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Obesity is the biggest driver of metabolic diseases lets focus on our waists

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Abstract---Obesity is the main determining factor of whole body reduced insulin sensitivity. This association has been demonstrated in multiple adult and pediatric cohorts. A close-fitting relation exists between typical lipid depositions patterns, exactly within the skeletal muscle and liver, as well as the intra-abdominal compartment and whole body insulin sensitivity causing different metabolic disorders. The effect of lipid deposition within insulin responsive tissues such as the liver and skeletal muscle relates to the ability of fatty acid derivate to inhibit elements of the insulin signal transduction pathway. Firming the relation of obesity and reduced insulin sensitivity are the annotations that weight gain reduces insulin sensitivity while weight loss increases it. This displays as the appearance of cardiovascular risk factor clustering with weight gain and its recovery in the face of weight loss. Both obesity and low insulin sensitivity, are independent determinants of the adverse metabolic phenotype characteristic of the metabolic syndrome.

Keywords---obesity, biggest driver, intra-abdominal, body.

Introduction

The metabolic syndrome (MS), also known as “Insulin Resistance Syndrome” or “Syndrome X” describes clustering of established cardiovascular risk factors in specific individuals [1]. These factors include altered glucose metabolism, elevated triglycerides, reduced HDL-cholesterol, elevated blood pressure and adiposity [1, 2] and have been shown to directly promote the development of atherosclerotic cardiovascular disease [3]. While the exact definition of the syndrome in the pediatric age group is still debated, it is well-established that adults who meet the criteria for the syndrome are at increased risk for the development of type 2 diabetes (T2DM) and cardiovascular diseases over time, compared to individuals who do not meet these criteria. It was Gerald Reaven who first proposed the name “insulin resistance syndrome” to this risk factor clustering as he noticed and later

demonstrated that adults with the metabolic syndrome tend to have lower insulin sensitivity (in other words—insulin resistance) compared to those who do not [4]. Moreover, insulin resistance seems to be the major driving force of the development of the cardiovascular risk factors characteristic of the syndrome. Other factors such as local inflammation within relevant tissues and surrounding blood vessels feeding them and systemic subclinical inflammation may play a substantial role in the development of MS via inducing vaso-regulatory effects of local lipid deposits around blood vessels, which may contribute both to insulin action and endothelial dysfunction [5]. In the presence of obesity, adipose tissue produces inflammatory cytokines in excess, whereas secretion of adiponectin is reduced highlighting the interplay between obesity and inflammation [6]. Cardiovascular risk factor clustering (CVRFC, termed by some as the metabolic syndrome), is not a discrete entity with a single underlying cause and is probably the result of multiple underlying factors, yet the syndrome identifies individuals at an elevated risk for accelerated atherosclerosis.

The DECODE study demonstrated that in adults without diabetes, cardiovascular risk factor clustering increases the risk of death from cardiovascular disease by 2.26 and 2.78 for men and women, respectively [7]. Taken together, these observations in adults show that clustering of cardiovascular risk factor clearly increases the risk of cardiovascular disease over time. It is well-established that longer exposure to obesity in childhood increases the risk for the presence of such clustering [8] thus it is plausible to assume that such clustering in obese children increases their risk for earlier development of cardiovascular morbidity. As indicated above, the postulated mechanistic driving force of CVRFC in childhood as well as adulthood is insulin resistance.

The Pathophysiology of Insulin Resistance and its Relation to Dyslipidemia

Insulin resistance describes a reduced effect of insulin on its target tissues. This reduced effect may be limited to some tissues while being preserved in others and can also be specific to part of the insulin signal transduction pathway but not to other parts of it within the same tissue [9]. For example, insulin receptors are widely distributed in the body in multiple tissues such as the traditional target organs liver and muscle as well as in tissues such as the kidney and the ovaries. In skeletal muscle, insulin's main role is to promote trafficking of the glucose transporter GLUT-4 to the cell membrane in order for glucose to enter into the myocyte. Muscle insulin resistance thus manifests as lower GLUT-4 expression on the membrane in response to insulin leading to reduced glucose uptake [10]. Insulin resistance within the signal transduction pathway may be present in muscle while being entirely normal in the ovary [11]. Within the liver, resistance may be present in segments of the pathway relevant to glucose metabolism (such as suppression of glycogenolysis and gluconeogenesis) but not in those related to lipid metabolism and proliferation [12]. This will manifest as reduced suppression of hepatic glucose production along with an increase of de-novo lipogenesis and VLDL production. In adipose tissue, the effect of insulin is to suppress lipolysis and adipose insulin resistance manifests as accelerated lipolysis [13].

There are multiple causes for the development of insulin resistance. These include a genetic background such as that observed in lean and healthy young adult offspring of patients with T2DM [14]. The effect of puberty on insulin sensitivity is suggested to be induced by growth hormone which causes increased lipolysis thus enhancing delivery of free fatty acids to skeletal muscle and liver. Supporting this hypothesis are the observations that in patients with growth hormone deficiency—insulin sensitivity is increased [15] while treatment with exogenous growth hormone in such patients reduces insulin sensitivity [16]. An additional factor that reduces insulin sensitivity is acute inflammation as observed during acute infections and trauma as well as the use of medications such as glucocorticoids [15, 16].

