CELIAC DISEASE IN CHILDREN WITHIN MODERN SOCIETY – A LITERATURE REVIEW

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Abstract

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Abstract

Celiac disease is an autoimmune reaction of the small intestine to dietary gluten. This reaction manifests itself in the form of chronic inflammation in the intestine, due to which the villi on the intestinal wall are smoothed out.

The consequences of the disease are mostly predominantly those of malnutrition due to maldigestion and malabsorption, such as diarrhoea, weight loss, and anaemia. Nevertheless, patients with celiac disease may also experience extra-intestinal symptoms - stomatitis, the appearance of polymorphic rashes, vitiligo foci and so on. Thus, it becomes really complicated to diagnose the disease. However, early diagnosis is crucial for the person's health, especially concerning children.

This review covers celiac disease in children. Discussed diagnostic markers revealing true potential celiac disease and considered risk factors of its uncontrolled progressing.

The evidence-based medical literature indicates that children with a genetic predisposition to celiac disease are at major risk. Infectious diseases in the neonatal period are considered as another risk factors of celiac.

Typical and no typical symptoms for celiac disease are identified by the inductive method of analysis and are described in a separate chapter of the thesis.

Based on the work done, generalized conclusions, as well as identified possible triggers of celiac disease and its early symptoms. A further review of the literature made it possible to determine the most effective method for diagnosing celiac disease in children today.

Keywords

small intestine disease, celiac disease in children, gluten, gluten-free diet

Contents

1 Introduction

Celiac disease (CD) is an autoimmune, genetically determined, chronic inflammation of the small intestine. Ingestion of gluten proteins provoke the inflammation of the small bowel mucosa and submucosa. Symptoms can be classic, they also can mimic to the symptoms of other diseases, or the disease can be completely asymptomatic (Garner 2011, 64; Barker & Liu 2008).

Celiac disease was previously considered as a rare disease. However, nowadays epidemiological studies have shown that celiac disease is quite common and affects about one person in 250 people. Recent statistics report demonstrates that 3 million people, or 1% of the population in the world, are affected by celiac disease. (Gallegos & Merkel 2019, 41-48.)

The wide range of mostly non-gastrointestinal symptoms complicates the diagnosis of celiac disease. However, in the past years, research has advanced in ability to diagnosis and treat celiac disease significantly (Leeds et al. 2008, 88).

Celiac disease is a life-long disease that requires to follow strict a gluten-free diet throughout patient's life. Not adhering to a diet leads to an adverse developing of the disease. And, as a result, lead to deep complications. Malabsorption is the most common reason for the next complications: malnutrition, lack of needed vitamins and minerals, weight loss, grow delay, diabetes, or even intestinal lymphoma (a type of cancer). (Violato & Gray 2019, 53.)

Usually, symptoms start to present in childhood and have a significant effect on child development and grow. Thus, it is crucial to determine disease at initial stages to prevent complications in a future (Mărginean et al, 2018).

Many questions arise, when patient diagnosed with celiac disease, especially concerning children. That is why this thesis focuses on celiac disease in children. The purpose of this thesis is to summarize risk factors that can provoke development of celiac disease, describe the Initial symptoms of celiac disease - gastrointestinal and non-typical.

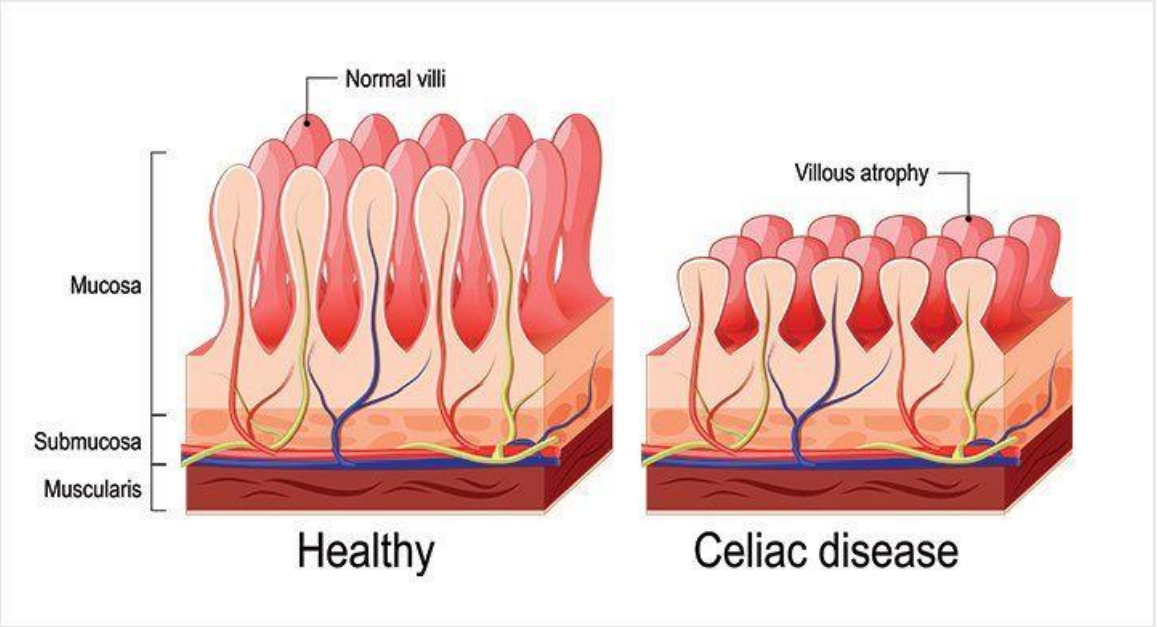
From the nursing point of view, it is essential to provide all-round support to recently diagnosed patients and family members / caregivers. Providing accessible evidence-based information from multi-professional team will help improve quality of patient's life with CD. The importance of a gluten-free diet and newest methods of treatment is highlighted, as a part of the review.

2 Background

2.1 Definition of Celiac disease

Coeliac or celiac disorder – food-related autoimmune disease that causes an allergic-like reaction in the small intestine to foods that contain gluten such as wheat, rye and barley, and it is considered as one of the most common long-term nutritional disease worldwide. (Lindfors et al 2019).

Due to malfunction in bowel, human body reacts to protein naturally found in some grains – gluten as a foreign antigen. In this way, the immune attacks the antigen and stimulates the production of white blood T- cells – lymphocytes playing major role in in acquired immune response – causes inflammation of the small intestine. This reaction trimmed of villi, paving in small intestine walls (Bower et al. 2014).



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Coeliac disease - normal villi and villous atrophy. Small bowel showing coeliac disease manifested by blunting of villi. Vector diagram for medical use

2.2 History of disease discovery

The first mentions of a mysterious disease were described in 250 AD. By the ancient Roman antique physician and philosopher, whose name was Areteus Cappadocia. In his writings, he described patients suffering from exhaustion, symptoms of weakness and diarrhoea that

he called "koiliakos", which comes from "koelia", in Greek "abdominal cavity". Celiac disease (coeliakia; Greek koiliakos intestinal, suffering from an intestinal disorder). (Losowsky 2008.)

