Adipocyte 2:3, 188–190; July/August/September 2013; © 2013 Landes Bioscience

# Does chronic low-grade endotoxemia define susceptibility of obese humans to insulin resistance via dietary effects on gut microbiota?

Daniel M Kemp
Diabetes & Endocrinology; Merck Research Laboratories; Kenilworth, NJ USA

**Recent studies, including one from our own lab, report that different subpopulations of obese individuals display a variable inflammatory signature in their visceral adipose tissue that may contribute significantly to their risk for developing insulin resistance, type 2 diabetes, and other metabolic diseases. Understanding the molecular mechanisms and signaling pathways that lead to these differences in susceptibility to insulin resistance will equip us with important targets to help stem the tide of such debilitating diseases. Here we discuss an emerging theory that chronic, low-grade endotoxemia may represent a causal factor in obesity-related inflammatory states, and that diet-induced changes in the gut microbiome may be a key regulator of metabolic health. The implications to both disease prevention and to therapeutic intervention are also highlighted.**

**Keywords:** inflammation, endotoxemia, type 2 diabetes, insulin resistance, obesity

Submitted: 04/03/13

Revised: 04/19/13

Accepted: 04/22/13

http://dx.doi.org/10.4161/adip.24776

Correspondence to: Daniel M Kemp;
Email: dmkemp@gmail.com

Commentary to: Qatanani M, Tan Y, Dobrin R, Greenawalt DM, Hu G, Zhao W, et al. Inverse regulation of inflammation and mitochondrial function in adipose tissue defines extreme insulin sensitivity in morbidly obese patients. Diabetes 2013; 62:855–63; PMID:23223024; http://dx.doi.org/10.2337/db12-0399

One of the key etiological factors that link obesity to type 2 diabetes is insulin resistance, which is characterized by the impaired ability of insulin to inhibit glucose output from the liver and to promote glucose uptake in fat and muscle. The search for physiological mechanisms that link obesity to insulin resistance has been intensely pursued in recent years resulting in the emergence of several hypotheses to explain the connection, such as (1) ectopic lipid accumulation in liver and muscle secondary to obesity-associated increase in serum free fatty acids (FFAs), (2) altered production of various adipocyte-derived factors (collectively known as adipokines), and (3) low-grade inflammation of white adipose tissue (WAT) resulting from chronic activation of the innate immune system.[1] Importantly, however, not all obese individuals are insulin-resistant, and in fact insulin sensitivity has been shown to vary up to 6-fold in this population, highlighting the importance of identifying genetic and environmental factors that place obese individuals at the greatest risk of obesity-related complications, such as type 2 diabetes.[2]

Current and emerging drug classes for the treatment of type 2 diabetes are generally aimed toward mechanisms that augment insulin secretion from the pancreas, suppress glucose re-absorption from the kidney, suppress glucose output from the liver, or increase glucose uptake in peripheral tissues such as skeletal muscle.[3] Though modestly effective and meaningful in terms of glycemic control, these mechanisms are essentially targeted toward lowering glucose levels over the short-term rather than impacting the underlying cause of the disease, and as such have been shown to simply delay the progression of diabetes rather than to stop it in its tracks.[4] In this regard, the pharmaceutical industry remains somewhat conservative, aiming for short-term biomarkers of glucose efficacy that provide proof of concept and incremental improvement in glucose control. Some suggest, however, that the aspiration of the entire research field needs to shift toward a more impactful assault on the underlying processes that drive hyperglycemia in the first place.

What is clearly beyond any doubt is the degree to which obesity is affecting westernized society, such that it underlies the

prevalence of type 2 diabetes, and serves as a leading indicator for metabolic dysfunction. In 2010, no state in the US had a prevalence of obesity less than 20%. Thirty-six states had a prevalence of 25% or more; 12 of these states (Alabama, Arkansas, Kentucky, Louisiana, Michigan, Mississippi, Missouri, Oklahoma, South Carolina, Tennessee, Texas, and West Virginia) had a prevalence of 30% or more.[5] By comparing these statistics with those from 1990, the explosion in obesity rate is striking, and the data strongly suggest that prevention (or reversal) of obesity would have a profound effect on the prevalence of type 2 diabetes. As such, many companies have focused their research efforts on anti-obesity programs as a means to treating obesity-related metabolic diseases such as type 2 diabetes. So the key questions are (1) how does obesity pre-dispose individuals to insulin resistance and type 2 diabetes? And (2) more importantly, how can we envisage a way to discover new therapeutic options that get right to the heart of the issue?