It is well-established that lipid partitioning, i.e., the pattern of lipid deposition, is a stronger determinant of whole body insulin sensitivity than the degree of obesity per se [17]. Lipid partitioning in this context refers to the intracellular accumulation of lipid within cells of insulin responsive tissues such as the liver and skeletal muscle. Such intracellular accumulation renders cells vulnerable to the molecular effects of fatty acid derivate that may interfere with the normal insulin signal transduction pathway. Fat can be stored in extracellular depots such as the subcutaneous area and can also be stored within cells of insulin responsive tissues such as skeletal muscle and liver. An additional fat storage site is the intra-abdominal (visceral) compartment. In the context of energy surplus, lipid deposition within insulin responsive tissues, such as liver and muscle, has been shown to negatively affect the glucose related portions of the insulin signal transduction pathway [17]. In this scenario, once the favorable fat depot (subcutaneous fat) exceeds its storage capacity, ectopic accumulation of lipid within the liver and skeletal muscle triggers molecular pathways that impair insulin signaling [15]. In addition, storage of fat within the visceral compartment is associated with an adverse metabolic phenotype characterized by increased inflammatory cytokines further reducing insulin sensitivity and sub-clinical inflammation along with an accelerated flux of free fatty acids into the liver resulting in intra-hepatic lipid deposition.

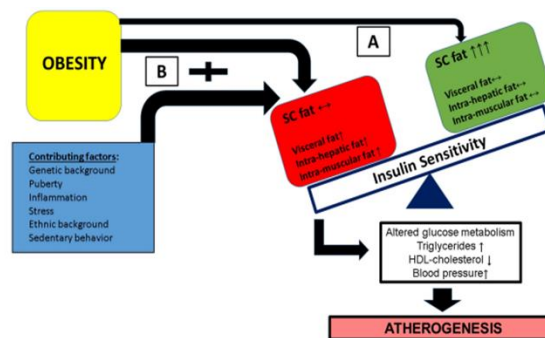


Figure 1. Obesity and Atherogenesis

Effect of obesity on lipid metabolism

Obesity is associated with increased basal lipolysis in adipose tissue, and elevated circulating FFAs[13]. Acute-phase serum amyloid A (SAA), a lipolytic adipokine in

humans, stimulates basal lipolysis. The lipolysis has been postulated to be an autocrine feedback mechanism by which increased SAA production from enlarged adipocytes A into the circulation may contribute to insulin resistance. The SAA act through the CLA-1 and the extra-cellular signal regulated kinase signaling pathway to stimulate lipolysis directly[14]. Alternatively, increased lipolysis by SAA may be indirect, i.e. through the stimulation of the lipolytic cytokines viz IL-6 and TNF- α .

Role of different fat depots in metabolism

Many studies have shown that excess fat in the upper part of the body, i.e. central or abdominal (android or male-type obesity) correlates with increased mortality and risk for disorders such as diabetes, hyperlipidemia, hypertension, and atherosclerosis of coronary, cerebral, and peripheral vessels more than the lower body or gluteofemoral or peripheral depot (gynoid i.e. female-type of fat distribution)[9,10,14,15]. Abdominal fat is composed of abdominal subcutaneous fat and intraabdominal fat (which includes visceral or intraperitoneal fat). The visceral fat is associated with disturbances in insulin-glucose homeostasis, alterations in plasma lipoprotein-lipid levels [174], particularly increased plasma triglycerides and low HDLcholesterol concentrations. These effects on the lipid profile may be due to the association of insulin resistance with disturbances in plasma lipid transport and lipoprotein levels [16]. Mobilization of FFAs is more rapid from visceral than from subcutaneous fat cells because of the higher lipolytic activity in visceral adipocytes compared to subcutaneous adipose tissue. This variation may be due to the increased expression and function of β -adrenoreceptors and a decreased insulin receptor affinity and signal transduction in visceral adipocytes [16, 17].

Summary

Weight gain reduces insulin sensitivity and weight loss increases insulin sensitivity. Both obesity per se and low insulin sensitivity are independent determinants of the adverse metabolic phenotype characteristic of the metabolic syndrome. The impact of obesity on metabolism is modulated by the lipid partitioning patterns yet it is accurate to say that increased adiposity is associated in most children with some degree of insulin resistance and that it is the strongest predictor of the presence of cardiovascular risk factors in this age group.

Conclusion

The newly identified function of the adipocytes has progressed from a simple energy storage tissue to a major endocrine system. The hormones secreted from adipose tissue influence energy homeostasis, glucose and lipid metabolism, vascular homeostasis, immune response, and reproductive functions. Newly discovered roles include the production of the cytokines IL-6, TNF- α , and leptin, which all play decisive roles in the development of obesity and insulin resistance. Thus, the enlargement of the adipose mass has pleiotropic effects on endocrine and metabolic events at whole body level that may contribute to the pathogenesis of the detrimental complications of obesity.

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