Obesity, Insulin Resistance, and Its Link to Non–Insulin-Dependent Diabetes Mellitus

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Studies have shown that obese patients have a lower tissue response to insulin than lean individuals, suggesting that obesity promotes the development of insulin resistance. The mechanisms linking obesity and insulin resistance are not known. Obese patients have decreased glucose oxidation and increased lipid oxidation compared with lean individuals, and are hyperinsulinemic, which may result in downregulation of insulin receptors. Studies in healthy subjects have shown that increased plasma levels of nonesterified free fatty acids resulted in a decrease in peripheral insulin-induced glucose uptake. Obese patients have increased plasma levels of nonesterified free fatty acids, which may be involved in the development of insulin resistance. Patients with central obesity have a greater degree of peripheral insulin resistance and higher plasma insulin levels than patients with lower body obesity. Patients with non–insulin-dependent diabetes mellitus (NIDDM) who become obese have a further reduction in insulin sensitivity. Studies in Pima Indians have shown that adiposity is the most important predictor for NIDDM in children with at least one parent who have diabetes. Insulin sensitivity improves with weight loss in obese patients.

INSULIN RESISTANCE

A SIMPLE definition of insulin resistance is the decreased ability of insulin, endogenous or exogenous, to suppress hepatic glucose production and to enhance glucose clearance, principally into skeletal muscle. This definition is useful, but restrictive, as it does not include other aspects of insulin resistance, such as decreased effects of insulin on lipid and protein metabolism.

Insulin resistance occurs in the normal population and decreased insulin sensitivity is not just confined to patients with non–insulin-dependent diabetes mellitus (NIDDM). Studies have shown that the response to insulin varies among healthy individuals with normal fasting plasma glucose levels, indicating a range of insulin sensitivity among subjects without NIDDM. This is almost certainly because insulin sensitivity is influenced by many variables, including obesity, physical activity, and dietary composition.

GLUCOSE METABOLISM

Obesity has an effect on the development of insulin resistance. Studies of obesity and insulin resistance have encountered difficulties because of the heterogeneous nature of the obese population, particularly as many obese people have abnormal glucose tolerance. A study was performed in obese patients with normal glucose tolerance, to assess the effects of pure obesity on insulin resistance.[1] The effect of insulin on glucose metabolism was compared in obese and lean populations. Insulin-stimulated glucose uptake was decreased in the obese patients (Fig 1), suggesting that obesity promotes the development of peripheral insulin resistance. However, the insulin resistance was not irreversible, and could be overcome by very high plasma insulin levels.

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The effect of obesity on hepatic glucose output has also been assessed.[1] Suppression of hepatic glucose output by insulin was diminished in obese patients compared with healthy controls, indicating that obesity is accompanied by hepatic insulin resistance.

FAT METABOLISM

The development of insulin resistance is accompanied by a reduction in the suppression of fatty acid metabolism and an increase in circulating nonesterified fatty acid (NEFA) levels. Plasma NEFA turnover in response to increasing concentrations of insulin was assessed in obese patients compared with healthy controls.[2] Suppression of fatty acid turnover by insulin was lower in the obese individuals (Fig 2). However, when the turnover rates were corrected for the fat mass of the patients, the curve for the obese group almost matched that of the control patients. This suggests that the increased NEFA turnover rate in obese individuals is due to the expanded fat mass, which in turn results in increased plasma NEFA levels and higher oxidation rates.

MECHANISM OF INSULIN RESISTANCE

The mechanisms linking obesity and insulin resistance are not known. One study compared glucose and plasma insulin levels in lean and obese individuals following an oral glucose load.[3] Plasma glucose levels were similar for obese and lean individuals, but insulin levels were higher in the obese group. It has been proposed that this hyperinsulinaemia may contribute to the insulin resistance in obese patients by the downregulation of insulin receptors.

The glucose–fatty acid cycle seems to play an important role in the development of insulin resistance in obesity. Rates of glucose oxidation and uptake have been shown to decrease in response to increased plasma NEFA levels. Studies in healthy volunteers showed that increasing the plasma NEFA levels resulted in a decrease in insulin-stimulated glucose uptake and decreased hepatic insulin sensitivity.[4] These features are seen in obesity, suggesting that increased plasma–free fatty acids levels may be involved in the development of insulin resistance.

