European Review for Medical and Pharmacological Sciences 2021; 25: 6613-6618

The role of gluten-free diet in nonalcoholic fatty liver disease development

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Abstract. – OBJECTIVE: Celiac Disease (CD) is an autoimmune disease involving the small bowel, generated by the ingestion of gluten-containing foods in genetically predisposed subjects. Currently, the unique therapy for CD is the absolute adherence to gluten-free diet, but this treatment has been related to the onset of non-alcoholic fatty liver disease (NAFLD). In this systematic review, we provide an update from the most recent studies on the risk of developing NAFLD patients adhering to GFD.

MATERIALS AND METHODS: According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) criteria, we performed a systematic literature search on PubMed and Google Scholar from 2012 to 2021.

RESULTS: In the present systematic review, eight studies investigated how GFD in CD patients may be a risk factor for the onset of NAFLD from a minimum of six months to the maximum follow-up period represented by a median of 10 years.

CONCLUSIONS: Present systematic review evaluates how GFD plays a key role in NAFLD for consumption of products rich in saturated fats and carbohydrates that promotes accumulation of lipids and lead to hepatic steatosis and inflammation.

Key Words:
Celiac disease, Non-alcoholic fatty liver diseases, Gluten free diet, Transient elastography, Liver stiffness, Controlled attenuation parameter, Metabolic syndrome, Gut microbiota.

Introduction

Celiac Disease (CD) is an autoimmune disease involving the small bowel; it is triggered and maintained by the ingestion of gluten-containing foods in genetically predisposed individuals[1]. Gluten proteins trigger two immunological pathways: innate immune response that induces mucosal damage characterized by atrophy of the villi and adaptive immunity through CD4 T cells that identify gluten peptide *via* antigen presenting cells[2]. CD affects 1% of the world population and it is often linked with other autoimmune disorder. Its incidence is higher in subjects who have a first-degree relative affected, with an estimated prevalence of 20% in siblings and 10% in other family members[3]. The CD is characterized by a broad spectrum of symptoms, such as diarrhea, steatorrhea, weight loss, bloating, flatulence, abdominal pain and also non-gastrointestinal alterations such as abnormal liver function tests, iron deficiency anemia, osteoporosis and dermatological disease[4,5]. CD diagnosis is based on increased values of anti-tissue transglutaminase and anti-endomysial antibodies associated with the distinctive histological abnormalities of duodenal mucosa[6]. Abnormal liver blood tests, in particular increase of alanine aminotransferase and aspartate aminotransferase, are common in clinical practice and hypertransaminasemia is often a subclinical finding that is gluten dependent[7]. Therefore, patients with an unexplained rise of liver blood test should be evaluated for CD[8]. The unique therapy for CD is the absolute adherence to gluten-free diet (GFD) improving not only clinical parameters, but also the quality of life of patients measured by patients reported outcomes, as well as in other inflammatory disorders of the digestive system[9,10]. The meaning of "gluten free" entails the total abolition of all food containing gluten, but this is not always feasible due to con-

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tamination of foods; hence GFD should contain a low level of gluten to be considered harmless. The exact amount of gluten not dangerous is unknown, but current literature indicates that less than 10 mg per day does not induce injury in most patients[11]. Patients should adhere to a GFD for life, and this entails the avoidance of all foods with the proteins from wheat, barley, and rye. Consequently, patients with newly diagnosis should undergo testing and treatment for micronutrient deficit such as iron, folic acid, vitamin D, and vitamin B12[12].

A strict adherence to a GFD will lead to resolution of clinical manifestations and to healing of duodenal mucosa in almost all celiac patients, therefore assessing the dietary compliance in CD patients is crucial during the follow-up[13].

Current literature reports a link between CD and non-alcoholic fatty liver disease (NAFLD) with a prevalence of CD in patients with NAFLD of 2-14% and vice versa a risk of 4-6 fold higher of developing NAFLD patients with CD compared to the general population[14,15]. NAFLD has been identified as the first trigger of alterations in liver blood test in the Western world[16]. It represents the major cause of chronic liver disease world-wide with a prevalence ranges from 6.3% to 33% and a median of 20% in the general population[17].

NAFLD is defined as an excessive hepatic fat accumulation with a presence of steatosis in >5% of hepatocytes[18]. Diagnosis requires the exclusion of both secondary causes and of a daily alcohol consumption[19]. NAFLD includes non-alcoholic fatty liver (NAFL) characterized by steatosis without necro-inflammatory injury, and non-alcoholic steatohepatitis (NASH) with active lesions of hepatocyte injury, cell death and inflammation[20].

