Journal of
Obesity & Weight Loss Therapy

Editorial **Open Access**

Endothelial Metabolic Inflammation: A Link between High Fat Feeding, Insulin Resistance, and Impaired Trans-Endothelial Insulin Transport

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Obesity and its associated metabolic syndrome and type 2 diabetes are becoming epidemics in the United States. The 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 deficiency of bio-available nitric oxide (NO), has been found to precede the development of type 2 diabetes and is significantly 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]. These HFD-fed rodents develop striking hyperinsulinemia with significantly 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 inflammation known as the metabolic inflammation characterized by elevated levels of pro-inflammatory cytokines (such as TNFα, IL-6, IL-1β, CCL2 etc.), accumulation of leukocytes within adipose tissue and other organs, activation of macrophages in both liver and fat and activation of pro-inflammatory signaling pathways in multiple organs or tissues [7,8]. The mechanisms causing the metabolic inflammation have been related to excess nutrient intake (metabolic stress) including HFD feeding [7,8]. Dietary fat intake not only significantly increases circulating free fatty acids (FFAs) concentration but also affects the composition of circulating FFAs [9]. Four-week HFD feeding has been shown to cause metabolic endotoxemia leading to the metabolic inflammation in mice [10]. The lipopolysaccharide (LPS) -induced inflammatory 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 inflammatory response like LPS through activation of TLR4 [12,13]. It has also been proposed that nutrients per se are naturally inflammatory [7]. While the flood 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 IKKβ/NFκB and c-jun N-terminal kinase (JNK) pathway activation, increased production of pro-inflammatory cytokines TNFα, IL-1β and IL-6 [13,17-19] and significant insulin resistance as reflected 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 first responder to the environmental insult, high fat feeding, leading to the vascular endothelial metabolic inflammation and insulin resistance.

Vascular endothelial cells (ECs) have pleiotropic functions and regulate a large variety of cellular processes including coagulation, fibrinolysis, angiogenesis, adhesion and transmigration of inflammatory 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]. This 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 diffusional 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 obesity or type 2 diabetes [22,23,25]. Current evidence indicates that insulin transendothelial transport (TET) is a saturable process being mediated by insulin receptor (IR) at a physiological concentration of insulin [26-28] and also involves IGF-1R (and IR/IGF-1R hybrid receptors) when a supraphysiological concentration of insulin is applied [28]. It has also been reported that insulin act on vascular ECs through its intracellular signaling to facilitate its own uptake and TET [29,30]. Inhibiting insulin signaling either by treatment of cultured vascular ECs with the specific inhibitor of insulin signaling pathways or by pro-inflammatory cytokines such as TNFα or IL-6 in vitro [30-32] or by HFD feeding [32] in vivo or by endothelium-specific knockout of IRS-2 in vivo [33] all severely impair insulin TET.

Several laboratories have also reported the increased expression of pro-inflammatory cytokines in the liver, skeletal muscle and adipose tissue which required between 8 and 16 weeks, respectively after starting HFD feeding [34-36]. The vascular EC appears particularly sensitive to HFD, for example, a single high-fat meal quickly provokes endothelial dysfunction in humans as measured by flow-mediated dilation and increases the plasma levels of TNFα,IL6, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in healthy humans [37,38]. In a study, HFD induced defects in the insulin signaling and increased the inflammatory responses in thoracic aorta as early as one week after starting the HFD [35]. This suggests that the vasculature may be the "first responder" to the HFD insult.

The activation of TLR4/IKKβ/IκBα/NFκB pathway has been implicated to play a central role in the pathogenesis of both HFD-induced vascular inflammation in mice [18,35] and SFAs-induced endothelial inflammatory responses in cultured vascular ECs [19,39,40]. Inhibiting TLR4 signaling can effectively suppress palmitate-induced

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inflammation both *in vivo* and in cultured vascular ECs [13,18,19]. In addition, SFAs stimulate NADPH oxidase-dependent reactive oxygen species (ROS) production, and inhibition of TLR4 signaling inhibits both SFAs-stimulated ROS production and HFD-induced NOX4 expression [19].

Taken together, current data indicate that HFD feeding causes a chronic low-grade inflammatory state via activation of TLRs that occurs much earlier in vascular endothelial cells than that in multiple peripheral tissues or organs such as adipose tissue and liver. The HFD-induced metabolic inflammation mediates extensive cellular pathology, e.g. insulin resistance, leading to the impairment in insulin transendothelial transport. Thus, the vascular endothelial metabolic inflammation induced by high fat feeding clearly constitutes a critical link between high fat feeding, insulin resistance, and impaired trans-endothelial insulin transport.