As mentioned earlier, not all obese individuals are insulin-resistant. Despite the increased awareness of the role inflamed adipose tissue plays in obesity related insulin resistance, there is limited understanding of the molecular signals that differentiate insulin-resistant from insulin-sensitive obese individuals. Since equally obese individuals can differ dramatically in their overall sensitivity to insulin, we decided to investigate how in fact these individuals differed at the molecular level, and performed a high powered transcriptome study on more than 800 obese individuals and identified molecular pathways associated with insulin sensitivity, independent of body mass.[6,7] Specifically, we conducted a comprehensive transcription profiling analysis on subcutaneous and visceral adipose tissue samples collected from this entire cohort of obese subjects during their bariatric surgery procedures. Our results emphasized the role of the immune and inflammatory system along with mitochondrial function in the etiology of insulin resistance in obese people. We confirmed that macrophage and T-cell gene signatures were upregulated in the insulin-resistant state, which coincides with the general recognition that obesity and insulin resistance are associated with a state of low-grade systemic inflammation. Our data also suggested the possibility that individuals with a higher basal inflammatory tone are more at risk of developing insulin resistance, diabetes and other metabolic diseases. This is not a novel concept, and many labs within industry and academia are focused on characterizing the role of inflammation on metabolic health, and identifying specific causal factors that may represent new therapeutic avenues. An area of intense interest is the relationship between the gut microbiome and respective levels of endotoxemia in patients that may result in a chronic systemic inflammatory response.[8] Evidence that chylomicrons can transport LPS across the gut epithelium strongly suggests that a high fat diet may facilitate chronic endotoxemia. One study that showcased this concept leveraged a human low-dose experimental endotoxemia model of inflammation-induced metabolic disturbance.[9] The authors defined the effects of endotoxemia on insulin sensitivity and focused on adipose inflammation because of its emerging relevance in dietary excess and adipose dysfunction in human insulin resistance. To summarize the results, the team demonstrated in humans that activation of innate immunity in vivo induces insulin resistance following modulation of specific adipose inflammatory and insulin signaling pathways. More evidence linking chronic endotoxemia to insulin resistance and diabetes comes from a clinical study where Roux-en-Y gastric bypass (RYGB) resulted, as often cited, in profound weight loss in a majority of patients, accompanied by a high resolution rate of type 2 diabetes.[10] However, as many similar clinical studies have reported, the resolution of the diabetic state was observed within days of the procedure and well before clinically significant weight loss had occurred, and this time course of resolution provided important evidence that the chronic inflammatory state may be mediated by a source other than the adipose tissue. Because LPS is a potential source of the persistent chronic inflammatory state (endotoxemia), the group hypothesized that plasma LPS concentration may be reduced after RYGB and that this reduction would be accompanied by a similar reduction in markers of oxidative and inflammatory stress. Indeed, RYGB was associated with a marked reduction in insulin resistance and indices of chronic inflammation. In addition, these improvements were accompanied by reduction in plasma LPS exposure, MNC CD14, TLR-2, and TLR-4 expression and NFκB DNA binding. The reduction in LPS exposure and proinflammatory mediators after RYGB may contribute significantly to the resolution of insulin resistance and type 2 diabetes. The proposed cumulative pathway that leads from gut microbiota to insulin resistance is captured in **Figure 1**.

