Inflammation, Insulin Resistance, and Type 2 Diabetes: Back to the Future?

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In this issue of *Diabetes*, two articles highlight the emergence of inflammation's contribution to insulin resistance and to chronic diseases in humans. The common feature in each article is the inflammation–obesity–insulin resistance connection, but each article approaches the investigation from a completely different perspective. Specifically, the study of Ortega Martinez de Victoria et al. (1) comments on factors related to macrophage activation in adipocytes as a source for cytokines for systemic inflammatory effects. In contrast, the study of Haus et al. (2) provides data on systemic effects resulting from inflammatory activation, namely, the relationship of cytokines with circulating lipid intermediates.

Approximately 2,000 years ago, Aulus (Aurelius) Cornelius Celsus, a Roman physician, was credited with the first recording of the cardinal signs of inflammation, which included calor (warmth), dolor (pain), tumor (swelling), and rubor (redness and hyperemia) (3). This general description of inflammation appears to have served clinical medicine well for most of the 2,000 years since it was first described. Until the recent past, no one would have ever envisioned that inflammation would be considered a root cause of the pathogenesis of metabolic abnormalities associated with obesity or a potential molecular target for diabetes therapies. But these statements for the inflammatory pathway represent present-day reality for basic and clinical human investigation.

The association of inflammation with carbohydrate metabolism can actually be traced back to reports from the 1800s. Shoelson et al. (4) describe these reports in a historical review. Specifically, they cite reports from over a century ago in which high-dose salicylates appeared to decrease glycosuria in individuals classified as diabetic (presumably type 2 diabetes). The works of Ebstein in 1876 and Williamson in 1901 were also cited. These works suggested remarkable benefits of salicylates for treating diabetes (4,5). In addition, clinical observations from the 1950s suggested that the use of high-dose aspirin in individuals with diabetes resulted in marked improvements in glycemia and, in at least one case, in the discontinuation of insulin (4,6). The mechanism behind these effects was not really identified because the focus on investigation at that time was clearly on insulin secretion.

The current-day investigations that link obesity, inflammation, and insulin resistance, including the articles featured in this issue of *Diabetes*, result from research findings from the early 1990s. Research reported at the time suggested that a protein called tumor necrosis factor-α, produced by adipocytes and overproduced with obesity, can attenuate metabolism locally and systemically (4,7,8). Since those initial reports, research on adipocyte secretions (e.g., interleukin-6, resistin, adiponectin, monocyte chemoattractant protein-1, plasminogen activator inhibitor 1, and angiotensinogen) and their role in whole-body insulin action has been aggressivley pursued. The investigations have focused on intracellular pathways modulated by these adipocyte products and have provided a total restructuring of concepts about obesity, insulin resistance, and development of type 2 diabetes. Specifically, research has established that the link between inflammation and insulin resistance resides at the level of the IκB kinase-β (IKKβ)/NFkB axis (4,9). As such, modulation of this system with regard to clinical treatment is being actively investigated.

The precise physiological events leading to initiation of the inflammatory response in obesity remain incompletely understood. However, one emerging hypothesis, as recently evaluated by Regazzetti et al. (10), envisions hypoxia as a novel mechanism participating in insulin resistance in adipose tissue of obese patients. It has been suggested that hypertrophic adipocytes become hypoperfused, creating regional areas of microhypoxia leading to increased expression of hypoxia-inducible factor-1. Activation of JNK1 and IKK/NFkB pathways along with increased expressions of genes involved in inflammation and endoplasmic reticulum stress appears to be enhanced in hypoxic adipose tissue. This may lead to the release of chemokines recruiting macrophages into the adipose tissue and end with the formation of crown-like structures and adipocyte death (11,12). Thus, microhypoxia is emerging as a mechanism suggested to exacerbate the proinflammatory nature of adipose tissue (10–12).

It has been suggested that obese individuals are associated with a greater rate of fatty acid breakdown and uptake compared with lean individuals, and this higher flux is postulated to be an important mediator of insulin resistance (13). When fatty acids are taken up by peripheral tissues, they can undergo β-oxidation in the mitochondria or be stored as intramuscular triglycerides. When there is increased fatty acid flux in obesity and the efficiency of skeletal muscle to dispose of fatty acids via oxidation or storage is maximized, various fatty acid "intermediates" (diacylglyerol, ceramide, etc.) accumulate in skeletal muscle (13). Ectopic lipid accumulation is postulated to impair insulin receptor signaling and to contribute to insulin resistance (13–16). It is believed, however, that the accumulation of intramuscular triglycerides may not be the direct cause of insulin resistance but

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is more an inert marker for the presence of other bioactive lipid species (diacylglyerol, fatty acyl-coenzyme A, and ceramides) that have been directly linked to defects in insulin signaling (4,9,13–16). Specifically, there is evidence to suggest that specific bioactive lipid species inside the muscle cell can activate protein kinase C, which in turn inhibits tyrosine phosphorylation of the insulin receptor and the insulin receptor substrates. In addition, ceramides activate specific protein phosphatases that dephosphorylate Akt/protein kinase B, resulting in inhibition of GLUT4 translocation and glycogen synthesis. More recently, Wang et al. (17) used skeletal muscle–specific lipoprotein lipase knockout mice and evaluated the impact of reduced lipoprotein delivery on insulin sensitivity. The data demonstrated that lipoprotein lipase–derived lipids modulated insulin signaling pathways, particularly basal and insulin-stimulated Akt activation. Thus, it is very clear that intramuscular lipid accumulation is detrimental to insulin signaling, but the cause of this accumulation is less evident.

The association of insulin resistance with lipid intermediates is not a novel idea; however, the novelty of the work by Haus et al. (2) really revolves around the quantification and identification of ceramide subspecies in the circulation. The results demonstrate that plasma levels are elevated in type 2 diabetes and that the lipid species appear not only to be associated with the severity of insulin resistance but also to be a marker of inflammation, i.e., tumor necrosis factor-α levels. So, what is the next step for this research? Are plasma ceramides now considered a surrogate marker for tissue lipid stores? Would they be valuable markers to assess the effectiveness of strategies to reduce inflammation at the myocellular level? If so, would they be viable markers that give us insight into muscle metabolism and eliminate the need to obtain muscle tissue by biopsy? Do plasma ceramides really serve to identify individuals at high risk to develop type 2 diabetes as suggested? Given the observations in this study, these are important questions that now need to be answered.

The most relevant question, however, is whether therapies that specifically target inflammation will evolve into future diabetes medications. This very idea is being actively investigated as suggested for ongoing National Institutes of Health trials such as Targeting INflammation Using SALsalate in Type 2 Diabetes (TINSAL-T2D) and other proof-of-concept studies (18,19). With the focus now clearly on modulating the inflammatory pathway as a potential target for future diabetes therapies, it is truly an exciting time for human investigation. However, let us not forget that the interesting reports from the 1950s appear to be the first to suggest modulation of inflammation as a therapy for diabetes. Given the lack of understanding of insulin action during the 1950s, it is understood why research into inflammation was not given more attention. In this regard, the present-day approach of modulating inflammation as a potential diabetes therapy reminds me of the movie from the 1980s, in which Michael J. Fox goes back in time and then returns to the present. In this regard, we can appreciate that the focus on inflammation in regard to diabetes is truly an area that is going "Back to the Future."

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