The Deadly Quartet

Upper-Body Obesity, Glucose Intolerance, Hypertriglyceridemia, and Hypertension

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- The contribution of obesity to cardiovascular risk has not been adequately appreciated because of a failure to recognize the involvement of upper-body predominance of body weight with hypertension, diabetes, and hypertriglyceridemia even in the absence of significant overall obesity. This article examines the evidence that upper-body obesity, as usually induced by caloric excess in the presence of androgens, mediates these problems by way of hyperinsulinemia. Because of these interrelationships, there is a need to identify and prevent upper-body obesity or, failing that, to provide therapies that will control the associated problems without aggravating hyperinsulinemia.

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Over the past 20 years, significant decreases in mortality from both stroke and coronary disease have occurred in the United States. The explanation for the decrease in coronary heart disease (CHD) remains uncertain,1 but improved control of hypertension has likely been the major factor responsible for the decrease in stroke.2

Awareness of these improvements in cardiovascular mortality has further increased enthusiasm for the application of preventive measures against the three major risk factors. The national campaign against hypertension, started in 1972, has been joined by a similar one against hypercholesterolemia, and smoking is being increasingly curtailed.

Despite our current enthusiasm for preventive measures, we likely face a future with even more people dying and disabled from CHD. A computer simulation model projects a marked increase in the total number of people who will suffer from CHD in the United States through the year 2010, even with the incorporation of continued reductions in risk factors as noted over the past 20 years.3 Although the model projects a further 10% decline in CHD incidence rates because of a more favorable risk factor status among younger people, the progressive aging of the United States population is responsible for the overall increase in projected rates of CHD events and mortality.

Moreover, the major risk factors continue to be both common and intractable. Despite our intense efforts to identify and to treat hypertension over the past 15 years, the average diastolic blood pressure for the population at large has changed little and, in fact, has risen among white males during this time.4 Similarly, there has been only a 3% to 4% reduction in mean serum cholesterol levels in representative samples of the United States population between 1960 and 1980.4 More than 50 million Americans still smoke cigarettes regularly.

For these reasons, the search for other remediable risk factors continues, particularly since a significant portion of those who develop CHD are not recognized by current techniques of assessment.5 The search has recently uncovered elevated plasma fibrinogen levels,6 but in the meantime we continue to underestimate the role of another common risk factor—obesity.

According to some authorities, obesity, by itself, is not a significant contributor to CHD, with the view that it becomes a problem only when it is accompanied by other risk factors, namely glucose intolerance or diabetes, hyperlipidemia, and hypertension8-9 (Fig 1). When multiple biases in the analysis of the role of obesity are taken into account, obesity does appear to be an independent risk factor for premature mortality.8-11 Nonetheless, many view moderate degrees of obesity as more of a social or cosmetic problem than a medical one, inadvertently leading to a serious oversight in the recognition of its importance as a major contributor to the other risk factors that so often accompany it. This oversight may be attributed to a lack of understanding as to how obesity leads to the other problems. Even more importantly, the role of obesity has been minimized because of the lumping of all excess body weight into one category. Although it was shown over 40 years ago that upper-body obesity is the major contributor to the risk of excess weight,12 most analyses of the role of obesity have used total weight, thereby diluting the importance of upper-body obesity.

In the last few years, new insights have made it possible to visualize the manner by which upper-body obesity connects to glucose intolerance, hypertriglyceridemia, and hypertension, with hyperinsulinemia being the key intermediary13-18 (Fig 2). This article examines these insights and proposes an overall hypothesis for their interrelationships, with the hope...
that greater awareness of the critical role of upper-body obesity will increase attention to the need to prevent it or, failing that, to correct it.

THE COMPONENTS OF THE QUARTET

Obesity, hypertension, hypertriglyceridemia, and glucose intolerance are common and they often coexist. Current estimates indicate that 35 million people in the United States are obese, defined as a body weight more than 20% above the ideal weight; 40 million are hypertensive, defined as a blood pressure above 140/90 mm Hg on repeated measurements; perhaps 10 million have diabetes, defined as fasting hyperglycemia, and an even larger number have impaired glucose tolerance.

The four conditions coexist more commonly than by chance. Among the obese, hypertension is three times and hypertriglyceridemia and diabetes at least two times more common than among the nonobese. Obesity and diabetes are both more common, perhaps twofold, among hypertensive than among normotensive people. Hypertriglyceridemia and low high-density lipoprotein cholesterol levels are often associated with obesity.

