Non-celiac Gluten Sensitivity (NCGS)

Pravin M Rathi, Vinay G Zanwar

Abstract

There has been increasing interest in the entity “Non-celiac gluten sensitivity” in recent years which was first of its in 1980s. This “re-discovered” disorder is characterized by intestinal and extra-intestinal symptoms which occur after ingestion of gluten containing food. The number of such patients who neither have celiac disease nor wheat allergy, but appear to benefit from gluten withdrawal is increasing substantially. However it still remains a controversial and its pathogenesis is not well understood. Lack of biomarkers is a major limitation making it difficult to differentiate it from other gluten related disorders. Recent studies have raised the possibility that, beside gluten and wheat amylase-trypsin inhibitors (ATI), low-fermentable, poorly-absorbed, short-chain carbohydrates can contribute to symptoms (at least those related to IBS) experienced by NCGS patients.

In this paper we will focus on the manifestations of NCGS and evidence for the condition. Also areas of controversy, major advances and future trends will be discussed.

Introduction

Real existence of the non-celiac gluten sensitivity has always been debatable issue due to its diagnosis of exclusion and lack of concrete pathogenesis. In contrast, Celiac disease (CD) is a heightened immune response to ingestion of wheat gluten and related cereal proteins in genetically predisposed individuals. The resulting inflammatory response in the small bowel leads to lymphocytic infiltration, villous atrophy, and crypt hyperplasia. Elimination of the gluten proteins from diet generally leads to clinical and histological improvement. CD is a multigenic disorder, the HLA-DQ2 and HLA-DQ8 molecules confer susceptibility for CD. The gold standard tool for the diagnosis of CD is the demonstration of villous atrophy on duodenal biopsies, with celiac serology playing a supportive role. Contemporary epidemiological studies have estimated the prevalence of the same in the European adult population to be 1%. Some of the CD-associated symptoms experienced in response to ingestion of wheat are also reported by individuals who are negative for typical serologic, histological, or genetic markers of CD, and who also do not experience the immunoglobulin E (IgE) serologic response associated with wheat allergy. These patients have frequently put themselves on Gluten-free diet (GFD) after negative experiences from eating gluten-containing foods and report significant improvements on a GFD.

The term nonceliac gluten sensitivity (NCGS) has been proposed to refer the spectrum of conditions reported by such patients. Gluten sensitivity (GS) was originally described in the 1980s. Number of papers have come up in recent past after the landmark work by Sapone and co-workers on GS in the year 2010. However, many aspects of its epidemiology, pathophysiology, clinical spectrum, and treatment are still unclear. Given the recent increase in the patients consuming gluten-free diet, revenue in the gluten-free market has increased from $100 million in 2003 to $1.31 billion (2011) to $1.68 billion by the year 2015 emerging as ‘big business’. Hence, there is a need of “separating the wheat from the chaff”.

In February 2011 at London, panel of experts developed a consensus on new nomenclature and classification of gluten-related disorders, a first met. The panel proposed a series of definitions and a diagnostic algorithm that has been recently published. An overlap between the irritable bowel syndrome (IBS) and GS has been suspected, requiring even more stringent diagnostic criteria.

Here we reviewed the international literature about this “new” disease, consulting PubMed and Medline, using the search terms “wheat allergy,” “wheat (hyper) sensitivity,” “wheat intolerance,” “gluten (hyper) sensitivity,” and “gluten intolerance;” and we will discuss current knowledge about NCGS.
**Wheat and Gluten: What are they?**

Gluten is the protein mixture of glutelins and gliadins (prolamines), which occurs in the endosperm of wheat and other cereals (such as barley, rye and spelt) and can be fractionated to produce alpha, beta, and gamma peptides. The ratio of glutelins to gliadins in the protein mixture is approximately 1:1. Gliadins, a group of proteins that are rich in proline and glutamine, have been identified as the main culprit gluten component that is toxic.\(^{16-18}\)

Globally nowadays, gluten is one of the principle dietary components particularly in western population. Mean daily gluten ingestion is 10–20 g in the Mediterranean area and even higher in other populations.\(^{19,20}\)