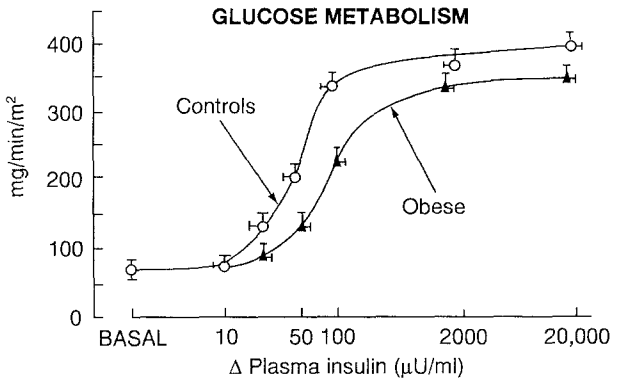

Fig 1. In obese subjects, the insulin dose-response curve is shifted to the right, indicating decreased insulin sensitivity for glucose uptake. (Reprinted with permission.[1])

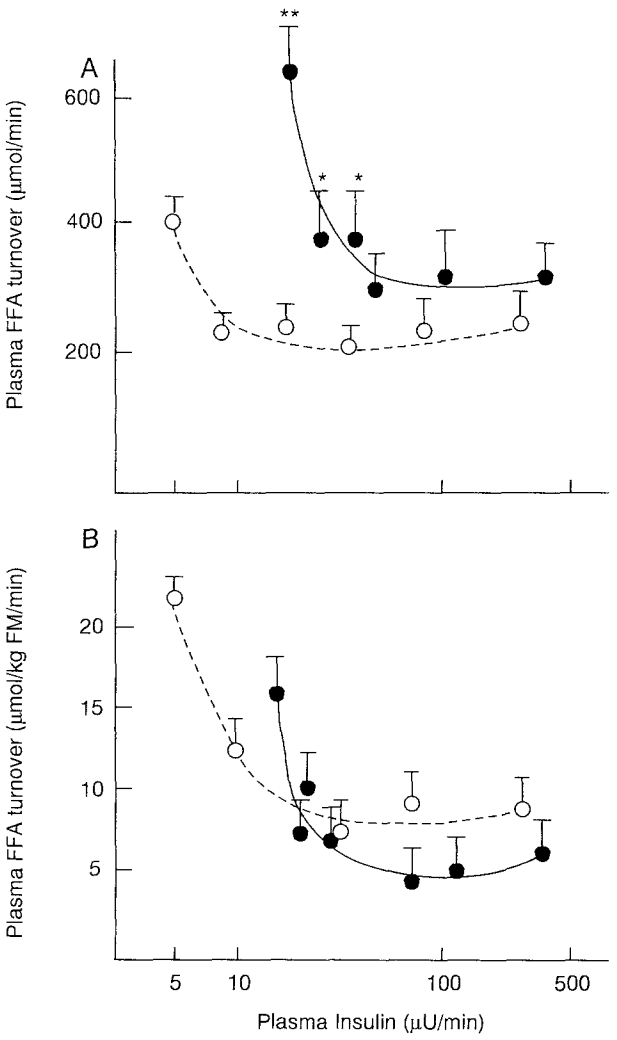

Fig 2. Absolute plasma NEFA rates are increased in obese people (A). However, when corrected for fat mass (B), the response to insulin in obese patients becomes more like that in non-obese controls. (—) Obese; (----) non-obese. (Reprinted with permission.[6])

CENTRAL OBESITY

The distribution of fat on the body influences the degree of insulin resistance that develops with obesity. Studies measured glucose utilization rates in response to increasing insulin concentrations (Fig 3). When the obese patients in the study were matched for body mass index (BMI), patients with central obesity had a greater degree of peripheral insulin resistance compared with patients with lower body obesity.[5]

Central obesity is associated with higher plasma insulin levels than lower body obesity. This appears to be due to diminished hepatic extraction of insulin from the portal circulation. Visceral adipose tissue has a greater metabolic activity compared with lower body fat, which results in a greater flux of NEFA to the liver. This in turn might interfere with the hepatic extraction of insulin.

NIDDM AND INSULIN RESISTANCE

NIDDM is also characterized by insulin resistance, which appears to be independent of the effects of obesity. Thus, in a study of lean NIDDM patients, there was decreased insulin-stimulated glucose uptake and decreased hepatic insulin sensitivity.[6] A reduction in the suppression of lipolysis by insulin was also observed in these patients. Studies have shown that nondiabetic relatives of NIDDM patients have an increased risk of developing NIDDM themselves, suggesting that the insulin resistance associated with this form of diabetes may be caused by an inherited abnormality. A postreceptor defect may account for these findings. Other proposed mechanisms include hyperglycemia, altered cell membrane composition, or altered limb blood flow.

However, the role of the glucose–fatty acid cycle in NIDDM does not appear to be as important as it is in obesity. In a study of lean NIDDM patients, nonesterified fatty acid levels were lowered using a nicotinic acid analog.

