Review Article

Association of adiponectin and visfatin in obesity with insulin resistance: A Non-systemic Review.

Bilal Aheed

Department of Biochemistry, Ziauddin Medical College, Karachi

ABSTRACT

Insulin resistance in chronic diseases including obesity and other metabolic diseases remains unanswered in health impairment.The release of adipocytokines from adipose tissue alters the insulin signaling pathway; in contrast some of the adipocytokines improves the insulin resistance, so it is important to understand the role and mechanism of individual adipocytokines in different condition. The adipocytokines (adiponectin and visfatin) are suggested to be a significant association between obesity and insulin resistance. Obesity increases the relative incidence of other diseases like diabetes mellitus, metabolic syndrome, and atherosclerosis and type 2 diabetes mellitus,whether or not obesity persists into the future. (Rawal Med J 2014;39:92-95).

Key words: Obesity, adipocytokines, visfatin, adiponectin, HOMA IR insulin resistance.

INTRODUCTION

The increase prevalence of obesity is an alarming condition especially in developing countries where there is scarcity of resources. According to World Health Organization, obesity is a major concern today worldwide and it is among the ten preventable health related consequences. Around 300 millions of people worldwide are obese, facing life threatening problems. Qidwaiet al reported that 6% of Pakistani school children were obese and almost 20% were overweight.[1] An study of Indian children concluded that the obesity was the leading cause for increasing insulin resistance.[2]

Obesity is considered as ongoing inflammation in human body which leads to metabolic disturbance.[3] Multiple factors including environmental, genetic and lifestyle plays an important role in the pandemic of obesity which leads to insulin resistance, diabetes mellitus and cardiovascular complications. Adipose tissue secretes multiple proteins known as adipocytokines that involved in the regulation of different metabolic and pathophysiological processes.[4]

Several adipocytokines like adiponenctin, visfatin, resistin and leptin have been discovered, which are helping explain the mechanism of insulin resistance in obese individuals.[3] It is believed that adipocytokines may contribute the development of obesity, which leads to insulin resistance. Out of these adipocytokines, adiponectin and visfatin act as an insulin sensitizer in human body. The role of these adipose derived proteins in the development of insulin resistance is still not fully discovered in obese individuals.[5]

METHODOLOGY

Selection of Articles: The key words were used including "insulin resistance," "serum adiponectin," and "obesity" for searching in the electronic databases including Google scholar, PubMed, and Medline (from last eight to ten year). Boolean Characters such as AND, OR and NOT were used in search engine. Studies that were selected must contain full text and, if needed search relevant article in the reference lists from original and review articles.

Measuring obesity and insulin resistance. Childhood and adolescence obesity were typically defined in terms of relative weight for height and age. Body weight, height, Body mass index (BMI) and waist hip circumference was measured by standardized procedures. Unfortunately, a cut-off point was not defined in childhood obesity in most of the countries. On study used the age-adjusted BMI cutoff points and defined overweight as a BMI between 21 and 23 and obesity as a BMI >23 in children.[6] Plasma glucose concentrations were measured by glucose oxidase method. Serum

insulin concentrations and adipocytokines were determined by enzyme immunoassays (ELISA) technique.

Insulin resistance was estimated by using HOMA-IR or Euglycemic clamp method. The euglycemic clamp methodis more accurate but is an invasive technique, whereas HOMA-IR is a reliable method used in obese children and adults.[7] HOMA-IR score was calculated by given formula: HOMA IR Score = fasting serum insulin (μU/ml) x fasting plasma glucose (mmol/l)/22.5. Patients with HOMA score values exceeding the 75th percentile (i.e., 2.0) were considered to have insulin resistance.[8]

DISCUSSION

The occurrence of obesity was high among children and adolescence that leads to the development of insulin resistance. The duration of obesity was an independent risk factor for the development of type 2 diabetes mellitus.[9] Obesity showed potential to develop insulin resistance in people having higher level of insulin.Obesity-associated insulin resistance was a major risk factor for development of multiple diseases includes type 2 diabetes and cardiovascular disease.[10] It was proposed that disturbed insulin sensitivity in obese has an important role in the progression of pathogenesis of obesity-related insulin resistance.[11]

The imbalance in deleterious and protective cytokines plays pivotal roles in the development and progression of pancreatic β-cell dysfunction under insulin-resistant conditions.[12] Various factors contribute insulin resistance in obese individuals, one of the possible models suggested that stimulation of adipocytokines enhancing the insulin resistance, and increasing the risk for development of different diseases including endothelial dysfunction causing atherosclerosis, dyslipidemia, metabolic syndrome and type 2 diabetic mellitus.[8]