References

1. Balletshofer BM, Rittig K, Enderle MD, Volk A, Maerker E, et al. (2000) Endothelial dysfunction is detectable in young normotensive first-degree relatives of subjects with type 2 diabetes in association with insulin resistance. Circulation 101: 1780-1784.

2. Barboriak JJ, Krehl WA, Cowgill GR, Whedon AD (1958) Influence of high-fat diets on growth and development of obesity in the albino rat. J Nutr 64: 241-249.

3. Barboriak JJ, Krehl WA (1958) Effect of dietary fats on glucose tolerance and alloxan diabetes. Am J Physiol 195: 639-642.

4. Kraegen EW, Clark PW, Jenkins AB, Daley EA, Chisholm DJ, et al. (1991) Development of muscle insulin resistance after liver insulin resistance in high-fat-fed rats. Diabetes 40: 1397-1403.

5. Anderson EJ, Lustig ME, Boyle KE, Woodlief TL, Kane DA, et al. (2009) Mitochondrial H2O2 emission and cellular redox state link excess fat intake to insulin resistance in both rodents and humans. J Clin Invest 119: 573-581.

6. Matveyenko AV, Gurlo T, Daval M, Butler AE, Butler PC (2009) Successful versus failed adaptation to high-fat diet-induced insulin resistance: the role of IAPP-induced beta-cell endoplasmic reticulum stress. Diabetes 58: 906-916.

7. Gregor MF, Hotamisligil GS (2011) Inflammatory mechanisms in obesity. Annu Rev Immunol 29: 415-445.

8. Glass CK, Olefsky JM (2012) Inflammation and lipid signaling in the etiology of insulin resistance. Cell Metab 15: 635-645.

9. Fielding BA, Callow J, Owen RM, Samra JS, Matthews DR, et al. (1996) Postprandial lipemia: the origin of an early peak studied by specific dietary fatty acid intake during sequential meals. Am J Clin Nutr 63: 36-41.

10. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, et al. (2007) Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes 56: 1761-1772.

11. Rhee SH, Hwang D (2000) Murine TOLL-like receptor 4 confers lipopolysaccharide responsiveness as determined by activation of NF kappa B and expression of the inducible cyclooxygenase. J Biol Chem 275: 34035-34040.

12. Lee JY, Sohn KH, Rhee SH, Hwang D (2001) Saturated fatty acids, but not unsaturated fatty acids, induce the expression of cyclooxygenase-2 mediated through Toll-like receptor 4. J Biol Chem 276: 16683-16689.

13. Shi H, Kokoeva MV, Inouye K, Tzameli I, Yin H, et al. (2006) TLR4 links innate immunity and fatty acid-induced insulin resistance. J Clin Invest 116: 3015-3025.

14. Schaeffler A, Gross P, Buettner R, Bollheimer C, Buechler C, et al. (2009) Fatty acid-induced induction of Toll-like receptor-4/nuclear factor-kappaB pathway in adipocytes links nutritional signalling with innate immunity. Immunology 126: 233-245.

15. Seimon TA, Nadolski MJ, Liao X, Magallon J, Nguyen M, et al. (2010) Atherogenic lipids and lipoproteins trigger CD36-TLR2-dependent apoptosis in macrophages undergoing endoplasmic reticulum stress. Cell Metab 12: 467-482.

16. Stewart CR, Stuart LM, Wilkinson K, van Gils JM, Deng J, et al. (2010) CD36 ligands promote sterile inflammation through assembly of a Toll-like receptor 4 and 6 heterodimer. Nat Immunol 11: 155-161.

17. Nguyen MT, Favelyukis S, Nguyen AK, Reichart D, Scott PA, et al. (2007) A subpopulation of macrophages infiltrates hypertrophic adipose tissue and is activated by free fatty acids via Toll-like receptors 2 and 4 and JNK-dependent pathways. J Biol Chem 282: 35279-35292.

18. Kim F, Pham M, Luttrell I, Bannerman DD, Tupper J, et al. (2007) Toll-like receptor-4 mediates vascular inflammation and insulin resistance in diet-induced obesity. Circ Res 100: 1589-1596.

19. Maloney E, Sweet IR, Hockenbery DM, Pham M, Rizzo NO, et al. (2009) Activation of NF-kappaB by palmitate in endothelial cells: a key role for NADPH oxidase-derived superoxide in response to TLR4 activation. Arterioscler Thromb Vasc Biol 29: 1370-1375.

