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# Elaboration of a risk score for celiac disease screening

## *Elaboração de escore de risco para rastreamento de doença celíaca*

**Abstract**

***Objective:*** This study aims to elaborate a risk score that will aid in the screening of celiac disease, based on the risk factors already described in the literature. ***Methods:*** It is a case-control study with two groups: individuals who reported having celiac disease and individuals who reported not having celiac disease. For data collection, a questionnaire was elaborated based on the bibliographic review, answered online by the research participants. The data collected were entered in the Excel program and analyzed in the SPSS 23.0 program. ***Results:*** Among these questionnaires, 72 were cases (with celiac disease) and 54 controls (without celiac disease). There was a significant difference, with p-value of 0.005, among the scores of the group of cases, 7.09 (standard deviation: 1.47), and of the control group, 4.59 (standard deviation: 1.94). ***Discussion:*** The main benefit is that, with more studies, the celiac patient can initiate treatment early, reducing the risk of complications and

associated comorbidities, and reduce the rate of death of undiagnosed or late diagnosed celiac patients. ***Conclusion:*** There is a significant difference between the risk scores, showing that the cases have a higher score in relation to the controls. It is important to make it clear that this score will be used only for screening study purposes and not for celiac disease diagnosis.

**Keywords:** Celiac Disease. Risk Factors. Mass Screening.

**Resumo**

***Objetivo:*** O objetivo deste estudo é elaborar um escore de risco que auxilie no rastreamento de doença celíaca, baseado nos fatores de risco já descritos na literatura. ***Métodos:*** Trata-se de estudo caso-controle com dois grupos: indivíduos que referem ter doença celíaca e indivíduos que referem não tê-la. Para a coleta de dados, foi elaborado um questionário com base na revisão bibliográfica, respondido de forma online pelos participantes da pesquisa. Os dados coletados foram digitados no programa Excel e analisados no programa SPSS 23.0. ***Resultados:*** Dentre estes questionários, 72 eram casos (com doença celíaca) e 54 controles (sem doença celíaca). Houve diferença significativa, com valor ***p*** de 0,005, entre os resultados dos escores médios do grupo de casos, 7,09 ± 1,47 , e do grupo de controle, 4,59 ± 1,94. ***Discussão:*** O principal benefício esperado é que, com mais estudos, o doente celíaco possa iniciar o tratamento precocemente, reduzindo o risco de complicações e de comorbidades associadas, além de reduzir o índice de morte de doentes celíacos não diagnosticados ou com diagnóstico tardio. ***Conclusão:*** Conclui-se que existe uma diferença significativa entre os escores médios, mostrando que os casos possuem maior escore em relação aos controles. É importante deixar claro que esse escore será usado apenas para fins de estudo de rastreamento, e não para diagnóstico de doença celíaca.

**Palavras-chave:** Doença Celíaca. Fatores de Risco. Programas de Rastreamento.





## INTRODUCTION

Celiac disease (CD) is a chronic autoimmune enteropathy that affects the small intestine of genetically susceptible individuals and is triggered by the ingestion of foods containing gluten.[1] Gluten is a mixture of proteins found in the endosperm of cereal seeds such as wheat, rye, barley and oats. The major gluten protein is gliadin, which corresponds to the toxic fraction and is directly involved in the CD pathogenesis.[2] It is estimated that the disease affects between 0.5 and 1% of the world population, with important regional variations,[3,4] but there are no recent studies addressing the epidemiological aspects of CD.

