

## Subclinical celiac disease and gluten sensitivity

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### ABSTRACT

Atypical presentation is the most common form of celiac disease (CD). Although the terminologies like *latent*, *silent* and *potential* have expressed different aspects of clinical and pathological behaviour of CD, they also have contributed in some extent to confusion between clinicians and patients due to the multiple definitions and uncertainty around them. In the light of new advances and the discovery of entities such as non-celiac gluten sensitivity, using *subclinical* instead of *silent* and *atypical* instead of *potential/latent* may simplify the understanding behind the clinical behaviour of atypical CD. The evidence behind a lower threshold for starting a gluten free diet (GFD) in non-celiac gluten sensitive patients would strongly support applying a GFD treatment strategy in any forms of CD.

**Keywords:** Subclinical, Celiac disease, Atypical, Microscopic enteritis, Gluten sensitivity.

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### Introduction

Using multiple terminology in defining atypical celiac disease (CD) has confused many of the clinicians to recognise atypical forms of this common disorder. CD is not considered an uncommon disorder any longer and is not a disease of essentially European origin (1). Nevertheless, recognising the existence of atypical forms known under the old terminologies like *latent*, *silent* and *potential* CD has introduced a new insight on clinical behaviour of this condition. That way the age of presentation of the disease has changed dramatically (1, 2) and the factors responsible for this change are mainly attributed to advances in

diagnostic tools in recognising atypical and subclinical forms of the disease. Adult presentation is increasingly common, and subclinical CD can occur at any age. Population screening with serological tests, have shown a CD screening prevalence of the order of 1% in the western hemisphere (3). European and Asian studies involving healthy blood donors found a prevalence rate of 1 in 166-330 (4, 5) subclinical CD. According to the previous studies, screening based on antibodies only would underestimate the prevalence of CD due to false-negative results caused by the low sensitivity of tests (6-10). However, some studies suggest that the overestimation of CD frequency could also result

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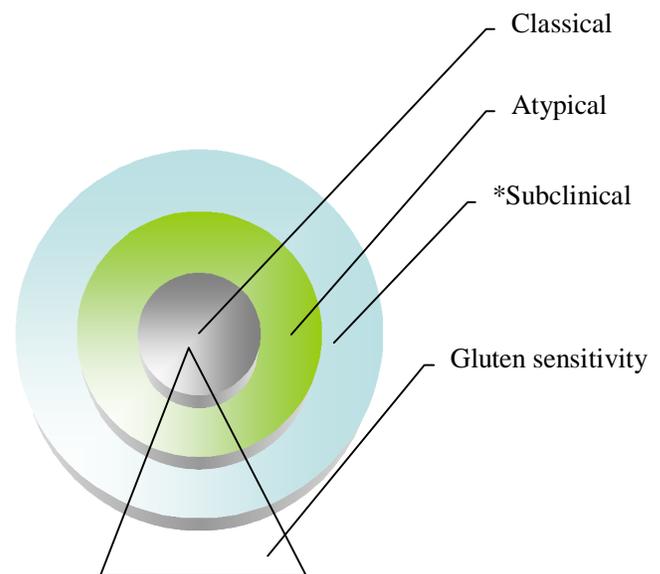
from antibody based screening programmes due to a high rate of false positives (11).

### Sub-clinical Celiac Disease

Terminologies like *latent*, *silent* and *potential* celiac disease can be confusing for clinicians and patients. *Silent* CD is not absolutely silent after all; patients show signs of CD with no significant symptoms. *Potential* and *latent* are defined differently in different studies. T-cell-mediated autoimmune processes are initiated by gluten exposure, leading to both intestinal and atypical extraintestinal manifestations. More and more diseases are proven to be associated with CD. In these conditions, screening is strongly recommended. However, a typical CD patient today has merely mild abdominal symptoms. Malabsorption can be silent like a mild anaemia (better defined under subclinical), or there is usually only moderate malabsorption, if any at all. Diagnostic difficulties may further emerge when minor mucosal changes are found (12). Should the presence of CD be ascertained in every symptomatic patient with atypical presentation? Since gluten sensitivity is no longer limited to overt villous atrophy, and given the results of many studies (13- 15), we believe the answer is yes.

