Physiological and Metabolic Consequences of Obesity

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Fasting plasma insulin levels provide an indirect indication of insulin resistance. Glucose utilization rate, measured by the euglycemic clamp technique, is a direct measure of insulin sensitivity. Insulin sensitivity decreases with increasing body mass index (BMI) in the range of 27 to 35 kg/m^2. A higher waist-to-hip ratio is associated with lower insulin sensitivity, after adjusting for BMI. Obese patients have higher plasma free fatty acid levels and less suppression of lipolysis by insulin than lean individuals. The increased supply of fatty substrates and their competition with glucose for oxidation constitute a component of insulin resistance in obesity. Both systolic and diastolic blood pressure are increased with BMI. The hemodynamic effects may be due to an increase in cardiac output and enhanced activity of the adrenergic nervous system.

INSULIN RESISTANCE is a reduction in sensitivity to the biological effects of insulin and, although more common in obese subjects, it is also found in the lean population.[1] Obesity provided the first recorded instance of insulin resistance, documented more than 30 years ago.[2] When insulin was infused through the brachial artery, the glucose uptake by forearm tissues in response to insulin was diminished in obese patients compared with lean individuals.

MEASUREMENTS OF INSULIN SENSITIVITY

Insulin resistance can be estimated indirectly from fasting plasma insulin as high fasting insulin levels are generally associated with low insulin sensitivity. However, it must be emphasized that circulating insulin concentrations primarily reflect β-cell secretion. In obesity, true hypersecretion of insulin is present both in the fasting and fed state.[3] In addition, reduced insulin clearance by the liver may exacerbate peripheral hyperinsulinemia in obese individuals.[4]

In the general population, fasting plasma insulin concentrations increase with body mass index (BMI) (Fig 1). Patients with a BMI greater than 27 kg/m^2 are generally considered to be obese; at approximately 27 kg/m^2, fasting insulin levels begin to increase, with further weight gain indicating a further reduction in insulin sensitivity.[5] Longitudinal studies have shown that changes in BMI affect insulin sensitivity. In the San Antonio Heart Study, 1,400 subjects were weighed at baseline and again after 8 years. Patients who had gained weight over the 8-year period had increased fasting plasma insulin levels, while those who had lost weight had reduced plasma insulin levels. There were also sex differences, as mean had higher plasma insulin levels for a given weight change than women.[6]

DIRECT MEASUREMENTS

The degree of insulin sensitivity can be measured directly using the euglycemic insulin clamp. The technique involves infusing insulin at a constant rate while maintaining plasma glucose constant at any desired level. The amount of glucose required to clamp the plasma glucose concentration is a measure of the sensitivity of the tissues to insulin. Insulin-resistant subjects have a low glucose utilization rate in response to insulin.

In a clamp study of nondiabetic, normotensive individuals, glucose utilization rate was significantly lower in obese patients compared with lean controls. The difference in the ability of insulin to stimulate glucose uptake was 20% on average, while the corresponding difference in fasting plasma insulin concentrations was 50% (unpublished data). This discrepancy indicates that often hyperinsulinemia reflects enhanced insulin secretion in the presence of normal insulin sensitivity. In the whole study group, patients with BMIs less than 27 kg/m^2 had little variation in glucose utilization (Fig 2). Insulin sensitivity declined as BMI increased in the range of 27 to 35 kg/m^2. At BMIs greater than approximately 35 kg/m^2, there was no further reduction in insulin sensitivity. The waist-to-hip ratio (WHR), an index of truncal versus limb fat distribution, was measured in a subgroup of the study population. After adjusting for BMI, the WHR was found to add significantly to insulin resistance in women, but not in men.

Hepatic glucose production, as assessed by the tracer glucose dilution technique, was about 10% greater in obese patients (in whom it averaged 875 μmol/min) compared with lean individuals (804 μmol/min, $P < .01$). Regardless of body weight, men had higher hepatic glucose production than women, further illustrating the sex differences. A major in vivo action of glucose is to suppress glucose production from the liver.[7] This effect is consistently found to be blunted in obese subjects, indicating the presence of hepatic insulin resistance.[8]

FATTY ACIDS AND INSULIN RESISTANCE

It has been postulated that differences in circulating levels of free fatty acids and fat oxidation may be involved in the development of insulin resistance in obesity.[9] Studies have shown that fasting free fatty acid levels are significantly higher in obese patients than lean individuals. This means that substrates for lipid oxidation are more abundant in obese subjects. When the expanded fat mass of obese patients is taken into account, the fasting free fatty acid concentrations are more than normalized. This suggests that the increase in free fatty acids is due to the increase in fat mass.