This disease can be classified as: classical CD, in which the intestinal symptoms are predominant; non-classical CD, with predominantly extraintestinal characteristics such as dermatological, hematological, endocrinological, reproductive, renal, psychiatric, skeletal and/or hepatic involvement; and silent CD, without evidence of clinical symptoms.[5,6] Asymptomatic patients often remain undiagnosed because screening tests are usually made only in persons with typical manifestations of the disease.[7]

Diagnosis of celiac disease is based on clinical tests, detailed anamnesis, histopathological analysis of the small intestine and assessment of serum markers.8 The major serological tests for detection of gluten intolerance are: antigliadin antibody, antiendomysial antibody and antitissue transglutaminase antibody.[9] They are useful to identify individuals who must undergo small intestine biopsy.[10] Final diagnosis is confirmed when the biopsy reveals villous atrophy, crypts elongation, and an increase of intra-epithelial linfocytes.[8]

Despite the variety of diagnosis techniques, some factors can contribute to misdiagnosis, considering that serological tests may result negative, the disease may have an irregular/nonuniform histological behavior or the number or sites of biopsies may not be adequate.[11] It is important to keep in mind that the investigation of CD for diagnosis must be carried out before starting the treatment, because a gluten-free diet may negatively alter the results of the serological tests and improve the histology. Some authors describe that half of adult celiac patients are diagnosed after age 50, and population-based studies suggest that 50-90% of people with CD remain undiagnosed.[12,13] Studies indicate that late diagnosis of CD increases the risk of complications and severity of the disease as well as the likelihood of associated comorbidities, conditions that can be prevented with early diagnosis and treatment.[14-16]

Thus, the aim of this study is to develop a risk score to aid in celiac disease screening based on risk factors already described in literature so that it may contribute to an early diagnosis for biopsy and treatment.

## METHODOLOGY

It is a case-control study, in which the sample was divided into two groups: individuals who reported having celiac disease and individuals who reported not having celiac disease. Both the diagnosis or absence of the disease were evaluated by self-reporting, without being requested confirmatory or excluding tests of the disease.

The inclusion criteria for the CD group (cases group) were individuals who reported having this disease; for the group without CD (control group), individuals who reported not having the disease. Exclusion criteria for both groups were individuals unable to answer the questionnaire. The sample size was calculated by the WinPepi 11.65 software, using the criterion of five valid answers for each item of the questionnaire, in addition to 100% of the cases identified in the cases group, 80% power and 5% significance level. The total sample was comprised of 15 individuals in each group, added by 10% for possible losses and refusals, totaling 34 individuals (17 in each group).

The project was approved by the Research Ethics Committee of the ***Universidade Federal de Ciências da Saúde*** (Federal University of Health Sciences) in Porto Alegre-RS, process number 2.025.716. All participants agreed to participate in the study by signing the Free Consent Form (FCF), which was available prior to the online questionnaire. The participants were allowed to answer the questionnaire only after submitting the FCF.

The questionnaires were answered online by individuals through social media platforms. It was developed based on a literature review on the Virtual Health Library (VHL), on the following databases: Lilacs, MEDLINE, SciELO, PubMed and CAPES Portal; and on source documents of the Ministry of Health and the specific organization for celiac disease, "Fenacelbra".

The questionnaire contained questions on demographic data (gender, age, skin color or race); nutritional status determined by the body mass index (BMI); any change in body weight in the last six months; change in weight in relation to diagnosis; following or not a gluten-free diet; CD heredity; symptoms; clinical signs; CD-associated diseases; time at which intestinal symptoms appear; and symptoms-related food(s), if present.

Each item included in the score was identified and scored according to specific literature on the subject. Several studies report a higher prevalence of celiac disease in women then in men. One of these studies point out an average CD prevalence of 2.9 women for each man.[17] To understand the weight history of individuals who reported having CD, three questions were asked: current weight and height, for subsequent calculation and classification of BMI; no weight change, loss or gain, weighted before and after the CD diagnosis; and no weight change, loss or gain, in the last six months. Abdominal bloating, edema and fluid retention are typical characteristics of celiac disease and may interfere with the weight assessment. So,





it is important to assess and make sure that the weight gain is due to an increased intake of energy or to bloating, edemas and fluid retention.

Genetic factors, given by the HLA DQ2 and HLA DQ8 surface markers, are found at high rates in the general population. Presence of HLA in the general population is more prevalent in relatives of celiac individuals – the closer the relative (first-degree relative), the greater the prevalence of the antigen histocompatibility.[2] So, it was considered one point for second-degree relatives, two points for those who have one first-degree relative and three points for those who have more than one first-degree relative with CD.

