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Insulin resistance: a key therapeutic target for cardiovascular risk reduction in obese patients?

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Abstract

The global obesity epidemic has emerged as one of the most important health care problems worldwide. Insulin resistance represents a prevalent pathophysiological abnormality that underlies mechanisms of cardiometabolic disease associated with obesity. Increasing basic, animal, and clinical data support a mechanistic link between insulin resistance and vascular dysfunction, and suggest that improving insulin sensitivity may represent a therapeutic target for combating atherosclerosis and cardiovascular disease. As clinical studies suggest that insulin resistance may play a key role in the cardiovascular benefit achieved with weight loss intervention, we will discuss our clinical perspective and provide evidence that obese individuals with hyperinsulinemia may derive the greatest improvement in vascular function with weight reduction. Lastly, we will address several important unanswered questions in the field that are likely to drive future clinical investigation.

Keywords

bariatric; endothelium; insulin resistance; obesity; weight loss

The current obesity epidemic is fueling a surge in the prevalence of systemic insulin resistance, which plays a key pathophysiological role in the development of type 2 diabetes mellitus. The global impact of the obesity–diabetes partnership recently termed ‘diabesity’ is presenting a major healthcare challenge, particularly in adolescent populations who are exposed to disease conditions at an early age [1,2]. Diabesity is already one of the leading causes of chronic disease in the world, and its impact is expected to rise dramatically in the next 25 years [3,4]. Clinical studies show that a state of insulin resistance, which is prevalent in most obese subjects, represents a fundamental pathophysiological abnormality associated with a number of atherosclerotic risk factors and metabolic dysfunction that are linked to dyslipidemia, hypertension, central obesity, systemic inflammation, hypercoagulability and

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glucose intolerance. As ischemic heart disease and stroke continue to be leading causes of death in obesity, elucidating mechanisms of obesity-associated cardiovascular disease are highly needed.

Insulin's metabolic actions on a wide range of tissues including adipose tissue, liver, skeletal muscle and vascular endothelium are mediated by a broad range of target-specific actions that involve a complex cellular signaling cascade and rapid changes in protein phosphorylation and bioaction [5]. While insulin resistance generally implies impaired actions of insulin in mediating glucose uptake, transport and storage, insulin also exerts direct effects upon the vascular endothelium regulating vascular tone and blood flow. An important vascular action of insulin involves stimulation of endothelial nitric oxide production that promotes vasodilation and increased blood flow to target tissues, and preservation of insulin signaling appears to be a key homeostatic mechanism of blood vessels. Vascular insulin resistance is associated with impaired endothelial nitric oxide synthase activation, arterial inflammation, oxidative stress, increased expression of vasoconstrictive and prothrombotic mediators including endothelin-1 and plasminogen activator inhibitor-1 and vasodilator dysfunction that collectively set stage for atherosclerosis [6,7]. Animal models demonstrate that endothelium specific insulin receptor deletion promotes atherogenesis by facilitating vascular-monocyte interactions and accelerating progression of advanced lesions [8]. In obese diabetic humans, endothelial cells isolated from the vascular wall exhibit impaired insulin-stimulated endothelial nitric oxide synthase phosphorylation and inflammatory activation that are associated with arterial vasomotor dysfunction [9]. Compelling evidence is thus mounting, supporting a mechanistic link between insulin resistance and endothelial dysfunction and suggesting that improving vascular insulin sensitivity may represent a therapeutic target for combating atherosclerosis and cardiovascular disease.

A clinical tool commonly used for assessing vascular function noninvasively involves utilization of high-resolution ultrasound to interrogate nitric oxide-mediated, endothelium-dependent flow-mediated dilation and reactive hyperemia as measures of macro- and microvascular functions of the forearm vasculature. Brachial artery vasodilator impairment correlates with endothelial dysfunction in the coronary circulation, relates to traditional risk factors, improves with targeted treatment and predicts risk of future cardiovascular events [10]. This method has become a valuable tool for elucidating mechanisms of arterial dysfunction and utilization as a surrogate of cardiovascular risk for intervention studies using novel therapies. Our group and others have demonstrated that endothelial function is impaired in obesity/insulin resistance states and improves with weight reduction treatment [11,12].