In 1856, Francis Adams for the Sydenham Society in England translated Aretheus observations of Cappadocia from Greek into English. In 1888, British paediatrician Samuel Gee published a monograph on celiac disease, which argued that dietary adjustments were a major part of treatment. This is how he became the first physician to be recognized for establishing the link between disease and diet. A variety of diets have become popular for the treatment of celiac disease, including carbohydrate and low-carbohydrate diets. (Losowsky 2008.)

However, the true causes of celiac disease remained a mystery to doctors. Mostly children suffered from this disease and there was a high mortality rate. The following symptoms were observed in children: delayed physical growth and mental development, rash, large swollen abdomen, dry limbs. There was a high mortality rate among children with similar symptoms (Houmich & Admou 2021).

For many years, scientists and doctors around the world have put forward various hypotheses of the causes of the celiac disease and methods of its treatment. So, in 1924, the American physician Sydney Haas suggested that complex carbohydrates such as starch were the culprit and began promoting the “banana diet” as a medicine. The diet did help the little patients get rid of their symptoms, but as soon as the patient started using gluten again, the disease returned (Haas 1924).

The real breakthrough in the study of celiac disease occurred during the Second World War. Due to lack of food people around Europe became malnourished and weakened. However, for children with celiac disease, it became a salvation, because, on the contrary, they began to recover during hunger. The Dutch pediatrician and doctor Willem-Karel Dicke, who took care of children with celiac disease, noticed this feature. When the children were given crackers, the disease returned. He had guessed that the reason instigate disease led to consumption of wheat. And, since 1936, subsequently he tested his theory for a long time. (Losowsky 2008.)

After the war, Dr. Dicke went into research to document and prove his observations. He found that during the war, the death rate of children with celiac disease in the Netherlands fell from 30% to almost zero, and after the end of the war, it returned to its previous level. This helped narrow down the question of which foods were causing celiac symptoms (Jabri & Green 2003).

In 1950, the doctor published his findings that wheat and rye flour exacerbate celiac disease symptoms. He also refuted the theory that complex carbohydrates could be the cause of celiac disease. As during the research, he was giving to patients' wheat starch and did not notice the harmful effects. In addition, Dr. Dicke described the histological damage to the intestinal mucosa as being associated with celiac disease. (Losowsky 2008.)

Later, with the help of colleagues, he established that gluten is the main reason for celiac disease. Subsequently, the medical community began to associate gluten with celiac symptoms and gluten-free food became the standard treatment for celiac disease in Europe and Australia (Garnier-Lengliné 2015).

Celiac disease was originally thought to be a type of food allergy. However, new methods of studying the small intestine have shown that not only the response of the immune system, but also the deformation of the intestinal walls, lies at the heart of celiac disease.

In the early 1970s, it began to be discovered that celiac disease might not be an allergic disease, but an autoimmune one. Dr. Daniel Leffer was surprised to see that the HLA-DQ2 gene, which is a component of the genetic immune response, is linked to celiac disease. It was already known then that this gene is associated with type 1 diabetes, which is an autoimmune disease. The HLA-DQ8 gene was also found to be associated with celiac disease. (Celiac Disease Foundation)

Since 1980s, research into the effects of gluten has started and continues to this day. Nowadays, celiac disease (CD), according to definition, is now an autoimmune disease that affects the small intestine. Caused by a reaction to gliadin, which is present in wheat, barley, rye, and oats.

Due to the malfunction of the small intestine, the body reacts to gluten as a foreign antigen. In this way, the immune system attacks the antigen and stimulates the production of T cells - white blood cells that play a crucial role in the acquired immune response - causes inflammation of the small intestine. It destroys mucosa and produce shortening of the villi lining in small intestine. Villous atrophy reduces absorption of nutrients from food. (Bower S. et al. 2014, 3.)

This mechanism of immune-mediated gut response is not yet fully understood, but involves a partial HLA-DQ2 or HLA-DQ8 T-cell immune response as well as an immune response in the intestinal epithelium (Jabri B. 2003, pp. 383-391).

2.3 Symptoms of CD

People are not born with CD. Genetically susceptible or trigger of the disease development might be pregnancy, bacterial infections or consumption of gluten.

Celiac disease can develop in early childhood following the introduction of wheat or other foods containing gluten into the diet, usually between 6-9 months of age with symptoms of chronic diarrhoea, prolonged growth, and development difficulties. It is not researching yet why some children become ill at an early age and others only after years of exposure. However, genetic factors, leukocyte antigens (HLA) type, environment influence and gluten intake caused the pathogenesis of disease. (Kamalova et al. 2020, 371-378.)

Many people face difficulties to identify a diagnosis, since the symptoms of celiac disease are like other gastrointestinal diseases. Typical symptoms of celiac disease in children are bowel problems such as constipation, diarrhoea, and abdominal pain (Silano et. al. 2016, 7).

Refusal of food due to loss of appetite, against the background of along with improper absorption of nutrients, water-salt and mineral imbalance - all those factors lead to problems in the entire body (Bower S., et. al., 2014). The age of first manifestation of CD could be various from infancy to the elderly. As well as the range of symptoms are very wide.

The classic signs are abdominal pain, foul-smelling stools, diarrhoea, or constipation, and even a swollen belly, cause by malnutrition. Child suffering from CD usually experience weight loss, slow growth pattern, irritability, fatigue, and listlessness. (Murray 2018.)

Children under 2 years old usually experience as a common symptom vomiting, chronic diarrhea, muscle weakness, poor appetite, and swollen belly. For older kids symptoms could be similar – diarrhea, loss of appetite and in addition constipation, weight loss, irritability, delayed puberty, some neurological symptoms, such as attention-deficit/hyperactivity disorder (ADHD), learning problems, lack of muscle coordination and seizures. (Murray 2018)

Systemically repetition-accompanying conditions such as anaemia, chronic fatigue, weight loss, obesity, osteopenia, osteoporosis and fractures, amenorrhea, infertility, muscle cramps, and dental enamel defects can also be potential symptoms of celiac disease.

Hidden symptoms of celiac disease can be the cause of neurological diseases such as seizures or unsteady gait (ataxia). A neurologist will not be able to track the occurrence of seizures because there is no brain damage. Celiac disease can also cause very itchy, scaly skin lesions. Similar symptoms are observed in the disease herpetiformis dermatitis. The

doctor will have a history of complaints of abdominal pain, bloating, constipation, diarrhea, chronic fatigue, gas, or even type 1 diabetes. However, the diagnosis with such symptoms may not be correct (Bauer S. et al. 2014).

Concluding, five main symptoms of celiac disease can be separated out from different resources. Many sources note that sometime after eating gluten with food, the child becomes lethargic, pale, and has a dull look. The body gives a quickly physical reaction, within up an hour to three, to the received gluten. This can manifest as an abdominal pain, vomiting, or diarrhoea. (Kamalova 2020.)