The common coexistence of these four conditions suggests a shared pathogenesis for at least some of those who suffer from two or more of these conditions. Obviously other genetic and environmental factors must be involved, since each of these conditions may occur in the absence of the others. This article examines the evidence that the combination may be related to insulin resistance with hyperinsulinemia, long recognized as a metabolic derangement of obesity. Since most of the recent evidence relates to the connection between obesity, glucose intolerance, and hypertension, and since there has been such a major emphasis in the recent literature about the dangers of the reduction of high-density lipoprotein cholesterol that usually accompanies hypertriglyceridemia, this fourth part of the deadly quartet is only touched on. The apparent association between insulin resistance plus hyperinsulinemia with hypertension in the absence of obesity is, however, noted. Emphasis is given to therapeutic maneuvers that may provide relief from the serious cardiovascular risks posed by these common conditions.

THE SCOPE OF THE PROBLEM

Not only is obesity common but it is increasing in prevalence despite repeated efforts to lose weight by millions of Americans. The problem is likely to continue to get worse; obesity has increased by 54% among 6- to 11-year-olds and by 39% among 12- to 17-year-olds in the United States over the past 15 years, and about 40% of children who are obese at age 7 years and 70% of obese adolescents will become obese adults.

Blood pressure tends to rise in concert with body weight. Both systolic and diastolic levels rise with weight gain and the association holds at all ages, although the overall rise in blood pressure with age is independent of weight gain. In the Framingham offspring study, increasing adiposity was the major controllable contributor to hypertension.

Some find that the hypertension that so frequently accompanies obesity may not be as dangerous in causing premature coronary disease as that seen in nonobese people. However, a 12-year prospective study of 7554 Japanese-American men found that coronary mortality rates were no lower and perhaps even higher in the hypertensive subjects with increasing obesity compared with normotensive subjects. The lean hypertensive subjects in this population did have higher mortality rates from cardiovascular diseases other than coronary disease, so that the increase in overall cardiovascular mortality in obese people with hypertension may be less than that seen among nonobese hypertensive subjects. Regardless, obesity must be taken seriously because of the risk factors that so often accompany weight gain.

Because of the association of hypertension, diabetes, and hypertriglyceridemia with obesity, overall mortality rises with every increment in body weight beyond the average. Mortality is minimal at weights at least 10% below the United States average. Mortality rises gradually until weights are more than 20% above the average but, considering the many millions of people involved, a little increase translates into large numbers of affected people.

THE DISTRIBUTION OF BODY FAT

However, as we have seen, there is more to obesity than just the amount of excess weight. Hippocrates classified people into two body builds: habitus apoplecticus and habitus phthisicus but not until after Sheldon and coworkers popularized the idea of categorizing body shape into three somatotypes in the 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. However, the importance of the distribution of body fat was really first clearly stated by Vague, in 1947 in French, and in 1956 in English. 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 these various diseases in both men and women.

Vague's observations were largely neglected other than for continued reports from Björntorp and coworkers in the 1970s of metabolic changes in association with greater abdominal fat, which they termed hypertrophic obesity. Only after the articles of Kissebah and coworkers and of Krotkiewski et al 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 (Table).

Of these, most investigators use one of two more objective measures, subcapular skinfold thickness, determined by calipers, or the waist-to-hip girth ratio, determined by measurement with a tape of the minimum waist circumference and the maximum hip circumference in the standing position. The two measurements usually, but not always, coincide.25,26 Of the two, waist-to-hip seems preferable since it should be more reliably measured in routine clinical practice and since some have found skinfold measurements not to be closely related to either blood pressure or cholesterol levels.27 Even more precise assessments can be obtained by computed axial tomography, but this hardly seems necessary since an increased waist-to-hip measurement is closely correlated with increased amounts of intra-abdominal fat seen by computed tomographic scans.28

ASSOCIATIONS WITH UPPER-BODY FAT

The following have all been shown to be more prevalent with increasing upper-body fat distribution: diabetes;29 hypertriglyceridemia and low high-density lipoprotein cholesterol;30 hypertension;31 and coronary disease.32,33 In all these conditions, the relationship is stronger with upper-body obesity than with total body obesity, usually defined as body mass index, ie, weight vs height squared.