Given the significant adverse healthcare impact of obesity, there is naturally great interest in investigating weight loss treatments as therapeutic intervention to improve cardiovascular risk. To date, bariatric surgical intervention stands alone as the sole weight loss intervention proven to reduce cardiovascular mortality, as recently reported by the 15-year follow-up of the prospective, observational Swedish Obesity Study cohort [13]. While a number of metabolic improvements and favorable changes in risk factor profiles occur with surgical weight loss, post hoc analyses have demonstrated that only baseline fasting insulin

concentrations, not BMI or other measured cardiac risk factors, related to the effectiveness of weight loss with regard to long-term mortality reduction. This is potentially a crucial observation because it suggests that elevated fasting insulin concentrations, which likely reflect a state of systemic insulin resistance, may serve as better selection criteria for aggressive weight reduction intervention than adiposity measures alone. This line of thinking is controversial, yet gaining ground as we have come to realize that obese individuals differ markedly in their degrees of insulin resistance and metabolic profiles, and thus cardiovascular risk. While at the clinical level, metabolic abnormalities tend to worsen as a function of excess weight, a significant subset of individuals who meet the standard BMI cut-point for obesity (BMI ≥ 30 kg/m²) are viewed as being ‘metabolically healthy obese’ defined by insulin sensitive profiles and absent metabolic syndrome and cardiovascular risk factor components [14]. This population comprising around 20–25% of obese individuals also displays clinical phenotypes characterized by reduced visceral fat accumulation, decreased hepatic fat deposition, favorable cardiopulmonary fitness, less proinflammatory adipose tissue expression patterns and preserved peripheral arterial vascular function similar to leans [14,15]. Importantly, observational studies suggest that the metabolically healthy obese may have mortality risk similar to normal weight individuals although this issue requires further study [16].

To potentially gain mechanistic understanding between blood insulin levels and cardiovascular risk in obesity, we recently examined whether the effects of weight loss on arterial function are differentially modified by baseline plasma insulin status in more than 200 overweight and obese individuals undergoing weight loss treatment over a 1-year period by either medical/dietary intervention or bariatric surgery [11]. In our study, obese individuals with high baseline plasma insulin levels (above median >12 μ U/ml) achieved significant improvement in both macro- and microvascular endothelial function following weight loss, as assessed by vascular ultrasound, while weight reduction did not confer vascular benefit to subjects with lower plasma insulin (≤ 12 μ U/ml). Our finding that insulin status predicted vascular improvement is strikingly concordant with longitudinal Swedish Obesity Study data and suggests that improved cardiovascular risk with weight loss may be intertwined with mechanisms of improved insulin sensitivity and arterial function. While additional clinical implications could be derived from our study, at least two points are worth emphasizing. First, our results demonstrated that at least 10% weight loss was required for improvement in integrated micro- and macrovascular measures of arterial health. Second, while it was much easier to achieve this degree of sustained weight loss with bariatric surgery, we ought to not conclude that therapeutic modulation was solely a function of surgical intervention. In this regard, however, recent findings from the Look AHEAD study, which reported only 6% weight loss with lifestyle modification failed to reduce cardiovascular events at 9.6 years of follow-up [17]. Several other dietary studies that achieved $<10\%$ weight loss reported no significant vascular improvement, which adds further debate to not only the optimal weight loss strategy but minimal amount of weight change required to improve vascular health.

While emerging basic, animal and clinical research supports that reversal of insulin resistance and/or hyperinsulinemia may represent a therapeutic target in cardiovascular risk reduction, there are many unanswered questions in the field. It remains unclear whether it is

insulin resistance *per se* or associated cardiovascular risk factors that are the pathogenic culprit. Additionally, while surrogate measures such as the homeostasis model of assessment are available, a clear and practical consensus definition of insulin resistance is lacking for the common practitioner. This is clinically important since a state of insulin resistance may be largely unrecognized and require treatment to avert or delay the development of overt diabetes. Also, whether insulin sensitization should be targeted with pharmacological therapy or behavioral lifestyle change and to what extent remains unclear. Since cardiovascular disease is the most important health risk associated with obesity, intervention studies targeted to improve insulin sensitivity should be designed with incorporation of hard cardiovascular endpoints. Another important question is whether metabolically healthy obesity can discriminate individuals who do not stand to gain cardiometabolic benefit from aggressive weight loss intervention. At the present time, based on increasing evidence, our personal opinion is that hyperinsulinemic and metabolically dysfunctional obese individuals are most likely to gain vascular benefit from sustained weight loss. The observation that hyperinsulinemia may serve as a biomarker of weight reduction efficacy is provocative and hypothesis generating for future clinical studies [18]. However, randomized, prospective intervention studies in obese subjects with varying strata of insulin concentration and/or sensitivity would be required to determine whether insulin status could ultimately be used in algorithms of clinical decision making.

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Biographies

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