Systematic review of safe level of gluten for people with coeliac disease

Summary of findings table

Comparison: Exposure to low amounts of gluten (equivalent to consumption of products with < 20 ppm gluten) versus higher amounts of gluten (equivalent to consumption of products with ≥ 20 ppm gluten)

Patients or population: The included trials (n=5) involved 186 adults, 13 adolescents and 20 children (total n=219) with a confirmed diagnosis of coeliac disease (small bowel biopsy). In most cases coeliac disease was well controlled on enrolment to the study.
Settings: Italy (3 trials), Finland (2 trials)
Intervention: Exposure to lower amounts of gluten administered in a capsule of purified gluten or gliadin (2 trials), a gluten containing product (3 trials), or a 'no gluten' placebo (2 trials) (some trials had multiple intervention groups, hence total > 5). Gluten containing products included wheat-starch based products, hydrolysed wheat flour, wheat-based starch hydrolsate products (glucose syrups, maltodextrin). Exposures ranged from one to twelve months (28 to 365 days).
Comparison: Exposure to higher amounts of gluten administered in a capsule of purified gluten (2 trials), or an alternative form of gluten containing product (3 trials).

Outcomes No of Participants (studies)	Intervention effects	Certainty of the evidence (GRADE)*	Interpretation
Small bowel histology	Direct evidence: gluten intake equivalent to consumption of products containing < 20 ppm vs products containing 20-100 ppm		
Mucosal morphology Follow up: immediately after 90 days of gluten exposure 38 participants (1 randomised trial[1])	Improvement in villous height to crypt depth ratio (Vh/Cd) with 'no gluten' compared to 50 mg gluten/day (0.33 increase in Vh/Cd ratio; 95%CI 0.73 increase to 0.07 reduction, n=26) and 10 mg gluten/day compared to 50 mg gluten/day (0.31 increase in Vh/Cd ratio; 95%CI 0.71 increase to 0.10 reduction, n=25). Both estimates encompass potentially important improvements (based on the point estimate and upper bound of the 95%CI), but also potentially small harms (based on lower bound of the 95%CI). Little or no difference with 'no gluten' compared to 10 mg gluten/day (0.02 increase in Vh/Cd ratio; 95%CI 0.42 increase to 0.38 reduction, n=25). [2(a), 2(b)]	⊕⊕⊖⊖ Low due to serious imprecision	It is uncertain whether 'no gluten' (≤ 20 ppm) compared to 10 mg gluten/day makes any difference to mucosal morphology. 50 mg gluten/day may reduce Vh/Cd compared to placebo and 10 mg gluten.
	Indirect evidence		
180 participants (4 randomised trials)	One trial (n=90) found little or no difference in Vh/Cd with wheat-based maltodextrin (0.005 mg gluten/day) compared to wheat-based glucose syrup (0.12 mg gluten/day; equivalent to consumption of < 100 g gluten/day of food containing 3 ppm gluten), and little or no difference with either of these wheat-based starch hydrolysate products compared to placebo. A second very small trial (n=13) found reduced incidence of mucosal atrophy with 1.6 mg gluten/day (fully hydrolysed flour) compared to higher gluten intakes (hydrolysed flour, 496 mg gluten/day; natural flour, 16 g gluten) (0 of 5 compared to 2 of 2 and 6 of 6 participants respectively). [3] Results of two further trials (n=77) were not usable because the lowest gluten intake was 40 mg gluten/day or greater. [4]	⊕⊖⊖⊖ Very low due to serious risk of bias, imprecision and indirectness	These findings are uncertain due to the very low quality of evidence, but are consistent with the study providing direct evidence.
	Direct evidence: gluten intake equivalent to consumption of products containing < 20 ppm vs products containing 20-100 ppm		
Intraepithelial lymphocytes (IEL) count Follow up:	Little or no difference in IEL count with placebo compared to 10 mg gluten/day (4.0 decrease in IEL count; 95%CI 3.4 increase to 11.4 decrease, n=25) or with 10 mg gluten/day compared to 50 mg gluten/day (3.8 decrease in IEL count; 95%CI 3.5 increase to 11.0 decrease, n=26).	⊕⊕⊖⊖ Low due to serious imprecision	It is uncertain whether 'no gluten' (≤ 20 ppm) compared to 10 mg gluten/day makes any