New variants of wheat have arisen as a result of agricultural modernisation and the growing use of pesticides and fertilizers, which could have a leading role in the adverse immunologic reactions to gluten. Moreover, the process of bread leavening has been progressively shortened, resulting in an increased concentration of toxic gluten peptides in bakery products.\(^{21,22}\)

**Nomenclature**

The term “gluten-related disorders” is the umbrella-term to be used to cover all conditions related to ingestion of gluten-containing food. Based on the discussion and the current evidence in literature, the panel generated a series of definitions and created the classifications and algorithms summarized below in Figure 1.\(^{14}\)

**Wheat Allergy (onset: minutes to hours after gluten exposure)** is defined as an adverse immunologic reaction to wheat proteins. WA is classified into classic food allergy affecting the skin, gastrointestinal tract or respiratory tract; wheat dependent exercise-induced anaphylaxis (WDEIA); occupational asthma (baker’s asthma) and rhinitis; and contact urticaria. Wheat specific IgE antibodies play a vital role in executing WA, however non-IgE-mediated WA does exist\(^{23}\) and make difficult to distinguish from GS.

**Celiac disease (onset: weeks to years after gluten exposure)** is an autoimmune enteropathy triggered by the ingestion of gluten in genetically predisposed individuals. The major antibody responses are targeted against deamidated gluten sequences, and the transglutaminase 2 (TG2) enzymes of gluten proteins.\(^{24}\) However, the immunoglobulin A (IgA) anti-TG2 antibody is currently considered the most sensitive and specific serologic marker of CD.\(^{25,26}\)

Diagnosis of CD is confirmed if at least four of the following five criteria are fulfilled:\(^{27}\)

1. Typical symptoms of CD
2. Positivity of serum IgA class auto antibodies at high titre
3. HLA-DQ2 and/or HLA-DQ8 genotypes
4. Classic histological findings on duodenal biopsy
5. Improvement on GFD

**Dermatitis herpetiformis** is a skin manifestation of CD presenting with blistering rash and pathognomonic cutaneous IgA deposits.\(^{28}\) Since DH is the cutaneous counterpart of CD (‘skin CD’), a proven diagnosis of DH in a patient should be taken as indirect evidence for the presence of small bowel damage.

**Gluten ataxia** was originally defined as otherwise idiopathic sporadic ataxia with positive serological markers for gluten sensitization.\(^{29}\) Like CD, it is an autoimmune disease characterized...
by damage to the cerebellum resulting in ataxia.

**Gluten sensitivity (Immune-mediated form with onset: hours to days after gluten exposure)** The recent rise of the gluten-free market in the USA, partially sustained by individuals who undertake a GFD, raises questions about possible gluten reactions alternative. These are generally defined as non celiac GS (NCGS) or more simply, GS in which neither allergic nor autoimmune mechanisms can be identified. Thus GS is defined as those cases of gluten reaction in which both allergic and autoimmune mechanisms have been ruled out (diagnosis by exclusion).

The “Uttering” of this disorder was a great deal among the panel experts. In order to avoid confusion with CD, sometimes defined as gluten-sensitive enteropathy, “non celiac gluten sensitivity” appeared as an improved definition. Doubtless this is still too vague a terminology, simply reflecting the poor knowledge of the pathophysiology of this condition. As triggering cereal proteins could include fractions other than gluten, some panelists were in favour of “non celiac wheat (protein) sensitivity”, a terminology that would however conflict with the possibility that other gluten-containing cereals (rye, barley) may be offensive for the “gluten sensitive” patient. Bearing these limitations in mind, the expert’s panel agreed that this entity can provisionally be defined as NCGS, a definition requiring refinement in the future.

**Epidemiology**

The overall prevalence of NCGS in the general population is still unknown, mainly because many patients are currently self-diagnosed and start a GFD without consultation. Whereas the “low-carb diet” was widely adopted in the years after 2000, which now has been on decline. On the other hand, the gluten-free diet has gained popularity and shown a steady rise since 2008 and is expected to increase further. In US study Di Giacomo et al. reported a 0.55% prevalence of persons on a self-reported GFD who participated in the National Health and Nutrition Examination Survey (NHANES) 2009–2010. The prevalence was higher in females and older participants. Many of the NHANES subjects on a GFD could indeed be affected by NCGS. Because (a) the possible relationship between gastrointestinal symptoms and gluten intake was not systematically explored in this population sample, and (b) the NHANES survey was conducted before NCGS was described in the medical literature, this likely to underestimate the original figure.

