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Review

Part of celiac population still at risk despite current gluten thresholds

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In order to assist celiac disease (CD) patients in making safe food choices, gluten-free food products are labelled as such. The exact meaning of the gluten-free label differs throughout the world. This paper discusses the different thresholds that are currently used to label products gluten-free and compares tolerable gluten levels to the gluten levels CD patients can be exposed to with these thresholds in place. Currently, the most applied gluten threshold to label products gluten-free does not protect the most vulnerable patients. Therefore, we propose to lower the threshold for products with a gluten-free label to 3 ppm gluten.

Introduction

Approximately 1% of the world population is afflicted with celiac disease (Lionetti & Catassi, 2011; Reilly & Green, 2012). These persons have an intolerance to gluten, a group of storage proteins found in wheat, rye and barley. When a CD patient ingests gluten, an inflammatory response is triggered in the intestinal tract. This inflammation can lead to atrophy of the mucosal villi and, as a consequence, to malabsorption and malnutrition. The symptoms of CD vary between persons. Symptoms in a typical manifestation are mainly gastrointestinal, whereas atypical manifestations have mostly extra-intestinal symptoms. Furthermore, CD can manifest asymptomatic. In this case, the patient does not show symptoms other than villous atrophy or serological changes. Especially in the asymptomatic cases, CD can remain undetected for a long period of time (Lionetti & Catassi, 2011). A wrong interpretation of biopsy results can also lead to a delay in CD diagnosis (Marsh, 2013). When left untreated, CD can lead to serious complications. In the worst case scenario, these can include lymphomas and intestinal adenocarcinoma (Green & Cellier, 2007). Although multiple new therapies are investigated, at this moment the only treatment is to adhere to a strict lifelong gluten-free diet.

In order to make safe food choices, CD patients rely heavily on the correct labelling of food products. This is not an easy task for the patient. Gluten are often added to foodstuffs which are naturally gluten-free, in order to improve product quality and stability (Day, Augustin, Batey, & Wrigley, 2006). Ingredients on the label are sometimes difficult to interpret for gluten presence, since gluten can be hidden in names as, for instance, 'flavourings' or 'hydrolysed vegetable protein'. A gluten-free label on a product makes finding the right products for a gluten-free diet much easier. However, labels can be confusing too. Gluten-free labelling legislations differ throughout the world and, as a result, the acceptable gluten content of a product labelled gluten-free can differ per country.

According to the Dutch Celiac Disease Association (NCV), CD-related complaints are still often reported by CD patients who have been following a gluten-free diet. Sometimes, the supposedly gluten-free product is found to be contaminated with gluten above the legal threshold, but often the reason for these complaints remains unknown as the products seem to comply with the current European legislation for gluten-free foods. The aim of this literature study is to investigate whether the currently applied gluten thresholds are suitable to protect CD patients, or adjustments should be considered.

Literature selection

Systematic literature searches were performed in order to investigate the gluten content of foods and the amounts of gluten tolerated by CD patients. The following databases

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were included: Medline, Cochrane Library and Scopus. Studies had to be written in the English language to be included.

Search terms for the gluten contents of food were "gluten traces" OR "gluten content" AND "gluten-free" AND "food". Subsequently, the reference lists of the studies identified by the electronic databases were searched to identify additional studies. Results were filtered to include only original research articles. Full manuscripts were obtained for all potentially relevant articles. Studies had to be performed in the last 10 years to be included. Studies that estimated instead of quantified the gluten content of foods were excluded, as were studies that did not specify if the tested products were intended for CD patients to use. Furthermore, studies that only assessed the gluten content of raw materials such as flour were excluded, as for this study the gluten content of final products is most relevant to determine exposure. Finally, studies assessing the gluten content of beer were excluded. Beer contains mostly hydrolysed gluten, which are known to be overlooked by the most commonly applied method to detect gluten in food; the sandwich format enzyme-linked immunosorbent assay (ELISA).

Search terms for the tolerated amounts of gluten were "coeliac disease OR celiac disease" AND "gluten" AND "threshold OR gluten challenge" NOT "*in vitro*". Again, the reference lists of the studies identified by the electronic databases were searched to identify additional studies. Results were filtered to only include original research articles and case reports describing effects on humans. Full manuscripts were obtained for all potentially relevant articles. Since only a limited amount of gluten threshold studies has been performed in total, the time frame for including these studies was increased compared to the studies evaluating the gluten content of food products. Studies had to be performed in the last 20 years to be included. Dietary recall studies concerning wheat starch intake were included if they made at least an estimation of the gluten content of the wheat starches. These dietary recall studies do not give an exact gluten content that CD patients are exposed to, due to their retrospective set-up. However, they do give relevant information on a different approach to gluten exposure; the effect of smaller doses of gluten spread over several meals per day, as compared to the effect of a single, larger dose. Studies concerning gluten challenges given in combination with pharmacological treatment were excluded.

The current applied legislations concerning gluten-free labelling of food products were retrieved for the European Union, the United States of America, Canada and Australia and New Zealand. For this, the websites of government authorities responsible for food standards and regulations were consulted.

Current thresholds for gluten-free labelling of food products

For the European Union, the United States of America and Canada, products with a gluten-free label cannot contain more than 20 mg/kg (ppm) gluten. However, there are some differences in legislation between these countries. In Europe, the definition of gluten-free products and the recommended limits of the Codex Alimentarius standard 118-1979 were implemented in Commission Regulation 41/2009 in 2012 (European Commission, 2009) and later the new Commission Regulation 1169/2011 in December 2014 (European Commission, 2011). Gluten is defined as "the protein fraction from wheat, rye, barley, oats or their crossbred varieties and derivatives thereof, to which some persons are intolerant and which is insoluble in water and 0.5 M sodium chloride solution". According to this legislation, in order to label a product gluten-free, the ingredients derived from gluten-containing cereals must have been processed to reduce the gluten content or these ingredients must have been replaced by gluten-free cereals. There is a specific addition for the use of oats. Oats must have been specially produced and processed in a way that avoids contamination by gluten-containing cereals and the maximum of 20 ppm gluten is still valid. The US adopted a legislation on gluten and gluten-free products in 2013. According to this legislation and contrary to the European legislation, the gluten-free label may also be applied to food that does not contain a gluten-containing grain, including naturally gluten-free foods, as long as the gluten content of the final product does not exceed 20 ppm (U.S. Food and Drug Administration, 2013). The Canadian legislation differs from both the European and American legislation by stating that gluten-free products cannot contain wheat, including spelt and kamut, or oats, barley, rye, triticale, or any part thereof (Health Canada, 2014). In this case, the 20 ppm threshold is used to set a maximum level of allowed cross-contamination with gluten.

The gluten legislation of Australia and New Zealand is very different from the above mentioned legislations and is considered to be most strict worldwide. Their definition of gluten is the main protein in wheat, rye, barley, oats, triticale and spelt, relevant to the medical conditions CD and dermatitis herpetiformis (Australia New Zealand Food Authority, 2012). A product can be labelled gluten-free if it contains no detectable gluten. This means that the tolerable amount of gluten in these products is decreasing over time as the detection methods become more sensitive. At this moment, the type I method R5 as recommended by Codex Alimentarius has a limit of detection (LoD) of 3 ppm.

Other thresholds concerning the gluten content of food products

Apart from the thresholds that are used to define gluten-free, the European Union, Australia and New Zealand have a second category for products that are low in gluten, yet exceed the threshold to be labelled gluten-free. In the European Union, a product may be labelled 'very low in gluten' if the gluten-containing cereals have been processed to reduce the gluten content, and the product does not contain