immediately after 90 days of gluten exposure 38 participants (1 randomised trial)	Reduction in IEL count with placebo compared to 50 mg gluten/day (7.8 decrease in IEL count; 95%CI 0.33 decrease to 15.2 decrease, n=25).		difference to IEL count. 50 mg gluten/day may reduce IEL count compared to placebo but not 10 mg gluten/day.
	Indirect evidence		
180 participants (4 randomised trials)	One trial (n=90) found little or no difference in IEL count with wheat-based maltodextrin (0.005 mg gluten/day) compared to wheat-based glucose syrup (0.12 mg gluten/day), and little or no difference with either of these wheat-based starch hydrolysate products compared to placebo. A second very small trial (n=13) found a reduction in IELs with 1.6 mg gluten/day (fully hydrolysed flour) compared to higher gluten exposures (hydrolysed flour, 496 mg gluten/day; natural flour, 16 g gluten/day) (0 of 5 compared to 2 of 2 and 6 of 6 participants respectively). Results of two further trials (n=77) were not usable because the lowest gluten intake was 40 mg gluten/day or greater. [4]	⊕⊖⊖⊖ Very low due to serious risk of bias, imprecision and indirectness	These findings are uncertain due to the very low quality of evidence, but are consistent with the study providing direct evidence.
Non-randomised and observational studies (11 studies)	Two studies included participants with gluten intake equivalent to consumption of products containing < 20 ppm, but did not use designs appropriate for addressing the review question. A further nine studies were not usable because the lowest gluten intake was above that typically consumed with products containing < 20 ppm gluten.	⊕⊖⊖⊖ Very low due to serious risk of bias and potential confounding	Studies did not use an appropriate design for addressing the review question.
Coeliac serology	Direct evidence: gluten intake equivalent to consumption of products containing < 20 ppm vs products containing 20-100 ppm		
Follow up: immediately after 90 days of gluten exposure 39 participants (1 randomised trial[1])	Little or no difference in anti-tissue transglutaminase (tTG) with 10 mg gluten/day compared to 50 mg gluten/day, or with placebo compared to either amount of gluten. Lower anti-gliadin antibodies (AGA) with placebo compared to 50 mg gluten/day (p=0.04), but the 50 mg group was within 'normal' range. Little or no difference in AGA with 10 mg compared to 50 mg gluten/day, or placebo compared to 10mg gluten/day.	⊕⊕⊖⊖ Low due to serious imprecision	It is uncertain whether 'no gluten' (≤ 20 ppm) compared to 10 mg or 50 mg gluten/day makes any difference to coeliac serology.
	Indirect evidence		
180 participants (4 randomised trials)	One trial (n=90) found little or no difference in seriological tests for coeliac disease (tTG-ab, EmA) with 'no gluten' placebo compared to wheat-based glucose syrup (0.12 mg gluten/day). Slight increase in positive seriological tests (tTG-ab) with wheat-based maltodextrin (0.005 mg gluten/day) (2 of 30 participants) compared to wheat-based glucose syrup (0 of 30 participants) or placebo (0 of 30 participants). A second very small trial (n=13) found a reduction in anti-Tg2 antibodies with 1.6 mg gluten/day (fully hydrolysed flour) compared to 16 g gluten/day (natural flour) (0 of 5 compared to 6 of 6 participants), but no "statistically significant difference" between 1.6 mg and 496 mg gluten/day. Results of two further trials (n=77) were not usable because the lowest gluten intake was 40 mg gluten/day or greater. [4]	⊕⊖⊖⊖ Very low due to serious risk of bias, imprecision and indirectness	These findings are uncertain due to the very low quality of evidence.
Non-randomised and observational studies (9 studies)	One study included participants with gluten intake equivalent to consumption of products containing < 20 ppm, but did not use a design appropriate for addressing the review question. A further eight studies were not usable because the lowest gluten intake was above that typically consumed with products containing < 20 ppm gluten.	⊕⊖⊖⊖ Very low due to serious risk of bias and potential confounding	Studies did not use an appropriate design for addressing the review question