A liver biopsy is the only procedure that differentiates this two pathologically distinct conditions[21]. Approximately 30% of patients with NAFLD develop NASH and 20% of those with NASH progress to cirrhosis. Of note, 30-40% of patients with cirrhosis die for liver failure in a 10 years period[22]. Excessive caloric intake, such as an abuse of saturated triglycerides, refined carbohydrates, sugary drinks, a high fructose intake and a Western diet have all been related to weight gain, obesity and NAFLD[23]. Indeed NAFLD is often linked with insulin resistance and metabolic syndrome defined as the presence at least three of the following five criteria: impaired fasting glucose (IFG) or type 2 diabetes mellitus (T2DM), high level of triglycerides, low level of high-density lipoprotein cholesterol, increased abdominal circumference and hypertension[24]. Obesity, insulin resistance, oxidative stress and cytokine action are identified as the major factors that lead to fat accumulation, promote inflammation, cell injury, apoptosis, fibrogenesis and carcinogenesis[25]. NAFLD is diagnosed in 60-95% patients with obesity, in 28-55% patients with type 2 diabetes mellitus and in 27-92% patients with dyslipidemia[26]. Moreover, a gluten-dependent hepatic involvement has been reported in CD patients and furthermore altered intestinal permeability promotes damage in the liver. Furthermore, malabsorption in CD could lead to chronic deficiency of a lipotropic factor with an associated pyridoxine deficiency giving rise to hepatic steatosis[27,28].

Histological alterations in liver parenchyma, when a liver biopsy has been performed, are often mild and non-specific and they include Kupffer cell hyperplasia, mononuclear cell infiltration, steatosis, and mild fibrosis. This reversible and gluten-related liver damage is known as "celiac hepatitis"[29]. Current studies suggest that GFD, due to higher lipid and carbohydrate intake, could play a role in NAFLD[30].

In this systematic review, we provided an update from the most recent studies on the risk of developing NAFLD patients adhering to GFD.

Materials and Methods

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) criteria, we performed a systematic literature search on PubMed and Google Scholar from 2012 to 1 March 2021[31]. A combination of the following keywords has been used: "Gluten free diet" and "Non alcoholic fatty liver disease" OR "NAFLD" OR "Liver steatosis". The inclusion criteria required that studies were: (1) dated between 2012 and 2021; (2) CD patients; (3) adult population (aged ≥18 years); and (4) human research only. Study selection process comprised three steps. Step 1 consisted of the identification of the studies from a database search, as described above. Screening of the records was performed in step 2. Full-text papers were evaluated in step 3. The Critical Appraisal Skills Programme (CASP) tools (i.e., Cohort Checklist and Case-Control Checklist; 31.05.2013 version) were used to assess the quality of the included studies. Questions 1-6 relate to the internal validity of the

studies, questions 7-8 relate to the validity of the results, and questions 9-11 relate to the external validity of the study.

Results

The flow diagram of the systematic research is shown in Figure 1. Of the 19 titles originally identified, 9 studies have been excluded because secondary (eight review articles) and one case report. Another three studies have been excluded because one described the frequency of CD among NAFLD patients, one evaluated response to GFD of seronegative CD and one described psoriasis-associated comorbidities. Seven studies were included in our review. Data including Authors, title, country, year of publication, patients, aim, design, and results are summarized in Table I.

Quality Assessment

A quality assessment was conducted according to CASP-2013 for all the included studies, and the results are shown in **Supplementary Table I**. All included studies – i.e., case-control study and cohort study – were considered of good quality. Prospective and cohort studies score 12 out of 13 of the CASP appraisal tool and retrospective and case-control studies presents 8 and 9, respectively, affirmative answers.

The Role for GFD in NAFLD Development

The effect of GFD in promoting NAFLD is still a matter of debate. The following articles have been selected in this systemic review and present data regarding GFD in CD patients and the onset of NAFLD (Table I).

A study conducted by Rispo et al[32], carried out a retrospective analysis on a dataset containing information on adult celiac patients; data were collected both at the time of diagnosis and at the end of the 2-year follow-up period. Diagnosis of CD was made by the presence of Marsh histology ≥2 associated with IgA anti-tissue transglutaminase (atTG) antibodies >7 U/mL and positive anti-endomysium antibodies (EMA). The results of the study indicated that at the time of diagnosis, CD patients presenting NAFLD were 29.4%, while at the end of the follow-up period the percentage of subjects presenting NAFLD had risen to 46.6%. In the study performed by Agarwal et al[33], patients were divided into two groups: 54 treatment-naïve CD patients and 130 CD patients treated with GFD for ≥1 year were recruited in the first and second group, respectively. All enrolled patients obtained an evaluation of anthropometric, metabolic and hepatic parameters.