However, new data confirm that this is not an uncommon disorder at all. In a selected (and, therefore, probably biased) series of adults with IBS, the frequency of NCGS, documented by a double-blind, placebo-controlled challenge, was 28% 31. According to an article in The Wall Street Journal, some experts think as many as 1 in 20 Americans may have some form of NCGS.32 The prevalence of non celiac gluten sensitivity was reported at 6% based on the Maryland secondary care clinic experience (where between 2004 and 2010, 5896 patients were seen with 347 fulfilling gluten sensitivity criteria).32 High-quality genetic studies on the NCGS population have not been performed as yet. There are no data suggesting that the condition follows the same HLA-DQ2/-DQ8 association as CD.33

**Historical Review**

The entity of non celiac gluten intolerance has been regarded as a new diagnosis 34 but it is better to consider it as an old diagnosis which has been recently rediscovered and embellished. A study in 1980 described 9 female subjects with abdominal pain and chronic diarrhoea who had dramatic relief on a gluten-free diet and a return of symptoms on gluten challenge.30 CD was ruled out by lack of villous atrophy on a gluten-containing diet, but it was noted that the gluten challenge induced a jejunal cellular infiltrate. The clinical description of these patients is similar to that for patients who are now frequently found in clinical practice and are thought to have NCGS. In a study using rectal challenge of gluten for investigation of CD, it was shown that about half of nonceliac siblings of CD patients respond to gluten, with epithelial changes and an increase in intraepithelial lymphocyte numbers.35 It is interesting that this rectal response was not dependent on the presence of HLA-DQ2. The observation suggests that an immune response to gluten can happen in the absence of the HLA-DQ2–restricted, gluten-specific T cells that are central to the development of CD. Kaukinen and colleagues36 observed further that intolerance to cereals is not specific for overt or latent CD. Ninety three adults reporting abdominal symptoms in response to ingestion of cereals were recruited. Only 8 patients were found to have CD, 7 could be said to have latent CD i.e. both an increase IELs and the presence of celiac disease-type HLA, and 19 were positive for allergy tests. In non-celiac patients, serum EmA (Endomyosia) and tTG tests were negative in all, whereas AGA (Anti gliad Ab) was seen in 40%.

Without villous atrophy, patients with a symptomatic response to a (GFD) that does not show tTG serological responses characterizing celiac disease are diagnosed as “IBS gluten sensitive,” particularly in the presence of genetic markers for celiac disease.37 In a non-randomised, prospective study of 41 patients who fulfilled
the Rome II diagnostic criteria for irritable bowel syndrome but with normal small bowel biopsies, a gastrointestinal symptom score decreased significantly in those treated with a gluten-free diet for six months, who were positive for DQ2, IgG AGA/tTG or DQ2 and IgG AGA/tTG, than in those who were negative for these markers (p<0.05-<0.01). Diarrhoea resolved more frequently in DQ2 positive patients with celiac disease associated antibodies (p<0.05). This investigation has identified a subgroup of patients with diarrhoea predominant irritable bowel syndrome who are likely to respond to a gluten-free diet. The most concrete evidence for NCGS existence comes from two recent double blind placebo controlled trials in patients with self-reported sensitivity to gluten or wheat.

The first study was a rechallenge trial. It included 34 patients with IBS, who met the ROME III criteria and were self-controlled on a GFD over a 6-week period. CD was excluded based on negative celiac serology plus either a HLA genotype incompatible with CD or a normal duodenal biopsy while on gluten containing diet. Patients were then subjected to either gluten or placebo in the form of muffins and bread that were low in fermentable oligosaccharides, disaccharides, monosaccharide, and polyols (FODMAPs). Those in the gluten containing group demonstrated a significant worsening of symptoms as compared to those on a GFD (p=0.001). There was no difference between the groups in tests that served as biomarkers of intestinal injury in the form of faecal lactoferrin, C-reactive protein and the dual sugar test for intestinal permeability. There was no change in celiac serology including gliadins antibodies on gluten challenge. This study indicates that gluten does trigger symptoms in individuals without celiac disease. The gluten used in this study did not contain FODMAPs which it is speculated cause symptoms in patients with IBS. The authors were therefore unable to elucidate a mechanism for the difference between the groups.

