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EVALUATION OF SERUM LEVEL OF TRACE ELEMENTS (IRON, ZINC) IN PATIENTS WITH CELIAC DISEASE

(An article review)

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SUMMARY

Celiac disease (CD) is known as coeliac disease , and it is considered to be one of the digestive disorders, and it is also an autoimmune disease that is caused by sensitivity to gluten [1], because it results from the inability to digest the protein gluten, which is one of the components of wheat, rye and barley [2].Allergy to gluten affects young and old, and may occur at any age and appears when the child is exposed for the first time to eating food containing gluten at about 3-4 months of age(1). Most of the studies that determine the prevalence of this disease are focused on Western societies in the United States of America and Europe, and these studies indicate that the incidence of disease in society in general ranges between 2-3%, and the prevalence of the disease in people who have a genetic predisposition to the disease reaches Up to 4% for patients with diabetes, 2% for relatives of patients with wheat allergy first-degree, 3% for patients with immune thyroiditis and 10-55% for patients with Down syndrome[3],[4].Celiac disease results from the presence of alpha-cladin, which is one of the components of gluten (wheat protein)[5], which affects the mucous layer lining the intestine, which causes damage to the villi lining the small intestine and thus leads to chronic inflammation and atrophy of the villi (1), and thus the body loses vitamins, minerals and glucose, and this results in malnutrition. Despite the adequacy of food due to chronic malabsorption, as well as loss of surface area for absorption, lack of digestive enzymes, as well as poor absorption of important micronutrients such as fat-soluble vitamins A, D, E, K, iron, zinc, B12 and folic acid [6].Untreated patients are more likely to have a deficiency of a number of micronutrients compared to healthy people, i.e. those who do not suffer from the disease, and include the following: iron [7],[8] zinc, folic acid[9] as well as B12, B6 [10],[11].
Celiac disease affects other important organs and systems in the body such as the liver, pancreas, thyroid gland, skin, connective tissue, heart, bones and the nervous system [12]. It has been proven that there is a strong relationship between celiac disease and the severity of damage to the liver, as eating gluten leads to the emergence of chronic liver disease in many patients, as one of the studies concluded that celiac disease is one of the most important causes that lead to the occurrence of hepatic failure [13] as it has been proven that The diet of a gluten-free diet improves the clinical aspects of the

patients' liver and also contributes to saving it even if it reaches the final stages of damage [14], so the only treatment for celiac patients is a gluten-free life[15].There are many studies confirm the relationship of celiac disease with renal diseases [16],[17]. Many cases may not show clinical symptoms and are not found only by discovering other diseases such as patients with type one diabetes and other autoimmune disorders [18].The aims of this study were evaluate the level of some trace elements (Iron & Zinc) through its estimation in the serum of patients who consume gluten and who donot consume it and compare them with healthy people.Explain the effect of gluten-free diet followed by celiac patients on their health status and the speed of recovery.

DEFINITION

Celiac disease occurs when gluten, a component of wheat, rye and barley, is consumed. This protein is rich in glutamine and proline as it is poorly digested in the digestive system [19] However, the soluble parts of alcohol that include proliamines from wheat are (gliadins), rye (secalins), and barley (Hordeins), which are among the protein components most dangerous for individuals suffering from digestive disorders [20]. Gluten protein consists of two main parts, and it can be divided, based on its solubility in alcohol, into the soluble gliadin protein and insoluble protein, and these parts are toxic to celiac patients . Gluten plays a major role in affecting the mucous layer of the small intestine of celiac patients, which leads to damage to the cilia lining the small intestine, but it is not known how the toxic effect of gluten on the small intestine and there are two main proposals for the mechanism of the toxicity of gluten are:

1.There is a decrease in the enzymatic activity or an enzyme deficiency that allows Toxic products accumulate in the mucous membrane layer.

2.The presence of a kind of immune response against gluten [21]

This disease occurs in people who have a genetic predisposition to infection, especially people who carry the genes HLA-DQ2 and HLA-DQ8, which are a type of protein encoding genes that are located on the short arm of the sixth chromosome, and thus this disease causes excitation of cells in the mucous membrane lining the small intestine , The cilia that absorb nutrients are damaged, which leads to an imbalance in the absorption process due to the lack of enzymes needed for both digestion and absorption [22]and the immune system is stimulated by the gliadin part, which is one of the components of the protein protein in wheat [23].