Children become irritable, capricious, lethargic, appetite decreases. Against this background, the main problem that forces parents to see a doctor is the deterioration of the stool character, which becomes thinner, more frequent, abundant, greasy, and fetid. Parents often note that the volume of stool in a child exceeds the amount of food eaten (polyfecal syndrome). Along with pathological stools, attention is drawn to increased gas formation, leading to flatulence and persistent bloating. In the other hand, severe constipation also can be a symptom of celiac disease. All mentioned above, obviously cause abdominal pain (Celiac Disease Foundation).

2.4 Celiac disease in children

Celiac disease is one of the most widespread chronic disorders among children, affecting 1 in 100 children. In recent years, celiac disease has been diagnosed more often. (Husby et al 2012.)

The most striking manifestations of celiac disease with a predominant lesion of the gastrointestinal tract, observed in children in the first years of life. With first introduction of gluten-containing foods into the diet, children may experience the first symptoms of celiac disease. At the same time, from the beginning of regular use until the development of the clinic of the disease, at least 8 - 12 weeks (about 3 months) usually pass, even in the case of an early onset of celiac disease. The duration of the latency period (from the onset of gluten consumption to the development of the clinical picture) can be different, ranging from several weeks to tens of years. Therefore, it is important to be alerted to predisposed people throughout life (Husby et all 2012).

In paediatric practice, the following clinical variants of the disease are distinguished:

- a typical variant of celiac disease

In children it occurs up to 2 years of age, usually 2-3 months after the introduction of gluten-containing products into complementary foods; manifested by polyfecal and steatorrhea, poor weight gain, emotional disorders.

- atypical variant of celiac disease

Occurs in children from 2 to 12 years old, in the clinic on the first planet there are deficient conditions (rickets-like skeleton, anaemia, convulsions, osteoporosis), bowel dysfunction during food load.

- hidden (latent) type of gluten enteropathy

Asymptomatic, the appearance of classical symptoms with gluten load in adulthood is possible. (See & Murray 2006.)

2.5 Assessment and diagnosis

Usually, doctors suggest anyone with a family history of celiac disease to check themselves in terms of celiac disease. This also comes into the place in case of other diseases, such as thyroid disease, anemia, diabetes, or other immune diseases (e.g., Downs syndrome). In all other cases patients can be checked on a case-by-case basis based on individual symptoms. The initial step to detect celiac disease usually starts with a blood test (Schuppan 2013).

A celiac disease blood panel includes several tests to determine whether someone has celiac disease. These tests are extremely specific because certain antibodies only appear in those with gluten sensitivity, celiac disease and/or dermatitis herpetiformis (Gallegos, Merkel, 2019).

The initial testing starts with an Immunoglobulin A (IgA) test. Based on the results of this test the decision is made about further proceeding. For example, if the results from the IgA test are normal, then a Tissue transglutaminase, antibody test is prepared. While a weak positive result should lead to some other test proceedings, such as Endomysia antibodies and Gliadin (deamidated) antibody. Further, if the results of the initial Immunoglobulin A (IgA) test are low, then Tissue transglutaminase antibodies (IgA and IgG profiles) and Gliadin (deamidated) antibodies evaluation (IgG and IgA) should be tested. Finally, if the initial IgA test has shown deficient results then Tissue transglutaminase (ITG) antibody (IgG) and Gliadin (deamidate) antibody (IgG) test should be arranged. It sounds complicated, but it is

standard procedure, and when blood screening is done this way the results for celiac disease are ~98% accurate. (Celiac Disease Foundation)

According American Gastroenterological Association tests reliable only if personal regularly take in gluten with the food. Otherwise, if gluten removed from diet for more than a month before test, either blood test and small intestine biopsy results could be incorrect, or CD may be hard to determinate.

Until now, about half of all children diagnosed with celiac disease have undergone a biopsy. Recently published guidelines from the European Society for Pediatric Gastroenterology, Hematology and Nutrition (ESPGHAN) recommend that clinicians perform a two-step blood test for most children with suspected celiac disease.

The new guidelines appear in the Journal of Paediatric Gastroenterology and Nutrition and call for clinicians diagnosing children with celiac disease to rely on accurate serology-based diagnosis without biopsy.

Being able to diagnose children without biopsy is a major advance in celiac disease diagnosis and will save millions of parents and children from what can be a costly, intimidating, and uncomfortable procedure.

2.6 Treatment

The main treatment for celiac disease is a gluten-free diet. All products with a gluten content of more than 1 mg per 100 grams of product are prohibited. (Murray, 2006.)

It should be remembered that gluten is found in some forms of medicines as well as in cosmetics. There is also hidden gluten in many food products. Thus, it is necessary check every time the product composition.

At the beginning of treatment, it is necessary to avoid milk, as well. Later, it is permissible to expand the diet and include in the diet of prohibited foods (in small quantities) (Ruchała et.al 2012).

Also, in the treatment of celiac disease, medications can be used - enzymes, vitamins (B1, B6, nicotinic acid - subcutaneously, iron, calcium, vitamin D - in tablets), drugs for symbiosis. (Vici et al. 2020.)

Other treatments for celiac disease are currently being sought. (Maglione 2016.)

2.7 Nursing point of view and family orientation

The diagnosis of CD can be incredibly stressful for patients and family members, as it is a life-long disease. Most adverse effects of CD related to malabsorption: such as malnutrition, lack of vitamins and minerals, osteoporosis, diabetes, or even intestinal lymphoma. (Violato M. And Gray A., 2019, 53.)

Celiac disease diagnosed at an early age gives the possibility to significantly influence the growth and development of the child.

In this case patient education is crucial. By providing information about celiac disease in general, how to cope with it, non-gluten diet nurses and other health care professionals can minimize anxiety level and reduce stress among patients and their close ones.

3 The thesis aims, purpose and research questions

The thesis **aims** to provide evidence-based information within qualitative research about celiac disease in children.

The **purpose** of this thesis is to describe the risk factors affecting the development of celiac in childhood, the symptoms, health effect to children, as well as the methods of testing to identify celiac disease in early age, which also can be in principle applied to adult people.

Research questions for this thesis were:

1. *What are the risk factors for development of celiac disease at an early age?*
2. *What are the initial symptoms of celiac disease - gastrointestinal and non-typical?*

4 Methodology

In the process of writing a scientific work, the researcher analyses a wide variety of literature. Finding reliable data, comparing, and analysing them called a systematic literature review. In other words, the systematic literature review is the summary of research literature that is focusing on topic question. It is statistically verified, observing many criteria and minimize errors (Mengist, et al. 2020, 76). This approach was assumed as an effective method for selecting information.

Systematic literature review consists of 4 stages: literature search, assessment, data synthesis and analysis. Literature search includes identifying databases where information will be searched by keyword. During the assessment, the researcher finds a source of information according to the specified criteria. Then one or another literature is included in the review or excluded from it. Quality is also assessed at this stage. Synthesis involves the assortment of data and their categorization, and during the analysis, the result is described, and the final conclusions are formed. (Murad et al. 2014, 35.)

A systematic literature review was carefully sorted and selected information from different resources. It is difficult to compare the available data. First, there is large amount of scattered information about celiac disease provided in diverse sources and with only partial information. Second, the authors of the studies apply different criteria for statistical data, thus coming to different conclusions. (Caio et al. 2019.)