The importance of upper-body fat predominance can be appreciated by examining the findings among the men in the Honolulu Heart program.34 Their 12-year incidence of CHD was little influenced by their degree of obesity, measured as body mass index. However, within each tertile of body mass index, the presence of higher upper-body fat, measured by subcapular skinfold thickness, was strongly related to the development of CHD. Waist-to-hip ratios have similarly been found to be more tightly correlated to the risk for coronary disease than have measures of weight and height.35,36 Moreover, the association of upper-body fat with increasing blood pressure can be identified even among children.37

THE PATHOPHYSIOLOGY OF UPPER-BODY FAT AND CARDIOVASCULAR DISEASE

The associations between upper-body fat and various disease states seem certain. The pathophysiology to explain these associations is not certain, but a unifying scheme can be constructed from available evidence (Fig 3). Much of this is taken from data of Kissebah and Björntorp and their coworkers,38,39 but many have contributed pieces of the overall construct. As this evidence is reviewed, we should remain aware that some of it comes from rather limited studies that obviously need confirmation and amplification. In particular, the intricacies of hepatic insulin extraction need to be more carefully dissected. Even if it is correct for some with these combined diseases, it may not apply to others who may share other pathophysiologic mechanisms.

UPPER-BODY FAT AND INSULIN

Obesity is usually accompanied by an increase in pancreatic insulin secretion and hyperinsulinemia. This is thought to reflect peripheral insulin resistance with a secondary increase in insulin secretion to maintain euglycemia.40 However, the degree of hyperinsulinemia is more striking in those with a predominance of upper-body fat.41 This has been shown both in adults and in children with upper-body fat predominance.42

Peiris et al43 provided evidence for another explanation for the increase in peripheral insulin levels seen in those with predominant upper-body obesity beyond the rise secondary to insulin resistance, namely an increase in posthepatic delivery of insulin because of a decrease in its hepatic extraction. They found a progressive decrease in the percent of hepatic insulin extraction with increasing waist-to-hip ratios in 16 obese women, suggesting that the presence of increasing upper-body fat leads to peripheral hyperinsulinemia both by hypersecretion of insulin secondary to peripheral insulin resistance and by delivery of more of the insulin that escaped hepatic extraction to the periphery.

In addition to confirming the dual mechanism for hyperinsulinemia in obesity, Peiris et al40 showed that with increasing upper-body obesity the fall in hepatic insulin extraction was inversely related to increasing levels of plasma-free testosterone, as would be expected in women with an android distribution of body fat. This finding is in keeping with the previously recognized hyperinsulinemia of both women with high endogenous androgen levels associated with polycystic ovaries and men who ingest androgenic steroids to enhance body strength.44

The next piece of this pathogenetic hypothesis relates to the considerable evidence that abdominal (upper-body) fat is metabolically more active than gluteal or femoral (lower-body) fat. When fragments of adipose tissue obtained from obese subjects were exposed to increasing concentrations of adrenaline, the stimulation of adenylate cyclase, the enzyme responsible for lipolysis, was greater in abdominal fat than in gluteal fat45 (Fig 4). This could then explain the various metabolic defects seen with increased abdominal fat, in keeping with the article by Björntorp46 that the excess of free fatty acids released during lipolysis of abdominal fat, in addition to causing hypertriglyceridemia, interferes with insulin clearance by the liver.

These data suggest that, in the presence of a positive energy balance, an increased androgenic activity, as seen in males in general and in certain women, leads to an increase in the deposition of fat within the abdomen and upper body. This increased intra-abdominal fat is more responsive to adrenergic agonists that stimulate lipolysis,47 resulting in greater release of free fatty acids into the portal circulation. These fatty acids or other accompaniments to lipolysis appear in some manner to inhibit the extraction of insulin by the liver, shunting more into the periphery. Whether or not this construct is the primary mechanism, there is little question that

![Fig 3 - A possible scheme for the development of hyperinsulinemia with upper-body obesity.](https://www.archinternmed.com/article_attachments/1516/fig3.jpg)

**Fig 3.** A possible scheme for the development of hyperinsulinemia with upper-body obesity.
upper-body fat predominance is associated with higher plasma insulin levels.

HYPERINSULINEMIA IN HYPERTENSION

This construct could explain the hyperinsulinemia of upper-body obesity and, as we shall see, hyperinsulinemia may exert numerous effects that would raise the blood pressure to explain the higher prevalence of hypertension with upper-body obesity. The association of obesity and, even more so, of upper-body obesity with hyperinsulinemia and hypertension is easily understood and expected.

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, confirmed by Berglund et al and highlighted in a large survey from Israel. In the last few years, the association has been amply documented.

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, Ferramini and coworkers 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. 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 has been reported by Shen and coworkers.

