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EDITORIAL

Three papers indicate that amount of gluten play a role for celiac disease – But only a minor role

Celiac disease (CD) is a chronic immune-mediated disorder that affects the small intestine.[1] It occurs in genetically sensitive individuals exposed to gluten. Over time it has become apparent that individuals with CD are at increased risk of both death and extra-intestinal comorbidity.[1,2]

While CD has a strong genetic component, concordance rates in monozygotic twins are only about 50%,[3] indicating that environmental factors play a role for disease etiology. Given that CD traditionally has an early-life onset, it has been natural to focus the search for risk factors in infant feeding, and other exposures occurring in the first year(s) of life. Initially suspected as major risk factors, both breastfeeding duration and age at gluten introduction were deemed less important or perhaps even irrelevant by two randomized clinical trials published in 2014 that failed to find an effect on various feeding strategies on the risk of CD.[4,5] Since then attention has shifted, and only in the last year, at least three papers have been published with the aim to illuminate the association between the quantity of gluten and risk of CD and CD autoimmunity (CDA; Table 1).[6-8]

In their latest study published in JAMA,[6] Andrén-Aronsson et al followed 6605 children for a median time of 9.0 years (Table 1). During that period, 1216 (18%) developed CDA, and 447 (7%) CD (an outcome with stricter criteria). The researchers' main finding was that in the joint modeling analysis, each additional gram of gluten consumption (per day) was associated with a 50% increased risk of CD at the age of 3 years. What this means is that within a child population, genetically at risk of CD, those consuming the reference amount of gluten, 20.7% developed CD by age 3 years, among those consuming another 1 g per day of gluten, 27.9% developed CD. It should be noted that the study participants were selected for their very high baseline risk of CD.

While these results seem clear-cut, this paper has several concerns, and the implications on a public health level are not clear. Andrén-Aronsson et al analyzed data from the TEDDY study. In that study, the researchers began by screening 424 788 newborn infants for HLA (a genetic predisposition to the development of CD). Of those 21 589 were eligible for screening but only 40% (n = 8676) agreed to participate. Of these, even fewer (n = 6757) were screened for CD, and roughly the same number participated in this study. This means that the current study was based on a sample that represented 1.55% of the pediatric population in the study area, and thus even minor selection biases might have affected the result. Furthermore, it is inappropriate to assume that the results of this study are applicable to the remaining 98.45%, even among the subset that carries the at-risk alleles for CD. What a 50% increased risk per gram gluten per day, in a highly selected group of patients representing <2% of the general population, means for the overall prevalence of CD in the population is hard to tell.

The authors chose to use a joint modeling analysis for their main analysis. When the authors used the more common Cox regression, the relative risks for CDA and for CD decreased to 1.14-fold increase per gram gluten/d, for both outcomes (in general, joint modeling tends to produce higher risk estimates than the traditional Cox regression). Joint modeling considers the total amount of gluten over time (in the case of this study, during the first 5 years), and therefore does not allow us to identify a window of sensitivity where it restricting the gluten amount is particularly important. Hence, though a study by Andrén-Aronsson et al was large and included systematic measurement of exposure and outcome, its results do not inform us on the particular question of when during the first five years of childhood, a lower gluten consumption might be beneficial.

Almost simultaneously, Mårild et al[8] published data from the US DAISY study in the *American Journal of Gastroenterology*. They followed 1875 at-risk children. Between 1993 and January 2017, 161 children (8.6%) developed CDA; of these, 85 (4.5%) had biopsy-verified CD or persistently high tissue transglutaminase antibodies (equal to CD in this study). The risk of CDA increased by 5% (HR = 1.05) for every gram of gluten consumed between 1 and 2 years of age. In addition, CD per se was linked to higher intake of gluten, but the increase per gram of gluten was not significant (HR = 1.04; 95%CI = 0.98-1.10). Comparing the highest tertile of gluten consumption with the lowest tertile, both the risk of later CDA and CD were around 2 (Table 1).

The DAISY study screened 31 766 newborns, of which 2547 (8%) were included in the study, and 1043 had analyzable data on gluten and a CD-associated HLA (3.3% of the screened number). The study used 24-hour dietary recalls to retrieve information on gluten amount, after which 62 food frequency questionnaire (FFQ) records were excluded for unrealistically high gluten intake (this is reported as a 0.4% missingness, but is rather >3%, if based on the 1875 with FFQ data). This study primarily used Cox regression, but also carried out joint modeling. One important finding of the study by Mårild et al is that the association with later CD/CDA was strongest for gluten intake at 1 year of age.

TABLE 1 Three studies on the amount of gluten and risk of celiac disease (CD) and celiac disease autoimmunity (CDA)