The risk score also considered the clinical aspects and the major symptoms of celiac disease contained in a review of the World Gastroenterology Organization Guidelines – 2012. In adults with classical celiac disease they were: chronic diarrhea, weight loss, anemia, bloating, lassitude, malaise and edema. In children with CD: stunted growth, weight loss, short stature, vomiting, diarrhea, recurrent abdominal pain, muscle atrophy, irritable bowel, hypoproteinemia, irritability and discomfort. In adults and children with non-classical CD, the disease may appear monosymptomatic or oligosymptomatic or with low intensity symptoms: bloating, abdominal pain, chronic fatigue, iron-deficiency anemia, chronic migraine, dermatitis herpetiformis, peripheral neuropathy, folic acid deficiency, reduction of bone density, unexplained infertility, late menarche and unexplained miscarriage.[18]

Despite the large number of symptoms, the clinical signs and CD-associated diseases described in literature, the risk score used in this study did not contain all of them, because they are numerous and would make the document very long and tiresome. Therefore, we selected those most common in the general population and which are more associated with CD, according to literature: recurrent miscarriages, repetitive mouth sores, food allergy, iron-deficiency anemia, anxiety, rheumatoid arthritis, asthma and atopy, muscle atrophy, muscle cramps, micronutrients deficiency, depression, skin rash (dermatitis herpetiformis), bipolar disorder, type I diabetes mellitus, thyroid disorder, numbness and/or tingling, edemas, migraine, epilepsy, fatigue, poor appetite, lassitude, infertility, lactose intolerance, irritability, lupus erythematosus, irregular menstrual cycles, osteoporosis, chronic pancreatitis, muscle loss, constipation, psoriasis, hair fall, fluid retention, Down syndrome, and ulcer.

In the questionnaire, there was clear instruction to those who reported having CD to answer the questions having in mind the clinical characteristics that they had before starting treatment, since a gluten-free diet minimizes or excludes symptoms, clinical signs and associated comorbidities.

Rather than assigning a point for each of the symptoms, we decided to score the symptoms in conjunction, as follows: zero point for none of these symptoms, one point for each of

these symptoms and two points for more than one of these symptoms, because according to the Fenacelbra's guide for celiac individuals, an individual with CD may have a single symptom or many ones.[19] However, according to what was found in literature, it is more common for individuals suffering from CD to have more than one symptom. All data (symptoms) of this study were self-reported.

With respect to ingested foods, which may be associated with the emergence of symptoms, it was decided to assign a higher score for gluten-rich foods (2 points), considering that the ingestion of these foods is one of the major triggering factors of celiac disease. It was assigned one point for milk and dairy products because lactose intolerance may be associated with celiac disease. Another question in this questionnaire was related to the time when these symptoms appear, as an attempt to differentiate between wheat allergy, which is an immediate reaction and CD, which has a late response.

The data collected from the questionnaire were typed in a spreadsheet of the Excel program and analyzed by the SPSS 23.0 program. The qualitative variables were described using absolute and relative frequencies. The quantitative variables were described by mean and standard deviation. To compare the score means of the groups, the student t-test was used. The level of significance was defined as 5%.

## RESULTS

A total of 135 questionnaires were answered online in a period of approximately one month in 2017. Those which were incomplete or not from Brazil were excluded, resulting in a loss of nine questionnaires. Of valid questionnaires, 72 were cases (with celiac disease) and 54 were controls (without CD). The mean age of the cases group was 35.04 years (standard deviation: 12.80) and of the control group was it 29.56 years (standard deviation: 11.88).

Table 1 describes the demographic variables, family history and nutritional variables of the cases and controls. Both groups were different regarding family history, gluten-free dietary practice, time at which the symptoms occur and kind of foods that trigger symptoms.





