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The Enigma of Oats in Nutritional Therapy for Celiac Disease

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Abstract Celiac disease (CD) is a life-long autoimmune condition affecting the small intestine of genetically susceptible individuals. Gluten is one of the offending inducers of the disease, with structurally related molecules found in barley, rye, and oats, where the offending peptides are called avenins. Avoiding toxic prolamins is the only established therapy but most patients have compliance difficulty on a gluten-free diet. Oats are considered less immunogenic than other cereals, and have high nutritional value, which is very desirable in an often undernourished celiac population; however, the consumption of oats by patients with CD is still controversial and debatable. Most clinical and in vitro studies favor oat consumption, but many of these studies were poorly designed and oat cultivar and purity was not considered. A recent study reported a wide range of susceptibility to avenin peptides in patients with CD. Oat cultivars can be subdivided based on toxicity and immunogenicity into none, partial, or highly immunogenic types. Furthermore, most commercial oat products are likely to be contaminated byprolamins. Those products should be avoided by the celiac population and well labeled for contaminants containing gluten. More basic and clinical research and active national celiac associations efforts are needed to characterize the place of oats in a gluten-free diet and to implement non immunogenic and uncontaminated oat products for the benefit of patients with CD. Great care should be taken when recommending consumption of commercial oat products to patients with CD.
The most important messages of the review are: 1. Immunogenic oat cultivars are present in oat products. Patients with CD should be cautioned about using them when on a gluten-free diet. 2. Many oat products are cross contaminated with toxic levels of gluten. 3. Interstudy comparisons are difficult because of variability in design, conditions during testing, and difference in oat cultivars studied. Several studies also had small cohorts or significant patient withdrawals during studies. 4. This review aims to encourage clinical and in vitro studies to investigate the benefits of recommending oats in a gluten-free diet.

Keywords: *celiac disease, oats, gluten-free diet, cultivar, contamination, gluten*

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1. Introduction

A1. Celiac Disease

Gluten-inducedenteropathy or celiac disease (CD) is a life-long autoimmune condition mainly of the gastrointestinal tract, affecting the small intestine of genetically susceptible individuals [1]. Gluten, which is the storage protein of wheat, and its alcohol-soluble gliadins, are the primary offending inducers of the disease together with structurally related molecules found in barley (hordeins), rye (secalins),and in oat, where the offending peptides are called avenins.

As in other autoimmune conditions, additional environmental factorssuch as infections or stress might play a role in CD induction [2].

Tissue transglutaminase (tTG) is the auto antigen against which the abnormal immune response is directed [3]. The two main auto antibodies to tTG, anti-tTG and anti-endomysium, are the serological markers most used to screen for the disease [4]. Two additional auto antibodies: anti-deaminated gliadin peptide and anti-neoepitope tTG, have recently been found to be reliable for use in CD screening [5]. The human leukocyte antigens (HLA) HLA-DQ2 and HLA-DQ8 are the most important predisposing genetic factors, but more than 60 additional susceptible genes have been described by genome-wide association studies. The treatment of CD is a strict, life-long adherence to a gluten-free diet (GFD), also excluding rye and barley products. Debate remains about whether oat products should be excluded from the diet of patients with CD.

In this article we review the controversy regarding oats and their consumption by patients with CD.

A2. Gluten-free Diet Adherence

In a large survey of children and adults with CD, 85% of responders reported difficulties in finding gluten-free foods, especially of good quality [6,7]. Given the

ubiquitous presence of gluten-containing cereals and grains in the Western diet, the strict avoidance of wheat and other sources of gluten is a lifetime challenge, causing a considerable burden to patients with CD. In fact, non-adherence to a GFD is prevalent in approximately 60% of patients [8]. However, the reported rate of non-compliance differs considerably in individual publications and ranges from 42-91% of patients [9]. The multiple difficulties encountered by patients with CD in adhering to a GFD are summarized in Table 1.