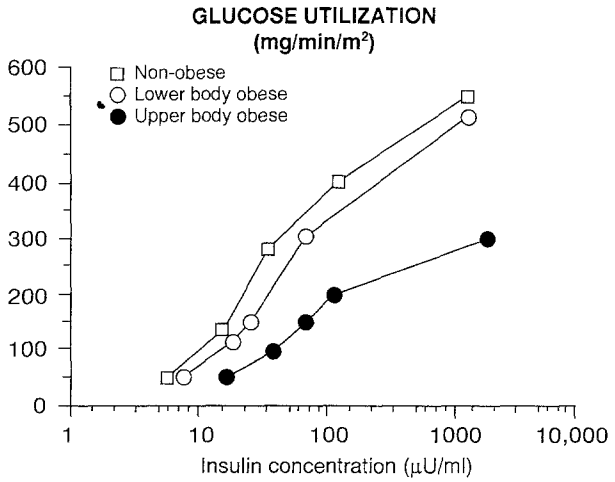

Fig 3. Glucose utilization in response to insulin is impaired in obese patients compared with non-obese controls. The defect is more marked in patients with central (upper) rather than lower body obesity. (Reprinted with permission.[5])

Hepatic insulin resistance improved, suggesting that there was an effect on the liver, but peripheral insulin resistance was unchanged.[7]

OBESITY AND NIDDM

At least a third of NIDDM patients are obese, with a BMI of greater than 30 kg/m^2. A study showed that obese NIDDM patients had a further decrease in hepatic insulin sensitivity and glucose oxidation rates compared with lean NIDDM patients.[8] Thus, the main effect of obesity in NIDDM patients was to increase hepatic insulin resistance.

Studies in Pima Indians have shown that adiposity is the most important predictor for the development of NIDDM in children with one diabetic parent.[9] It was suggested that by preventing the development of obesity in these children, it could be possible to reduce their risk of developing NIDDM. Similar studies in white families with a history of NIDDM have also shown that obesity appears to be an important early predictor for the development of NIDDM.

WEIGHT LOSS

There is limited research on the effects on health of weight loss in obese patients. One study assessed the effects of dietary intervention in obese patients.[10] There was a mean weight loss of 14 kg as body weight was reduced from 150% to 125% of the ideal. This weight loss was associated with a decrease in lipid oxidation, an increase in glucose oxidation rate, and the return of post–oral glucose insulin levels to normal. This provides indirect evidence that weight loss is associated with a lowering of insulin resistance.

SUMMARY

Obesity is associated with insulin resistance and hyperinsulinemia. Insulin resistance is more severe in patients with central obesity. Obesity also increases the insulin resistance associated with NIDDM. Studies suggest that weight loss in obese patients may lower insulin resistance.

REFERENCES

1. Bonadonna RC, Groop L, Kraemer N, et al: Obesity and insulin resistance in humans: A dose-response study. Metabolism 39:452-459, 1990

2. Groop LC, Bonadonna RC, Simonson DC, et al: Effect of insulin on oxidative and nonoxidative pathways of free fatty acid metabolism in human obesity. Am J Physiol 263:E79-E84, 1992

3. Felber JP, Haesler E, Jéquier E: Metabolic origin of insulin resistance in obesity with and without type 2 (non–insulin-dependent) diabetes mellitus. Diabetologia 36:1221-1229, 1993

4. Ferrannini E, Barrett EJ, Bevilacqua S, et al: Effect of fatty acids on glucose production and utilization in man. J Clin Invest 72:1737-1747, 1983

5. Kissebah AH: Insulin resistance in visceral obesity. Int J Obesity 15:109-115, 1991 (suppl 2)

6. Groop LC, Bonadonna RC, DelPrato S, et al: Glucose and free fatty acid metabolism in non-insulin-dependent diabetes mellitus. J Clin Invest 84:205-213, 1989

7. Walker M, Aguis L, Orskov H, Alberti KGMM: Peripheral and hepatic insulin sensitivity in non-insulin-dependent diabetes mellitus: Effect of nonesterified fatty acids. Metabolism 42:601-608, 1993

8. Groop LC, Saloranta C, Shank M, et al: The role of free fatty acid metabolism in the pathogenesis of insulin resistance in obesity and non-insulin dependent diabetes mellitus. J Clin Endocrinol Metab 72:96-107, 1991

9. McCance DR, Pettitt DJ, Hanson RL, et al: Glucose, insulin concentrations and obesity in childhood and adolescence as predictors of NIDDM. Diabetologia 37:617-623, 1994

10. Golay A, Felber JP, Dusmet M, et al: Effect of weight loss on glucose disposal in obese and obese diabetic patients. Int J Obesity 9:181-190, 1985