**Table 1.** Demographics, family history and nutritional variables of the cases and control groups. Brazil, 2017.

| Variable | Cases (72) N (%) | Control (54) N (%) | p-value |
|---|---|---|---|
| **Females** | 59 (81.9) | 50 (92.6) | 0.08 |
| **Skin color/race** | | | 0.52 |
| Whites | 62 (86.1) | 50 (92.6) | |
| Not whites | 10 (13.9) | 4 (7.4) | |
| **BMI/Nutritional status** | | | 0.58 |
| Underweight | 3 (4.2) | 5 (9.3) | |
| Normal | 38 (52.8) | 30 (55.6) | |
| Overweight | 23 (31.9) | 13 (24.1) | |
| Obesity | 8 (11.1) | 6 (11.1) | |
| **Do you have any family member with CD?** | | | 0.03 |
| No | 24 (33.3) | 31 (57.4) | |
| I don't know | 21 (29.2) | 12 (22.2) | |
| Other relative | 14 (19.4) | 8 (14.8) | |
| Father, mother or brother | 13 (18.1) | 3 (5.6) | |
| **Has your weight changed in the last six months?** | | | 0.26 |
| No | 29 (40.3) | 16 (29.6) | |
| Yes, intentional weight loss | 12 (16.7) | 5 (9.3) | |
| Yes, involuntary weight loss | 3 (4.2) | 2 (3.7) | |
| Yes, weight gain due to inadequate diet | 13 (18.1) | 19 (35.2) | |
| Yes, weight gain due to fluid retention or edema | 3 (4.2) | 1 (1.9) | |
| Yes, weight gain and loss oscillation | 12 (16.7) | 11 (20.4) | |
| **Do you practice a gluten-free diet?** | | | <0.001 |
| No | 5 (6.9) | 52 (96.3) | |
| Yes | 67 (93.1) | 2 (3.7) | |

Table 1 continued

| Variable | Cases (72) N (%) | Control (54) N (%) | p-value |
|---|---|---|---|
| **If you have symptoms, when they occur?** | | | <0.001 |
| I don't have symptoms | 5 (6.9) | 19 (35.2) | |
| I don't know | 5 (6.9) | 7 (13.0) | |
| After eating, and it usually takes a while to appear | 19 (26.4) | 9 (16.7) | |
| After eating and appear right afterwards | 43 (59.8) | 14 (25.9) | |
| There is nothing to do with eating | -- | 5 (9.2) | |
| **If there is a relationship with a food eaten, which food is it?** | | | <0.001 |
| I do not have symptoms | 2 (2.9) | 20 (37.7) | |
| There is no relationship with what I eat | -- | 4 (7.5) | |
| I don't know | 10 (14.5) | 17 (32.1) | |
| Gluten-rich foods | 52 (75.4) | 3 (5.7) | |
| Milks and dairy products | 4 (5.8) | 8 (15.1) | |
| Others | 1 (1.4) | 1 (1.9) | |

Among the cases, 28.6% gained weight after the CD diagnosis; 13.5% lost weight and 11.9% reported no weight change after the CD diagnosis.

The symptoms prevalence is shown in Fig. 1 to 3, which were divided into clinical characteristics of classical CD (Fig. 1), typical symptoms of non-classical CD (Fig. 2) and CD-associated diseases (Fig. 3), cited on the online questionnaire.