The manner by which insulin resistance and hyperinsulinemia occur in hypertension is unknown and will obviously be the focus of considerable research in the future. It appears to be independent of both obesity and glucose intolerance as measured by standard glucose tolerance tests. Some who are not obese by usual criteria may be "metabolically obese," perhaps because of an increase in intra-abdominal fat. However, the hypertensive patients and control subjects studied by Ferramini et al had similar body composition. In the absence of studies on hepatic extraction such as have been performed in subjects with upper-body obesity, the possible role of this component of insulin dynamics remains unknown. However, the degree of peripheral resistance to insulin noted by Ferramini et al seems sufficient to explain the hyperinsulinemia as purely a compensatory mechanism to maintain euglycemia.

Sympathetic nervous system overactivity could be involved in insulin resistance. Epinephrine, at levels seen during mild to moderate stress, will antagonize the effects of insulin on peripheral glucose utilization. In one study, glucose metabolism fell by 41% during the infusion of epinephrine, the same decrement as noted by Ferramini et al in their study of patients with hypertension. Although plasma epinephrine and norepinephrine levels may be somewhat elevated in patients with essential hypertension, they certainly are not at "stress" levels so that, by the relatively crude measurement of circulating concentrations of catecholamines, insulin resistance in hypertension cannot be attributed mainly to sympathetic nervous hyperactivity.

HYPERTENSIVE EFFECTS OF HYPERINSULINEMIA

However it arises, hyperinsulinemia may elevate the blood pressure in at least three ways and, possibly, in a fourth way.

Renal Sodium Retention

Insulin reduces urinary sodium excretion during a solute or water diuresis in a manner that reflects an increase of sodium reabsorption in the distal tubule. Insulin also increases sodium chloride reabsorption in proximal tubules in vitro so that multiple sites within the kidney may be involved in the retention of sodium that insulin induces in the absence of changes in overall renal function.

The hypertension in patients with diabetes or obesity tends to be associated with volume expansion and considerable evidence supports a role of body sodium and volume expansion in the pathogenesis of essential hypertension. Thus, the hyperinsulinemia seen in all three of these conditions could contribute to the elevation of blood pressure via sodium and volume expansion.

Sympathetic Nervous Activation

Increased levels of insulin in the presence of normal blood glucose levels increase plasma norepinephrine. Sympathetic nervous activation and hypertension may be induced in rats by overfeeding carbohydrates or fats, providing another amplifier for the interactions between obesity, hyperinsulinemia, and hypertension.
**Hypertrophic Effect on Smooth Muscle**

The third manner by which insulin could be involved in the pathogenesis of hypertension is via induction of vascular smooth-muscle hypertrophy. The persistence of hypertension, in whatever manner it is initiated, likely involves hypertrophy of resistance vessels, a process that could be induced by numerous humoral or neural stimuli. Insulin has been clearly shown in vitro to be a potent stimulus for the growth of vascular endothelial and smooth-muscle cells and there are receptors for insulin and insulinlike growth factor 1 on blood vessels. The greater stimulation by insulin of the in vitro growth of endothelial cells obtained from retinal capillaries than on those obtained from aorta may help explain the particular vulnerability of retinal vessels to proliferative angiopathy in diabetics who are exposed to high levels of exogenous or endogenous insulin.

**Increased intracellular Calcium**

A fourth possible way by which insulin could raise blood pressure has been postulated but not documented. In adipocytes, insulin increases cytosolic free calcium concentration. Insulin has not been shown to increase calcium within vascular or cardiac smooth-muscle cells, but it has been shown to inhibit the activity of the membrane (calcium plus magnesium)-adenosine triphosphatase in red blood cells as well as in adipocytes. In view of the primacy of calcium for smooth-muscle contraction, more information about the effect of insulin on calcium movements will surely be forthcoming to determine if this, too, is a way by which insulin could raise blood pressure.

**THE HEMODYNAMICS OF HYPERTENSION WITH OBESITY**

With the recognition that hyperinsulinemia is present in both obesity and hypertension and that hypertension is commonly associated with obesity, a logical next question is: are the hemodynamic features of hypertension seen with obesity compatible with the postulated effects of hyperinsulinemia? The answer is clearly yes, with perhaps the best evidence coming from a study of obesity induced in dogs. In nine animals fed enough beef fat to cause a 20% weight gain over 5 weeks, the mean blood pressure rose from 90 to 112 mm Hg in association with an increase in plasma volume, cardiac output, and peripheral resistance. The fasting and post-glucose plasma insulin levels rose and there was a close correlation between the rise in blood pressure and fasting plasma insulin levels. All of these features returned to control values when the extra calories were stopped and the body weights fell to control over the ensuing 6 weeks.

