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Obesity and its associated metabolic syndrome and type 2 diabetes are becoming epidemics in the United States. e most recent data show that nationwide incidence of obesity (BMI > 30 kg/m^2) and type 2 diabetes has reached to 27.8% and 8.7%, respectively (CDC Behavioral Risk Factor Surveillance System 2012). Endothelial dysfunction, characterized by a de ciency of bio-available nitric oxide (NO), has been found to precede the development of type 2 diabetes and is signi cantly correlated with insulin resistance [1]. Early studies have shown that feeding rodent animals with a high fat diet (HFD) (~60% of calories) produces not only obesity [2] but also a state of insulin resistance [3]. ese HFD-fed rodents develop striking hyperinsulinemia with signi cantly reduced whole body insulin sensitivity and glucose disposal rates, severe impairments in both muscle and adipose tissue insulin signaling and glucose uptake and an impairment of insulin-mediated suppression of hepatic glucose output [4-6]. Moreover, obesity has been shown to be a state of low-grade chronic systemic in ammation known as the metabolic in ammation characterized by elevated levels of pro-in ammatory cytokines (such as TNF ., IL-6, IL-1 , CCL2 etc.), accumulation of leukocytes within adipose tissue and other organs, activation of macrophages in both liver and fat and activation of pro-in ammatory signaling pathways in multiple organs or tissues [7,8]. e mechanisms causing the metabolic in ammation have been related to excess nutrient intake (metabolic stress) including HFD feeding [7,8]. Dietary fat intake not only signi cantly increases circulating free fatty acids (FFAs) concentration but also a ects the composition of circulating FFAs [9]. Four-week HFD feeding has been shown to cause metabolic endotoxemia leading to the metabolic in ammation in mice [10]. e lipopolysaccharide (LPS) -induced in ammatory responses in macrophages have been shown to be mediated by Toll-Like Receptor-4 (TLR4) (pattern recognition receptors that sense lipopeptides and lipopolysaccharides of bacterial walls) [11]. Interestingly, saturated fatty acids (SFAs), but not unsaturated fatty acids, can induce an in ammatory response like LPS through activation of TLR4 [12,13]. It has also been proposed that nutrients per se are naturally in ammatory [7]. While the ood of nutrients in a short period of time may induce a brief episode of stress signaling in the target cells, long-chain SFAs, particularly palmitate, have been shown to directly activate TLR4 that may require CD36 (a class B scavenger receptor) [14-16], leading to IKK /NF NB and c-jun N-terminal kinase (JNK) pathway activation, increased production of pro-in ammatory cytokines TNF D, IL-1 and IL-6 [13,17-19] and signi cant insulin resistance as re ected by impairments in insulin-stimulated tyrosine phosphorylation of IRS-1, serine phosphorylation of Akt and eNOS, and NO production. Interestingly, recent studies have shown evidence that vascular endothelium that line up the inner wall of vasculature appear to be the rst responder to the environmental insult, high fat feeding, leading to the vascular endothelial metabolic in ammation and insulin resistance.

Vascular endothelial cells (ECs) have pleiotropic functions and regulate a large variety of cellular processes including coagulation, brinolysis, angiogenesis, adhesion and transmigration of in ammatory cells and vasculature hemodynamics. Another very important vascular endothelial function is providing a barrier that regulates entry of nutrients and hormones into the interstitium of peripheral tissues [20,21]. is is particularly true for skeletal muscle, a major site of fuel use, where its continuous vascular endothelium has well-developed junctional structures and abundant caveolae that provides a relatively tight di usional barrier. Muscle's tight endothelium has constituted the structural basis for a strong argument that the transit of insulin from the vascular to the interstitial compartment within skeletal muscle is rate limiting for insulin's metabolic action [21]. Most importantly, this rate-limiting step for peripheral insulin action is delayed in insulin-resistant obese subjects [22-24] and it has been estimated that slow trans-endothelial insulin transport may account for 30-40% of insulin resistance seen with human obes[(i)8(b)1turibi unc(io)12(I(w)6-5(l)e

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Received November 19, 2012; Accepted November 22, 2012; Published November 25, 2012

Citation: Wang H (QGRWKHOLDO 0HWDEROLF ,QÀDPPDW Fat Feeding, Insulin Resistance, and Impaired Trans-Endothelial Insulin Transport. - 2EHV :W /RVV 7KHU H GRL 10.4172/2165-7904.1000e110

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