Epidemiology

Celiac disease occurs in adults and children, estimated at about 1% of the total population in the world [24],[25]. It occurs in 1-2% of the western population. Celiac disease is not only spreading to European societies, but also in the Middle East [26],[27]. Despite the increase in the diagnosis of celiac disease [28], most of the infected people remain undiagnosed , and global statistics indicate that the sensitivity caused by wheat components reaches 1 out of every 2,800 people in Iraq [29]

The relationship of celiac disease with other diseases

Although celiac is known to be an infection to the small intestine and results in malnutrition, in recent times this disease has been characterized as a disorder that occurs in many systems in the body, including the nervous system, bones, skin, especially the heart and liver [30].In a study it was observed that celiac disease had an effect on other

important organs and systems in the body such as the liver, pancreas, thyroid gland, skin, connective tissue, heart, bones, nervous system (12), as well as an enlarged spleen caused by cirrhosis (13),[31].It was found that there is a direct relationship with the celiac patient's affliction with other diseases, including: that there is an increased risk of malignancies such as adenocarcinomas in the small intestine, esophageal cancer, and lymphocyte cancer of celiac patients [32].

Studies have shown that women with celiac disease have an increased risk of infertility, spontaneous abortion or preterm birth with low infant weight during childbirth, and when these women were treated, these risks were reduced

[33],[34]. There is evidence that celiac disease is more common in patients with type 1 diabetes than in the general Caucasian population, with estimates ranging between 3 and 10% [35,[36]. Patients with type 1 diabetes who are undergoing upper endoscopy should also undergo a duodenal biopsy to rule out celiac disease if they have not been tested before. After the onset of gastrointestinal symptoms, the second most common phenomenon among people with diabetes and celiac disease is weak bone mineralization [37], and it has been observed that parents of children with type 1 diabetes or their children are at an increased risk of developing celiac disease to approximately 4% [38],[39], so laboratory tests must be carried out immediately for patients with type 1 diabetes if they have any gastrointestinal symptoms that are similar to those of celiac disease [40].

There is a relationship between celiac disease and patients who have a disorder in thyroid hormones and growth hormone in patients with Turner syndrome[41] andDown syndrome[42] and patients with type 1 diabetes, as it has been proven that the emergence of these diseases has a great relationship with its existence[43]. There is also a close relationship with the emergence of autoimmune diseases in a large percentage of celiac patients compared to the general population [44]. It was also found that there is a relationship between celiac disease and Graves' disease[45] (Buzduff's disease) or the so called toxic goiter, which is one of the autoimmune diseases that affect the thyroid gland and the most common cause of hyperthyroidism [46].

The researchers found that the proportion of mental illness, depression and infertility increases in celiac patients [47]. It was also observed that there was a relationship between celiac and Autisum, as children with autism were more likely to have self-immunodeficiency disease, such as the disease of gastrointestinal disorders [48], and in another study on autism patients in Iraq showing 3cases suffering from celiac disease [49].

Family history of the disease

Some cases were diagnosed by studying the family history of the disease with the clinical symptoms appearing on the patients [50], as celiac disease increases dramatically in patients in whom one of the first-degree family members has it [51],[52]. The incidence of the disease increases in monozygotic twins [53], and the disease occurs at a lower rate in second-degree relatives [54]. Family members who have more than one person

who has already been diagnosed with celiac disease have a higher risk factor for the disease, and examinations should extend to all other family members, including second-degree relatives [55] history of the disease

Environmental Factors of the disease

Some epidemiological studies have suggested that environmental factors play an important role in the development of celiac disease, including the protective effect of breastfeeding [56] and exposure to gluten after weaning [57],[58]. The initial exposure

to gluten before the age of four months increases the risk of developing celiac disease, as for the introduction of gluten into the diet of the child after the age of seven months is associated with secondary risks [59], and if gluten is introduced into the food while breastfeeding the child, it will be an important preventive factor in reducing the incidence of the disease [60]. Gastrointestinal infections such as Rotaviral infection also increase the risk of developing celiac disease in childhood [61].

In addition, studying environmental factors may facilitate the development of strategies for primary prevention of celiac disease [62].

Clinical Manifestations

The clinical manifestations of celiac patients vary greatly according to age groups, as infants and young children usually develop diarrhea, flatulence, failure to thrive, vomiting, colon irritation, loss of appetite and constipation, while older children and adolescents often have other apparent symptoms. In addition to intestinal symptoms such as short stature, neurological symptoms and anemia [63], stunted sleep and failure to thrive should be monitored regularly in children [64],[65]. As for adults, the incidence of disease occurrence in women is estimated to be three times higher than that found in men, and in the majority of women, the disease decreases considerably after the age of 65 years, and the prevalence of autoimmune diseases in women is higher than in men, as well as iron deficiency and osteoporosis, And every one of these symptoms leads to Celiac disease [66].

Among the most important clinical symptoms in adults are diarrhea, abdominal pain and discomfort, as diarrhea is one of the main symptoms in less than 50% of the cases studied in the past decade [67]. There are also silent symptoms of the disease in adults represented by iron deficiency anemia, osteoporosis and GERD [68], and there are other symptoms that include

abdominal pain, constipation, weight loss, neurological symptoms, lack of protein in the blood and calcium deficiency with high levels of liver enzymes [69].