The second study was a larger study of 920 patients suffering from IBS. After a 4-week elimination diet, patients were rechallenged using a crossover double blind placebo control challenge DBPCC of wheat or placebo capsules. A total of 276 patients were identified as having wheat sensitivity of whom, 206 were identified as suffering from multiple food sensitivities. However, there is confusion in this terminology. Some of these may well go on to develop overt celiac disease if they remain on gluten containing diet. It is possible therefore that some of the patients enrolled in the study may have had CD without villous atrophy, particularly as some patients had reduced wheat on enrollment in the study, which may have led to some improvement in histology. However, wheat sensitivity also affected those who did not have celiac disease in any form and will not develop it because the necessary HLA markers were absent. Those with multiple food sensitivity had features more in keeping with food allergy.

What these studies point towards? Clearly, gluten sensitivity do exists as an entity beside overt celiac disease. Some patients fall into the spectrum of celiac disease, because they have the genetic predisposition, necessary HLA markers and also celiac disease associated antibodies, although a macroscopically normal small bowel mucosa and fall in as having potential or latent celiac disease. About half of patients do not have celiac disease in any of its forms because they do not have the necessary HLA profile.

**Clinical Features**

As name implies NCGS symptoms usually occur soon after gluten ingestion, disappear with gluten withdrawal and relapse following gluten challenge, with varying symptom interval. The “classical” presentation of NCGS is a combination of IBS-like symptoms, including abdominal...
pain (68%), altered bowel habits (33%), and systemic manifestations such as, dermatitis (eczema or skin rash 40%), headache (35%), “foggy mind” (34%), fatigue (33%), depression (22%), leg or arm numbness (20%), and anaemia (20%), joint and muscle pain (11%) (Figure 2). In children, NCGS manifests with typical gastrointestinal symptoms, such as abdominal pain and chronic diarrhea, while the extra-intestinal manifestations seem to be less frequent, the most common extra-intestinal symptom being tiredness. In recent years several studies suggested a relationship between NCGS and occurrence of neuropsychiatric disorders like schizophrenia, Cerebellar ataxia and autism spectrum disorders (ASD). Table 1 lists the most commonly reported symptoms associated with NCGS in comparison with those of CD and wheat allergy.

No major complication of untreated NCGS has so far been described; especially autoimmune comorbidity, as observed in CD. However, natural history data on NCGS are still lacking. Therefore it is difficult to draw firm conclusions on the outcome of this condition.

**Labotary Evaluation**

**Serology**

At present, there are no known specific serologic markers for NCGS. Wahnschaffe and colleagues reported that a high proportion of NCGS patients have increased levels (56.4%) of IgG antibodies to gliadins. The prevalence of IgG AGA detected in NCGS, although lower than that found in CD (81.2%), was much higher than other pathologic conditions such as connective tissue disorders (9%) and autoimmune liver diseases (21.5%) as well as in the general population and healthy blood donors (2%–8%).

More recently, Volta and colleagues studied 78 patients with NCGS and 80 patients with untreated CD in a tertiary referral setting. The prevalence of IgA AGA in GS patients was very low (7.7%). Noteworthy, the “gold standard” CD markers, namely IgG deamidated gliadins peptide (DGP) antibodies, IgA tTG, and IgA EMA, were always negative in NCGS patients, except for an isolated positivity at a very low titre for IgG DGP. The consistent negativity for IgG DGP-AGA, whose synthesis “in vivo” is an expression of the interaction between tissue transglutaminase and gliadins peptides, is particularly interesting because the absence of these antibodies seems to exclude the involvement of adaptive immunity. Interestingly enough, ELISA activities of IgA tTG in GS patients were very low with 30% of them displaying values <1AU (none of them had IgA deficiency).

In Majamaa et al study serum total IgE concentration and wheat-specific IgE antibodies (RAST) were used to rule out wheat allergy with specificity of 93% but with poor sensitivity of 20%.

