Antihypertensive Drugs and Insulin Resistance in Obesity

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Obesity increases the risk for hypertension. Several studies have demonstrated that weight gain raises blood pressure and weight loss reduces blood pressure. The mechanisms leading to hypertension in obese individuals are not completely understood, however the primary metabolic abnormality is insulin resistance and this has been implicated in both the hemodynamic and metabolic consequences of obesity (1). Other proposed mechanisms of obesity-related hypertension are activation of renin-angiotensin system and increased sympathetic nervous system activity.

Formerly it is reported that the short-acting calcium channel blocker, nifedipine, deteriorates insulin resistance via acceleration of the sympathetic nervous system (2) in contrast to angiotensin-converting enzyme (ACE) inhibitor (3) and that diltiazem and verapamil have no effect on insulin resistance (4). Regarding therapeutic guidelines for hypertension with diabetes from the Japan Hypertension Association and Japan Diabetes Society, calcium channel blocker is one of the first choice treatments for hypertension with diabetes. In contrast, calcium channel blocker is not the first choice treatment in the Guidelines from the American Diabetes Association, which is based on the results of IDNT.

However, the long-acting calcium channel blockers, amlodipine and nitrendipine, improve glucose tolerance (5), reduce fasting and glucose-stimulated serum insulin levels, increase serum DHEA-S and androstenedione levels, and decrease circulating cortisol (6, 7) and manidipine, improves insulin resistance as assessed by glucose clamp technique (8). These findings have been confirmed by the authors in hypertensive obese patients (9).

An elevated intracellular calcium level and its suppression effect of insulin have been reported in obese subjects (10) and an increased intracellular calcium level seems to be associated with insulin resistance. Therefore, decreased intracellular Ca²⁺ following a long-acting calcium channel blocker treatment might be possibly related to insulin resistance (11).

The authors suggested that reduced dehydroepiandrosterone (DHEA) and DHEA-sulfate level in hypertensive obese patients was caused by the shift in adrenal steroid synthesis. Although the sex ratio was similar among the groups in this paper, the finding of a sex-based disparity in DHEA-S and DHEA responses to insulin reduction suggests that the metabolism of these steroids may be regulated differently in men than in women (12) and these data render interpretation difficult.

DHEA and DHEA-S are the most abundant adrenal steroids in man. The metabolism of these hormones is unique and the serum concentration of DHEA-S in human plasma is about 300 times higher than that of DHEA and 20 times higher than that of any other steroid hormone. DHEA is considered to be a weak androgen and its concentration has a greater diurnal variation than DHEA-S. Peak serum DHEA and DHEA-S levels occur around age twenties and decrease gradually to 5% of these peak values by the age of ninety. Since Yen et al reported an antiobesity effect of DHEA in an experimental animal model (13), many other studies have disclosed a variety of other potential physiological effects of DHEA. In particular, the antidiabetic effect of DHEA has been well evaluated. DHEA reduces the hyperglycemia and/or hyperinsulinemia of diabetic mice and obese Zucker rats, suppresses the elevated hepatic glucose-6-phosphatase and fructose-1,6-bisphosphatase activities, and increases tissue sensitivity of insulin in aged rats (14, 15). In the obese group, DHEA-S levels showed a significant positive relationship with insulin (16). The authors showed insulin, DHEA, and DHEA-S were decreased in two months after the administration of calcium channel blocker in both this paper and in another trial (17). It is, however, difficult to conclude whether insulin regulated DHEA and DHEA-S or these steroids regulate the insulin level from the data. Further evaluation will be needed because the correlation between DHEA/DHEA-S and insulin is still controversial (18, 19).

TNF-α plays a major role in the pathogenesis of obesity-induced insulin resistance. Several studies have demonstrated that the production of TNF-α by adipose tissue increases in obesity-induced insulin resistant states. Complete absence of the TNF gene or both of its receptors results in significant improvement in insulin sensitivity in mice with dietary, hypothalamic, or genetic obesity. Nicardipine, amlodipine and manidipine significantly inhibit TNF-alpha production in mice at doses of more than one or ten times higher than those used clinically (20) and DHEA treatment reduces body weight and serum TNF-alpha independently, and both may ameliorate insulin resistance in obese Zucker fatty rats (21). Measuring the serum TNF level of patients may be interesting pre and post treatment with calcium channel blocker in this relevant trial.

Sympathetic nervous activity is hyperactive in obesity and furthermore hyperinsulinemia increases sympathetic nerve tone. Cilnidipine treatment did not significantly increase serum norepinephrine levels, which suggests that cilnidipine
improves insulin resistance, possibly due to its exerting a vasodilatory action without stimulating sympathetic nervous activity (22). Alvarez et al reported that sympathetic nerve activity is elevated in men with visceral obesity which is consistent with the idea that abdominal visceral fat is an important adipose tissue depot linking obesity with sympathetic neural activation in humans (23). Although the authors did not show the leptin level, it may be also interesting because leptin has an important link between obesity, sympathetic activity, and hypertension (24).

From these findings, long acting calcium channel blocker can be one of the first choice treatments for hypertensive obese patients, which the authors showed in this trial.

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References