**Figure 1.** Graphic representation of intestinal symptoms, in percentage (%).

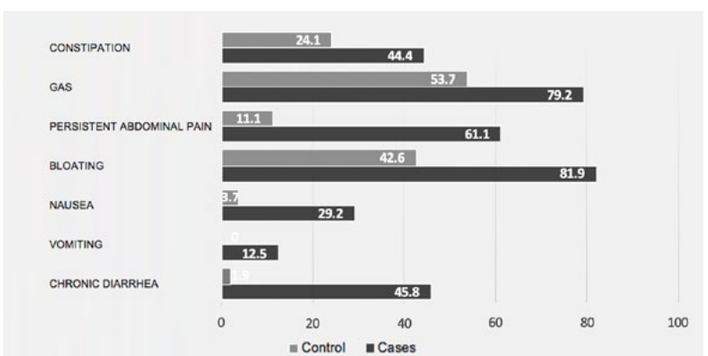







**Figure 2.** Graphic representation of CD-related diseases.

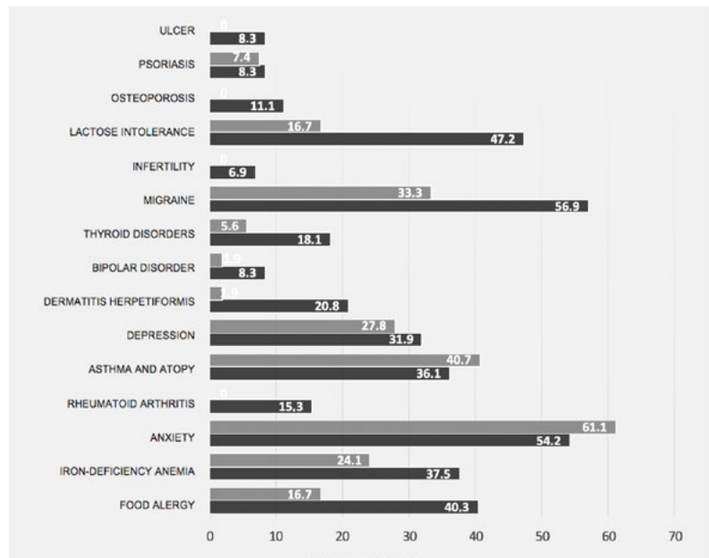
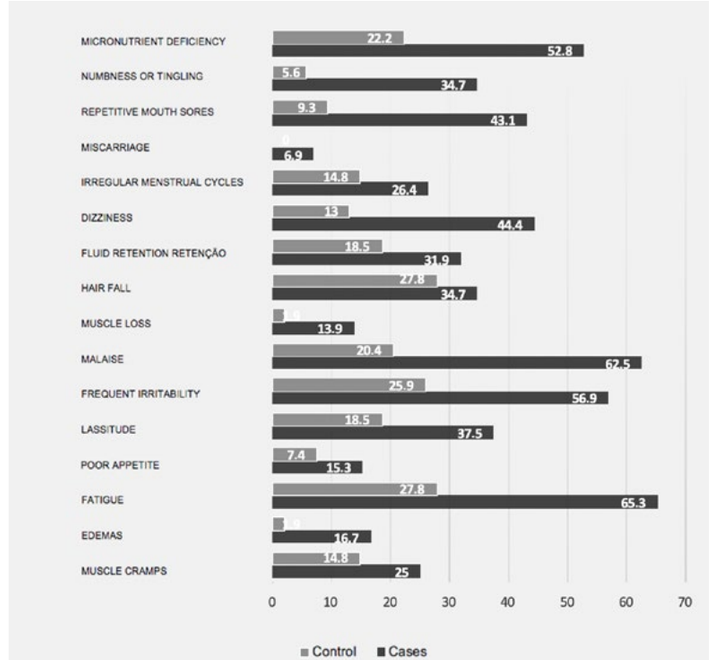
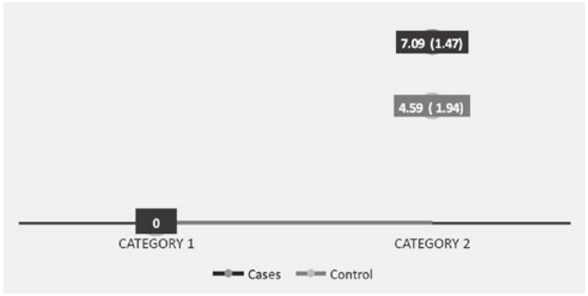



**Figure 3.** Symptoms and clinical characteristics associated with CD



The results of the risk score of the cases group, 7.09 (standard deviation: 1.47) and the control group, 4.59 (standard deviation: 1.94), indicated a significant difference, with p-value of 0.005 (Fig. 4).

**Figure 4.** Comparative demonstration of risk score and standard deviation




## DISCUSSION

The aim of this study was to develop a score for CD screening. The items contained in the score are considered risk factors, according to literature. The nutritional variables, which consisted of weight change and current nutritional status, are typical conditions of CD. However, in this study, there was no difference in the current body mass index of celiac and non-celiac individuals. The majority was classified as having normal weight in both groups, cases and control.