Subclinical or so called silent CD cases are being detected in increasing numbers because of raised awareness of the disease. Presentations with atypical symptoms are the dominant form of disease manifestation and these comprise the sole and main part of the celiac iceberg (16). Whether they have positive serology with negative biopsy

or increased  $\gamma\delta$  T Cells receptors with symptoms compatible with CD they could be classified as atypical CD. We are moving towards a lower threshold in implementing a gluten free diet (GFD). Villous atrophy is not mandatory any longer to qualify a patient for GFD. In fact a large number of patients present with non-celiac gluten sensitivity with completely normal biopsy and negative serology. They also seem to benefit from a GFD. In such circumstances there is a need to re-define the terminologies according to the modified treatment strategy in gluten related disorders. The main strategy for treatment should target symptomatic typical or atypical patients, and not asymptomatic cases. We propose a simplified classification by dividing and replacing previous terminology to *typical*, *atypical* and *subclinical* instead of *silent/latent* and *potential*. (See figure 1).



**Figure 1-** Celiac and non-celiac gluten sensitivity  
\* Subclinical: previously known as silent and atypical as known under latent and potential CD

## Immunogenetics involvement in Celiac Disease

The spectrum of gluten related disorders seems to be beyond HLA DQ2-8. Our knowledge of CD pathogenesis has made significant progress in the last decade. The disorder is now considered the result of a complex interaction between genetic and environmental factors such as gluten that classified from subclinical to severe malabsorption. In contrast to gluten sensitivity celiac disease development has a strong genetic component with a sibling relative risk ( $\lambda$ ) of 30. Recent studies using the human genome screening technique in families with multiple siblings suffering from CD have suggested the presence of at least 4 different chromosomes in the predisposition to suffer from CD (17). One susceptibility locus is the MHC (major histocompatibility complex) region, with a particular association with the HLA-DQ alleles DQA1\*0501 and DQB1\*0201. However, shared-haplotype studies suggest that genes within the MHC complex contribute no more than 40% to the sibling familial risk of disease. Early studies showed that gliadin elicits an inflammatory T-cell reaction when added to intestinal biopsy specimens of celiac patients *in vitro* and a link to the genetic predisposition was provided by the isolation of gliadin-specific HLA-DQ2-restricted T-cell clones from CD mucosa (18, 19). However, the prevalence of HLA-DQ2 is high in the normal population (25-45%), suggesting the involvement of additional, and probably non-HLA-linked genes in CD pathogenesis.

## Microscopic enteritis

The pathologic spectrum of the mucosal abnormalities seen on small intestinal biopsies, range from microscopic enteritis (Marsh 0-II) to macroscopic forms (Marsh IIIa-c) (20). Not every gluten-sensitized individual inevitably develops CD and not every celiac patient develops the destructive lesions such as Marsh III. Celiac disease is not exclusively due to antibody production either. A large proportion of the patients present with microscopic enteritis (Marsh I-II) whose diagnoses may actually be missed (20-23). Five major histopathological features that define CD have been recognized in the previous study. These 6 distinct and sequential phases of the CD are microscopic enteritis (ME) Marsh (0-II). Marsh 0 with normal small bowel mucosa where intraepithelial lymphocytes are below 25/100 enterocytes. Some patients could still have subtle abnormalities at this stage like increased  $\gamma\delta$  T cell receptors or alteration of enterocytes and microvillous. i) Recruitment of T-lymphocytes > 25/100 enterocytes (intestinal-intraepithelial lymphocyte or IEL; Marsh I), ii) lymphocyte infiltration and crypt hyperplasia (Marsh II), iii) macroscopic enteritis (Marsh IIIa-c) partial villous atrophy (Marsh IIIa), iv) subtotal villous atrophy (Marsh IIIb) and v) total atrophy (Marsh IIIb) and total villous atrophy (Marsh IIIc) (6,8). This sequential cascade suggests that a T-cell response to gliadin precedes, and very likely produces, the complete pattern of CD. The statistical comparison between antibody-positive and antibody-negative cases shows that the appearance

of antibodies was seen predominantly in cases with serious mucosal damage in which IELs was highly increased. However, it is hard to rule out the contribution of antibodies in genesis of an autoimmune condition like CD.