4.1 Data search

Theoretical part obtained from evidence-based internet sources and educational textbooks. The literature review for this thesis was done in April 202, and then repeated in June 2021 and November 2021.Qualitative methods were used for this research. The data is being analysed using inductive content analysis.

Academic databases, like PubMed, LAB Library, MEDLINE, EBSCO were searched for reviews published between 2011 and 2021. Letters to the editor, abstracts and proceedings from scientific meetings were excluded from the analysis. Articles were narrowed by language. Only scientific articles in English were considered. Abstracts, scientific essay, letters to author were excluded from literature review.

Data was selected from similar type of systematic review, primary studies included in the review, as well as medical research about celiac disease were included.

Following terms were used for search in databases ”celiac” or ”coeliac” or ”sprue” or” gluten entreropathy”; ”risk factors of celiac” or ”children’s risk factors of celiac”; ”complementary feeding” or ”infant feeding” or ”gluten introduction”. (See appendix 1)

In PubMed was found 28166 results. Sources was narrowed by publication date. 2011 - 2021 years was settled, as 10 years - period that recommended for academicals researching (Stephan, Smith, 2019, 25-26). The database found 10,743 results. It is also important to mention that during this period the largest number of literature work on this topic was published. Next filter for narrowing articles was free full text of article and review, systematic review. 513 peer reviewed journal articles were found.

In funded articles, it was necessary to highlight articles related to research among children. The results were 222 articles. Selected articles were retrieved and assessed the potentially relevant ones.

14 articles have been selected for this thesis (see appendix 2).

Research Databases EBSCO became another database for evidence-based information research for this literature review. It was necessary to login with LAB University ID to start the academic research in that platform.

Next step was to identify keywords for search. As the EBSCO database has 3 optional fields for key words was chosen: celiac disease, celiac disease in children, gluten sensitivity.

To specify articles was picked "Boolean/Phrase" as a model of search with applying all related words, also search within the full text of the articles.

To limit results by publication date was set up from January 2011 till October 2021, full text with available references. Special limiters for academic search elite were elected all articles in English in PDF full text. Search results was 25 articles. All of them were assessed and reviewed. As a result, only 3 of those articles were chosen for analysis. The information gained from those articles became the basis for authoring this thesis.

Databases	Search words	Delimitations	Results	Selected articles
PubMed	Celiac disease in children	Free full text, English, Review, in the last 10 years (2011-2021)	222	2
	Celiac disease children diagno-sis		129	1
	Celiac disease gluten		513	2
EBSCO	Celiac disease	Free full text, English, 2011-2021 years	25	1
	Celiac disease in children		17	1
	Gluten sensitiv-ity		13	1
Google Scholar	Celiac disease in children	Free full text 2011 - 2021 years	296	2
LAB Primo	Celiac disease	Free access avail-able online books	22	2
Evidence-based open infor-mation internet resources	Celiac disease	Free access		2
				14

4.2 Data synthesis and reliability

During literature analysis were found many well done texts and articles with the qualitative approaches. Nevertheless, most of them are focused to data collection instead of analysis process (Divan, et al. 2017)

The reviewer independently assessed the studies for potential relevance. Any type of primary data report was included in this systematic review. Previous systematic reviews and meta-analyses were excluded.

Prospective studies had to enroll infants/children at increased risk of developing CD. In the analysis different studies regarding the assessment of CD risk should be included. This can cover analysis of the factors which increase the risk of celiac disease in childhood, distribution of celiac disease within society, and gluten consumption at different ages including the first time of receiving it by people.

4.3 Data analysis

The dualism propounded in Qualitative Content Analysis (QCA), suggests the adoption of “inductive” or “deductive” approaches or modes of reasoning in the process of qualitative data analysis (Elo & Kyngäs, 2008).

In a primary evaluation articles were selected by title, abstract and keywords. The next phase was scouting of the full text of possible relevant trials. The reviewer individually assessed of each potentially range with the use of inclusion/exclusion considerations

The symptoms of celiac disease described in reviewed articles by inductive data analysis were divided into three groups: metabolic, somatic and mental. Metabolic and part of the somatic symptoms are considered as classic symptoms. Mental and partially somatic symptoms of celiac disease are less common. All symptoms are described in table 2 (see appendix 3)

Based on the work done, generalizing conclusions were made to identify trigger of celiac disease and its early symptoms. A further review of the literature made it possible to determine the most effective method for diagnosing celiac disease in children today.

5 Results

After content analysis of the selected articles, the following patterns can be distinguished - typically, celiac disease manifests itself 1.5 to 2 months after administration the child's diet of gluten-containing products (crackers, bread, dryers, bagels, semolina (wheat) porridge, multigrain porridge).

According Sciurti Martina's research HLA genes help the immune system to distinguish proteins that belong to our body from proteins produced by foreign invaders such as viruses and bacteria. About 99% of people with celiac disease have one of the following HLA gene variants: HLA DQ2.5, HLA DQ8, or HLA DQ2.2, which sometimes trigger an anti-gluten reaction. (Kaswala et al., 2015)

Having one of these genes does not mean that celiac disease will develop. In fact, about 30% of the population carries these risk genes, but only 1% of them will develop celiac disease. (Guandalini, 2017)

Since the formation of modern knowledge about celiac disease, in addition to genetic factors, the role of environmental factors in the development of the disease has been actively discussed. (Valitutti et al., 2019) Interest in this issue is associated with the possibility of developing preventive measures in risk groups, that is, where the genetic predisposition to the disease is beyond doubt, and alleles are present in the genotype. The researchers believe that the possible reasons for the development of celiac disease in the risk group may be the peculiarities of the course of pregnancy in the mother and complications of the neonatal period. For example, viral intestinal infections that a child suffered in the first days of life can trigger the development of celiac disease. (Savvateeva et al., 2018)

Sometimes manifestation of celiac disease in children occurs after the transferred infectious diseases (intestinal or respiratory infections), however, the disease often begins for no apparent reason. (Therrien et.al. 2020)

The largest number of studies among children is aimed at studying the effect of feeding in infancy and early age on the risk of developing celiac disease, as well as determining the age of the first symptoms of celiac disease. The research in this direction was based on the phenomenon of the "Swedish epidemic". In Sweden, in the mid-1980s, there was a significant increase in the number of newly diagnosed cases of celiac disease among children in the first two years of life. In the next 10 years, the incidence reached a record level, and by the mid-90s had dropped to its original level (Popp & Mäki 2019).

The incidence of celiac disease during the analysed period increased almost 3 times, while baby girls were susceptible to the disease. This fact determined special attention to the nature of infant feeding. The researchers pointed out that the onset of the epidemic coincided with a change in the way babies were fed: foods high in gluten were introduced to babies from 6 months, exactly when most mothers stopped breastfeeding. In the 1990s, nutritional recommendations for children changed again towards the earlier introduction of gluten-containing cereals from the age of 4 months, while the amount of gluten in industrial products was reduced (Popp & Mäki 2019).