20. Barrett EJ, Eggleston EM, Inyard AC, Wang H, Li G, et al. (2009) The vascular actions of insulin control its delivery to muscle and regulate the rate-limiting step in skeletal muscle insulin action. Diabetologia 52: 752-764.

21. Barrett EJ, Wang H, Upchurch CT, Liu Z (2011) Insulin regulates its own delivery to skeletal muscle by feed-forward actions on the vasculature. Am J Physiol Endocrinol Metab 301: E252-263.

22. Castillo C, Bogardus C, Bergman R, Thuillez P, Lillioja S (1994) Interstitial insulin concentrations determine glucose uptake rates but not insulin resistance in lean and obese men. J Clin Invest 93: 10-16.

23. Miles PD, Li S, Hart M, Romeo O, Cheng J, et al. (1998) Mechanisms of insulin resistance in experimental hyperinsulinemic dogs. J Clin Invest 101: 202-211.

24. Sjöstrand M, Gudbjörnsdottir S, Holmäng A, Lönn L, Strindberg L, et al. (2002) Delayed transcapillary transport of insulin to muscle interstitial fluid in obese subjects. Diabetes 51: 2742-2748.

25. Yang YJ, Hope ID, Ader M, Bergman RN (1994) Importance of transcapillary insulin transport to dynamics of insulin action after intravenous glucose. Am J Physiol 266: E17-25.

26. King GL, Johnson SM (1985) Receptor-mediated transport of insulin across endothelial cells. Science 227: 1583-1586.

27. Schnitzer JE, Oh P, Pinney E, Allard J (1994) Filipin-sensitive caveolae-mediated transport in endothelium: reduced transcytosis, scavenger endocytosis, and capillary permeability of select macromolecules. J Cell Biol 127: 1217-1232.

28. Wang H, Liu Z, Li G, Barrett EJ (2006) The vascular endothelial cell mediates insulin transport into skeletal muscle. Am J Physiol Endocrinol Metab 291: E323-332.

29. Wang H, Wang AX, Barrett EJ (2012) Insulin-induced endothelial cell cortical actin filament remodeling: a requirement for trans-endothelial insulin transport. Mol Endocrinol 26: 1327-1338.

30. Wang H, Wang AX, Liu Z, Barrett EJ (2008) Insulin signaling stimulates insulin transport by bovine aortic endothelial cells. Diabetes 57: 540-547.

31. Wang H, Wang AX, Barrett EJ (2011) Caveolin-1 is required for vascular endothelial insulin uptake. Am J Physiol Endocrinol Metab 300: E134-144.

32. Wang H, Wang AX, Aylor K, Barrett EJ (2013) Nitric Oxide Directly Promotes Vascular Endothelial Insulin Transport. Diabetes.

33. Kubota T, Kubota N, Kumagai H, Yamaguch S, Kozono H, et al. (2011) Impaired insulin signaling in endothelial cells reduces insulin-induced glucose uptake by skeletal muscle. Cell Metab 13: 294-307.

34. Xu H, Barnes GT, Yang Q, Tan G, Yang D, et al. (2003) Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest 112: 1821-1830.

35. Kim F, Pham M, Maloney E, Rizzo NO, Morton GJ, et al. (2008) Vascular inflammation, insulin resistance, and reduced nitric oxide production precede the onset of peripheral insulin resistance. Arterioscler Thromb Vasc Biol 28: 1982-1988.

36. Tateya S, Rizzo NO, Handa P, Cheng AM, Morgan-Stevenson V, et al. (2011) Endothelial NO/cGMP/VASP signaling attenuates Kupffer cell activation and hepatic insulin resistance induced by high-fat-feeding. Diabetes 60: 2792-2801.

37. Vogel RA, Corretti MC, Plotnick GD (1997) Effect of a single high-fat meal on endothelial function in healthy subjects. Am J Cardiol 79: 350-354.

38. Nappo F, Esposito K, Cioffi M, Giugliano G, Molinari AM, et al. (2002) Postprandial endothelial activation in healthy subjects and in type 2 diabetic patients: role of fat and carbohydrate meals. J Am Coll Cardiol 39: 1145-1150.

39. Iwata NG, Pham M, Rizzo NO, Cheng AM, Maloney E, et al. (2011) Trans fatty acids induce vascular inflammation and reduce vascular nitric oxide production in endothelial cells. PLoS One 6: e29600.

40. Kim F, Tysseling KA, Rice J, Pham M, Haji L, et al. (2005) Free fatty acid impairment of nitric oxide production in endothelial cells is mediated by IKKbeta. Arterioscler Thromb Vasc Biol 25: 989-994.