The screening value of autoantibodies has been too optimistically overestimated, especially those on tissue transglutaminase antibodies (tTGA) (24, 25). However, comparing the tTGA to EMA and AGA, the sensitivity of tTGA does not offer any advantages over EMA for screening of the populations at high risk of CD (26- 28). It is time to re-evaluate our perception of intestinal pathology (29) in such terms, rather than by continued use of subjective degrees of villous atrophy (VA), since absence of VA is not evidence of absence of CD. Such terminology obscures the recognition of fundamental changes occurring within small bowel mucosa. In simple words, increased density of IEL's and crypt hyperplasia form an essential phase in the disease pathogenesis sequence of progression. As CD with milder enteropathy is the most common form, histology cannot be considered as the gold standard any longer. Therefore, treatment should target the symptoms and not the immunohistology (29-32).

### Gluten sensitivity and Celiac disease

Gluten sensitivity (GS) is characterised by negative antibodies and normal histology; it is defined as a non-allergic and non-autoimmune condition in which the consumption of gluten can lead to symptoms similar to those seen in CD. Until recently the terms GS and CD were used synonymously in

literature (33) and it is not clear yet whether patients affected by GS will have some subtle intestinal and mucosal changes consistent with microscopic enteritis. Yet we know very little about the pathogenic mechanism behind gluten sensitivity. Some GS patients would tolerate even more than 5g gluten/day and still remain symptom free with negative serology (34, 35).

GS patients are gluten intolerant and gluten consumption does not lead to small intestinal damage, so it is not accompanied by the concurrence of tTG autoantibodies or autoimmune disease. In the study by Kaukinen et al. out of 94 adults with GI symptoms, 63% were affected by gluten foods and neither classified as CD nor as allergic (36).

On the other hand around 50% of the GS patients were DQ2/DQ8 positive, which is similar to that of the general population, while celiac patients carry more than 95% in most regions of the world. However, while the prevalence of CD is roughly 1% within the general population, GS is thought to affect 6 to 10% of the general population (37). In some cases GS can present with normal or milder enteropathy seen as increased intestinal permeability, IBS, abdominal discomfort, pancreatic disorders, pain or diarrhoea; or it may present with a variety of extraintestinal symptoms including lymphoma, attention deficit disorder and neuropathy, autism and schizophrenia, infertility, IBD, muscular disturbances as well as osteopenia and osteoporosis (38-42). According to current literature, a GFD is recommended to gluten sensitive cases with/without enteropathy. This policy includes a range of symptomatic gluten sensitive cases with atypical

presentation including those with small bowel microscopic changes (Marsh 0-II) who are antibody negative or show characteristic features of other conditions.

## Conclusion

The spectrum of gluten related disorders is widening. This is because these common systemic disorders have multifactorial etiology with a multitude of symptoms and complications inside and outside the small bowel. We still don't know how seriously subclinical CD will be affected by the long term complications if they are not treated with GFD.

A marked increase in the prevalence of CD, especially the subclinical CD forms and non-celiac gluten sensitivity, seem to become a major health problem (43-46). The clinician may often face the variability of histological and clinical aspects of CD (46) with uncertainty, as they might not quite fit into the diagnostic models in the current guidelines. Accumulated evidence supports that decreasing the treatment threshold for cases with atypical CD and those with gluten sensitivity, as the life quality of these cases will improve with GFD and the long-term health benefit of this strategy, would perhaps be also cost effective.

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