Inflammation in the intestinal layer is one of the hallmarks of celiac disease, as inflammation is lead to the symptoms of malabsorption through the occurrence of diarrhea, and failure to absorb glucose leads to weight loss and as a result of malabsorption , flatulence and pain in the abdomen occurs [70]. Dyspepsia is also one of the clinical signs of the disease [71], The treatment of dyspepsia is one of the clinical challenges [72], however it responds easily to GFD [73],[74]. Therefore, patients with clinical symptoms or signs or laboratory evidence such as malabsorption, chronic diarrhea with weight loss, emaciation or steatorrhea, abdominal pain immediately after eating and abdominal bloating should be Immediately take tests for the disease [75].

A large proportion of patients who were diagnosed with the disease were noted to have pre-existing irritable colon syndrome [76],[77]. Usually, infected patients suffer from the appearance of symptoms and go to the doctors for a very long time before they are diagnosed with this disease accurately [78], [79]. In another study indicated that the symptoms of this disease include diarrhea, weight loss, and children with sensitivity to gluten gain weight slowly, less than the normal range, or they may suffer from weight loss and loss of appetite [80].

In other studies it has been indicated that this disease is usually characterized by diarrhea and malabsorption, but nowadays many patients may suffer from another group of symptoms that often appear on a large scale outside the digestive system such as dermatitis herpetiformis, infertility, neurological problems, osteoporosis, and liver failure [81], [82].

Diagnosis

Confirmation of the diagnosis of celiac disease must be based on a set of findings that include the patient's medical and family history, serology examinations, and upper endoscopy with histological analysis of a biopsy of the duodenum [83].

Serological tests

Accurate diagnosis of the disease includes first subjecting to serological tests and then undergoing an intestinal biopsy, although the diagnosis of this disease is very easy by doctors if the serological tests are performed in a timely manner, there are
10% of cases that are difficult to diagnose due to the incompatibility between the serological tests And histological as well as clinical manifestations or symptoms [84].
One of the most important serological tests that was used to diagnose the disease is the IgA antibody test. These include Antigliadin antibody (AGA-IgA) and connective tissue antibodies that include Antireticulin (ARA-IgA) and Antiendomysial (AEA-IgA) and the antibodies directed against the tTg enzyme that is present in the intestinal layer, but at the present time the Antigliadin antibody AGA-IgA test is insensitive and not specific enough to be used as a diagnostic test for the disease except in children under the age of 18 months [85], [86]. The Antireticulin ARA-IgA test is also considered to be an insensitive test, it is rarely used to detect the disease after it has been passed by using the AEA-IGA and tTg-IgA tests, as the diagnostic criterion for celiac disease at the present time is based on the antibody test against tTg-IgA and AEA-IGA, as this test is considered one of the specific indicators for high disease accuracy, where it has a specialized accuracy of 100% ,it is recommended as a single diagnostic test [87].
In some special cases, some levels of these indicators may appear within the normal range, and if there is great suspicion that the patient has celiac disease, a total IgA test should be performed, and it is not necessary to rely solely on the lack of IgA antibody as a diagnostic indicator of celiac disease as it may ,The deficiency appears due to other diseases that cause villi atrophy, such as Giardiasis disease, bacterial overactivity in the small intestine. Therefore, biopsy examination should be resorted to even if the serological examinations are negative [88].

Biopsy

The intestinal biopsy remains a very important matter and is the standard used in the diagnosis, as an accurate diagnosis of this disease requires examination of the patient by colonoscopy for a biopsy taken from the duodenum area of the intestine, Where the injury of intestinal epithelial cells and lymphocytes appears, as well as the disappearance or atrophy of the intestinal villi, which helps to diagnose the disease, the positive response of the patient's body by its followers to the GFD system, A biopsy should also be performed, especially if there are medical suspicions of the possibility of the disease, regardless of the results of the serological tests in order to determine the age of the disease as well as the time required to follow the GFD system , the diagnosis of celiac disease requires three intestinal
biopsies: the first is a biopsy of a diet containing gluten for the purpose of diagnosis, the second is a biopsy at the end of the gluten-free diet, and the third is a biopsy after consuming products that contain gluten [89], Also, a biopsy taken from the small intestine is useful in the differential diagnosis between celiac disease and malabsorption disorders [90], [91].
To determine how severely the small intestine is affected by celiac disease by biopsy, it is based on the Marsh classification, which has five stages:
Stage 0: normal mucous membranes.
Stage 1: The number of lymphocytes increases in the intestinal epithelium, and the number is often more than 20 lymphocytes per 100 intestinal cells.
Stage 2: Increased crypts in the intestinal wall.