There is no evidence to prove protective effect of breast feeding. However, it must be noted that should be implemented whenever possible for new-borns babies, including those who have a genetic risk of CD. Many reports mention also benefits of breastfeeding also aa method of building a maternal-infant contact. There was evidence that the introduction of gluten to infants before 3 months or after 7 months significantly increases the risk of developing the disease compared with a period of 4-6 months. This period in one of the researchers' works was called the "critical window" - the time of tolerance to potential allergens by introducing them into the diet. (Silano et al., 2016)

However, there is currently no evidence to recommend avoiding either an early (at 4 months of age) or a late (at or after 6 or even 12 months) gluten introduction in children at risk of CD.

Celiac disease is more common in at-risk people, such as having a biological relative with CD, having HLA-DQ2 and HLA-DQ8 genes, having CD symptoms or having some autoimmune disorders. (Samasca et al. 2014)

Next of kin relatives the main risk group for celiac disease. First-degree relatives of someone diagnosed with celiac disease should always be screened, even if they are not experiencing any symptoms. Second-degree relatives and families with several people with celiac disease also have an increased risk of developing the disease. (Samasca et. al. 2014)

The sooner celiac disease is diagnosed, the easier it will be to avoid serious health problems because of that.

Symptoms vary widely. For many children, symptoms begin within minutes or hours after consuming gluten and last only a few hours. In other situations, symptoms persist for days or even weeks.

The clinical symptoms of celiac disease appear, in most cases, gradually. Copious, frothy, greasy, fetid stools, characteristic of celiac disease, impaired appetite, gratuitous vomiting,

and weight loss. Parents pay attention to behavioural disorders - irritability, negativism, apathy appear, sleep is disturbed, and interest in the environment disappears. (Kelly, et al., 2015)

Many children have mild symptoms and are easy to miss. For example, excessive gas, abdominal pain, or constipation. Other children have more severe symptoms that will lead to an earlier diagnosis. The most noticeable signs are the baby's inability to develop fully, weight loss, and vomiting. Older children complain of abdominal pain, which are more often fickle, "dull" character and are localized in the umbilical region. Most of the symptoms related to problems with the digestive system (Meijer et al. 2018).

Later, child experience disturbances in the digestion of food, continues stomach pain, lack of appetite. Children does not gain weight and height, their muscle weakness increases, physical activity decreases, and the normal pace of psychomotor development is disrupted. As the disease progresses, patients acquire a characteristic appearance: against the background of a lack of body weight, thinning of the subcutaneous fat layer, and a decrease in muscle tone, a significantly increased abdomen appears (Silano et al. 2016).

It is worth noting that quite often in children, celiac disease occurs in the absence of any manifestations from the gastrointestinal tract, and the symptoms caused by the presence of deficiency states due to impaired absorption of micro- and macronutrients in the intestine come to the fore. The pathological process in celiac disease can involve the skin and mucous membranes with the development of stomatitis, the appearance of polymorphic rashes, vitiligo foci, and the formation of focal and total alopecia against the background of increased hair loss. Among the skin manifestations of celiac disease, special attention should be paid to dermatitis herpetiformis - a chronic skin disease characterized by dry skin and the presence of vesicular-papulosis rashes on the elbows and knees, accompanied by severe itching. (Houmich & Admou 2021)

Children suffer not only physically, but also mentally: isolation, increased excitability, mood swings are observed.

Medicine has not yet found ways to regulate the body's sensitivity to gluten. Therefore, in case of illness, a non-prolamin diet becomes the most crucial factor. (Penagini at al. 2013) The more carefully a suitable diet is followed, the higher the quality of life, as well as its duration. (Murray, et al., 2018)

The disease in adults often does not manifest itself for many years and proceeds secretly, while the signs of celiac disease in children are more pronounced, but it is difficult to suspect this disease due to the typicality of its symptoms for many other diseases.

6 Conclusion

Summing up the results of the work done, it can be concluded that there is still no exact reason was discovered why celiac disease can develop. Nevertheless, according to the research results, children with a genetic predisposition are most susceptible to the development of celiac disease. Also at risk are children who have suffered infectious diseases in the neonatal period of life. (Samasca, et al., 2014)

Several studies describe the role of breastfeeding and the introduction of complementary foods containing gluten. However, it is not fully understood whether there is a connection between the introduction of gluten into food at an early age and the development of celiac disease. This issue requires further research. (Silano et al., 2016)

Most often, celiac disease manifests itself in the form of problems with the gastrointestinal tract. Among other information about the symptoms of celiac disease, it was necessary to find non-typical manifestations of the disease at an early age. From the total amount of information obtained by inductive analysis, three groups of celiac disease symptoms were identified, which are described in detail in the chapter 2.4 of the thesis. (Kamalova A., et al., 2020, 371-378)

The study of celiac disease in recent decades has advanced significantly. Previously, the diagnosis was possible only after a biopsy of the small intestine. This diagnostic method is difficult to apply to children. Therefore, many children suffer from the symptoms of the celiac for years, but albeit the fact that remain without treatment. Nowadays, newest guidelines make it possible to determine the presence of celiac disease by blood tests. This makes the diagnosis much easier, even at an early age (Rostom et.al 2006).

The main treatment for celiac disease is a gluten-free diet. Other treatments for celiac disease are currently being sought. (Maglione 2016)

7 Discussion

Investigation of celiac disease brings quite controversial results, where only one aspect about the disease can be considered as straightforward information agreed within the medical society, which is actual treatment of patients having celiac disease. The only verified treatment of celiac disease suggested in the most designated sources is a strict non-gluten diet. While information regarding symptoms of the disease and actual harm to health might vary from case to case, which opens a speculation about disease effect to the health condition of an adult person.

However, celiac disease has a clearer harm effect on children, which is often related to their growth development. Therefore, it can be considered that the determination of celiac disease among children in good timing is especially important and critical to avoid any significant harmful effect to the health of children. While nowadays, there is no clearly specified proceeding of celiac disease determination in a systematic way in most of the countries. It means that there could be a few children suffering from celiac disease worldwide without any knowledge of what type of disease they are having and how to treat it. Even in the regions where medicine system involves determination of celiac disease, often without proper actions from parents (who could start observing some symptoms that can be observed only within critical time) and medicine personal (who should justify blood checking based on description of the situation by parents) it can take a significant period before proper actions are implemented.

For example, in our case it took more than a year before it was discovered that our son has celiac disease, which can be considered as a momentous time for a 4 - c5 years old child, because already now there is straightforward evidence that growth development has significantly slowed down during this period (before the disease was diagnosed and proper diet is applied). The time delay for a correct diagnosis of celiac disease can be increased by varied factors such as Covid19 (which was the main reason of late diagnosis in our case), absence of periodic growth development checking, non-evident symptoms (e.g., only related with child behavior and growth development) and other personal aspects.

None of the circumstances described above should affect the fast diagnosis of celiac disease in children, because especially for small children it is critically important to make a fast diagnosis of celiac disease, as each time delay it takes for diagnosis of celiac disease worsens the health of children and slows down the correct growth development. Therefore, it can be discussed what should be done to make a systematic diagnosis of celiac disease among children, especially in cases with genetic predisposition.

