The Global Phenomenon of Self-Reported Wheat Sensitivity

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Abstract: Celiac disease affects about 1% of the population and is treated with a gluten-free diet. However, the last decade has seen a huge rise in individuals self-reporting wheat sensitivity, and consuming a gluten-free diet, despite not having a doctor-diagnosis of celiac disease. A recent flurry of observational studies from across the globe suggests that approximately 10% of the population is self-reporting wheat sensitivity. They describe a constellation of intestinal and extra-intestinal symptoms attributed to ingestion of gluten-based products. This phenomenon poses a significant challenge to clinicians with regards to adequately excluding celiac disease, identifying the culprit agent, understanding the pathophysiology, and providing safe aftercare.

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The Neolithic revolution saw a transition from hunter-gatherer to settled agriculture, with the first signs of wheat cultivation being attributed to the Fertile Crescent in the Middle East. The nutritional properties of wheat, its palatability and storage capabilities, led to an expansion in its agricultural production through artificial breeding and selection of wheat variants with better adaptation to extreme climate conditions, bread-making qualities, and resistance to diseases [1]. This has contributed to a change in the immunogenic quality of wheat over time. Hence, from a philosophical standpoint, it has been suggested that gluten is a relatively novel introduction to a man's primitive immune system, and that with the rise of gluten has now come its fall! [1]

The most commonly recognised gluten-related disorder is celiac disease (CD), a gluten sensitive enteropathy that occurs in genetically susceptible individuals [2, 3]. All patients with CD carry the human leukocyte antigen (HLA) DQ2 and/or HLA-DQ8 genotypes, although these alleles are present in around 40% of the general population. Historically, CD was considered to be rare with a prevalence of 1 in 8000 being reported in the 1950s. However, contemporary epidemiological studies estimate a worldwide prevalence of approximately 1% and potentially rising. The change in prevalence is partly due to the increasing immunogenic properties of gluten, but also through better diagnostic modalities and a paradigm shift in our conceptual understanding of the CD patient. We now recognise that CD can present in adults, not just in children, and that non-classical symptoms (such as anaemia or symptoms compatible with irritable bowel syndrome) are seen more often than classical malabsorption. The diagnosis of CD in adults is based upon a positive celiac serology and demonstration of enteropathy on duodenal biopsies, with subsequent treatment being a strict lifelong gluten-free diet (GFD) [2, 3]. Another gluten-related disorder is IgE-mediated wheat allergy which will not be discussed further in this editorial, as it is seen in up to 0.1–1% of children but rarely progresses into adulthood [4–6].

Prior to a decade or so ago there was little awareness within the public domain of CD and the need for a GFD [7]. This left patients with CD frustrated by the lack of gluten-free products in food stores, restaurants, and at social functions. Indeed, many would avoid dining out but when faced to do so would not disclose their condition and, in the fear of stigmatisation, digress and consume a gluten-containing diet which inevitably provoked their underlying disease inflammation [8]. However, the last 10 years has seen a drastic societal change with regards to the availability and awareness of a GFD and gluten-related disorders [7]. Whilst this has provided a euphoria moment for the patient with CD in terms of food choice, the rising availability of the GFD was mainly driven through public demand (and celebrity endorsement) choosing to adopt this lifestyle as it supposedly alleviated a myriad of physical and cosmetic ailments. This gluten-free boom and its necessity outside of CD have been repeatedly championed in the commercial industry, with retail sales in the United States going from $0.9 billion in the year 2006, to exceeding $10 billion in the year 2015, and projected to reach almost $24 billion by the year 2020 [9].

However, the scientific committee have largely remained sceptical in accepting that such dietary behaviour was anything more than a fad. This mindset changed somewhat following a seminal study published in the AJG showing gluten-based products to induce symptoms in the absence of CD [10]. Since then, controversy has simmered as to the constituent in wheat that evokes symptoms.

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Following rigorous double-blind placebo-controlled crossover trials, it seems that gluten-per-se accounts for 1-in-6 cases [11], with the remaining majority either due to fructans (a type of FODMAP) or a nocebo effect [11, 12]. There is also experimental data implicating non-gluten proteins (such as amylase trypsin inhibitors and wheat germ agglutinins) to induce inflammation, although this has yet to be explored in bedside studies [13]. Given the absence of biomarkers to detect the culprit agent, and the impracticality of performing dietary elimination followed by double-blind placebo-controlled challenges in daily clinical practise, this entity may initially be termed "self-reported wheat sensitivity (SRWS)", and in those where CD has been excluded, "self-reported non-celiac wheat sensitivity (SR-NCWS)" [14].