Table 1. Barriers to dietary adherence of CD patients to GFD

Social, cultural or peer pressures.
Financial restrictions, high cost of products
Low availability.
Poor palatability.
Insufficient education, inadequate dietary counseling
Misinformation.
Food labeling variability.
Absence of symptoms while non-adherence
Inadequate medical and nutritional follow up
Dining out of home
Transition to adolescence
Cross contamination.
Anger, sadness, despair\depression.
No consensus on minimal amount of gluten permitted.
Individual variations in gluten sensitivity.

Due to the high rate of non-compliance and the daily difficulties experienced in adherence to a GFD, several potential therapeutic strategies are being developed to circumvent these problems and improve the patients' quality of life [10].

2. Oat Composition and Importance in Celiac Disease

Extending the GFD with alternative cereals remains highly desirable. Incorporation of oats into the GFD is important from a quality of life standpoint to the celiac population. Oat is distinct among the cereals due to its multifunctional characteristics and nutritional profile [11,12]. Oat grains are a good source of dietary fiber, especially β-glucan (2.3-8.5 g/100g), B-complex vitamins, proteins, fats, minerals (calcium, phosphorus, iron, magnesium, zinc, and iodine) and other nutrients. The β-glucan has important functional properties that affect human health. Due to its viscosity, it attenuates postprandial plasma glucose and insulin response, enhances the transport of bile acids to the distal intestine, thus increasing bile acid excretion and resulting in decreased serum cholesterol levels. Oat consumption is helpful in treating diabetes and cardiovascular diseases [11]. In addition, oat possesses different pharmacological activities including antioxidant and anti-inflammatory effects [13]. Oats upplementation attenuates alcohol-induced disruption of intestinal barrier integrity by inhibiting oxidative stress and oxidative tissue damage [14].

Natural unprocessed oats do not contain gliadin, but do contain its prolamin counterpart avenin. The percentage of prolamin of the total proteins in wheat, rye, barley, and oat is 40-50%, 30-50%, 35-45%, and 10-15%, respectively. It is estimated that 60 grams of oat contains 1.2 g of avenin.

Due to the lower content of prolamins in oats, the lower number of proline-glutamine residues, the less efficient binding to HLA-DQ2, oats is thus considered to be less toxic to patients with CD. Moreover, oats have high nutritional value and the high fiber content may in particular be beneficial in the celiac population. Patients with CD on long-term GFD are at increased risk of having an unbalanced diet, leading to nutritional deficiencies in fiber, vitamins and minerals. They are more likely to suffer constipation, become obese, and potentially can develop metabolic syndrome. The qualities of oats, mainly because of its high fiber content can counteract the consequences of the unhealthy consequences of a GFD. If the prolamin avenin is non-toxic then inclusion of oats in a GFD is advantageous.

3. Clinical Studies of Oat Consumption in Celiac Disease

A1. In children

Table 2 summarizes the clinical studies performed on CD children consuming oats in their GFD.

Table 2. The clinical studies performed on CD children consuming oat in their GFD

No of children	Study design	Oat gr/day	Duration of oat	Safety of oat	reference
10	Uncontrolled	24	6m	yes	15
116	Rand. Double blind	15	12m	Yes, majority	16
86	Rand. Double blind	5-40	12m	Yes, majority	17*
87	Rand. Double blind	5-40	12m	Yes, majority	18*
32	Randomized controlled	50	2y	yes	19
23	Randomized controlled	50	2y	yes	20
306	Rand. Double blind, placebo-controlled	Up to 40	15m	yes	21

*part of study of [16]. Adopted from [20].

A2. In Adults

Table 3 summarizes the oat consumption trials in adults with celiac disease while on GFD.

Table 3. Oat consumption trials in adults with celiac disease (adapted from [9])

No of patients	Study design	Oats gr/day	Duration of oat	Safety of oat	reference
20	uncontrolled	93	2y	Yes, majority	22,23*
19	uncontrolled	50	12w	Yes, majority	24
9	uncontrolled	50	12w	no	25,24*
276	controlled	24	6m	yes	26
15	uncontrolled	50	12w	yes	27
106	uncontrolled	20	8y	yes	28
92	randomized	50-75	6/12m	yes	29-31
10	uncontrolled	50	3m	yes	32
32	Randomized, controlled	100	1y	yes	33
39	controlled	50	1y	no	34
423	uncontrolled	Not mentioned	Not mentioned	Yes, majority	35#

*Shared patients, #patients survey.