Clinical symptoms	Direct evidence: gluten intake equivalent to consumption of products containing < 20 ppm vs products containing 20-100 ppm		
Follow up: immediately after 90 days of gluten exposure 39 participants (1 randomised trial[1])	One of 13 participants showed clinical signs of relapse (e.g. vomiting, diarrhoea, abdominal distension) with 10 mg gluten/day compared to 0 of 13 with 50 mg gluten/day and 0 of 13 with 'no gluten' placebo.	⊕⊕⊖⊖ Low due to serious imprecision	It is uncertain whether 'no gluten' (≤ 20 ppm) compared to 10 mg or 50 mg gluten/day makes any difference to GI symptoms.
	Indirect evidence		
180 participants (4 randomised trials)	Little or no difference in gastrointestinal symptoms (GSRS[5]) with one wheat-based starch hydrolysate product compared to another (glucose syrup, 0.12 mg gluten/day or maltodextrin, 0.005 mg gluten/day), or with either of these wheat-based starch hydrolysate products compared to placebo. There were more withdrawls due to abdominal symptoms among those receiving wheat-based maltodextrin (3 of 30) or placebo (3 of 30) compared to wheat-based glucose syrup (1 of 30 participants). Adverse events were reported (n=21), but not by group. A second very small trial (n=13) found a reduction in symptoms (e.g. malaise, abdominal pain, diarrhoea) with lower gluten exposures (hydrolysed flour, 496 mg gluten/day; fully hydrolysed flour, 1.6 mg gluten/day) compared to the highest gluten exposure (natural flour, 16 g gluten/day) (0 of 5 and 0 of 2 participants compared to 2 of 6). Results of two further trials (n=77) were not usable because the lowest gluten intake was 40 mg gluten/day or greater. [4]	⊕⊖⊖⊖ Very low due to serious risk of bias, imprecision and indirectness	These findings are uncertain due to the very low quality of evidence.
Non-randomised and observational studies (8 studies)	Two studies included participants with gluten intake equivalent to consumption of products containing < 20 ppm, but did not use designs appropriate for addressing the review question. A further six studies were not usable because the lowest gluten intake was above that typically consumed with products containing < 20 ppm gluten.	⊕⊖⊖⊖ Very low due to serious risk of bias and potential confounding	Studies did not use an appropriate design for addressing the review question.

* GRADE Working Group grades of evidence

High = This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.
Moderate = This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.
Low = This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.
Very low = This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

† Substantially different = a large enough difference that it might affect a decision

Footnotes

1. Catassi 2007. Participants in all three arms (groups) of this trial were able to consume gluten-free products (< 20 ppm as per regulations in Italy) throughout the intervention. The investigators estimated the average background gluten consumption from the products to be < 5 mg/day based on consumption of 300 g of gluten-free product per day (data from 30-day food diaries from a separate sample of people with coeliac disease, and measurement of gluten levels in a sample of the products consumed with sensitivity limit reported as 3 ppm of gluten).
2. (a) 10 mg gluten/day is equivalent to consumption of 500 g per day of food containing 20 ppm gluten; 50 mg is equivalent to consumption of 500 g per day of food containing 100 ppm gluten. (b) Effect estimates are adjusted mean difference in Vh/Cd ratio between groups where the adjustment is for baseline (calculated by Cochrane Australia based on data reported in Catassi 2007).
3. 0.12 mg gluten/day is equivalent to consumption of < 100 g per day of food containing 3 ppm gluten; 0.005 mg gluten/day is equivalent to consumption of < 1 g per day of food containing 3 ppm gluten.
4. 40 mg gluten/day or greater is equivalent to consumption of at least 400 g of food containing 100 ppm gluten.
5. GSRS: Gastrointestinal Symptom Rating Scale