According to the understanding of the Author of this thesis work, proper systematic actions should take place for an effective fight against harm done by celiac disease. For example, proper information should be provided to parents once they have a born child. The information should include some details about celiac disease such as symptoms and possible harmful effects caused by it. In our case, we did not have this information beforehand, and we did not even know that celiac disease exists. While if we had been informed properly in advance, it would have helped us to take actions faster based on the very initial symptoms.

As it has been discussed above, currently there is no large share of children which have celiac disease (about 1%). This is one of the main reasons why celiac disease is not taken seriously enough in many regions of the world. However, considering the overall population of the world, it is understood that the total number of people that have celiac disease can be compared with a whole population of an average country. Naturally, quite large share of these people can still be not aware of the main reason of their health suffering and cannot treat the disease properly. Therefore, it can be considered that millions of people (especially children) have problems with the health because of not considering celiac disease seriously enough, or because of lack of information about it.

Finally, as was discussed in the thesis, the number of children having celiac disease is gradually increasing during recent years. One probable reason of that can be better and faster ways of diagnosing celiac disease developed and applied in practice recently, which allows to make a proper diagnosis of the disease among larger number of people. However, another reason of that can be related to habits of parents, new diets of pregnant women, practical approaches during birth of the child, etc. While naturally it will take time before, the actual reasons of celiac disease growth would be discovered. Therefore, it is especially important to prepare a proper action plan to reduce the overall harm effect of celiac disease within society.

7.1 Results

Celiac disease is a multifactorial disease, that is, genetic factors and environmental factors play a role in its development. A person may be at a higher risk of developing the disease due to their genetic makeup, but this does not mean that they will develop the disease. In other words, parents can pass genes on to their children, but genetic predisposition is only one of the factors that cause celiac disease in a person.

The importance of celiac disease was previously underestimated, and it is still not widely recognized in different countries. However, it was found that celiac is one of the most common genetic diseases on the planet with a prevalence about 1% within the undivided population (Rostom & Murray 2011, 24).

Results suggest that CD occurs frequently not only in patients with gastrointestinal symptoms, but also in first- and second-degree relatives and patients with numerous common disorders even in the absence of gastrointestinal symptoms. Celiac disease is a more common but neglected disorder than has been recognized (Irvine et al. 2017)

In this regard, over the past decade, there has been put a significant effort on the scientific research on celiac disease. The output of this research is distributed within different scientific publications, reports, and conference presentations. Further studies should be aimed to identifying risk factors and early latent symptoms of CD.

A gluten-free diet nowadays the only one possible treatment for celiac disorder or similar food-related symptoms. According to a February 2005 report by the World Organization of Gastroenterology (WOG-OMGE), celiac patients should not consume any form of wheat, rye, or barley. Compared with the population without chronic diseases, the rate of death of patients with chronic diseases increases. However, in accordance with a strict gluten-free diet during three to five years, the mortality of celiac patients returned to normal.

7.2 Thesis process

Before starting work on the draft of this thesis, the author experienced difficulties in choosing a relevant topic. Finally, my 5 years old son helped me with the choice. In April 2021, he was diagnosed with celiac disease, and even after a brief investigation of the disease (history, symptoms, treatment) it became clear that celiac disease is getting more attention nowadays and its investigation with further detailed description would be quite relevant research topic.

He had no prerequisites for the development of the disease - in the family until the third generation, no one has had such a diagnosis before.

One of the purposes of this work was to describe the initial, typical, and non-typical symptoms of the disease, its effect to health, as well as the reasons why the disease can develop in certain children or adults.

During the research, it was found that many people face the difficulty of identifying a diagnosis, since the symptoms of celiac disease are like some other gastrointestinal diseases. Typical symptoms of celiac disease in children are bowel problems such as constipation,

diarrhea, and pain in abdomen. Refusal of food due to loss of appetite, along with improper absorption of nutrients, and a water-salt and mineral imbalance, lead to problems with physical development and delayed growth.

In the process of selecting the available literature, a lot of related information was worked out. For example, the relationship between breastfeeding and the development of celiac disease was studied.

Further, large share of the material was dedicated to the investigation of history of celiac disease and to the study/discovery of the medical history of patients of different ages, which shows quite different effect of the disease on human health as well as different symptoms people have faced.

Many patients in their notes mention that before being diagnosed with celiac disease, they suffered from many different symptoms. But none of the diagnoses was correct. In addition, the treatment that was assigned did not lead to the desired result, but only aggravated the course of the disease. And only after establishing the correct diagnosis, following a gluten-free diet helped to get rid of the symptoms, and significantly improve the health condition.

7.3 Validity and reliability

During the creation of a scientific work, the researcher must ensure that all sources of information are valid and reliable. Reliability assumes that all materials used while writing a scientific work are reasonable and verified.

To write this work, materials were used from electronic databases, like MEDLINE and EBSCO. MEDLINE is a bibliographic database of life sciences and biomedical information. It includes bibliographic information for articles from academic journals covering medicine, nursing, pharmacy, dentistry, veterinary medicine, and health care. [43]

MEDLINE is a wide scope resource for biomedical researchers all over the world, as it provides evidence-based information. Likewise, EBSCO provides high-quality content for academic libraries including academic research databases.

MEDLINE resource is an evidence-based information retrieval resource for healthcare professionals. Both EBSCO and PubMed are rigorously reviewed by research professionals and have strict criteria for selecting articles for publication on their platform.

According to information at the official website EBSCO provides access to trustworthy information, offer the most comprehensive coverage of content from many regions, in an array of languages, across a multitude of subject areas. They apply strict curation processes that

users are accessing diverse and trustworthy content. EBSCO references top citation indexes, such as Web of Science and Scopus, and subject indexes, such as APA PsycInfo and SciFinder, to determine relevance and quality.

PubMed also has strict criteria for publishing on their resource. According to the rules, PubMed databases are committed to publishing a publisher to conform to guidelines and best practices published by relevant professional organizations. Additionally, participating journals and selective deposit programs are required to meet PMC's technical quality requirements, which includes deposit of full-text XML for every article.

Writing a scientific work is always accompanied by experiment, which may be theoretical or practical. When confirming scientific results in practice, the coincidence of the phenomena in practice with the constructed theoretical propositions is considered.

The symptoms of celiac disease described in this thesis were compiled from a selected list of research articles. The author of the thesis was able to experience practical symptoms, diagnosis and treatment of celiac disease in a child recently diagnosed with celiac disease. Symptoms similar those described in the thesis were manifested in other patients describing cases of CD in several research papers and on the website dedicated to CD – celiac.org

Unfortunately, it is not possible to conduct a firsthand survey of celiac disease symptoms during research work since there is no access to the personal data of celiac patients due to the privacy policy.

8 Conclusion

As mentioned before, there has been an increased number of studies on celiac disease in recent years. This is primarily due to the increased number of patients suffering from this disease. The youngest age when the disease manifested itself is from 1 to 2 years (the period when gluten was introduced into food). Less often, the disease develops in adulthood and older age. However, this may be due to the asymptomatic development of the disease.

