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Letter to the Editor

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Possible Mechanisms of Insulin Resistance in Obese Subjects

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Obesity is characterized by excessive triglyceride accumulation in adipose tissue cells (adipocytes); the adipocytes are not just a reservoir for storage of energy in the form of triglyceride, but more importantly act as endocrine cells; they secrete several hormones as leptin and adiponectin, also secrete adipokines as TNF-α, Interleukin 6 (IL-6) and Plasminogen activator inhibitor-1 (PAI-1). In obese subjects, adipocytes release high levels of free fatty acids (FFA) and its metabolites; Diacylglycerol (DAG) and ceramide.[1]

Acquired insulin resistance is associated with obesity. Insulin resistance is classically defined as impaired insulin-mediated glucose disposal in skeletal muscle. There are several mechanisms responsible for insulin resistance in obese subjects, which can be classified into either to activation of inflammatory pathways or changes in lipoproteins and apoprotein concentrations as result of associated dyslipidemias.[1,2]

Those mechanisms include; inflammatory pathways through activation of (IKKβ) (inhibitor of nuclear factor κB) and c-Jun N-terminal kinase 1 (JNK1): They play a role in feedback inhibition of the insulin signaling cascade. Their activation occur by increased secretion of free fatty acids (FFA) and its metabolites, which together adipokines (TNF-α), reactive oxygen species in both liver and adipose tissue. The resultant activation of JNK1 stimulates serine phosphorylation of insulin receptor substrate 1 (IRS-1) with a resultant decline in insulin signaling.[3] The second is inhibition of Peroxisome proliferator-activated receptor gamma (PPARγ) by TNF-α; PPARγ is a nuclear receptor that stimulates enzymes and/ proteins involved in fatty acid esterification and triglyceride synthesis and degradation. Its inhibition decreases triglyceride storage in adipocytes and increases lipid distribution to skeletal muscle and liver which consequently contributes to insulin resistance.[4] Also Leptin and adiponectin under normal conditions promote FA oxidation, lower lipid stores. Those effects are mediated through AMP-activated protein kinase. However; some degree of resistance to each of these adipokines in skeletal muscle develops in obese subjects leading to accumulation of DAG and ceramide, with resultant increase in FFA uptake and decreased oxidation, leading to impaired insulin signaling.[5]

Moreover, hepatocytes and adipocytes are the major sources of apolipoproteins. Apoproteins are the proteins of lipoproteins. They have several functions, for example some are known to regulate lipolytic enzyme activities and lipoprotein uptake into cells. Also some ratios of those apoproteins may be used as indicators of dyslipidemias. In addition, they exert an influence on insulin sensitivity either directly or through lipoproteins.[2]

There are several types of apoproteins:

Apolipoprotein (Apo A) is a major component of high density lipoproteins (HDL-C); apolipoprotein A-I (ApoA1) indirectly modulates insulin sensitivity through their antioxidant and anti-inflammatory action. apoA-I and apoA-II are reported to have incretin-like properties; incretins such as glucagon-like peptide-1 (GLP-1) and the glucose-dependent insulinotropic (GIP), are small peptides secreted from the gut in response to glucose, they stimulate insulin secretion from β-cells of pancreas. In addition, apoA-I and apoA-II both increase insulin secretion under basal as well as high glucose concentrations. In contrast to incretins which

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stimulate insulin secretion from β-cells only under high glucose concentrations. Also apoA-IV is similar to endogenous incretins, it stimulates insulin secretion from β-cells only under high glucose concentrations.[2,6]

The mechanism of apoA-I and apoA-II in insulin secretion is dependent on the ATP-binding cholesterol transporter, ABCA1, which is expressed on the β-cell surface, which through a series of reactions promote insulin synthesis and secretion. In addition, the effect on insulin resistance may be through decreased FA oxidation in skeletal muscle.[2]

Apolipoprotein (ApoB 100) is the major constituent of very low density lipoprotein (VLDL) and low density lipoprotein (LDL). Insulin decreases ApoB 100 secretion by promoting its degradation in the hepatocyte. Also insulin promotes clearance of circulating ApoB 100 particles by the hepatocytes through low-density lipoprotein receptor (LDLR), LDLR-related protein 1 (LRP1). Consequently, the insulin-resistance is associated with increased concentration and decreased clearance of ApoB100 and LDL-Cholesterol.[7]