The concept of SRWS is now being reported globally, with a flurry of observational studies since the year 2012 evaluating its prevalence and clinical characteristics within the general population (Fig. 1) [15–22]. These studies share a common theme, in that the prevalence of SRWS is much higher than the prevalence of known CD. On pooling these observational studies, the average prevalence of SRWS - from a total of 11,211 subjects across eight countries and spanning four continents—is approximately 10% (range 4.3–14.9%). In contrast, the prevalence of known CD is 0.7% (range 0–1.26%) [15–22]. Outside of the general population setting, an Australian sports research institute noted a remarkably higher prevalence of SRWS in non-celiac athletes (~33%), particularly those doing endurance events where gastrointestinal dysfunction can be common [23]. Nevertheless, the clinical phenotype is characteristically young to middle aged women who attribute wheat-based products to give rise to a constellation of intestinal and extra-intestinal symptoms. The intestinal symptoms reported include abdominal pain, discomfort, bloating, and altered bowel habit, with many fulfilling criteria for irritable bowel syndrome. The extra-intestinal manifestations reported include fatigue, headaches, depression, musculoskeletal pains, and foggy mind [13].

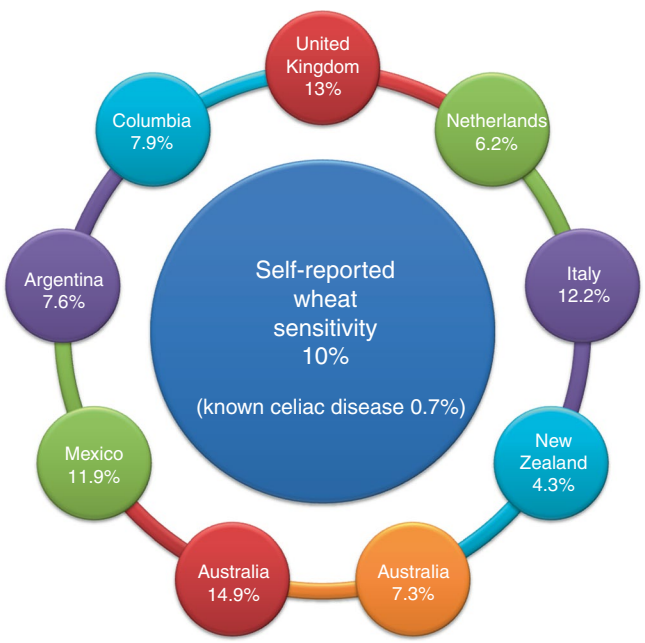

Fig. 1 The general population prevalence of self-reported wheat sensitivity. Note: Studies have been performed in adults, except for in New Zealand (children) and Italy (age 14–18 years) [15–22]

In this month's issue of the AJG, Potter et al. report the prevalence and associations of SRWS from a large population-based postal survey conducted in Eastern Australia [22]. Their findings are largely in concordance with those previously reported for SRWS, with regards to the clinical phenotype and lower intestinal symptoms [15–22]. Extra-intestinal symptoms were not inquired for. However, a novel observation made by the investigators was the strong association between SRWS and symptom-based Rome III functional dyspepsia. In their cohort, 31.3% of subjects with SRWS fulfilled criteria for functional dyspepsia, compared to 13.6% in those without SRWS [22]. Based on previous studies showing raised duodenal eosinophils in (a) NCWS [24], and (b) the postprandial distress syndrome variant of functional dyspepsia [25], the investigators propose a unifying hypothesis [22]. They speculate that wheat may be the environmental allergen implicated in the pathogenesis of postprandial distress syndrome [22]. This could be a crucial observation, particularly as functional dyspepsia affects approximately 10% of the population—of which postprandial distress syndrome represents the majority—and that these patients incur significant health impairment with current therapies largely being suboptimal [26]. However, the investigators acknowledge an association, not causation, and that their proposed hypothesis will require further research [22].