NAFLD increased from 14.3% at baseline to 29.5% after 1 year of GFD (p=0.002). Furthermore, in the second group it was observed that 30 of 114 patients (26.3%) presented metabolic syndrome and 30 of 130 patients (23%) had hepatic steatosis. In the case-control study carried out by Tovoli et al[34], 202 CD patients were compared with 202 controls and the prevalence of NAFLD was 34.7% in the CD group and 21.8% in the control group, respectively (p= 0.006). Moreover, Remes-Trochè et al[35], showed metabolic effects in 22 CD patients compared with 22 patients with non-celiac gluten sensitivity

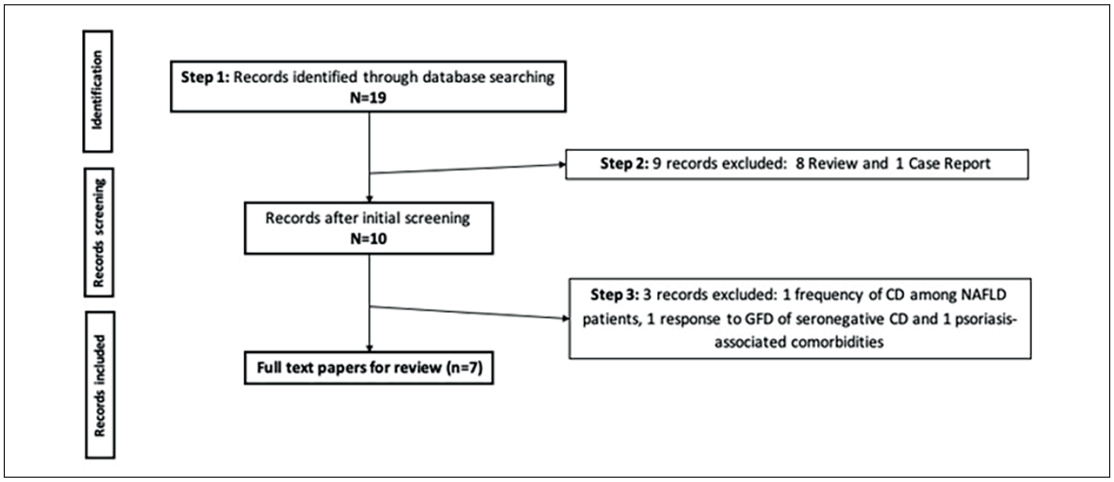

Figure 1. Study flow diagram.

and 22 healthy controls, highlighting how after GFD, 25% of CD patients developed hepatic steatosis. Similarly, Tortora et al[36], have shown that GFD for a period of one year caused an increase in severe hepatic steatosis, moreover, Reilly et al[37], in a cohort study performed from 1997 to 2009 in 26,816 CD individual compared to 130,051 reference individuals have shown an increased risk of NAFLD of 13.3 (95% CI 3.5-50.3) in the first year after CD diagnosis and even beyond 15 years after CD diagnosis (HR= 2.5; 95% CI 1.0-5.9). Finally, data are consistent with a study performed by Ciccone et al[38], indicating that after a 2-year treatment period with GFD, CD patients have an increased risk of developing fatty liver disease.

Conclusions

In recent years, the scientific literature reports a continuously increasing incidence of CD and NAFLD. Despite research efforts, the pathophysiological mechanisms for both CD and NAFLD remain to be elucidated. All studies included in this systematic review are of good quality and highlight how GFD can represent a risk factor for the onset of NAFLD, Although GFD represents the only treatment currently available for the CD. Processed GFD is nutritionally imbalanced and a higher intake of carbohydrates and saturated fat, used to make gluten free food palatable, promotes hyperglycemia, elevated triglyceride levels and raised blood pressure[39]. Furthermore, majority of gluten-free foods have a high glycemic load due to the high content of flour derived from rice and potatoes. Large amount consumption of these products can increase the occurrence of hyperinsulinemia and insulin resistance[40]. Therefore, GFD promotes onset of metabolic syndrome, obesity, diabetes and cardiovascular disease. Next to, it remains to better define as well as inflammatory bowel diseases[41], also on CD, pathogenesis could be related to changes in the liver-gut axis, in which a pivotal role could be played by the gut microbiota.

Patients with CD should be evaluated for nutritional and metabolic characteristics at regular intervals by a health care team with hepatic, nutritional and immunological expertise. Patients should be educated on a diet low in excess fat and sugar, which are crucial factors in the onset of NAFLD. Both CD and NAFLD represent fundamental challenges for future scientific research and should be evaluated in a perspective of relationship, allowing to better clarify mechanisms of this close relationship.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

This research received no external funding.

Authors' Contribution

Conceptualization: Tiziana Larussa, Ludovico Abenavoli; Methodology: Tiziana Larussa, Ludovico Abenavoli, Anna Caterina Procopio; Resources: Tiziana Larussa, Anna Caterina Procopio, Chiara Iannelli; Writing-original draft preparation: Tiziana Larussa, Anna Caterina Procopio Chiara Iannelli; Visualization: Natale Polimeni, Rocco Spagnuolo, Patrizia Doldo, Francesco Luzza; Supervision: Ludovico Abenavoli, Rocco Spagnuolo, Patrizia Doldo, Francesco Luzza. All authors read and approved the final version of the manuscript.

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