The release of adipokines in inflammatory condition like obesity was derived from macrophages and was associated with insulin resistance.[13] Several studies showed that progression of insulin resistance provided a major rise to a hyperglycemic state that it was a risk factor for the development of diabetes mellitus type 2 in obese individuals.[14,15] It was also thought that the stored energy in adipose tissue was regulated by adipocytokines in obesity.[11]

Several studies found elevated level of some adipocytokines in obesity and impaired glucose tolerance,[16] whereas some adipocytokines stimulate glucose uptake in adipocytes and myocytes and inhibits glucose release from liver cells.[17] Pro-inflammatory cytokines possibly trigger cell signaling protein that may actually lead to insulin resistance.[18] Several studies linked obesity to the activation of pro- inflammatory cytokine and its signaling pathways that consequently lead to diabetes mellitus and other metabolic problems.[19]

Adiponectin and visfatin are the protein derived hormones or adipokines secreted by adipose tissue which exert action on insulin receptors. Several studies showed that adiponectin may exhibit antidiabetogenic properties.[20] Adiponectin also had several antiatherogenic functions, involving antiadhesive, antiproliferative, antioxidant[21] as well as anti-inflammatory effects.[20]

Adiponectin had two distinct type of receptors AdipoR1 and AdipoR2, which behaved differently in different tissues.[20] AdipoR1 mostly expressed in muscle whereas AdipoR2 expressed in liver.

The expressions of adiponectin receptor behaved in inverse association with insulin resistance condition.[22] Activation of adipoR1 and adipoR2 enhanced the AMP-activation protein kinase pathway, which possibly augmented certain diseases. It had been reported that AdipoR1 increases the expression of APPL1 protein that activated AMP-activate Kinase, which indirectly controls the insulin signaling leading to increase glucose uptake.[23] In contrast, AdipoR2 activated peroxisome proliferator- activated receptor that results in anti-inflammatory action and enhanced fatty acid oxidation.[23] Both receptor of adiponectin behave differently with hepatic glucose metabolism as Adipo1 decreases liver glucose production while hepatic expression of Adipo2 increases the uptake of glucose.[24]

Some animal studies had demonstrated that serum adiponectin level decreased with occurrence of obesity and insulin resistance.[25] Some studies also

reported that deficiency of adiponectin receptor altered the immune function as well as glucose and lipid metabolism.[26]AdipoR1 and AdipoR2 destructions inhibit the AMP-activation protein kinase signaling and peroxisome proliferator activated receptor (PPAR)-α signaling pathway that leads to insulin resistance.[22]Some of the studies reported that treatment of adiponectin activated AMPK and PPAR- α signaling pathway, improved the insulin signaling and decreased inflammatory process as well.[27]

Visfatin bonded to and activated insulin receptors at a site distant from insulin.[17,27] and decreases insulin resistance.[17] Some studies concluded that the association of visfatin level is mostly found in obese individuals with impaired glucose homeostasis.[29] Furthermore, it may be suggested that visfatin does not exhibit insulin like activity in insulin resistant state rather it imitates the effects of insulin through a binding site on insulin receptor and is a marker of visceral adiposity rather than obesity.[30]

Visfatin is a novel adipokines whose expression and plasma concentration increases with increasing levels of obesity and diabetes.[29]It significantly correlates with visceral obesity, which is known to be an early sign of metabolic syndrome and a major risk factor for the development of diabetes mellitus and insulin resistance.[28] However, there is conflicting information on the relationship of visfatin with visceral obesity and insulin resistance.[31] Some studies showed that visfatin mimics insulin like action and exerts hypoglycemic effect by reducing glucose release from hepatocytes and also stimulates glucose utilization in peripheral tissues.[28]

Debatable data regarding increased levels of plasma visfatin had been published in various studies, which showed correlation with insulin resistance and vice versa.[28,32]Adipose tissue derived proteins such as adiponectin and visfatin were found in significant association in the obese individuals.[33] The possible mechanism of development of insulin resistance is due to inhibition of phosphorylation of insulin receptorsubstrat – 1 (IRS-1) and of phosphatidylinositol-3- kinase (PI3K).[34]The biological responses of the adiponectin and visfatin had opposite effect on insulin resistance. However, both of the adipokines are believed to have antidiabetogenic properties,[23] because they exert their effect by improving insulin sensitivity through regulating glucose and lipid metabolismin peripheral tissues.[35]

CONCLUSION

Insulin resistance in obesity leads to increased risk of development of type 2 diabetes. The low level of adiponectin and its negative correlation with insulin resistance in obese individualspossibly acts asa contributing factor for development of diabetes mellitus type 2 and other complications. Serum level of visfatin showed significant association with obesity. Therefore, further research is required to determine the mechanism of other adipocytokines involved in the development of insulin resistance.

Corresponding author email: bilal_aheed@yahoo.com
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