A3. In-vitro Studies

Recent in-vitro studies have significantly expanded our knowledge on the mechanisms and effect of oat consumption in patients with CD [9]. Avenin did not induce anti-endomysial antibodies when cultured with duodenal biopsies of adult patients with CD in remission [36]. However, when checked, the variety of oats used was found to have low immunogenic potential for peripheral lymphocytes in children with CD [37]. Cultured duodenal biopsies of adults with CD with a peptic-tryptic digest of avenin for 4 hours did not exhibit a significant interferon (IFN)-gamma or interleukin (IL-2) response, when compared with the response to a gliadin digest [38]. The same group of researchers reported on investigations of T-cell lines from duodenal biopsies treated with peptic-tryptic digests of various prolamins and showed T-cell proliferation and cytokine production with exposure to all of the prolamins studied, including avenin. Pretreatment with tTg antigen decreased the impact of the avenin stimulation of the immune response [39]. The pivotal study by Arentz-Hansen et al.provided some novel information with respect to avenin toxicity. Some patients with CD have avenin-reactive mucosal T-cells that can cause mucosal inflammation and villous atrophy [25]. Avenin reactive T-cells recognize avenin peptides rich in proline and glutamine that are recognized by HLA-DQ2, and that are similar in structure to gluten epitopes.

In some patients, oat-derived peptide has been shown to cross-react with wheat-gluten-reactive T cell lines [40]. Different oat cultivars may display different biological properties relevant to CD pathogenesis. Avena Genziana and Avena Potenza did not display any in vitro activities related to CD genesis [41]. A Spanish group further elucidated and clarified oat toxicity. They found a direct correlation between the immunogenicity of different oat varieties and the presence of specific peptides with higher/lower potential toxicity, suggesting that there is a wide range of variation of potential immunotoxicity of oat cultivars that could be due to differences in the degree of immunogenicity in their sequences [42]. The reactivity of monoclonal antibodies against the main immunotoxic33-mer peptide is proportional to the potential immunotoxicity of oat cultivars [43]. The most recent in vitro study further substantiates the diversity of oat cultivars [44]. The authors found significant differences among oat cultivars in eliciting the tTG2-mediated events of inflammation in patients with CD. Summarizing the latest in vitro study, one can conclude that the safety of an oat cultivar in CD might be screened in vitro, using biochemical/biological assays, before starting a clinical trial to definitely assess its safety.

The following paragraph provides several explanations for the potential harmful effects of oat consumption in patients with CD.

4. The Toxic Peptides in Oats

The suitability of oats to be part of a GFD remains controversial. In contrast with most clinical trials of oat consumption in children and adults with CD, several studies have demonstrated that oat intolerance does exist in some patients with CD. A subgroup of patients with CD develops an immune reaction to oats that is similar to the reactions to wheat, barley, and rye.

Arentz-Hansen et al. studied 4 patients with CDwith an intolerance to oat consumption and established an avenin-specific and-reactive intestinal T-cell lines that recognized avenin peptides in the context of HLA-DQ2 [25]. These peptides had sequences rich in proline and glutamine residues, and which closely resembled wheat gluten epitopes. Furthermore, deamination by tTG was involved in the avenin epitope formation.

A Spanish research group [13,42,43] investigated the reactivity of different oat varieties to monoclonal antibodies against the main immunotoxic 33-mer peptide, and their 33-mer concentration, T-cell proliferation and interferon γ production. Comino et al. showed that reactivity of the monoclonal antibody is proportional to the potential immunotoxicity of the cereal cultivar [43]. In a seminal in vitro study, Realet al. [42] showed a direct correlation of the immunogenicity of the different oat varieties with the toxicity of peptides present in their avenin sequences. The results from these studies suggested that the differences in the protein sequences of different oat cultivars could explain why certain varieties of oats are toxic for patients with CD, while others are not.

