Reviewer’s report

Title: Effects of cow’s milk beta-casein variants on symptoms of milk intolerance in Chinese adults: a multicentre, randomised controlled study

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Reviewer: Anu Turpeinen

Reviewer's report:

This paper presents data from a cross-over trial on the effects of milk beta-casein variants on gastrointestinal symptoms in Chinese subjects with self-reported lactose intolerance. A single dose of conventional milk containing A1 and A2 beta-casein or milk containing only A2 beta-casein was consumed in a cross-over manner and symptoms were followed for 12 h. Urinary galactose was used to assess lactose absorption.

Milk intolerance and milk-related gastrointestinal symptoms are interesting issues, which require more research. Regarding this study, I have some concerns related to the study design and interpretation of results.

Study design

Baseline gastrointestinal symptoms were defined as those experienced when last consuming milk. The subjects were non-regular users of milk products who had generally not consumed milk for at least a month.

It is very difficult to reliably assess different stomach symptoms after several weeks and effect of other causes of gastrointestinal symptoms cannot be excluded. Why were baseline symptoms not measured at the study site before consuming the milks? Also, the scores for baseline gastrointestinal symptoms should be shown.

Breakfast (which was not identical in the three study sites) was eaten already after 1 h of consuming the milk and after 3 h, the subjects were allowed to leave the study site and eat and drink freely (only dairy products were prohibited). Therefore, regarding both the 3h and 12 h data it is not possible to distinguish between stomach symptoms caused by the milk and other foods and drinks consumed.

Were illnesses and use of temporary medications during the study asked and recorded?
Abstract:

- "… conventional milk reduced lactase activity and…" Can you really say that conventional milk reduced lactase activity? According to Table 5, urinary galactose concentrations increased after consumption of both milk relative to baseline.

- "galactose absorbers and malabsorbers", should be lactose absorbers and malabsorbers

Urinary galactose (page 7):

No reference is given for the method for the analysis of urinary galactose. Where does the cut off value 0.27 mmol/l, which was used to divide the subjects into lactose absorbers and malabsorbers come from? Please provide references.

Were galactose concentrations adjusted for urinary creatinine?

Results

Did FFQ show adherence to the dairy-free diet? The results are not presented or discussed.

Discussion

The authors propose that gastrointestinal symptoms associated with the conventional milk are caused by local inflammation in the gut. It seems plausible that milk proteins (like any dietary proteins) may cause local inflammatory reactions in sensitive individuals. However, A2 milk also caused gastrointestinal symptoms and since both milks contained lactose, the question remains whether symptoms were mainly due to lactose. Removing lactose generally alleviates stomach symptoms in lactose intolerants and some studies have even shown dose dependency (Bedine & Bayless 1973, Gudmand-Hoyer & Simony 1977). Also, in another study (Turpeinen et al. J Dairy Res 2016; 83(2):256-60), the benefits attributable to removing lactose were greater than the additional effect of protein hydrolysation in subjects with a sensitive stomach.

The authors propose that a single dose of A2 milk would significantly enhance lactase activity in lactose-intolerant subjects compared to conventional milk, but no mechanism for this is proposed. As this is a highly speculative issue and as lactase activity was assessed using the indirect urinary galactose method, I would be careful with conclusions. I would recommend to omit mentioning lactase activity in the title and to emphasize in the discussion that an indirect method to assess lactase activity was used.
Minors points

Table 3: Scale for symptoms should be shown

Table 3: Baseline symptom scores are not shown

Table 4. Does the group "No difference" also include those who experienced worsening of the symptoms? They should be presented separately.

Table 5. The unit for the data is not shown

Table 6. Title should be "Effects of lactose malabsorption on gastrointestinal symptoms"

Figure 1 Study design: There are several inconsistencies between this figure and the text:

- It is mentioned in the text that the urinary galactose test was done during screening (before randomization). It is not shown in the figure.

- According to the figure, 200 subjects in each study site were screened whereas the text states that 1200 subjects were initially screened and 642 started the study

- The figure indicates that in Phase 1, baseline VAS was done before consumption of the study milk. Why not in Phase 2? However, according to the text, VAS completed during screening was used as the baseline symptom score.

Page 13, line 303: "Accordingly, the objectives of the present study were to compare the effects of consuming milk…"

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