Thus, the question that remains is which was the BMI classification before starting the treatment. It is assumed that the current BMI of celiac individuals is due to weight recovery after starting treatment. Of the total sample of this study, 28.6% answered that they gained weight after receiving the CD diagnosis.

It is worth recalling that CD treatment consists of a gluten-free diet, and a strict adherence to this diet is vitally important because the ingestion of minimum amounts of gluten can trigger reactions, due to the severe injury that gliadin produces in the intestine. In this study, almost all individuals of the cases group responded that they follow a gluten-free diet, and almost no one in the control group does it. A study conducted in Canada showed similar results: 88.0% of celiac individuals maintain a gluten-free diet.[20] In the present study, of those who reported having CD, the majority follows a gluten-free diet recommended by a professional, while the remaining individuals do it by free choice.

In the cases group of this study, there was a greater number of women than men. In a similar study involving members of Acelbra - São Paulo Section, there was also a prevalence of women: 62% of the associates were women and 38% were men.[21]





In the general population that does not have a diagnosis of CD, markers HLA DQ2 and/or HLA DQ8 are present in nearly 40% of the total population, a percentage that increases in patients who do not have CD but have first-degree relatives with CD. In celiac patients with active CD and have these markers, gluten interacts with HLA, causing an abnormal immunologic response in the intestinal mucosa and tissue injury.[2] In this study, this is represented by the first- and second-degree family history in the cases group. Oliveira et al.,[22] in a study conducted with children, concluded that the prevalence of celiac diseases in first-degree relatives of celiac children was 3.1%, 4.5 times higher than the general Portuguese population (0.7%). In other study, the incidence varied according to the kinship degree, 70% in monozygotic twins, 10% in first-degree relatives and 2.5% in second-degree relatives.[23]

In a study carried out by Cecilio & Bonatto,[2] allele HLA DQ2/DQ8 was present in 98.4% of celiac patients; in 89.6% of relatives of celiac individuals; and in 55.4% of the general population without CD relatives. Although the absence of the specific marker HLA may have a high negative predictive value for the disease development, these markers do not act as a criterion for confirmation of diagnosis since they are also present with high prevalence in the general population.

In the present study, all typical symptoms of classical CD had a higher prevalence in the cases group. Other studies found in literature also reported the presence of gastrointestinal symptoms in individuals with CD. One of these studies is by Barbero et al.,[24] conducted with 119 adults: 87.3% had gas and bloating symptoms; 79.5%, abdominal pain or cramps; 65%, diarrhea; 42.7%, nauseas; 62.1%, constipation; and 11.1%, vomiting. And in the study conducted by Silva et al.,25 74.19% of the patients reported some kind of gastrointestinal manifestation, mostly diarrhea (51.61%), followed by vomiting (19.35%), weight loss (16.13%) and abdominal discomfort (16.13%).

Most of the clinical characteristics of non-classical CD also had a higher prevalence in the cases group. In the study cited above, conducted by Barbero et al.[24] with 119 adults, 78.8% of the individuals had fatigue; 60.2%, muscle cramps; 57.6%, joint pain; 52.5%, numbness or tingling in the fingers or toes; 49.6%, depression symptoms; 48.3%, anxiety; 47.9%, recurrent headache or migraine; 41.9%, skin rash; 33.9%, repetitive mouth sores; 33.1%, bone pain; 31.1% had diagnosed depression; 26.9%, irritable bowel syndrome; 22.2%, dental enamel defects; 21%, iron-deficiency anemia; 17.1%, non-intentional weight loss; 16%, autoimmune thyroid disease; 10.3%, infertility; 6.7%, infertility of unknown cause; 5.9%, B12- or folate-deficiency anemia; 2.6%, seizures; and 1.7% had dermatitis herpetiformis.

