathologies, the prevalence of CD among patients with DM1 has been estimated at approximately 4.0%. This association between the two pathologies occurs due to the presence of the human histocompatibility antigen (HLA) DQ, encoded by the DQ2 and DQ8 genes on chromosome 6, which suggests a genetic cause for the simultaneous occurrence of the two diseases, since such genes are shared by DM1, CD and other autoimmune diseases. **Goal**: To carry out an integrative literature review to seek to understand the relationship between celiac disease and type 1 diabetes, as well as the pathophysiology and immunopathogenesis involved in the association between these two pathologies. **Method**: PubMed, SciELO, and LILACS databases were methodically searched from 2000 to 2021 to identify all studies that evaluated the relationship between celiac disease and type 1 diabetes. **Results**: According to the studies analyzed, celiac disease was associated with a statistically significant increase in the risk of subsequent type 1 diabetes before age 20. In addition, prevalence of biopsy-confirmed celiac disease was also found in about 6% of the population with T1DM. In this study, the prevalence was lower in adults with type 1 diabetes (2.7%) and in mixed populations with children and adults with type 1 diabetes (4.7%) than in children (6.2%) with type 1 diabetes. 1.

The correlation between the prevalence of patients with Type I Diabetes Mellitus and Celiac Disease is notorious, and CD often manifests itself asymptomatically, which may worsen the clinical picture regarding DM1. Diagnosis and adequate treatment of CD are essential for the reduction of possible complications and risks resulting from diabetes to be possible, promoting an improvement in the quality of life of patients with both comorbidities. Celiac Disease may be responsible for accelerating the worsening of Type I Diabetes Mellitus, with the onset of chronic complications of DM1 prematurely. An example of a complication is Diabetic Nephropathy (DN), which appears earlier in patients with CD at the same time, since the role of the disease in the development of chronic hyperglycemia is suspected, which, in addition to culminating in a thickening of the glomerular basement membranes, in the kidneys, also has other repercussions in different body systems, as in the case of Diabetic Nephropathy. In addition, the state of hyperglycemia generated in the body is a triggering factor for Peripheral Neuropathy, a condition characterized by a change in the conduction of nerve impulses, due to the excessive entry of glucose into the cells of the neuronal and endothelial tissues. The association between both diseases is also responsible for causing a greater cardiovascular risk for the patient, since it was identified that individuals with both diseases have lower levels of HDL-cholesterol, associated with possible more severe conditions of atherosclerosis, in due to a greater thickening of the intima-media layer.

Conclusion: In many cases, celiac disease

symptoms go undiagnosed, as most individuals assume they are just symptoms of diabetes. Therefore, for a better control of type 1 diabetes mellitus to be carried out, it is imperative that the underlying cause of any symptom experienced by the patient be discovered. People who have DM1 and CD concomitantly have difficult diabetes control. The complexity of treating T1DM in patients with celiac disease is due to the fact that gluten in food causes inflammation in the intestine, which changes the way food is absorbed. This causes blood sugar fluctuations to be carried out more frequently and also with greater intensity. Thus, for individuals who have both autoimmune diseases, it is critical that a strict diet be followed to reduce the risk of diabetes and untreated celiac disease.

Keywords: "Celiac disease"; "HLA antigens"; "Diabetes Mellitus Type 1".

INTRODUCTION

Type 1 Diabetes Mellitus (DM1) consists of an autoimmune disease, where there is destruction of pancreatic beta cells by T cells, so there is a deficiency and even absence of insulin (hypoglycemic hormone that is produced by the pancreas). The lack of this hormone is characterized by high levels of blood glucose and disturbances in the metabolism of carbohydrates, fats and proteins. At the same time, this endocrinopathy causes structural alterations in several organ systems, including microangiopathy (retinopathy, nephropathy and neuropathy) and macroangiopathy (coronary disease, peripheral arterial insufficiency, among others). (FERREIRA et al., 2011). It is noteworthy that patients with DM1 are at greater risk of developing other autoimmune diseases, one of which is Celiac Disease (CD) (LUDVIGSSON et al., 2006).