An alternate view could be that as postprandial distress syndrome is characterised by early satiety and fullness, the high-residue content of a wheat-based diet exacerbates symptoms in these patients; indeed small-particle meals are amongst the first line treatment recommendations for postprandial distress syndrome [27], and in the context of diabetic gastroparesis have been shown to provide symptom benefit compared to large-particle meals [28]. A similar question has been posed in inflammatory bowel disease, given that SR-NCWS is common in those with severe or stricturing disease; is it a wheat-based immune reaction driving inflammatory bowel disease or, more plausible, that inflammatory bowel disease is symptomatic to the high-residue content and fermentation properties of wheat? [29]. Hence, associations in SR-NCWS require further studies to establish causation, which has been shown for gluten ataxia where the neurodegenerative process can be halted by a GFD but progresses with a gluten-containing diet [13]. Even in irritable bowel syndrome, where up to 25% of patients SR-NCWS [30], the direction of causality is not necessarily straightforward; [31] in the majority, it appears that a wheat-based diet is provoking the underlying dysfunctional brain-gut axis of irritable bowel syndrome through the fermentable properties of fructans [12, 32]. However, in a subset it may be a gluten-per-se effect, as demonstrated by intestinal cell damage, altered barrier function, elevated antigliadin antibodies, increased systemic immune activation, which reverse following a GFD and provide clinical improvement [33, 34].

Finally, as clinicians how should we approach SRWS? The initial aim is to exclude CD (thus diagnose SR-NCWS), although this can be tricky as many will have already placed themselves

on a GFD and not be willing to undertake a gluten challenge. A negative HLA-DQ2/8 excludes CD, which will be the case in about 50% of cases [13, 16, 35]. If HLA-DQ2 and/or DQ8 is positive, then a discussion needs to be had whether the patient is willing to undergo a gluten challenge prior to embarking on celiac serology and duodenal biopsies [35]. There is no consensus on the dosage and duration of the gluten challenge in this setting, leading to differences amongst international cohorts with regards to the prevalence of CD in those SRWS [36]. There have been four studies, of which three yielded a diagnosis of CD between 2 and 9%, with one giving a prevalence of 42.4% [36]. Recent insights suggest the way forward may be via the HLA-DQ-gluten tetramer blood test, which accurately identifies patients with and without CD even in the absence of gluten consumption; however, large-scale validation studies are needed [37].

It is also currently unclear how to manage SR-NCWS. As previously mentioned, we cannot establish the culprit associated with symptom provocation due to the absence of a diagnostic biomarker and the impracticality of performing cumbersome double-blind placebo-controlled dietary challenges in routine clinical practise. Although studies mainly point towards a fructan or nocebo effect rather a gluten-per-se effect [11, 12], it is not known whether we should be transferring patients from a GFD to the arguably more stringent low-FODMAP diet, especially if their symptoms are well controlled on the GFD. Alternatively, asking patients to stop such dietary interventions may lead to a breakdown in patient–physician relationship, given that we do not have an alternate non-dietary remedy. A long-term follow-up study reports that symptoms persist, with 75% still having to adhere to a GFD at 8 years [38]. Of the 25% who no longer adhere to a GFD, in one half it is due to symptom resolution, and in the other half it is influenced by cost/personal choice at the expense of symptom exacerbation [38]. However, the greatest concern is whether these diets are safe in the long-run, given the emerging data suggesting cardiovascular, nutritional, metabolic, and microbial changes [39, 40]. In light of this information, it could be argued that these patients should be under a dietician, which is not standard practise. Moreover, whether we can gradually re-introduce gluten back into their diets is unknown. Future studies will hopefully provide clarity. However, amid all the uncertainty, caution must be advised in those who take a GFD as a supposed "healthy lifestyle option" but do not SRWS, which is the case in almost 20% of gluten-free consumers [18].

In summary, SRWS has become a global phenomenon affecting approximately 1-in-10 people. It is associated with a constellation of intestinal and extra-intestinal manifestations, and poses a diagnostic and therapeutic dilemma. Further studies are needed to validate methods to easily diagnose CD, and then for those without CD identify a biomarker for the culprit agent, understand the pathogenesis and direction of causality, and establish long-term management.

CONFLICT OF INTEREST

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