As a result of atrophy of the mucosal cells of the small intestine, there is malabsorption of iron, folic acid, vitamin B12, calcium and vitamin D, which can give origin to iron-deficiency anemia, megaloblastic anemia and osteoporosis.[26] More than half of the cases group

(52.8%) and less than half of the control group (22.2%) reported having some micronutrient deficiency. Thus, it is possible to associate this prevalence in the cases group with CD physiopathology. Iron-deficiency anemia, as a common extraintestinal manifestation of celiac disease, could be demonstrated in this study, with a percentage of 37.5%.

In a study conducted by Baghbanian et al.,[27] of 402 patients with iron-deficiency anemia, 42 (10.4%) had positive serology for celiac disease. At the same time, the study points out that clinicians should consider celiac disease as a possible cause of anemia in all patients with iron-deficiency anemia. Low bone mineral density is also considered an extraintestinal manifestation of celiac disease, due to intestinal malabsorption, resulting in reduced bone mass, increased bone fragility and risk of fractures. In the cases group of this study, 11.1% reported having osteoporosis, while no individual of the control group had this disease (0%).

Silva et al[28] also stated that CD is a high-risk condition for secondary osteoporosis and commented that a bone density test is very important for the clinical management of patients. A study conducted by these authors found that of the assessed celiac patients, 69 (68.3%) had low bone mineral density, 47% had osteopenia, and 32% osteoporosis.

It was found in the literature a relationship between celiac disease and the female reproductive tract dysfunction, such as recurrent miscarriages, restricted intrauterine growth, prematurity and infertility.[29-31] With respect to the results related to recurrent miscarriage, it can be seen that it may actually be associated with CD; while 6.9% of the cases group reported having recurrent miscarriages, no one in the control group had it. Khoshbaten et al.[32] and Pellicano et al.[33] concluded that nutritional imbalance, especially malabsorption of nutrients such as zinc, selenium, iron and folic acid may be the reason for CD-mediated reproductive disorders, especially infertility. Whereas 6.9% of the cases group reported having infertility, no one in the control group had this condition.

In this study, it was possible to find prevalence of dermatitis herpetiformis in the cases group (20.8%). This is a chronic skin disease characterized by blisters, intense itchy skin rash and burning sensation in erythematous papules and plaques with urticariform appearance, grouped vesicles with centrifugal growth. The same J chain of protein IgA1 is found in the small intestine mucosa in adult patients with celiac disease, suggesting a strong association with dermatitis herpetiformis. Treatment of choice is dapsone and gluten-free diet.[34]

In the present study, there was no case of type I diabetes mellitus (DM), but Kordonouri et al.[35] report that the CD prevalence rates vary from 1 to 10% in children/adolescents with type I DM, with an incidence rate of nearly 8 cases per 1,000 patients/ year. In addition, these authors comment that children and adolescents with type I DM should be tested for CD at the time of diagnosis of type I DM and every 1-2 years while the result remains negative.[36] In one of the studies conducted by Gonçalves et al.,[9] the mean time for the onset of CD in patients who were diagnosed with type I DM for the first time was 3.6 ± 3.9 years.[10]





Down syndrome (DS) is a genetic condition characterized by the trisomy of chromosome 21. This study did not present any case of DS, but Pavlovic et al.[36] refer that, due to the high prevalence of the disease, universal screening of children with DS is recommended. Correct and early diagnosis can avoid untreated CD complications such as low weight and short stature, anemia, osteoporosis and risk of malignant disease, besides offering better quality of life.

The score result in the comparison between the cases group and the control group was significant, showing that the individuals in the cases group have a higher score compared to the control. The main expected benefit is that, with more studies, the celiac patient may initiate treatment early, reducing the risk of complications and associated comorbidities, and reduce the death rate of undiagnosed celiac people or those with late diagnosis. It is important to make it clear that his score should be used only for screening study purposes and not for CD diagnosis.

## CONCLUSION

Most of the data related to risk factors in this study is in agreement with what has been described in literature. It is concluded that there is a significant difference between the risk scores for the cases and control groups. We consider important to develop more studies on risk factors and Celiac disease (CD) screening.

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**Contributors**

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