Publication	Andrén-Aronsson et al (2019)[6]	Mårild et al (2019)[8]	Lund-Blix et al (2019)[7]
Study type	Cohort study	Cohort study	Cohort study
Setting	Finland, Germany, Sweden, United States	United States	Norway
Exposure groups	Gluten intake (g/d) Gluten intake of 2 g/d at age 2	Gluten intake between age 1 and 2	Gluten intake at 18 mo (quartile)
Mean gluten intake	2 y: 3.71 g/d	Between age 1 and 2 y: 10.9 g/d	18 mo: 8.8 g/d
Covariates in model	HLA haplotype, country, sex, first-degree relative with celiac disease, energy intake	HLA haplotype, sex, family history of CD, race-ethnicity, maternal age at the time of delivery, breastfeeding duration, timing of infant gluten introduction, total energy intake and the timing of islet autoimmunity	Age at gluten introduction, breastfeeding duration, parental CD, sex, and age at the end of the study, parity and maternal age at the time of delivery, education, pregnancy-related smoking, caesarean section, child's birth weight, and prematurity
Follow-up time	Birth until 15 y Median follow-up: 9 y	Median 13 y (controls)	Mean 11.5 y
Screening for celiac disease	Yes	Yes	No
Number (%) who developed celiac disease	447 (7%)	85 (4.5%)	738 (1.1%)
Risk estimate for celiac disease autoimmunity	g/d: HR 1.30 (1.22-1.38)	T3 vs T1: HR 2.17 (1.22-3.88)	Not applicable
Risk estimate for celiac disease	g/d: HR 1.50 (1.35-1.66)	T3 (highest tertile) vs T1: HR 1.96; (0.90-4.24)	Q4 (highest quartile) vs Q1: RR 1.27 (1.04-1.55)
Risk estimate for celiac disease per extra gram of gluten intake per day	g/d: HR 1.50 (1.35-1.66) (Joint modeling) g/d: HR 1.14 (1.35-1.66) (Cox regression)	g/d: HR 1.04 (0.98-1.10) (Joint modeling)	g/d: HR 1.03 (1.01-1.05) (Cox regression)

Finally, the *American Journal of Gastroenterology* recently published a study from the MoBa-cohort (Mor-far og Barn-undersøkelsen).[7] This study was truly population-based and did not consider HLA (though in paper the researchers additionally carried out a nested case-control study that explored the interaction between gluten intake and HLA). Of some 113 000 children initially enrolled, 67 608 were included in the study, 738 (1.1%) of whom were subsequently diagnosed with CD. Data on CD were obtained from the Norwegian Patient Register. As opposed to the Andrén-Aronsson et al study,[6] Lund-Blix et al[7] from Norway also adjusted for breastfeeding duration (and found that longer breastfeeding was linked to lower amount of gluten at 18 months, $P < .001$). The Norwegian researchers used binary regression to analyze their data. This study found that for each gram of extra gluten intake per day, the risk of CD increased by 3% (95%CI = 1.01-1.05). Of note, the association between gluten amount and future CD was strongest in children with HLA of intermediate/low risk of CD (HR = 1.20) rather than in those with HLA signaling a high risk of CD (HR = 0.75). Finally, the researchers reported that children introduced to gluten ≥6 months of age were at a significantly higher risk of CD than those introduced 4-<6 months (adjusted relative risk = 1.34; 95%CI = 1.10-1.64).

1 | COMMENT

Three recent studies[6-8] suggest that amount of gluten is associated with future CDA and CD. All studies report the relative risk for CD per gram of extra gluten intake (Table 1). Taken together, one extra slice of bread (some 2 g of gluten) per day seems to be linked to a 20%-50% increased risk of CD.

The study that has received most attention so far (Andrén-Aronsson et al[6]) evaluated cumulative gluten intake during childhood. It does not specify an age when gluten amount should be kept at a low level. In fact, research from the same group, trying to identify a window of sensitivity/opportunity has reported some surprising results.[9] While a high amount of gluten in the first 2 years was linked to later CD, looking specifically at 9 months of age when many parents start introducing gluten, having a high gluten consumption actually seemed *protective* against CD, although the results were based on few cases and did not attain statistical significance (odds ratio = 0.63; 95%CI = 0.19-2.05). It is therefore difficult to issue any recommendation as to when at-risk children should consume less gluten.

It is also important to keep in context the fact that, except for the Lund-Blix et al study[7] that included children independent of HLA,

the other two studies were limited to *at-risk* child populations. The paper by Andrén-Aronsson, et al was based on 1.55% of all children initially screened for the TEDDY study, and the study by Mårild et al included 3.3% of the children screened for the DAISY study. It might be questioned if any infant feeding recommendations should be based on findings from such highly selected samples, unless such feeding recommendations are targeted at children undergoing prior HLA testing.

Public health interventions in infant feeding have not always been beneficial. For instance, the change in gluten and breastfeeding recommendations in Sweden in the 1990s was once linked to a dramatic increase in CD, the so-called celiac epidemic (reported in *Acta Paediatrica* some 20 years ago[10]). We therefore urge caution and strongly agree with the recommendations of Andrén-Aronsson et al[6]: "A randomized clinical trial of different amounts of gluten during early childhood in genetically at risk individuals would be warranted to confirm our findings." A second concern is whether any study in genetically at-risk children should motivate changes in infant feeding recommendations in individuals *not at risk* of CD (ie, those without a celiac-permissive HLA haplotype). Withholding gluten-containing foods may have unexpected and unwelcome consequences outside the celiac arena. In a recent study published in the *British Medical Journal*, we found in adults without CD, a low-gluten diet, if accompanied by a reduction in dietary whole grains, might be associated with an increased risk of cardiovascular disease.[11] The effects of a low-gluten diet on children who are not at risk of CD are unknown. Though the authors of these studies are to be congratulated for moving science forward in wake of two negative clinical trials,[4,5] their results should spur new trials of interventions prior to our endorsing or recommending new dietary strategies.

CONFLICT OF INTEREST

Dr Ludvigsson coordinates a study on behalf of the Swedish IBD quality register (SWIBREG). This study has received funding from Janssen corporation. Dr Lebwohl has no conflict of interest.

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