**Haplotype**

CD-predisposing HLA-DQ2 and DQ8 genotypes were found in 50% of NCGS patients, a prevalence that was lower than CD (95%) and only slightly higher than the general population (30%). It was statistically not significant. HLA-DQ2 and HLA-DQ8 has an excellent negative predictive value for CD.

**Duodenal Biopsy**

In a study done by Sapone and co-workers, all subjects (11 patients with NCGS, 13 with CD, and 7 controls), underwent endoscopy for duodenal biopsy. Those with NCGS revealed normal to mildly inflamed mucosa (Marsh 0 to 1), while all CD patients showed partial or subtotal villous atrophy with crypt hyperplasia. Also, CD patients had increased numbers of CD3+ IELs (>50/100 enterocytes) compared to controls, while NCGS patients had a number of CD3+ IELs intermediate between CD patients and controls in the context of a relatively conserved villous architecture. Recently, activation of circulating basophils and increased infiltration of duodenal lamina propria with eosinophils have been described.

**Skin Testing**

Skin-prick testing is an additional tool for ruling out wheat allergy.

**Diagnosis**

In western countries, it is typical to find people who have commenced a gluten-free diet GFD on their own without formal evaluation for food sensitivity. Various reasons to adopt this diet include suggestions from family members and relatives who may have CD. Others have received advice from dieticians. Physicians may then concur if there has been the exclusion of other forms of
gluten-induced disease (CD and WA) by appropriate serological and/or biopsy tests.

The clinical workup for diagnosis of NCGS usually focuses initially on the exclusion of CD and wheat allergy. The task of exclusion is difficult in the case of a patient already on a strict gluten-free diet (GFD). If the patient in fact has CD, the mucosa may have recovered and the serology could also be negative. However, in many cases the mucosal damage persists for a definite diagnosis, so a small intestinal biopsy can be taken and serologic tests performed, even if the patient is on a gluten-free diet already. In other cases, a short gluten challenge may be necessary.

The finding that symptoms disappear after gluten elimination adds weight to the diagnosis of NCGS, which is definitely proven by a double-blind (or open) oral gluten challenge performed after at least three weeks of GFD. Gluten challenge is initiated once patient’s symptoms are reasonably under good control. The clinical response after gluten challenge might be variable but usually overlaps with symptoms of CD to a large degree. The need for performing a (DBPCC) is a controversial issue. A single-day DBPCC with capsules containing wheat flour has been used and is recommended, but has been disappointing in the authors’ hands (Rudihagen J, unpublished results, 2006). The American Gastroenterological Association technical review from 2001 recommended a DBPCC, and this was also recommended in a recent review and a workgroup report. Others have emphasized the limitations and impracticality of the DBPCC and consider it unsuitable in clinical setting. Virtually none of these publications have addressed the investigation of NCGS as the clinical entity encountered today.

The authors generally perform an open challenge with 4 slices of white sandwich bread (approximately 4 g gluten per slice). As this challenge is not blinded, one could expect a substantial placebo effect. However, the clinical responses picked up by this method seem to overlap with those seen after blinded challenge. There is no clear agreement on how to perform symptom evaluation after challenge. The authors have used symptom scoring with the following questionnaires: Short Form (36) Health Survey (SF-36), Scoring System for Subjective Health Complaints (SHC) and Gastrointestinal Symptom Rating Scale for IBS (GSRS-IBS),

None of the validated CD-specific symptom questionnaires have been applied to NCGS investigation. A consensus among clinicians on how to diagnose NCGS is urgently needed. Figure 3 shows a proposed algorithm for the diagnosis of NCGS.

Pathophysiology

Although many questions about the mechanism of CD remain unresolved, the disease is one of the best understood autoimmune disorders. By contrast, little is known about the pathophysiology...
Fig. 4: Proposed mechanisms of non-celiac wheat sensitivity

The triggers of mucosal events leading to NCGS are not necessarily represented by the same array of gluten peptides responsible for CD development. Unlike the duodenal mucosa from patients with CD, upon incubation with gliadins, mucosa from patients with NCGS does not express markers of inflammation, and their basophils are not activated by gliadins. In vitro studies suggest that wheat ATIs (amylase-trypsin inhibitors) could play a major role as triggers of the innate immune response in intestinal monocytes, macrophages and dendritic cells eventually leading to NCGS. Wheat ATIs are a family of five or more homologous low-molecular-weight proteins highly resistant to intestinal proteolysis. They are known to be the major allergen responsible for baker’s asthma. ATIs engage the TLR4-MD2-CD14 complex and lead to up-regulation of maturation markers and elicit release of pro-inflammatory cytokines in cells from celiac and non-celiac patients and in celiac patients’ biopsies.