In humans with obesity hypertension, all of the same hemodynamic features have been found in cross-sectional observations. Moreover, when weight loss accomplishes a fall in blood pressure, plasma insulin levels fall.

With the addition of the possible ways by which hyperinsulinemia can lead to hypertension, the pathogenetic hypothesis can cover all three of the major risk factors associated with upper-body obesity (Fig 5).

**MANAGEMENT OF THE DEADLY QUARTET**

Weight loss, however it can be accomplished, is then the obvious way to correct obesity and its attendant hyperinsulinemia and hypertension. Even limited amounts of weight loss may be helpful; since the metabolically more active intra-
abdominal fat cells would be expected to respond more rapidly than fat cells elsewhere, greater benefit in correction of the metabolic abnormalities might be achieved than would be assumed from the degree of weight loss. However, the use of a low fat-high carbohydrate diet, as usually recommended for weight reduction, has been found to accentuate both the hyperglycemia and hyperinsulinemia present in eight nonobese patients with hypertension. Therefore, large amounts of carbohydrate may best be avoided and more of the reduced number of calories provided by unsaturated fats. There may be a special place for omega-3 fatty acids found in fish oils in that they prevented the insulin resistance that developed in rats fed a high linoleic fatty acid diet.\(^9\)

Exercise may be especially beneficial, both in helping to lose weight and in reducing hyperinsulinemia even without weight loss. As shown first by Krotkiewski and associates,\(^9\) repetitive aerobic exercise is associated with falls in plasma insulin and increased insulin sensitivity, even if body weight does not fall. If, after a concerted effort, weight loss and isotonic exercise are not adequate, antihypertensive drugs may be needed. The two techniques most frequently used to treat hypertension in the United States, diuretics and \(\beta\)-blockers, may be less attractive choices for obese patients with a high prevalence of glucose intolerance and hypertriglyceridemia. Diuretics and \(\beta\)-blockers may worsen glucose tolerance;\(^9\) the former may elevate cholesterol while the latter may raise triglycerides and lower high-density lipoprotein cholesterol levels.\(^9\) These metabolic perturbations may be responsible for the overall inability to show a reduction in CHD mortality by the treatment of hypertension with these two agents.\(^9\)

Of four other major classes of antihypertensive drugs, there is little that either favors or discredits the use of central \(\alpha\)-agonists, angiotensin converting enzyme inhibitors, or calcium entry blockers. All three of these groups seem to have no deleterious effects on appetite regulation, glucose tolerance, or lipid levels. Angiotensin converting enzyme inhibitors may have an exceptional ability to lower intraglomerular pressures by reducing efferent arteriolar resistance, thereby providing additional protection against progressive glomerulosclerosis that is a common and serious problem with long-term diabetes.\(^9\) The fourth class, \(\alpha\)-antagonists, have two favorable characteristics; they may lower plasma cholesterol levels\(^9\) and the use of prazosin for 12 weeks was shown to significantly reduce plasma glucose and insulin levels after an intravenous glucose tolerance test and to increase glucose utilization during a euglycemic clamp study.\(^9\)

**PREVENTION**

Better than diet, exercise, or antihypertensive drugs would be the prevention of upper-body obesity with its associated hyperinsulinemia and hypertension. The cardiovascular risk factors that accompany obesity are present before the gain of weight and they appear in parallel with the increase in weight.\(^9\) What needs greatest emphasis is the alarming rate of development of these risk factors even in children who gain excess weight and become even minimally obese.\(^9\) Moreover, those children whose parents are obese, hypertensive, or diabetic have a greater likelihood of following in their footsteps, either because of genetic or environmental sharing.\(^9\)

Greater emphasis on prevention seems essential to reduce the serious complications of the increasing upper-body obesity that so often develops in middle-aged American men. To prevent the problem, it first must be recognized. The assessment of body fat distribution, easiest and best done by simple measurement of the ratio of waist to hip circumference, should be a routine portion of all health examinations, along with body weight. Patients should be made aware of increases in waist size and warned of the potential consequences. Even in the absence of significant overall excess weight, the presence of upper body predominance, with a waist-to-hip ratio above 0.85, should be used as motivation to reduce caloric intake and to increase physical activity. Even small amounts of upper-body obesity must be recognized as a potential hazard, particularly if accompanied by other risk factors. We have nothing to lose but our paunches and a great deal to gain.

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