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Celiac disease and non-celiac gluten or wheat sensitivity and health in later life: A review

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ABSTRACT

Celiac disease (CD) and non-gluten (or wheat) sensitivity (NCGS) are two gluten-related disorders, the treatment of which relies on dietary withdrawal of gluten (absolute and lifelong in the case of CD patients). However, these conditions differ in their pathophysiology and impact on health. CD is an autoimmune disorder of the intestine, and is associated with a wide range of disorders, pre- and post-diagnosis. Its autoimmune and inflammatory nature raises concerns about its potential effects on mortality and morbidity. Here we review the data on the health impact CD or NCGS may have prospectively, and report on the role of a gluten-free diet (GFD) in this respect. Since study designs have been heterogeneous, we focus on studies of treated patients with a biopsy-proven diagnosis of CD, to eliminate possible bias from misdiagnosis. The review revealed a moderately increased mortality risk among CD patients, mainly attributed to cardiovascular disease and malignancy. Other long-term morbidities of CD include autoimmune disorders, nutritional deficiencies, impaired bone health, reproductive abnormalities, and neurologic and neuropsychiatric disorders, which are substantially improved, and some of them even completely treated, after strict adherence to a GFD. For NCGS, the literature is too limited and its long-term complications are unknown.

1. Introduction

Celiac disease (CD) and Non-Gluten (or Wheat) Sensitivity (NCGS) are two clinical conditions with different pathophysiologybut with similar treatment i.e. the withdrawal of gluten from the diet [1]. In CD ingestion of gluten a generic term describing a diverse group of proteins present in wheat barley rye and oats causes both innate and adaptive immune responses resulting in an increase of gut permeability inflammation cryptal hyperplasia and villus atrophy. In CD following a life-long gluten free diet (GFD) aims at a reversal of the pathogenesis process leading to an almost full regression of the clinical manifestations. On the other hand NCGS is diagnosed in individuals who do not have celiac disease or wheat allergy. An important role of the intestinal innate immune system in the pathogenesis of NCGS has been also suggested although no adaptive immune responses have been described [1]. In this condition intestinal and/or extra-intestinal symptoms related to ingestion of gluten-containing grains are recorded with symptomatic improvement on their reduction or withdrawal from the diet.

The individual on a GFD needs to select foods naturally free of glutento find gluten free alternatives to cereals (e.g. “minor cereals” like millet or “pseudo-cereals” like quinoa), and relies much on the gluten-free products (GFPs) available in the market [2]. In addition concerns exist regarding potential gluten ingestion from drugs. According to the relative guidance developed by the Food and Drug Administration gluten as excipient or contaminant would rarely be present in an oral drug but even if so the amount would rather fall within the levels defined for a gluten-free food product [3]. However CD individuals might choose to avoid drugs potentially containing gluten. In that case they should consult drug labeling to find ingredients indicating primarily a wheat origin such as wheat starch modified starch pregelatinized starch sodium starch glycolate starch hydolysates (e.g. dextrates maltodextrin dextrose maltose) sugar alcohols (e.g. sorbitol xylitol maltitol mannitol). Moreover gluten is not expected to impact CD individuals through routes of drug administration other than oral or enteral ingestion [3].

It is widely adopted that treatmenteven at high adherence level to the GFD remains a great challenge due to accidental ingestion of gluten or to the not seldom contamination of GFPs with gluten resulting often in refractory symptoms and persistently abnormal histology in CD [4]. Given the implication of the immune system and inflammation

Abbreviations: ATIs, amylase-trypsin inhibitors; BMD, bone mineral density; CD, celiac disease; CVD, cardiovascular disease; EATL, enteropathy-associated T-cell lymphoma; GFD, gluten free diet; GFPs, gluten-free products; IBS, irritable bowel syndrome; IgA tTG, immunoglobulin A anti-tissue transglutaminase antibodies; IgA EMA, immunoglobulin A anti-endomysial antibodies; IgG AGA, immunoglobulin G antigliadin antibodies; NCGS, non-celiac gluten sensitivity

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processes along with a doubtful nutritional adequacy and quality of the GFD [5] concerns have been raised regarding potential increased health risks that patients with either CD or NCGS may encounter in the long term. Thus the aim of the present work was to review available data on the impact on health (or morbidity) these conditions may have prospectively in adult life and report on the role GFD could play in this regard.

2. Literature search

Literature search was based on the principles of systematic reviews, i.e., PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses); however, a systematic review was not carried out due to the great heterogeneity of published studies regarding CD diagnosis. A great number of large epidemiological studies use serologic tests to confer a CD diagnosis, diluting possibly the results on morbidity and mortality rates. Moreover, although undiagnosed or clinically silent CD may also affect health, in the current review we confined our search to studies based on a biopsy-proven diagnosis of CD, to eliminate misdiagnosis bias emanating from relying exclusively on serologic tests. Additionally, given that the increased risk of mortality and morbidity noted during the first year of CD diagnosis may be attributed to surveillance bias, we tried to emphasise on data coming from patients been in long-term GFD to avoid overestimation. At last, in accordance to the scientific interest of the journal we excluded studies on childhood populations.