Despite the selected terminology for NCGS, there is no clear evidence pointing that gluten proteins are the sole culprit molecules for the condition. It is also possible that non-gluten proteins of wheat are partially responsible for the associated symptoms in at least a subset of patients. Better characterization of the trigger molecules in NCGS will be a major step toward gaining a better understanding of the pathogenic mechanism of the condition, identifying specific biomarkers, and devising more effective treatment strategies.

**NCGS and IBS: A Complex Relationship**

Irritable bowel syndrome (IBS) ranks among functional gastrointestinal disorder, in the sense that the patients’ complaints cannot be explained by laboratory or biopsy testing. However, the Rome criteria emphasize pain as a dominant and necessary feature of IBS. The experience with NCGS, however, shows that while some of these patients may have pain, bloating, flatulence, and diarrhoea
are much more prominent. Thus it is difficult to give such patients a diagnosis of IBS. In addition, the diagnosis of IBS in patients who experience full recovery after withdrawal of gluten from their diet raises a semantic question: do they suffer from food intolerance with IBS-like symptoms or do they suffer from food-induced IBS? It is likely that careful investigations of NCGS patients would reveal subgroups both with and without IBS.

Vazquez-Roque and co-workers demonstrated gastrointestinal symptoms after gluten ingestion in subjects affected with the D variant (diarrhoea-predominant) of IBS recently. Subjects on a gluten containing diet (GCD) had more bowel movements per day, particularly those with HLA-DQ2 and/or DQ8 genotypes. The GCD was associated with higher small bowel permeability. Patients on the GCD had a small decrease in expression of zonula occludens 1 in small bowel mucosa, and significant decreases in expression of zonula occludens 1, claudin-1, and occludin in recto sigmoid mucosa; again the effects of the GCD on expression were significantly greater in HLA-DQ2/8—positive patients. On the other hand, the GCD vs. GFD had no significant effects on gastrointestinal transit or histology. It was concluded that gluten alters bowel barrier functions in patients with IBS-D, particularly in HLA-DQ2/8—positive patients. Another reason why a GFD would have a positive effect in IBS is because a GFD is deficient in dietary fibre, making it more easily digestible, even in patients without any gluten sensitivity. These data provided mechanistic explanations for the observation that gluten withdrawal may improve patient symptoms in IBS.

In addition, subsets of NCGS and IBS patients could have somatisation disorders as a common denominator. It has been found that the IBS population suffers from substantial psychiatric comorbidity. In a study of CD and HLA-DQ21 NCGS patients, however, the authors found that the NCGS patients did not exhibit a tendency for general somatisation. In addition, the psychometric profiles of the 2 cohorts were completely overlapping, as was their quality of life as measured by SF-36.

Questions Still to be Answered Despite Increasing Awareness

How specific the effect of gluten withdrawal from the diet of patients with IBS is, still remains to be elucidated. Besides gluten, wheat, and wheat derivatives contain other constituents that could play a role in triggering symptoms in IBS patients, e.g., amylase-trypsin inhibitors (ATIs) and fructans.

Biesiekirski et al studied IBS/self-reported NCGS patients and investigated by a double-blind crossover trial. Study subjects were randomly allocated to groups given a 2-week diet of reduced FODMAPs and then placed on gluten or whey protein for 1 week, followed by a washout period of at least 2 weeks. In all participants symptoms consistently improved during reduced FODMAP intake, but significantly worsened on gluten or whey protein. FODMAPS list includes fructans, galactans, fructose, and polyols that are contained in several foodstuffs, including wheat, vegetables, and milk products. These results raise the possibility that the positive effect of the GFD in patients with IBS is an unspecific consequence of reducing FODMAPs intake, given that wheat is one of the possible sources of FODMAPs. However, it should be stressed that FODMAPs cannot be entirely attributed for the symptoms scenario, since these patients experience a resolution of symptoms while on a GFD despite continuing to ingest FODMAPs from other sources, like legumes (a much richer source of FODMPs than wheat). Nevertheless, based on the data published by Biesiekirski et al. it is also possible that there are IBS cases entirely due to FODMAPs that, therefore, cannot be classified as affected by NCGS.

