

Alterations in human milk leptin and insulin are associated with early changes in the infant intestinal microbiome

Dear Editor:

We read with great interest the study by Lemas et al. (1) that reported early changes in the gut microbiota composition and functions of exclusively breastfed infants born from obese mothers compared with infants from normal-weight mothers, in relation to leptin and insulin concentrations in human milk (HM).

The authors indicated that the microbiome of these infants at 2 wk of age was dominated by the Firmicutes (30.5%), Proteobacteria (28.8%), Bacteroidetes (23.8%), and Actinobacteria (5.6%) phyla, which was different from the data provided in Supplemental Table 1. It is noteworthy that the proportion of Actinobacteria, mainly represented by *Bifidobacterium* species, was rather low (6.7%), considering that the infants were exclusively breastfed. It is generally accepted that the microbiota of exclusively breastfed infants, after the first week, is dominated by *Bifidobacterium* species (2, 3), with the growth of these bacteria being promoted by the oligosaccharides and nucleotides present in HM. These discrepancies possibly could be due to the methodology used, as previously shown by Walker et al. (4), but it would have been interesting to know the opinion of the authors on these controversial observations.

On the other hand, the authors reported a lower proportion of Proteobacteria in the infants born from obese mothers than in those from normal-weight mothers (35.8% compared with 18%). They also reported that the HM concentrations of insulin and leptin were significantly higher in obese mothers than in normal-weight mothers, with a positive correlation between these hormonal values and the maternal BMI before pregnancy. However, after normalizing the γ -Proteobacteria abundance by maternal BMI, a positive correlation between this bacterial family and HM insulin was finally observed. Taken together, these results are difficult to understand, considering that the normalization process generally makes a previously undetected effect significant, or indicates that a significant effect is, in reality, overestimated. Consequently, it is disturbing that normalization gave opposite results, as observed in this study; the real meaning of these observations is not clarified in the discussion.

Furthermore, the authors stated that high concentrations of HM leptin and insulin may improve intestinal integrity, because these hormones decreased the occurrence of bacterial genes coding protease and pyruvate kinase, which are involved in gut barrier alterations and inflammation, respectively. Surprisingly, this gives the final impression that infants born from obese mothers would have an improved intestinal barrier compared with those from normal-weight mothers. We think that this conclusion should be tempered, because it does not take into account the fact that leptin may also act as a proinflammatory mediator involved in intestinal diseases, among other things (5). In consequence, exposure of the gut mucosa to high concentrations of luminal leptin during breastfeeding by the obese mother might be damaging to the infant.

Finally, other factors not considered in this study could be present in altered concentrations in the HM of obese mothers. These include other hormones, such as adiponectin, resistin, or ghrelin, and dietary components, such as oligosaccharides and nucleotides (6), that may explain the current results from this study.

Neither of the authors had a conflict of interest.

Martin Gotteland
Fabien Magne

From the Department of Nutrition (MG) and the Microbiology and Mycology Program, Institute of Biomedical Sciences (FM, fabienmagne@med.uchile.cl), Faculty of Medicine, University of Chile, Santiago, Chile.

REFERENCES

1. Lemas DJ, Young BE, Baker PR, Tomczak AC, Soderborg TK, Hernandez TL, de la Houssaye BA, Robertson CE, Rudolph MC, Ir D, et al. Alterations in human milk leptin and insulin are associated with early changes in the infant intestinal microbiome. *Am J Clin Nutr* 2016;103:1291–300.
2. Bäckhed F, Roswall J, Peng Y, Feng Q, Jia H, Kovatcheva-Datchary P, Li Y, Xia Y, Xie H, Zhong H, et al. Dynamics and Stabilization of the Human Gut Microbiome during the First Year of Life. *Cell Host Microbe* 2015;17:690–703. Corrected and republished from: *Cell Host Microbe* 2015;17:852.
3. Avershina E, Storrø O, Øien T, Johnsen R, Pope P, Rudi K. Major faecal microbiota shifts in composition and diversity with age in a geographically restricted cohort of mothers and their children. *FEMS Microbiol Ecol* 2014;87:280–90.
4. Walker AW, Martin JC, Scott P, Parkhill J, Flint HJ, Scott KP. 16S rRNA gene-based profiling of the human infant gut microbiota is strongly influenced by sample processing and PCR primer choice. *Microbiome* 2015;3:26.
5. Sitaraman S, Liu X, Charrier L, Gu LH, Ziegler TR, Gewirtz A, Merlino D. Colonic leptin: source of a novel proinflammatory cytokine involved in IBD. *FASEB J* 2004;18:696–8.
6. Savino F, Benetti S, Liguori SA, Sorrenti M, Cordero Di Montezemolo L. Advances on human milk hormones and protection against obesity. *Cell Mol Biol* 2013;59:89–98.

doi: 10.3945/ajcn.116.140129.

Reply to M Gotteland and F Magne

Dear Editor:

We thank Gotteland and Magne for their insightful comments on microbial colonization of the infant gut in exclusively breastfed infants born to obese and normal-weight mothers. Specifically, the authors highlight the low abundance of *Bifidobacterium* observed in our cohort at 2 wk of life, and our general interpretation of how exposure to leptin in human milk (HM) during early life may