COMMENTS AND RESPONSES

Response to Comment on: Harte et al. High Fat Intake Leads to Acute Postprandial Exposure to Circulating Endotoxin in Type 2 Diabetic Subjects. Diabetes Care 2012;35:375–382

ALISON L. HARTE, PHD
PHILIP G. MCTERNAN, PHD

From the Division of Metabolic and Vascular Health, Warwick Medical School, University of Warwick, Coventry, U.K.

Corresponding author: Philip G. McTernan, p.g.mcternan@warwick.ac.uk.

DOI: 10.2337/dc12-2301

The letter from Hansen et al. (1) raises an interesting question regarding the complexity of metabolic endotoxinemia and inflammation in vivo. Hansen et al. suggest endotoxin activity should induce an inflammatory response in our cohorts, as noted in a previous in vivo study, where healthy patients were inoculated with endotoxin (1,2). This has two elements to consider: firstly, the impact of endotoxin on inflammation in subjects, and secondly, the measurement of circulating endotoxin.

Firstly, in understanding the inflammatory response, it is often tempting to directly compare in vivo situations, but the context is key (1–3). Our article (3) examined circulating endotoxin derived from the gastrointestinal tract, which induced a physiological meal-related response, whereas Taudorf et al. (2) inoculated endotoxin, which bypasses such gut-related processes. From this, direct comparison of endotoxin levels, across the two studies, examining the two healthy groups showed a differential response over time (2,3). Specifically, a high-fat meal did not significantly induce circulating endotoxin postprandially or tumor necrosis factor-α (TNF-α) (3), whereas inoculation of endotoxin raised TNFα levels (2). This aside, a high-fat meal induced circulating endotoxin (0–4 h) in obese, impaired glucose tolerant, and type 2 diabetic subjects (2) while lowering TNF-α, whereas in contrast the subjects of Taudorf et al. (3) had increased TNF-α levels, rising from 2 ng/mL to 5 ng/mL after 4 h. As such, our data appears to contradict the potential inflammatory effect posed by inoculated endotoxin (1). However in our study, the context and complexity is very different, as the influence of insulin would appear to have a more fundamental effect postprandially on metabolism. In such a postprandial state, reducing TNF-α, which is known to impair insulin signaling through the inhibition of the tyrosine kinase activity of the insulin receptor, appears critical for glucose homeostasis. As such, a decline in circulating TNF-α concentration could lessen its impact on insulin sensitivity at a time when it is most required—after feeding (4). This apparent decline in TNF-α postprandially, noted in our studies, appears to match previous high-fat meal studies (2,4).

Secondly, defining endotoxin units (EUs) is not a new undertaking; it is difficult to assess when using an enzyme derived from a horseshoe crab where batch-to-batch variation can occur. Also, different companies vary what their EU mL equates to and how this is assessed. In this case of endotoxin assessment, in our study, the team has had a consistent approach to endotoxin analysis across multiple cohorts. The assay is not used as for clinical assessment but as a research tool to highlight cohort changes, as others have observed (3–5). However this does not mean that endotoxin will not influence the proinflammatory state in vivo, as other studies suggest, but there is a clear complexity to understanding metabolic endotoxemia and inflammation impacted by metabolic state (3–5).

Acknowledgments—No potential conflicts of interest relevant to this article were reported.

References

1. Hansen HS, Moesby L, Timm M, Hansen EW. Comment on: Harte et al. High fat intake leads to acute postprandial exposure to circulating endotoxin in type 2 diabetic subjects. Diabetes Care 2012; 35:375–382 (Letter). Diabetes Care 2013;36:e42. DOI: 10.2337/dc12-0813
2. Taudorf S, Krabbe KS, Berg RMG, Pedersen BK, Møller K. Human models of low-grade inflammation: bolus versus continuous infusion of endotoxin. Clin Vaccine Immunol 2007;14:250–255
3. Harte AL, Varma MC, Tripathi G, et al. High fat intake leads to acute postprandial exposure to circulating endotoxin in type 2 diabetic subjects. Diabetes Care 2012;35: 375–382
4. Manning PJ, Sutherland WH, Hendry G, de Jong SA, McGrath M, Williams SM. Changes in circulating postprandial proinflammatory cytokine concentrations in diet-controlled type 2 diabetes and the effect of ingested fat. Diabetes Care 2004;27: 2509–2511
5. Lassenius MI, Pietiläinen KH, Kaartinen K, et al.; FinnDiane Study Group. Bacterial endotoxin activity in human serum is associated with dyslipidemia, insulin resistance, obesity, and chronic inflammation. Diabetes Care 2011;34:1809–1815