Natural History, Prognosis and Treatment for NCGS

Knowledge of natural history and progression of NCGS is still lacking.

Whether intestinal lymphoma or other gastrointestinal neoplasm can complicate NCGS is yet to be determined. Same commercially available gluten-free products used by CD patients can be prescribed to NCGS patients. Considering the lack of knowledge as to whether NCGS is a permanent or a transient condition, periodic reintroduction of gluten (?) yearly) on GFD might be an advise.
The increase in interest in NCGS is testified by the decreased. NCGS/CD publication ratio that dropped from 1:438 in the period 1950–70 to 1:10 in the period 2010–13 (Table 2).

Recent studies raised the possibility that, beside gluten and wheat ATIs, low-fermentable, poorly-absorbed, short-chain carbohydrates can lead to symptoms overlap experienced by NCGS patients. These new findings need corroboration through additional studies involving larger numbers of subjects. If these studies will confirm these new findings, they will probably prompt a change in nomenclature from wheat sensitivity to gluten sensitivity. (Table 2).

To surprise there are still lists of questions about NCGS that should be addressed.

1. Is NCGS permanent or transitory?
2. How frequent is NCGS?
3. Is the threshold of sensitivity the same for everybody, or change from subject to subject and in the same subject over time?
4. Is any reliable biomarker for NCGS diagnosis

There is need of dedicated input and ample of fund to explore the pearls in the world of NCGS. High yield research fields for NCGS overshadowing next couple of years would be

2. Actual evaluation of small bowel before and after dietary gluten challenge by imaging modality
3. Search for serum markers of gluten sensitivity
4. Evaluation of hormonal response after activation by gluten challenge

At the end of review, we would let the readers know about the common foodstuffs having gluten in it (Table 3).

### References


### Table 2: Number of research papers on NCGS in last couple of years

<table>
<thead>
<tr>
<th>Timeline</th>
<th>CD</th>
<th>NCGS</th>
<th>NCGS/CD ratio</th>
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<tbody>
<tr>
<td>1951-70</td>
<td>2632</td>
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<tr>
<td>1991-2010</td>
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<td>733</td>
<td>1:13</td>
</tr>
<tr>
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<td>2014</td>
<td>188</td>
<td>1:10</td>
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### Table 3: Common foodstuffs having gluten in it

<table>
<thead>
<tr>
<th>Gluten containing food</th>
<th>Gluten free food</th>
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<tbody>
<tr>
<td>Barley</td>
<td>Amaranth</td>
</tr>
<tr>
<td>Beer</td>
<td>Arrowroot</td>
</tr>
<tr>
<td>Bread</td>
<td>Beans</td>
</tr>
<tr>
<td>Candy e.g. licorice</td>
<td>Buckwheat</td>
</tr>
<tr>
<td>Cakes, cookies, cereals</td>
<td>Corn (maize)</td>
</tr>
<tr>
<td>French fries</td>
<td>Fresh eggs, fish, meat and poultry</td>
</tr>
<tr>
<td>Graham flour (Besan)</td>
<td>Fruits</td>
</tr>
<tr>
<td>Imitation bacon (flavoured meat)</td>
<td>Millet (Bajara)</td>
</tr>
<tr>
<td>Malt</td>
<td>Milo (commercial sorghum; Jawar)</td>
</tr>
<tr>
<td>Pastas</td>
<td>Oats</td>
</tr>
<tr>
<td>Sauces, gravies</td>
<td>Potato flour</td>
</tr>
<tr>
<td>Rye</td>
<td>Rice (all varieties)</td>
</tr>
<tr>
<td>Triticale (cross between wheat and rye)</td>
<td>Saffron (Kesar)</td>
</tr>
<tr>
<td></td>
<td>Sago</td>
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<tr>
<td></td>
<td>Sorghum</td>
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<td></td>
<td>Soy (soybean)</td>
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<td></td>
<td>Tapioca</td>
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intolerance (gluten sensitivity or wheat sensitivity?)


