The Deadly Quartet and the Insulin Resistance Syndrome:
An Historical Overview

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Since the original observations by Vague almost 50 years ago, a massive literature has documented the pathologic consequences of upper body or visceral obesity. These consequences likely relate to the presence of hyperinsulinemia. More recently, the presence of hyperinsulinemia has also been recognized in nonobese hypertensives as a feature of the insulin resistance syndrome. This paper will provide an historical overview of the two clinical syndromes. (Hypertens Res 1996; 19 Suppl. 1: S9–S11)

Key Words: insulin resistance, hyperinsulinemia

Insulin resistance and subsequent hyperinsulinemia are present in virtually all obese hypertensives and in half of non-obese hypertensives. Although there is considerable overlap between obese and non-obese hypertension, I will review the history of the two clinical syndromes separately.

The Deadly Quartet

As I noted in 1989 (1), although Hippocrates 2000 years ago classified people into two body builds: habitus apoplecticus and habitus phthisicus, not until after Sheldon and coworkers popularized the idea of categorizing body shape into three somatotypes in 1930s was there mention of a relationship between body build and serum lipids or blood pressure, with broad or stocky people having higher levels of both. The importance of the distribution of body fat was really first clearly stated by Jean Vague in 1947 (2). By comparing with calipers the thickness of the subcutaneous fat over the nape of the neck to that over the sacrum and over the arm to that over the thigh, Vague determined an “index of masculine differentiation” that was much higher in the normal male than in the normal female. He called the male pattern, “android,” the female pattern, “gynoid,” and provided evidence that the android pattern was much more likely to be associated with atherosclerosis and diabetes in both men and women.

Vague’s observations were largely neglected other than for continued reports from Bjontorp and coworkers in the 1970s of metabolic changes in association with greater abdominal fat, which they termed hypertrophic obesity (3). Only after the articles of Kissebah and coworkers (4) and Krotkiewski et al. (5) further confirmed the relation between body fat distribution and metabolic complications of obesity did interest begin to mount. Since, then, numerous measurements and terms have been used to differentiate the two patterns of fat distribution.

Assessment of Fat Distribution

A number of techniques have been used to assess body fat distribution (Table 1). Although computerized tomography (CT) and magnetic resonance imaging (MRI) have been shown to be most accurate for research purposes (6), the amount of intraabdominal (visceral) fat has been shown to be accurately assessed for routine clinical use by the simple tape measurement of waist circumference (7).

The Risks of Visceral Obesity

All of the following have been shown to be more prevalent with increasing visceral fat distribution: diabetes; hypertriglyceridemia and low high-density lipoprotein cholesterol; hypertension; and coronary disease. In all these conditions, the relationship is stronger with visceral obesity than with total body obesity as has recently been documented in middle-aged Japanese men (8).

The Mechanisms for the Association

The associations between upper-body fat and various disease states seem certain and a hypothesis to explain these associations can be easily constructed (Fig. 1). This construct could explain the hyperinsulinemia of visceral obesity and, hyperinsulinemia may exert numerous effects that would raise the blood pressure to explain the higher prevalence of hypertension with visceral obesity. The association of obesity and, even more so, of visceral obesity with hyperinsulinemia and hypertension is easily understood and expected.

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Subsequent presentations in this supplement will explore the various possible mechanisms by which hyperinsulinemia could result in hypertension.

Insulin Resistance in Nonobese Hypertension

The scenario, however, unexpectedly goes beyond hypertension with upper-body obesity; increasingly strong, and surprisingly uniform, evidence documents an association of hyperinsulinemia with hypertension in the absence of obesity, whether it be upper body or nondefined. The presence of higher plasma insulin levels in nonobese hypertensive patients was first described in 1966 (9), confirmed by Berglund et al. (10) and highlighted in a large survey from Israel (11). In the last few years, the association has been amply documented (12).

In addition to high insulin levels, and perhaps responsible for them, a significant degree of peripheral resistance to insulin has been described in nonobese patients with primary (essential) hypertension. With various measures of hepatic and peripheral actions of insulin, Ferrannini and coworkers in 1987 demonstrated a 40% reduction of whole-body glucose uptake that was accounted for by a decrease in nonoxidative disposal involving impaired glycogen synthesis and glycolysis (13). The degree of peripheral insulin resistance was correlated with the severity of the hypertension. Other metabolic effects of insulin were normal, including those on splanchnic glucose release, fatty acids, and potassium transport. The authors, therefore, assume that the high plasma insulin levels after glucose loading in nonobese hypertensive subjects are compensatory to peripheral insulin resistance. Similar insulin resistance in hypertension was reported by Reaven and coworkers (14).

As research on the relationships between insulin resistance and hypertension has progressed, the absence of the usual vasodilatory action of insulin has been recognized as a cardinal feature of the syndrome (15, 16). A current hypothesis connecting various components of the syndrome is shown in Fig. 2.
Conclusion

The associations between hyperinsulinemia and insulin resistance and hypertension have been extensively explored over the past 10 years, as will be portrayed in subsequent papers in this supplement. Regardless of the mechanisms, a number of new pharmacological agents are being developed which reduce insulin resistance (17). The availability of such “insulin-sensitizers” offers the exciting potential of overcoming the many adverse effects of insulin resistance.

References