Celiac disease (CD) is an autoimmune inflammatory bowel disease triggered by gluten ingestion. This protein induces an inflammatory immune response in the patient's intestine, and the withdrawal of gluten from the diet results in remission of the disease. The intestinal inflammation caused by this pathology can result in the complete destruction of the intestinal epithelium, with crypt hyperplasia, loss of villous structure and lymphocyte infiltration, with consequent malabsorption of nutrients, vitamins and minerals. (LUNDIN et al., 2015) This disease has a wide spectrum of symptoms and multifactorial causes. (LUDVIGSSON et al., 2006). Furthermore, the disease is characterized by being difficult to diagnose, in part due to the wide range of symptoms and the variation in their clinical expression. (LUNDIN et al., 2015)

Both type 1 diabetes and CD share a similar genetic basis, with high susceptibility associated with the HLA-DQ2/DQ8 genotype. This haplotype is present in over 95% of patients with celiac disease and 55% of those with T1DM, compared to only 20%-25% of the general population of European descent. It is noteworthy that several other genes are also implicated in susceptibility to both diseases (LUDVIGSSON et al., 2006).

Therefore, as CD is often linked with Type 1 Diabetes (T1D), genetic analysis may be of substantial value in monitoring those individuals who, from a genetic point of view, are at high risk of developing celiac disease, but who have not yet present evident manifestations, thus allowing a diagnosis as well as early treatment, which is very beneficial for the health and well-being of these patients.

METHOD

Conducting an integrative literature review, with articles indexed in the Scielo, PubMed and Lilacs databases from the years 2005 to 2020. Articles published in English, Portuguese and Spanish, whose theme was compatible with the proposed theme, were used as inclusion criteria. The descriptors

used were: "Gluten"; "Gluten-Free"; "Celiac disease"; "Celiac diagnosis"; "HLA antigens"; "Diabetes Mellitus Type 1".

RESULT AND DISCUSSION

Type 1 Diabetes Mellitus (DM1) is said to be one of the most severe forms of autoimmunity that is directly associated with Celiac Disease. (LEFFLER et al., 2015). Recent studies have shown that the prevalence of biopsy-confirmed CD in a population of patients with DM1 was 6%. In this study, the prevalence was lower in adults with type 1 diabetes (2.7%) and in mixed populations with children and adults with type 1 diabetes (4.7%) than in children (6.2%) with type 1 diabetes. 1. In addition, approximately 6% of patients with CD also have DM1 (ELFSTRÖM et al., 2014). In individuals who have T1DM, the pancreatic beta cells, which produce and secrete insulin, are destroyed by an autoimmune attack. The two diseases are related through a complex interaction based on genetic susceptibility and exposure to the environment, thus associating with the main histocompatibility complex, DQ2 class II antigen, and sharing the non-HLA loci (SMYTH et al, 2008).

Approximately 50% of individuals who develop DM1 are diagnosed before the age of 15. Children with DM1 are at increased risk of celiac disease, with the prevalence of biopsy-confirmed celiac disease ranging from 1 to 11% (DUBÉ et al., 2005). Thus, pediatric diabetes guidelines and gastroenterology societies are already recommending the screening of children with DM1 for CD (SILVERSTEIN et al., 2004). From the patient's point of view, there are several advantages to early screening of T1DM patients, including, among them, the potential to improve diabetes control and avoid the long-term manifestations of CD. Furthermore, it has also been suggested that early introduction of gluten may be a common risk factor for celiac disease and type 1 diabetes (NORRIS et al., 2005).

The correlation between the prevalence of patients with Type I Diabetes Mellitus and Celiac Disease is notorious, and CD often manifests itself asymptomatically, which may worsen the clinical picture regarding DM1. Diagnosis and adequate treatment of CD are essential for the reduction of possible complications and risks resulting from diabetes to be possible, promoting an improvement in the quality of life of patients with both comorbidities.