Classic symptoms, associated with gastrointestinal problems - abdominal pain, foul-smelling stools, diarrhoea, or constipation, and even a swollen belly. (Murray, 2018) But it also possible that the disease manifest in the form of complications due to malabsorption, poor absorption of food, lack of minerals and vitamins. Usually it is weight loss, slow growth pattern, irritability, fatigue, and listlessness (Murray 2018).

However, celiac disease symptoms are not always the result of deformation of the villi on the walls of the small intestine. Many researchers in their works note that the symptoms were mimicked for other diseases. So, for example, a rash on the skin cannot always be associated with a malfunction of the intestines. However, improper absorption of nutrients in the intestines can provoke dry skin and, as a result, instigate skin rashes. A neurologist will treat seizures or unsteady walking (ataxia) but may not be able to discover an obvious reason for the episode because the patient's electroencephalogram does not show brain lesions. One form of CD causes very itchy, scaly skin lesions. When the skin is biopsied, CD can be identified through the antibodies present. This is called dermatitis herpetiformis, and it also causes the intestinal damage. The family practitioner will have on file the symptoms of abdominal pain, bloating, constipation, diarrhoea, chronic fatigue, gas, or type 1 diabetes. (Bower S., et al. 2014) As a result of all above, the patients were treated for a long time from the misdiagnosis.

Certain associated conditions serve as potential systemic symptoms of celiac disease, including persistent anaemia, chronic fatigue, weight loss, obesity, osteopenia, osteoporosis and fractures, amenorrhea, infertility, muscle cramps, and tooth enamel defects (Murray 2018).

Concerning children under 2 years old, celiac symptoms often include vomiting, chronic diarrhoea, failure to thrive, muscle wasting, poor appetite, and swollen belly. (Kelly, Bai, et al, 2015) Older children may experience diarrhoea, constipation, weight loss, irritability, short stature, delayed puberty, and neurological symptoms, including attention-deficit/hyperactivity disorder (ADHD), learning disabilities, headaches, lack of muscle coordination and seizures. (Murray 2018)

In conclusion, diagnosis of celiac disease can help avoid many problems with health. The diagnosis is especially important at an early age to avoid delays in the development of the growing organism.

Unfortunately, total prevention from developing of celiac, as a genetically determined disease, nowadays is impossible. Therefore, medical personnel should pay more attention to children at risk and carry out timely diagnosis of the disease by mass screening before the symptoms of celiac disease develop to severe forms.

9 Suggestions for further studies

Despite the large amount of information about celiac disease, scientific works and articles on this topic, there are still many questions arise according to disease. For example, the research about relation to the prevention of celiac disease and introduction of gluten after first year of life, in groups the risk children's, has not yet been carried out.

The exact reasons of celiac disease development has not been discovered, despite of clear trend that the number of disease cases has been increased significantly during the latest decades. While most of the assumptions regarding the possible trigger of celiac disease development has not been properly validated within an extensive number of cases. Therefore, one of the important research questions which remains mostly undiscovered up to date (despite the one concerning the genes) is related to the actual reasons that cause celiac disease development. Consequently, further studies should include this aspect to be discovered.

Further, as the main reasons of celiac disease development has not been clearly identified it leads to questionable recommendations given by experts to avoid celiac disease development. For example, considering the suggested age of the child when gluten should be first included in the diet (to minimize the risk of the disease development) does not have any comprehensive justification from theoretical point of view and based on relatively limited database analysis of disease cases.

Concerning the symptoms of celiac disease it could be suggested that one common symptom or a set of most frequent symptoms for every case is searched and widely distributed among medical personal (which would give a good enough reasoning of making a blood test), as the currently observed and provided symptoms can significantly vary from case to case and easily can mislead the correct identification of celiac disease.

Finally, because celiac disease (with its harmful effect to human health and its possible symptoms) was discovered relatively recently, the distribution information about it worldwide (including medical society) still can be improved. This can help people living in certain countries and regions which are not much aware of celiac disease details in timing detection of the disease to avoid very harmful effect caused by it. At the same time study activities of celiac disease in those regions can be also improved as nowadays it is mostly concentrated in Europe and USA, as it can be observed from a reference list provided in the thesis work.

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Picture 1 took from online source, 2022: https://www.istockphoto.com/stock-illustrations

Online source, 2022: https://www.nlm.nih.gov/medline/medline_overview.html

Appendix 1

Searching words

‘Celiac’ OR ‘coeliac’ OR ‘sprue’ OR ‘gluten enteropathy’

’Risk factors of celiac’ OR ’children’s risk factors of celiac’

‘Genetically determinate celiac’

‘Celiac disease in children’

‘Classic symptoms with celiac’ OR “common symptoms of celiac disease’

‘Celiac disease symptoms’

‘Gluten’ OR ‘Introduction of gluten’

‘Infant feeding’ OR ‘dietary with celiac disease’ OR ‘gluten free diet’

‘Diet therapy for celiac disease’

‘Treatment for celiac’

Appendix 2

List of reviewed articles:

AUTHOR	YEAR OF PUBL.	TITLE	USED METHOD	PURPOSE AND AIMS	IMPORTANT FINDINGS
Francesco Valitutti, Salvatore Cucchiara Alessio Fasano	2019	Celiac Disease and the Microbiome	Literature review and meta-analysis	This paper summarizes the preclinical (basic scientific evidence) and clinical (cross-sectional and prospective studies) data that explained the link between the gut microbiome and celiac disease.	The article discusses the risk factors of the development celiac disease. According to some reports, exposure to antibiotics during the first year of life is associated with an increased risk of CD.
Annette K Taylor, Benjamin Lebwohl, Cara L Snyder, Peter HR Green Margaret P Adam, Holly H Ardinger, Robert Pagon, Stephanie E Wallace, Lora JH Bean, Karen W Gripp, Ghayda M Mirzaa, Anne Amemiya	2019	Celiac Disease	Literature review	This research describes celiac disease classic symptoms, and non-typical as well. Genes have also been studied, the presence of which may be associated with a predisposition to celiac disease.	Celiac disease is a multifactorial disease resulting from interactions between HLA-DQA1 and HLA-DQB1 allelic variants known to be associated with a predisposition to celiac disease, lesser-known variants in non-HLA genes, gliadin (a subcomponent of gluten), and other factors environment. Classical celiac disease, characterized by mild to severe gastrointestinal symptoms, is less common than nonclassical celiac disease, characterized by no gastrointestinal symptoms.
Joseph A. Murray, M.D., Mark R. Frey, Ph.D., Maria Oliva-Hemker, M.D	2018	Celiac disease	Article	This research paper examines the influence of many factors on the development of celiac disease, as well as finding the triggers for the development of the disease.	Diet therapy is by far the most effective treatment for celiac disease. Specific triggers inducing celiac disease supply a powerful platform for investigating the mechanisms of epithelial-immune interactions, autoimmune responses, and reparative responses in the gastrointestinal tract.
Stefano Guandalini	2017	The approach to Celiac Disease in children	Article	The purpose of this article was to describe the possible environmental factors that provoked the initiation of celiac disease.	Like most multifactorial diseases, CD is the result of a complex interaction between genes, host immune status, and environmental triggers. Celiac disease affects an increasing number of children around the world for yet unclear reasons: the role of environmental factors, such as infections caused by reovirus, is being actively studied.