One of the most potent actions of insulin is to suppress lipolysis, thereby restricting the provision of fatty substrate

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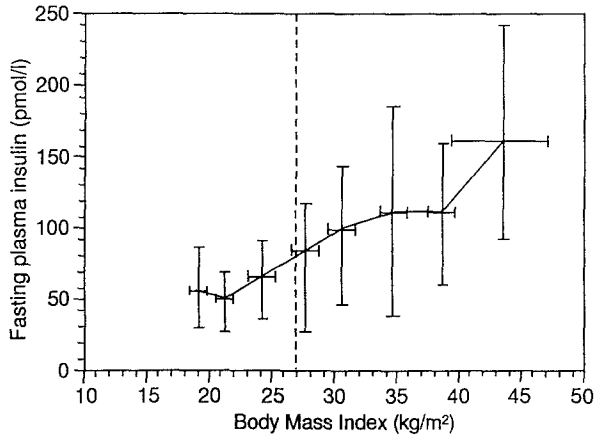

Fig 1. Fasting plasma insulin concentration as a function of BMI in 700 nondiabetic, normotensive men and women. Vertical bars are ±1 SD. Dotted line marks the conventional cut-off for the definition of obesity (BMI > 27 kg/m²).

for oxidation. Studies have shown that obese individuals suppress lipolysis less efficiently than lean controls. In a group of around 400 nondiabetic subjects, suppression of fasting free fatty acids during a euglycemic insulin clamp was significantly impaired in subjects with a BMI ≥ 27 kg/m² compared with those with BMIs below that level (72 *v* 82%, $P < .001$, unpublished data). This was still apparent when the increased fat mass was taken into account (the decrease in free fatty acids being 15 μmol/l/kg of body fat in the obese *v* 27 μmol/l/kg of body fat in the lean, $P < .001$). Thus, obese patients have an increased fat mass and less suppression of lipolysis, providing a constant surplus of free fatty acids. These excess free fatty acids compete with glucose for oxidation and may contribute to insulin resistance.

These results show that at least one component of insulin resistance in obesity is metabolic in origin. In fact, during a euglycemic clamp, whole-body glucose oxidation averaged

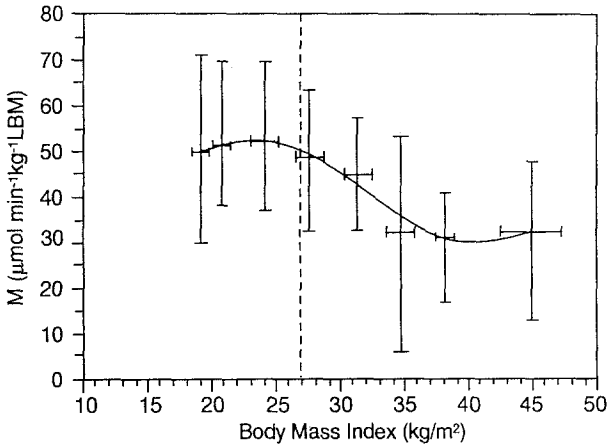

Fig 2. Insulin sensitivity (M value) as a function of body mass index in the same individuals as Fig 1. Vertical bars are ±1 SD. Dotted line marks the conventional cut-off for the definition of obesity (BMI > 27 kg/m²).

19 μmol/min/kg of fat-free mass in obese subjects versus 22 μmol/min/kg of fat-free mass in lean subjects ($P < .001$). The reduced glucose oxidation in response to insulin was probably a result of competition between fat and glucose, as simultaneous lipid oxidation rates were higher in obese patients compared with lean controls. Support for this mechanism comes from studies in vivo in normal subjects comparing the effects of a lipid infusion with saline infusion. It was found that providing an excess of fatty substrates induced insulin resistance (in terms of reduced glucose uptake, glucose oxidation, and glycogen synthesis).[10]

ENERGY EXPENDITURE

In absolute terms, obese patients have greater resting energy expenditure than lean individuals. When resting energy expenditure is adjusted according to lean body mass, there are no differences between lean and obese individuals. Obese patients have increased fat mass, but also more lean mass, which accounts for their increased resting energy expenditure.

