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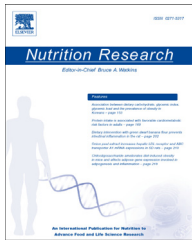

Oat safety for celiac disease patients: theoretical analysis correlates adverse symptoms in clinical studies to contaminated study oats

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ABSTRACT

Inclusion of oats in a gluten-free (GF) diet can provide whole grain nutritional benefits to celiac disease (CD) patients, but there has been debate regarding oat safety for these individuals. This is because of conflicting research findings, with inconsistencies attributed to varying CD subject's sensitivities to "pure" oats. Clinical trials to date have assumed oats provided to subjects to be lightly contaminated, if at all. This assumption is challenged here since oat's propensity to be "kernel" contaminated with gluten sources like wheat and barley has recently been shown to significantly complicate confirmation of a GF state. We therefore hypothesize that clinical studies may have inadvertently provided pill-like gluten kernels intermittently to study subjects, leading to adverse outcomes that could potentially explain inconsistencies between study conclusions. To test this theory, potential gluten contamination of oats used in a cross-section of 12 important oat feeding studies has been estimated, done according to descriptions of oats used, published contamination rates for various oat types, and study oat dosages. Expected gluten exposures were found to be at levels to elicit clinical effects in a large portion of CD patients, correlating with observed clinical reaction rates in those studies (P value = .0006). Estimated gluten doses were found insufficient, however, to affect morphological outcomes, whereas only 1 study had 1 case. Our analysis provides a new perspective with which to view oat safety study conclusions and justifies new clinical trials using today's higher-purity GF oats to settle the oat safety for CD patient debate.

1. Introduction

Currently, the only available treatment for celiac disease (CD) is lifelong adherence to a strict gluten-free diet (GFD) [1]. In addition to CD patients, GFDs are also followed by others as a lifestyle choice. GFDs, however, have been shown to present some nutritional limitations. These limitations include deficiencies in fiber and other nutrients like protein and iron due primarily to a reduced consumption of whole grains [2-5]. Recently, it has been shown that GFDs are associated with an increased risk of cardiovascular disease as well [6], with those authors discouraging GFDs except for those suffering with CD.

Oats appear to be an excellent addition to a GFD, countering these nutrient deficiencies. They are naturally gluten-free and an excellent source of fiber, iron, and proteins [7,8]. Oat consumption has also been associated with reduced risk of cardiovascular disease [9].

Abbreviations: CD, celiac disease; GF, gluten free; GFD, gluten-free diet.

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But there have been questions as to whether oats can be safely consumed by CD patients. This is due to inconsistent clinical findings, where a handful of studies have suggested that some CD patients possess sensitivity to oat proteins [10]. In contrast, other studies have shown that even high amounts of oats are well tolerated by CD subjects [10,11]. This has led to an unsettled debate about the safety of oats as a dietary component for CD patients, with many clinicians and some regulatory authorities, such as Food Standards Australia New Zealand, recommending against routine oat consumption.

Recent investigations have revealed the significant difficulties in accurately confirming a gluten-free state in oats [12,13]. This, along with recently published marketplace GF labeling noncompliance for GF oatmeal [14], has led us to theorize that adverse effects attributed to oats in CD dietary studies could potentially be due to oats assessed as "pure" but actually being contaminated with gluten containing wheat, barley, or rye kernels [15]. Herein, we explore this hypothesis that oats are potentially contaminated with gluten from other grains. The research objectives are to determine whether gluten from common oat contamination could theoretically be at levels to affect CD patients in a cross section of important clinical trials and, if so, whether this suspected contamination correlates to adverse reaction rates encountered in those studies. The approach is to estimate gluten exposure based on oat description, assessment description, published oat contamination rates, and stated study consumption dosages; compare these to CD patient "pure gluten dose study" reaction results; and finally use linear regression to assess the strength of relationship between estimated gluten loading and actual adverse reaction rates encountered in these studies.

This theoretical approach has merit in that it adds a new perspective by which to interpret and compare key clinical studies' results to date, putting them in a more proper context based on gluten assessment difficulties recently revealed. Our analysis can therefore justify new studies using today's purer oats, which hopefully lead to settling the debate regarding oat safety for CD patients.

2. Methods and materials

The approach used to investigate if inadvertent gluten contamination could bias published assessments of dietary oat safety in CD patients consisted of 3 steps: (1) compilation and screening of data from applicable oat feeding studies; (2) estimation of potential contamination-driven dietary gluten exposures per day; and (3) assessment of whether estimated gluten exposures correlate to clinical and/or morphological responses, comparing observed correlations to those reported in CD patients from pure gluten dose response studies.

2.1. *Screening and selection of oat clinical studies*

A search using the Medline Database with keywords *oats*, *celiac*, and *review* produced 3 recent reviews as potential sources of oat feeding studies [10,11,16]. The Pinto-Sanchez et al review [10] was used as the source for study selection herein based on its comprehensiveness, having identified and evaluated 433 studies and finding 28 appropriate for comparative meta-analysis. Additionally, the Pinto-Sanchez et al review [10] was the most current and assessed clinical studies from a greater chronologic range than the other 2 systematic review articles [11,16].

The 28 oat clinical studies identified in the review were further evaluated based on the following characteristics: (1) subjects confirmed to have CD either by serology or biopsy, (2) subjects not known as oat sensitive or insensitive prior to the study, (3) subjects symptomatic but in remission on a GFD prior to the study, and (4) known dosage and source of oats. Twelve of the 28 studies were found to meet these additional criteria.

2.2. *Estimation of gluten exposure per day due to contaminated oats in oat feeding studies*

Detecting the type of highly concentrated, intermittent contamination requires special sampling and testing approaches to accurately characterize GF status [12,13]. Clinical studies to date, including those assessed in the present analysis, used (if at all) the typical approach of randomly selecting a modest quantity of servings and evaluating a small amount (eg, 0.25 g) from each sample. This typical method has been found inadequate to assess purity in this "needle in the haystack" type of circumstance [12,13], and this is the assumed case with these 12 studies because they state use of "oats" or "rolled oats" exclusively, except one (Baker and Read) that used a blend of flour and flakes and was not assessed for gluten. With this circumstance in mind, we estimated how much contamination may have been present in the included oat feeding studies using the descriptions of oats listed in each study as a guide to probable impurity. We found 3 broad categories of oats used in the studies examined. Those categories were commercial oats, GF oats under a specification of 200 ppm maximum (~1979-2008), and GF oats under a specification of 20 ppm maximum (~2008-present). Estimates of potential gluten contamination were determined. These contamination estimates are based on research to date, which is admittedly sparse. Because of this, gluten content cited in the studies examined could in fact be biased for one or more of these categories. If this was significant, conclusions drawn could be altered.

Using these oat contamination categories, along with the stated oat consumption per day per subject for studies presented herein, we estimated average gluten (mg/d) for each study according to the following formula: gluten mg/d = (# of 50-g servings/d) × (prob. 50-g serving contaminated) × (mg gluten/50-g contaminated serving).

The resultant estimated average gluten (mg/d) is presented in the "Results" section. Included are details regarding oat source, gluten testing done, results of those tests if described, and the specific oat classification assigned based on these descriptions.

2.3. *Statistical analyses*

Linear and logistic regression analyses [17] were performed using MiniTab 17 statistical software, State College, PA, USA. An Excel (Microsoft, Redmond, WA, USA) macro was used to estimate the average outgoing quality limit for attribute-based acceptance sampling [18], and Excel was also used for a