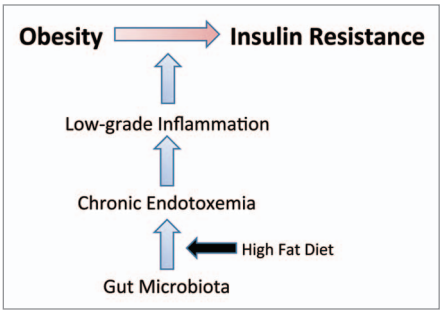


**Figure 1.** Cartoon of the proposed pathway underlying insulin resistance in obese individuals.

In summary, our recent study showed that the inflammatory tone in visceral adipose tissue is directly associated with whole body insulin sensitivity, and given the breadth and complexity of the inflammatory pathway suggests that new therapeutic strategies for type 2 diabetes, and other inflammatory diseases may include targeting upstream mediators of the inflammatory pathways, or enhancing endogenous molecular defense systems such as the stress response pathway.

Finally, it is worth considering the implications of a common microbial cause of chronic inflammatory states in human disease, and the potential for overlapping opportunities across research field to identify common therapeutic targets for such diverse disease indications as type 2 diabetes, Alzheimer disease, atherosclerosis, multiple sclerosis, and rheumatoid arthritis. A corollary to the chronic inflammatory state may also be inferred from the acute example of sepsis, wherein the root cause is systemic infection that rapidly

triggers a cytokine storm and inflammatory response leading within days to multiple organ failure and death. Notably, sepsis patients often display acute insulin resistance and impaired metabolic control, and outcomes have been shown to significantly improve with aggressive glucose control in the ICU. Thus, the microbial influence on metabolism underscores an important relationship that may introduce novel avenues for therapeutic intervention in both acute and chronic diseases that were once assumed to be quite distinct in nature.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

### References


1. Qatanani M, Lazar MA. Mechanisms of obesity-associated insulin resistance: many choices on the menu. Genes Dev 2007; 21:1443-55; PMID:17575046; http://dx.doi.org/10.1101/gad.1550907
2. Reaven G. All obese individuals are not created equal: insulin resistance is the major determinant of cardiovascular disease in overweight/obese individuals. Diab Vasc Dis Res 2005; 2:105-12; PMID:16334591; http://dx.doi.org/10.3132/dvdr.2005.017
3. Kemp DM. Type 2 Diabetes: Disease Overview. In: Jones R, ed. New Therapeutic Strategies for Type 2 Diabetes. RSC Publishing, 2012; 1-14.
4. Turner RC. The U.K. Prospective Diabetes Study. A review. Diabetes Care 1998; 21(Suppl 3):C35-8; PMID:9850487.
5. Data from the Office of Surveillance, Epidemiology, and Laboratory Services, Behavioral Risk Factor Surveillance System, CDC.
6. Greenawalt DM, Dobrin R, Chudin E, Hatoum IJ, Suver C, Beaulaurier J, et al. A survey of the genetics of stomach, liver, and adipose gene expression from a morbidly obese cohort. Genome Res 2011; 21:1008-16; PMID:21602305; http://dx.doi.org/10.1101/gr.112821.110
7. Qatanani M, Tan Y, Dobrin R, Greenawalt DM, Hu G, Zhao W, et al. Inverse regulation of inflammation and mitochondrial function in adipose tissue defines extreme insulin sensitivity in morbidly obese patients. Diabetes 2013; 62:855-63; PMID:23223024; http://dx.doi.org/10.2337/db12-0399
8. Laugerette F, Vors C, Peretti N, Michalski MC. Complex links between dietary lipids, endogenous endotoxins and metabolic inflammation. Biochimie 2011; 93:39-45; PMID:20433893; http://dx.doi.org/10.1016/j.biochi.2010.04.016
9. Mehta NN, McGillicuddy FC, Anderson PD, Hinkle CC, Shah R, Pruscino L, et al. Experimental endotoxemia induces adipose inflammation and insulin resistance in humans. Diabetes 2010; 59:172-81; PMID:19794059; http://dx.doi.org/10.2337/db09-0367
10. Monte SV, Caruana JA, Ghanim H, Sia CL, Korzeniewski K, Schentag JJ, et al. Reduction in endotoxemia, oxidative and inflammatory stress, and insulin resistance after Roux-en-Y gastric bypass surgery in patients with morbid obesity and type 2 diabetes mellitus. Surgery 2012; 151:587-93; PMID:22088821; http://dx.doi.org/10.1016/j.surg.2011.09.038