Celiac Disease may be responsible for accelerating the worsening of Type I Diabetes Mellitus, with the onset of chronic complications of DM1 prematurely. An example of a complication is Diabetic Nephropathy (DN), a condition characterized by the presence of lesions in the renal blood vessels, resulting in an abnormal elimination of proteins from the body, through the urine, during the metabolic process of filtration and excretion performed by the kidneys. This complication appears earlier in patients with concomitant CD, identified, on average, 24.1 years after the onset of diabetes in 25% of patients with both comorbidities, in contrast to the 30.2 years of DM progression, which culminated in the development of Diabetic Nephropathy, in patients with only DM1 (DAMASCENO; DOMINGUETI, 2017). The role of Celiac Disease in the development of chronic hyperglycemia is suspected, as a result of higher levels of glycated hemoglobin presented by the patient, being responsible for being a difficulty in the glycemic control of individuals with both diseases. Chronic hyperglycemia culminates in the formulation of final products resulting from a process known as advanced glycosylation, which allow the establishment of crosslinks between proteins, modifying their structure and their functions performed in the basal membrane, in the endothelium and in the

extracellular matrix, resulting in a thickening of the glomerular basement membranes and subsequent endothelial vascular injury, with progression of the clinical picture in the kidneys. In addition, hyperglycemia also has other repercussions on different body systems, as in the case of Diabetic Retinopathy.

Diabetic Retinopathy (DR) is one of the most common complications of DM1, and the most frequent cause of acquired blindness, in which studies indicate that almost 100% of individuals with metabolic disease will progress to some stage of retinopathy after 15 years of the disease (BOSCO et al., 2005). The etiopathogenesis of this complication is due to a state of chronic hyperglycemia in the organism, generating microvascular alterations in the retinal tissue, with consequent circulatory changes, such as loss of vascular tone, alteration of blood flow, increased permeability of vessels, in addition to of subsequent extravasations and edemas, ultimately resulting in vascular obstruction, culminating in neovascularization, with the formation of extremely fragile vessels. Newly formed vessels are very susceptible to rupture, causing hemorrhages in the region and consequent retinal detachment, which may lead to visual loss for the patient, an important morbidity factor resulting from Diabetes Mellitus.

In addition, the state of hyperglycemia generated in the body is a triggering factor for Peripheral Neuropathy, which has several clinical manifestations, including asymptomatic conditions, with emphasis on distal symmetrical polyneuropathy, with the known and most prevalent development of the diabetic foot. The etiopathogenesis of this complication is due to the hyperglycemic state presented by the organism, inducing too much glucose entry into the cells of the neuronal and endothelial tissues, with subsequent deposition of sorbitol and fructose in the intracellular environment, since glucose depends on insulin for its transport in the intracellular environment, culminating in an intracellular hypertonicity, in a cellular influx and in a cell lesion, generating alteration in the conduction process of nervous impulses.

The association between Celiac Disease and Type I Diabetes Mellitus is also responsible for causing a greater cardiovascular risk for the patient, since it was identified that individuals with both diseases have lower levels of HDL-cholesterol, associated with possible conditions more severe cases of atherosclerosis, due to a greater thickening of the intima-media layer. HDL is capable of transporting cholesterol in reverse, that is, it removes it from the cells and sends it to the liver, with the aim of excreting it later. of LDL molecules on artery walls, reducing the potential atherogenic risk presented by lipoprotein. As a result of the lower levels of HDL-cholesterol in patients with CD and DM1, the previously described process becomes more active, leading to a greater chance of developing cardiovascular diseases in the patient. It is suspected that individuals with both comorbidities have lower levels of intestinal Apo-A1, an apoprotein produced by intestinal cells and one of the main compositions of HDL-cholesterol, helping in the reverse transport of cholesterol. The enteropathy resulting from the ingestion of gluten, in celiac patients, is responsible for the atrophy of intestinal cells, resulting, consequently, in lower levels of Apo - A1.

Finally, it was identified that patients with celiac disease have higher levels of glucose, leading to the appearance of chronic hyperglycemia, and, due to the stimulation of an advanced glycosylation process, the end products of this phenomenon are capable of resulting in a direct tissue damage to the arterial wall, culminating in a progression to atherosclerotic vascular disease, affecting

the coronary arteries and leading to the emergence of cardiovascular comorbidities.