In a more recent in vitro study Silano et al. [44] strengthened the idea of the variability of different oat cultivars in eliciting CD inflammatory events. They showed that Nave oat cultivars elicited early gliadin-dependent events, whereas Irina and Potenza varieties did not. They suggested screening oat cultivars in vitro before starting clinical trials to definitely assess their safety for inclusion in GFD in patients with CD.

5. Contamination of Oat Products

One of the major problems in clinical studies of oat products is the potential for cross contamination. Similarly, this potential for contamination with gluten in oat products offers a potential for toxicity in patients with CD on GFD including oats.

In the United States, when selected brands of oats were analyzed for gluten contamination, 75% of the products sampled had gluten levels above the allowed upper limit, and ranging from 23-1807 ppm [45]. In view of the risks of cross contamination of oats with gluten, a position statement by the Canadian Celiac Association concerning pure oat consumption in CD was published in 2007 [46]. The Canadians established the requirements for growing, processing, purity testing, and labeling of pure oats. In a survey of national societies for CD, clear variations were demonstrated in the advice given to their members [47]. Two societies recommended cautious use of oats for patients with CD and five associations recommended that patients with CD avoid oats completely while on GFD. The Canadian commercial oat supply is heavily contaminated with levels of gluten above 20ppm, [48] and approximately 88% of 133 oat samples examined were found to be contaminated with even higher gluten levels. In a recent study, gluten contamination of natural gluten-free flours and starches used by Canadians with CD was investigated by the same group [49]. The researchers found that 61 of the 640 (9.5%) samples were

contaminated with gluten levels above 20ppm,a range of 5-7995 ppm. When examined for wheat, barley, and rye contamination, 109 out of 134 grains and commercial oat products were found to be contaminated, [50] with barley being the most predominant contaminant.

6. Study Limitations and Future of oat Consumption in Patients with Celiac Disease

Several limitations of published clinical studies can be highlighted.

1. More adults were investigated compared to children (920/660)

2. In adults, most of the studies were uncontrolled.

3. Oat ingestion was higher in children when grams of oats per kg body weight were considered.

4. Most of the studies documented the safety of oat ingestion; however, few patients in the studies exhibited disease deterioration or clinical symptoms

5. It is very difficult to compare different studies because of differences in study designs, variable conditions used in the testing, small numbers of patients included or withdrawn and reasons for dropout, difference in the size of cohorts, and insufficient reporting of gastrointestinal symptoms in some studies.

6. In most of the studies the information on the oat variety used and purity of the oat products used is missing.

7. The follow-up period of studies was insufficient and relatively short considering a lifelong adherence to GFD.

Based on the limitations of published studies and the recent information, several pathways of future research are recommended:

- Comparison of various analytical methods such as specific serology, biochemical, or biological assays should be performed to select the most reliable way to measure the immunogenic peptides levels in the prolamins and\or in commercial oat products

- Further research is necessary to characterize and select the immunogenic peptide of the different oat cultivars. Efforts should be made to recommend only products with non-toxic oat cultivars for consumption by patients with CD on GFD.

- Legislators, the scientific community, and the national celiac associations should join forces to improve and implement non-toxic oat product consumption and reliable food composition labeling.

Since patient surveys are positive for oat consumption during GFD, and oat is a good nutritional food with many beneficial qualities, any future research to introduce the correct oat cultivars into patients' diets will improve their compliance and quality of life.

7. Summary

Until future therapeutic strategies are established [10], GFD remains the corner stone of CD therapy. However, two thirds of patients have difficulty in implementing GFD for various reasons. The inclusion of oats in the restrictive gluten-free food is highly desirable as it will improve the palatability and nutritional value of a GFD. However, several key issues still remain before widely recommending inclusion of oat in the GFD:

1. Most commercial oat products are contaminated by prolamins. These products should be avoided by patients with CD and labeled for contaminants

2. Patients with CD have a wide range of susceptibility to avenin peptides. The non immunogenic ones should be allowed and the immunotoxic ones be omitted by the celiac population consuming GFD.

3. More basic and clinical research and active national celiac associations efforts are needed to characterize the role of oats in GFD and to implement non immunogenic and uncontaminated oat products for the benefit of the patients with CD.

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