Our search included scientific papers, letters or correspondence, in peer reviewed journals, archived in PubMed and Scopus. No restriction was made for publication dates, language or publishing status. The search was completed using cross referencing from the papers found. The search terms, mainly following MeSH, were combinations of the terms celiac disease, gluten free diet, non-celiac gluten/wheat sensitivity, and mortality, morbidity. In total, n = 5279 scientific papers were retrieved; of them, n = 5005 were disregarded from the present work on the basis of irrelevant title/abstract or content. Among the rest (n = 274) studied, n = 52 were finally included in the present narrative review.

3. Celiac disease

Epidemiological data reveal CD is a rather common disorder met worldwide, affecting all ages, even the elderly. In Europe and USA, as well as globally, the estimated mean prevalence is 1% of the general population, yet showing great regional variance, as well as an increasing incidence, attributed to a synergy of genetic and environmental factors [6]. CD diagnosis ultimately comprises of positive serologic tests [detecting mainly immunoglobulin A autoantibodies: immunoglobulin A anti-tissue transglutaminase (IgA tTG) and immunoglobulin A antiendomysial (IgA anti-EMA) antibodies], to be definitely verified by the characteristic histopathologic findings of an intestinal biopsy [6]. Intestinal damage and systemic inflammation being the ground of CD explain the wide range of symptoms which accompany CD diagnosis and/or follow-up. Persistence of this pathophysiology, even after the initiation of GFD, is perceived to contribute to the increased morbidity and mortality recorded in CD patients.

3.1. Mortality

A fundamental parameter studied regarding impact of CD is mortality, both overall and specific-cause one. In general, most studies record an increased mortality rate in CD patients compared to the general population. The largest study examining CD mortality to date by using biopsy-based diagnosis, from a prospectively kept database in Sweden, reports a moderately increased mortality risk of 39% in CD patients compared to the general population, falling to 26% after the first year of diagnosis [7]. Other cohorts from UK [8,9] and Sweden [7], with biopsy proven diagnosis, report a somewhat less than 40% increase in risk for all-cause deaths, while a two-fold increase has also been reported, in an Italian cohort [10]. Regarding the specific-cause mortality, the most common cause of death among biopsy proven CD patients is either malignancies [8,10] or vascular disease [7,9,11], followed by respiratory diseases [7,8,11].

A consistent observation of the aforementioned studies is that mortality is higher at the peridiagnosis period and seems to gradually decrease with longer follow-up [7–9]. However, time of diagnosis may modify mortality risk [7,9,10]. Solaymani-Dodaran et al. [9], found an almost three-fold decrease in mortality risk after five years compared to the first year of diagnosis, and an even nonsignificant increase after 15 years of diagnosis, but this applied only to adulthood diagnosed patients. Childhood diagnosed ones showed another pattern, with higher risk after 25 years of follow up compared to general population. Other factors positively associated with mortality risk include diagnostic delay, more severe clinical presentation and uncertain GFD adherence [10]. The last remains a major limitation of several cohorts reporting both mortality and morbidity data, which have not included dietary data.

3.2. Malignancies

Malignancies are regarded a common morbidity in CD patients, the incidence of which differs depending on the type and site of cancer, as well as the period relative to diagnosis. Although some studies report no increase in the overall incidence of cancer [11–13] compared to the general population, a higher risk for developing any lymphoproliferative disease [14,15], and especially non-Hodgkin lymphoma (NHL), is unanimously reported by studies using a histopathology CD diagnosis, usually ranging from a 3-fold to 6-fold increase [11,12,14–16]. T-cell type lymphomas are found to prevail in some studies [14], of which enteropathy-associated T-cell lymphoma (EATL) appears to be specifically linked to refractory CD [17], but B-cell type are more frequent in other studies [16], whereas small-intestinal lymphomas seem to be highly associated with CD [11,12,16]. However, even though relative risks for NHL or small bowel lymphoma are substantially high, authors comment that the absolute rates are practically small, meaning they refer to rare diseases [12].

Malignant risk may differ according to number of years relative to diagnosis. While a decrease in the risk for overall incidence [12], solid cancers [14] and all gastrointestinal cancers [18] has been reported after the first year of diagnosis, being equal to that of the general population, the risk for any lymphoproliferative malignancy and for NHL specifically, has been found to remain significantly higher [14]. In addition, the impact that adherence to the GFD may have on malignancies' risk remains contradictory. A high lymphoma risk has been found independently of adherence to GFD [13,19], while Elfstrom et al. [18] comment that the reduction noted post-diagnostically could be hardly attributed to GFD initiation, as the same pattern of cancer incidence was found in individuals with inflammation but no villus atrophy, who do not follow GFD. On the contrary, an impressive decrease in the risk for gastrointestinal cancers and NHL was seen in patients with CD [20] or dermatitis herpetiformis (DH) [21], so that the excess morbidity rate did not differ from that of the general population for those patients strictly adhering to GFD for more than five years.

3.3. Cardiovascular diseases and related risk factors

Focusing on studies with a biopsy-proven CD diagnosis, incidence of cardiovascular disease (CVD) comes essentially from the study of Ludvigsson et al., which reported an increase in the risk for myocardial infarction of 11%, for angina pectoris of 27% and for stroke of 10% in CD patients compared to the general population [22,23]; however no data regarding adherence to a GFD were available to test either the level of adherence or the overall diet quality, known to affect CVD.

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