DIAGNOSIS

Early diagnosis of Celiac Disease in patients also affected by Type I Diabetes Mellitus is crucial in order to delay the appearance of future complications, such as Diabetic Nephropathy and Peripheral Neuropathy. When gluten is ingested, in allergic people, it promotes an inflammation process in the intestine, altering the absorption of food, causing fluctuations in blood glucose more frequently and more intensely, making glycemic control difficult in patients who concomitantly have DM1, being Early diagnosis is essential for controlling the patient's diabetes.

The diagnosis of CD presents complications, due to possible disagreements between the serological, clinical and histological findings of the affected patient, the suspicion being based on reported signs and symptoms, such as chronic diarrhea, iron deficiency anemia, flatulence, folic acid deficiency and fat-soluble vitamins, in addition to their association with several diseases, especially DM1. One of the tests used is the serological one, in which there is the evaluation of specific antibodies, the EMA and anti-tGT, indicative of histological damage of the affected intestinal region, which may be negative after the suspension of the ingestion of foods with gluten, not being a diagnostic exclusion criterion for the disease.

Biopsy is the gold standard used for the diagnosis of CD, obtained through endoscopic examination, used for specific cases, with clinical suspicion with positive serology, risk patients with positive serology and clinical suspicion with negative serology. There is an evaluation of the presence of lesions in the tissue sample taken, classifying according to the lesion found, following the classification of Marsh, subdivided into infiltrative lesion, hyperplastic lesion or destructive lesion.

Furthermore, molecular biology is also used, mainly as a diagnostic exclusion criterion tool, used in cases of ill-defined diagnosis or when biopsy will not be performed for diagnostic certainty. The genetic markers evaluated are HLA-DQ2 and DQ8, genes responsible for contributing to the genetic predisposition of the disease, being present in more than 95% of celiac patients (LIU et al., 2014).

TREATMENT

The treatment of Celiac Disease, still the only one currently available, is given by the suspension of the ingestion of foods that contain gluten, and such restriction in the diet must be permanent and definitive. The non-intake of gluten by patients with CD and DM1, concomitantly, is of paramount importance for the individual's glycemic control, taking into consideration, that the ingestion of protein by celiac people has repercussions on higher levels of glucose in the body, with possible progression to chronic hyperglycemia. In addition, the patient must also maintain the treatment recommendations to be followed in Type I Diabetes Mellitus, through the regular administration of insulin, diet control, frequent monitoring of blood glucose by the individual and the practice of physical exercises, aiming at maintaining glycemic levels and glycated hemoglobin within acceptable parameters. Proper treatment of both diseases is of paramount importance so that possible complications and risks arising from diabetes are possible, promoting less morbidity in the life of the patient with both comorbidities.

CONCLUSION

From the surveys carried out by more than 20 studies it was possible to conclude that more than one in twenty patients with type 1 diabetes has celiac disease verified by biopsy.

This prevalence is high enough to motivate screening for celiac disease among patients with type 1 diabetes. In many cases, symptoms of celiac disease go undiagnosed, as most individuals assume they are just symptoms of diabetes. Therefore, for better control of Type 1 Diabetes Mellitus, it is imperative that the underlying cause of any symptom experienced by the patient be discovered. People who have DM1 and CD concomitantly have difficult diabetes control.

The complexity of treating T1DM in patients with celiac disease is due to the fact that gluten in food causes inflammation in the intestine, which changes the way food is absorbed. This causes blood sugar fluctuations to be carried out more frequently and also with greater intensity. Thus, for individuals who have both autoimmune diseases, it is critical that a strict diet be followed to reduce the risk of diabetes and untreated celiac disease.

REFERENCES

1. BOSCO, Adriana et al . Retinopatía diabética. Arq Bras Endocrinol Metab, São Paulo, v. 49, n. 2, p. 217-227, Apr. 2005 . Available from <http://www.scielo.br/scielo.php script=sci_arttext&pid=S0004 27302005000200007&lng=en&nrm=iso>. access on 01 Feb. 2021.