Recently it was taken into consideration that ApoB and ApoB/ApoA-I ratio rather than on low density lipoprotein-cholesterol (LDL-C) is considered as early predictors of insulin resistance and reflects the balance of cholesterol transport ; ApoB/ApoA-I ratio (≥1.12 in men and ≥1.0 in women).[6] Apolipoprotein (ApoCIII) is produced by hepatocytes,it modulates the lipoprotein metabolism by inhibiting lipoprotein lipase. Increased expression of ApoCIII results in impaired regulation of pancreatic β-cell function; with increased cytoplasmic free Ca^{2+} concentration, inflammation and hyperglycemia.[8]

Apolipoprotein (Apo E) is one of the most widely studied apoproteins; There are three common isoforms of (Apo) E; (E2, E3, and E4) ApoE3 is the most common isoform with frequency of about 80%, while ApoE4 (12%) and ApoE2 (8%).[9] (ApoE) is plays a major role in lipid and lipoprotein transport. It is mainly involved in the metabolism of dietary lipids and the removal of chylomicron remnants and very low density lipoproteins (VLDL), from the circulation, through binding to LDL-receptor (LDLr). In obesity, associated dyslipidemias is characterized by slow rate of lipolysis, leading to lower and undetectable apoE exchange between lipoproteins fractions. Also increased free fatty acid plasma level, enhances hepatic VLDL and thus VLDL apoE production, with further contribution to insulin resistance and hyperglycemia.[9]

In conclusion there are several hypotheses for the pathogenesis of obesity-associated insulin resistance, including chronic inflammation and its contribution to decreased insulin secretion and dyslipidemia. Moreover, the possible role added by lipoproteins and their associated apoproteins; that help in modulating insulin sensitivity. Better understanding the above mentioned mechanisms would facilitate the development of new pharmacological strategies targeting those pathways that prevent obesity-associated diabetes and its complications.

REFERENCES

1. Muoio DM. Intramuscular triacylglycerol and insulin resistance: guilty as charged or wrongly accused? *Biochim Biophys Acta*. 2010; 1801(3): 281-288. doi: 10.1016/j.bbalip.2009.11.007

2. Vergès B, Petit JM, Duvillard L, et al. Adiponectin is an important determinant of apoA-I catabolism. *Arterioscler Thromb Vasc Biol*. 2006; 26: 1364-1369. doi: 10.1161/01.ATV.0000219611.50066.bd

3. Sun X, Liu F. Phosphorylation of IRS proteins. Yin-Yang regulation of insulin signaling. *Vitam Horm*. 2009; 80: 351-387. doi: 10.1016/S0083-6729(08)00613-4

4. Odegaard J, Ricardo-Gonzalez R, Red E, et al. Alternative M2 activation of Kupffer cells by PPARδ ameliorates obesity-induced insulin resistance. *Cell Metabolism*. 2008; 7(6): 496-507. doi: 10.1016/j.cmet.2008.04.003

5. Yadav A, Kataria M, Saini V, Yadav A. Role of leptin and adiponectin in insulin resistance. *Clin Chim Acta*. 2013; 18(417): 80-84.

6. Demerdash H, Sharara G, Katri K. Differential effects of gastric bypass and banding on the cardiovascular risk profile in morbidly obese subjects: The correlation with plasma apolipoprotein A-IV concentration. *Alexandria Journal of Medicine*. 2013; 49(1): 17-23. doi: 10.1016/j.ajme.2012.07.002

7. Haas M, Attie A, Biddinge S. The regulation of ApoB metabolism by insulin. *Trends in Endocrinology and Metabolism*. 2013; 24(8): 339-397. doi: 10.1016/j.tem.2013.04.001

8. van der Ham RL, Alizadeh Dehnavi R, Berbée JF, et al. Plasma apolipoprotein CI and CIII levels are associated with increased plasma triglyceride levels and decreased fat mass in men with the metabolic syndrome. *Diabetes Care*. 2009; 32: 184-186. doi: 10.2337/dc08-1330

9. Bach-Ngohou K, Ouguerram K, Nazih H, et al. Apolipoprotein E kinetics: influence of insulin resistance and type 2 diabetes I Apolipoprotein E kinetics: influence of insulin resistance and type 2 diabetes. *Int Journal of obesity*. 2002; 26(11): 1451-1458. doi: 10.1038/sj.ijo.0802149