Stage 3: partial or total villous atrophy.
Stage 4: Hypoplasia of the intestine [92]

Gluten free diet GFD

In addition to the treatments mentioned previously, nutritional therapy remains the only safe treatment for celiac patients to follow the gluten-free diet for life, which includes avoiding eating wheat, barley and rye in food and any products containing gluten in their composition, but maintaining this system is complicated. It requires a great deal of effort and commitment, so the diet is often nutritionally lacking in vitamins, calcium, iron and fiber [94], [95].

Eating oats is safe for celiac patients and can improve the nutritional content of the diet [96], as oats can easily be incorporated into diets as a good source of nutrients, as a study indicated that consuming oats improves the nutritional content of patients and they are committed to gluten-free diets by increasing the amount of fiber , vitamin B, manganese and iron [97]. In the past, there was great concern that consuming oats could cause damage to the intestinal mucosa in celiac patients, but recent research indicates that pure oats not contaminated with other grains containing gluten could be safe for celiac patients, provided they are
taken in limited quantities [98], [99]. In another study, it is not recommended to eat oats alone as a substitute, because most commercial oats are susceptible to gluten contamination during the process of grinding, transportation, and milling in the factories [100].

The food that patients eat is devoid of foods that contain gluten, such as wheat and its products, the most important ofwhich is the bread that forms the main food for the human being and which provides him with most of his daily energy and calorie needs, so these foods must be replaced with other energy-producing sources such as potatoes, corn and rice [101]. because of the lack of many vitamins in patients, doctors also advise taking vitamin supplements with eating meat, dairy products, fruits and vegetables because they are naturally gluten-free and help to make the diet good, varied and nutritious [102]. When gluten eating is stopped, it leads to clinical improvement within days or weeks, and despite this, tissue recovery may last for months or even years, especially in adults [103]. People who have apositive celiac disease result may become negative within weeks after a gluten-free diet [104], and after 6-12 months of GFD, 80% of serological tests are negative [105], and after five years of GFD, more than 90% of Serological tests are negative [106].

The effect of celiac disease on the level of some Trace elements

Trace elements are elements that enter the structure of the organism and help it perform its vital functions, they are mainly found in the normal tissues of the body, and their concentration is almost constant from one person to another, and any deficiency in one of these elements causes an imbalance of what is treated mainly by eating this element with diets Also, these elements play a role in the biochemistry of the body, and trace elements are essential chemical elements for the body, and they are trace in the sense that they are present in the human body at a rate of less than 50 milligrams / kg, unlike the larger elements.

A person obtains his needs of trace elements from his food completely if he is keen on eating various fresh vegetables and fruits, as well as being keen on cooking fresh vegetables and not boiling them again and again, because the heat changes the composition of useful materials and loses them with multiple boiling and their nutritional benefit.

Trace elements such as zinc and iron are essential components of biological structures, but at the same time they can be toxic at concentrations beyond those necessary for their biological functions [108]. Some trace elements, especially zinc, are indeed involved in both humoral and cellular immunity. Antibody production, neutrophil function, and natural killer cell activity decrease in trace element deficiency .

The mineral zinc is an essential nutrient. It is a key trace element for the growing organism and is found in almost every cell of the body. High levels occur in specific organs such as the brain, middle ear, eye, skin, hair, and nails. It plays vital role in the activity of approximately 100 enzymes, and supports a healthy immune system. This micronutrient is involved in wound healing, DNA synthesis, energy metabolism, hemoglobin production, carbon dioxide transport, prostaglandin function, synthesis of collagen, protein synthesis, and vitamin A metabolism. It supports normal growth and development during pregnancy, childhood, and adolescence. Several symptoms such as retardation of physical growth, poor appetite, impairment of sexual maturation and impaired taste acuity have been illustrated in zinc-deficient individual .

Zinc is absorbed throughout the small intestine. The small intestine has a fundamental role in maintaining zinc homeostasis. CD significantly affects the proximal small intestine. So, zinc deficiency in patient suffering from CD may result from a cumulative loss of insoluble zinc complexes with fat and phosphate, exudation of zinc protein complexes into the intestinal lumen and massive loss of intestinal secretions or impaired zinc absorption because of damaged intestinal epithelial cell membrane. Some symptoms of CD (e.g. anorexia and reduced growth rate) also occur in zinc deficiency .Iron belongs to the micronutrient group that a person needs in a small amount, and it plays an important role in growth, well-being and disease prevention, and it is one of the minerals that cannot be synthesized inside the body, and must be consumedthrough the diet, while it causes deficiency Its levels have dangerous effects, and pregnant women and children are more susceptible to this. Iron is an important mineral in the human body, and it has a major role

in the process of transporting oxygen from the lungs to all parts of the body by hemoglobin, which is found in red blood cells, and constitutes two-thirds of the iron source. Inside the body, this means that iron deficiency affects various body functions starting from brain functions and ending with the immune system and its ability to fight infection.

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