Amelie Therrien, Ciaran P Kelly, Jocelyn A Silvester	2020	Celiac Disease: Extra intestinal Manifestations and Associated Conditions	Overview	This review summarizes common vitamin and mineral deficiencies associated with CD and their clinical manifestations, then supplies a system-oriented overview of the various EIM of CD.	Since celiac disease affects the small intestine, most of the minerals and vitamins the body needs are not absorbed. In this way, all organ systems become. The article describes in detail how the symptoms of celiac disease can manifest and which organ systems these symptoms will affect.
Ciarán P Kelly, Julio C Bai, Edwin Liu, Daniel A Leffler	2015	Advances in diagnosis and management of celiac disease	Review	It describes the signs of celiac disease, which tests will blur the disease, and by what means of which test results can a diagnosis be made.	Diagnosis of CD can be made without biopsy in certain circumstances, especially for children. Although some symptoms are overt and easy to recognize, others may be subtle or only become manifest as long-term complications of untreated disease. Many new diagnoses are now made through screening individuals considered to be at risk because of a family history of celiac disease, type 1 diabetes mellitus, autoimmune thyroid or liver disease, or Down Syndrome. Many of these people are asymptomatic (or have subclinical symptoms). Symptoms, mortality, and risk of malignancy can each be reduced by adherence to a gluten-free diet. This treatment is a challenge, however, as the diet is expensive, socially isolating, and not always effective in controlling symptoms or intestinal damage.
Caroline Meijer, Raanan Shamir, Hania Szajewska, Luisa Mearin	2018	Celiac Disease Prevention	Article	To name the relationship between early introduction of gluten into the diet of infants and the development of celiac disease	Early infant feeding practices have been suggested as one of the factors influencing the risk of CD in genetically susceptible individuals. Since CD is significantly underdiagnosed and a substantial proportion of CD patients

					are asymptomatic at the time of diagnosis, secondary prevention will not show all CD patients, if mass screening has not been introduced.
Alina Popp, Markku Mäki	2019	Gluten-Induced Extra-Intestinal Manifestations in Potential Celiac Disease-Celiac Trait	Review	Name diagnostic markers reveal true potential celiac disease.	Patients with normal biopsies may suffer from the same extra-intestinal gluten-induced complications before the disease manifests at the intestinal level. The other extra-intestinal manifestations occurring in celiac disease are also found at the latent disease stage.
Dharmesh H Kaswala, Gopal Veeraraghavan, Ciaran P Kelly , Daniel A Leffler	2015	Celiac Disease: Diagnostic Standards and Dilemmas	Overview	An overview of the history and current state of celiac disease diagnosis and supply guidance for evaluation of CD in difficult diagnostic circumstances	While modern celiac serologist is extremely sensitive, a small percentage of patients with CD will be seronegative at diagnosis and others may show an extremely slow resolution of histological findings, despite a gluten free diet, making the diagnosis uncertain. Most patients with villous atrophy on duodenal biopsy will have a serologic test consistent with CD. Differentiation of seronegative CD from alternate causes of enteropathy is a clinical challenge and requires integration of clinical, genetic, and histopathologic criteria
Gabriel Samasca, Genel Sur, Iulia Lupan, Mariana Tilinca, Diana Deleanu	2014	Celiac disease as an autoimmune condition	Review	The aim of our study was to follow the changes in the clinical autoimmunity picture of the celiac disease from recent years.	The study of autoimmunity in celiac disease has focused on associated diseases with the disease: type 1 diabetes mellitus, thyroid autoimmunity disease, Graves' disease, Hashimoto's disease, systemic lupus erythematosus, systemic sclerosis, spondylarthritis, hyperprolactinemia, Turner syndrome, Addison's disease, sensory neuropathies. Immune reactivity to tissue transglutaminase targeted autoantibodies and other autoantigens, including transglutaminase 3, actin, ganglioside, collagen, calreticulin or zonulin which have been reported in the celiac disease.
Marco Silano, Carlo Agostoni, Yolanda Sanz, Stefano Guandalini	2016	Infant feeding and risk of developing celiac disease: a systematic review	Systematic review	To review the evidence for the association of breast feeding, breastfeeding duration or the timing of gluten introduction and the later development of celiac disease (CD).	Currently, there is no evidence on the best breastfeeding duration or the effects of avoiding early (<4 months of age) or late (≥ 6 or even at 12 months) gluten introduction in children at risk of CD. So, no specific general recommendations about glu-

					ten introduction or best breastfeeding duration can be presently provided on evidence-based criteria to prevent CD.
Francesca Penagini , Dario Dilillo, Fabio Meneghin, Chiara Mameli, Valentina Fabiano, Gian Vincenzo Zuccotti	2013	Gluten-free diet in children: an approach to a nutritionally adequate and balanced diet	Article	Focuses on the nutritional adequacy of GFD at the pediatric age, with the aim being to increase awareness of the potential complications associated with this diet, to find strategies to avoid them and to promote a healthier diet and lifestyle in children with CD.	Gluten-free diet, the only available treatment for CD, if not carried out with attention, may paradoxically lead to nutritional imbalances, which should be avoided, particularly at the pediatric age, the phase of maximal growth and development. Increasing awareness on the possible nutritional deficiencies associated with GFD may help healthcare professionals and families tackle the issue by starting from early education on GFD and clear dietary advice on how to choose the most proper gluten-free foods
Taoufik Ben Houmich, Brahim Admou	2021	Celiac disease: Understandings in diagnostic, nutritional, and medicinal aspects	Literature review	The aim of this review is to shed light on the diagnostic, nutritional, and medicinal aspects of CD with an emphasis on practical issues in the management of celiac patients.	The main challenge in managing CD is the implementation and compliance with a gluten-free diet (GFD). This explains the key role of the dietitian and the active participation of patients and their families throughout the disease-management process.
Lyudmila V Savvateeva, Svetlana I Erdes, Anton S Antishin, Andrey A Zamyatnin	2018	Current Pediatric Coeliac Disease Screening Strategies and Relevance of Questionnaire Survey	Article review	Discussed the data on the current strategies for CD detection among pediatric populations and the role of questionnaire-based discovery of CD cases in interest.	Mass screening is a preferable strategy for finding CD cases within the pediatric population because this could uncover symptomatic, oligo symptomatic, and asymptomatic CD cases. However, under conditions of limited financial resources, screening for CD in risk groups, members of which can be named using questionnaires, is essential.

Appendix 3

Table of Celiac disease symptoms

SIMILAR PHRASES	SUB CATEGORY	UPPER CATEGORY
Weight loss	Metabolic symptoms	Common
Swollen belly		
Excessive gas		
Abdominal pain		
Constipation		
Diarrhea		
Anemia		
Headache	Somatic symptoms	
Dry skin		
Rashes		
Vitiligo		Uncommon
Stomatitis		
Alopecial		
Ataxia		
Osteoporosis		
Infertility		
Puberty delay	Mental symptoms	
Negativism		
Apathy		
ADHD		
Fatigue		
Sleeping problems		