2. DAMASCENO, Jésus Augusto; DOMINGUETI, Caroline Pereira. Associação entre doença celíaca e complicações do diabetes em pacientes com diabetes mellitus tipo 1: revisão sistemática. Rev Soc Bras Clin Med., [s. l.], jul/set 2017. Disponível em: https://docs.bvsalud.org/biblioref/2017/11/875538/sbcm_153_206-213.pdf. Acesso em: 1 fev. 2021.

3. DUBÉ, Catherine; ROSTOM, Alaa; SY, Richmond; CRANNEY, Ann; SALOOJEE, Navaaz; GARRITTY, Chantelle; SAMPSON, Margaret; ZHANG, Li; YAZDI, Fatemeh; MAMALADZE, Vasil. The prevalence of celiac disease in average-risk and at-risk Western European populations: a systematic review. Gastroenterology, [S.L.], v. 128, n. 4, p. 57-67, abr. 2005. Elsevier BV.

4. ELFSTRÖM, P.; SUNDSTRÖM, J.; LUDVIGSSON, J. F.. Systematic review with meta-analysis: associations between coeliac disease and type 1 diabetes. Alimentary Pharmacology & Therapeutics, [S.L.], v. 40, n. 10, p. 1123-1132, 1 out. 2014. Wiley.

5. FERREIRA, Leandro Tadeu et al. Diabetes melito: hiperglicemia crônica e suas complicações. Arquivos Brasileiros de Ciências da Saúde, [s. l.], v. 36, ed. 3, p. 182-188, 2011.

6. LEFFLER, Daniel A.; GREEN, Peter H. R.; FASANO, Alessio. Extraintestinal manifestations of coeliac disease. Nature Reviews Gastroenterology & Hepatology, [S.L.], v. 12, n. 10, p. 561-571, 11 ago. 2015. Springer Science and Business Media LLC.

7. LIU, Shinfay Maximilian et al. Doença celíaca. Rev Med Minas Gerais, [s. l.], 2014. DOI 10.5935/2238-3182.20140037. Acesso em: 2 fev. 2021.

8. LUDVIGSSON, J. F.; LUDVIGSSON, J.; EKBOM, A.; MONTGOMERY, S. M.. Celiac Disease and Risk of Subsequent Type 1 Diabetes: a general population cohort study of children and adolescents. Diabetes Care, [S.L.], v. 29, n. 11, p. 2483-2488, 25 out. 2006. American Diabetes Association.

9. LUNDIN, Knut E. A.; WIJMENGA, Cisca. Coeliac disease and autoimmune disease —genetic overlap and screening. Gastroenterol. Hepatol. advance, [*s. l.*], 25 ago. 2015. DOI doi:10.1038/nrgastro.2015.136. Disponível em: https://pubmed.ncbi.nlm.nih.gov/26303674/. Acesso em: 14 fev. 2021.

10. NORRIS, Jill M.. Risk of Celiac Disease Autoimmunity and Timing of Gluten Introduction in the Diet of Infants at Increased Risk of Disease. Jama, [S.L.], v. 293, n. 19, p. 2343-2349, 18 maio 2005. American Medical Association (AMA).

11. SILVERSTEIN, J.; KLINGENSMITH, G.; COPELAND, K.; PLOTNICK, L.; KAUFMAN, F.; LAFFEL, L.; DEEB, L.; GREY, M.; ANDERSON, B.; HOLZMEISTER, L. A.. Care of Children and Adolescents With Type 1 Diabetes: a statement of the american diabetes association. Diabetes Care, [S.L.], v. 28, n. 1, p. 186-212, 22 dez. 2004. American Diabetes Association..

12. SMYTH, Deborah J.; PLAGNOL, Vincent; WALKER, Neil M.; COOPER, Jason D.; DOWNES, Kate; YANG, Jennie H.M.; HOWSON, Joanna M.M.; STEVENS, Helen; MCMANUS, Ross; WIJMENGA, Cisca. Shared and Distinct Genetic Variants in Type 1 Diabetes and Celiac Disease. New England Journal Of Medicine, [S.L.], v. 359, n. 26, p. 2767-2777, 25 dez. 2008. Massachusetts Medical Society. http://dx.doi.org/10.1056/nejmoa0807917.