Diet-induced thermogenesis is the increase in energy expenditure that occurs after food intake. Studies have shown that diet-induced thermogenesis is lower in obese patients compared with lean individuals. In a series of euglycemic clamp studies, the insulin-induced change in energy expenditure was 0.84 kcal/min/kg of fat-free mass in

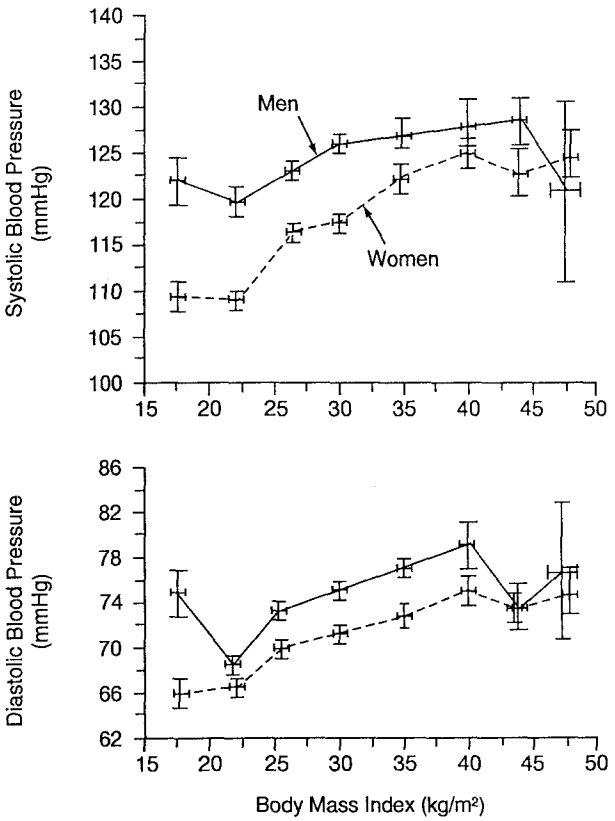

Fig 3. Systolic and diastolic arterial blood pressure values as a function of BMI in 3,000 subjects surveyed by the San Antonio Heart Study (data from reference 11).

lean subjects and 0.29 kcal/min/kg of fat-free mass in obese patients ($P < .05$), the difference being largely accounted for by women rather than men.

BLOOD PRESSURE

Hypertension is associated with obesity. Epidemiological data have shown that both systolic and diastolic blood pressure increase with BMI (Fig 3).[11] The San Antonio Heart Study data showed that normotensive, nondiabetic obese patients have a higher average blood pressure than lean individuals, regardless of age and sex. A BMI of ≥ 25 kg/m^2 results in a linear increase in blood pressure, both systolic and diastolic, until a BMI of 40 kg/m^2 is reached. The effects of BMI on blood pressure are greater in women than men.

Cardiac output increases in proportion to the expansion of body mass.[12] Expanding adipose tissue would be expected to be associated with a decrease in blood pressure due to the increase in vascular volume. However, a feedback mechanism compensates for the expansion of body tissues by increasing cardiac output. The increase in cardiac output is greater than required and pushes the blood pressure up.[13] Individuals who lose weight show a reduction in both cardiac output and blood pressure.[14]

One proposed link between obesity and the hemodynamic changes is adrenergic nervous system activity. Studies have shown that the adrenergic branch of the sympathetic nervous system is preferentially activated in obese subjects.[15,16] This stimulates cardiac output to a greater extent than required for maintenance of blood pressure.[13]

The vascular resistance of fat is actually less than that of lean tissues[17] and the increase in blood pressure is lower when weight is gained as fat rather than as lean tissue.[13] From a hemodynamic view at least, it may be advantageous to gain fat mass rather than lean tissue. Epidemiological studies, in fact, show that mortality is lower in obese hypertensives than lean hypertensives, even when adjustments are made for other factors, such as age, sex, and alcohol consumption.[18]

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