Medical Grand Rounds

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The Deadly Quadrangle: Upper Body Obesity, Glucose Intolerance, Hypertriglyceridemia and Hypertension

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 (1,2) but improved control of hypertension has likely been the major factor responsible for the decrease in stroke (3).

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 death and disability from CHD. Even with the incorporation of continued reductions in risk factors as noted over the past 20 years, a computer simulation model projects a marked increase in the incidence, prevalence and mortality from CHD in the United States population through the year 2010 (4) (Table 1). Although the model projects a further 10 percent 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.

Table 1: Projection of Coronary Heart Disease Incidence, Prevalence, and Mortality by Computer Simulation Model

Year	Incidence	Prevalence	Mortality
1980	692,117	5,977,405	432,613
1990	759,583	7,230,904	540,557
2000	834,522	7,973,869	596,777
2010	953,750	8,939,816	632,304

(from Weinstein et al. AJPH 1987;77:1417-26)

Moreover, the major risk factors continue to be both common and intractable. Despite our intense efforts to identify and 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 (5). Similarly, there has been only a 3 to 4 percent reduction in mean serum cholesterol levels in representative samples of the United States population between 1960 and 1980 (6). Over 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 (7). The search has recently uncovered elevated plasma fibrinogen levels (8), but in the meantime we continue to neglect the role of another very common risk factor - obesity.

The prevailing opinion is that obesity, by itself, is not a contributor to CHD and that it becomes a problem only when it is accompanied by other risk factors, namely diabetes, hyperlipidemia, and hypertension (9,10). When multiple biases in the analysis of the role of obesity are taken into account, obesity does appear to be an independent risk for premature mortality (11). Nonetheless, I believe the prevailing opinion that obesity per se is unimportant, more of a social or cosmetic problem than a medical one, has inadvertently led to a serious oversight in the recognition of its importance as a major cause of the other risk factors that so often accompany it. This neglect may be attributable 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 has been clear for over 40 years that upper body obesity is the major contributor to the risk of excess weight, almost all analyses of the role of obesity have utilized 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 intermediator. This review will connect these insights into an overall hypothesis, with the hope that greater awareness of the critical role of upper body obesity will increase attention to the need to prevent it and, failing that, to correct it.

THE COMPONENTS OF THE QUADRANGLE

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 20 percent or more above the midpoint for medium-frame people in the 1983 Metropolitan Life Insurance Company tables (12). About 40 million Americans are hypertensive, defined as a blood pressure persistently above 140/90 mm Hg (13). The prevalence of elevated triglycerides with the usually accompanying low HDL-cholesterol has not been determined for the total population. About 6.8% of the adult United States population has diabetes and another 4.6% impaired glucose tolerance (14).

The 4 conditions coexist more commonly than by chance. Among the obese, hypertension is 3 times, hypertriglyceridemia and diabetes at least 2 times more common than among the non-obese (12,15). Obesity and diabetes are both more common, perhaps two-fold, among hypertensive than among normotensive people (13,16). Hypertriglyceridemia and low HDL-cholesterol levels are often associated with obesity (17).

The common coexistence of these 4 conditions suggests a shared pathogenesis. This review will examine the evidence that the combination is 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, deservedly, so much interest about lipid abnormalities at this medical school, this fourth part of the deadly quadrangle will only be touched upon. The apparent association between insulin resistance plus hyperinsulinemia with hypertension in the *absence* of obesity will, however, be described. Emphasis will be given to therapeutic maneuvers which 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 percent among 6 to 11 year-olds and by 39 percent among 12-17 year-olds in the United States over the past 15 years and about 40 percent of children who are obese at age 7 and 70 percent of obese adolescents will become obese adults (18).

The increase in obesity likely reflects a number of factors: little physical activity in school and elsewhere by most children who are increasingly addicted to television; an increasingly sedentary lifestyle by most adults; and an increase in the number of black and poor people in the United States with both race and poverty being independent predictors of obesity (12).

Blood pressure tends to rise in concert with body weight (Table 2) (19). 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 (20). In the Framingham offspring study, increasing adiposity was the major controllable contributor to hypertension (21).

Table 2: Age-Adjusted Mean Blood Pressure and Percent Hypertensive, by Quintile of Body Mass Index

	Quintile of Body Mass Index				
Variable	1	2	3	4	5
Mean body mass index, kg/m^2	19.6	22.2	23.8	25.4	28.3
Systolic blood pressure, mm Hg	125	131	134	136	142
Diastolic blood pressure, mm Hg	76	80	83	84	88
% Hypertensive	11.3	16.5	21.4	25.6	36.4
Taking antihypertensive medication	3.5	6.1	7.9	10.4	13.8

(from Bloom et al. JAMA 1986;256:2972-5)

The Risk for Obese Hypertensives

Because of the association of hypertension, diabetes and hyperlipidemia with obesity, overall mortality rises with every increment in body weight. Mortality is minimal at weights at least 10 percent below the United States average (11). Mortality rises very gradually until weights are more than 20 percent above the average but, considering the many millions of people involved, a little increase translates into large numbers of affected people.

If hypertension, diabetes, or hyperlipidemia do not accompany obesity, the excess weight per se poses much less risk for atherosclerosis (10). Moreover, the hypertension that so commonly accompanies obesity may not be as dangerous as that seen in non-obese people. In three large surveys, obese male hypertensives were found to have significantly lower rates of coronary mortality over 9 to 15 years of observation than did equally hypertensive but lean subjects (22-24) (Figure 1). On the other hand, a 12 year prospective study of 7554 Japanese American men found that coronary mortality rates were no lower and perhaps even higher in the hypertensives with increasing obesity compared to normotensive subjects (19) (Figure 2). In this study, however, lean hypertensives had higher mortality rates from cardiovascular diseases <u>other</u> than coronary disease, probably in large part stroke which is particularly common in Japanese hypertensives. Thus, the increase in overall cardiovascular mortality in obese people with hypertension may be less than that seen among non-obese hypertensives. Regardless, obesity must be taken seriously because of the risk factors that so often accompany weight gain.

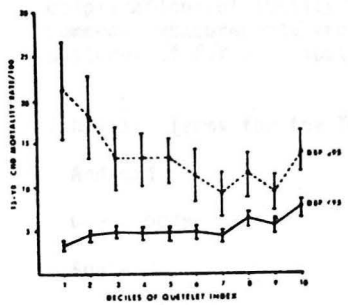

Figure 1: 15 year age-adjusted CHD mortality in normotensive (——) and hypertensive (---) subjects by deciles of body weight [Quetelet, index = weight (g) ÷ height (cm)^2]. (from Goldbourt et al, 1987, reference 24)

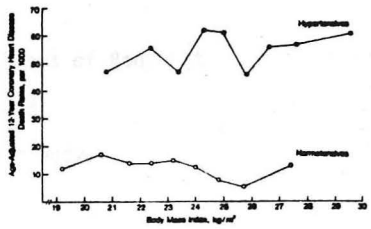

Figure 2: Age-adjusted 12-year coronary heart disease death rates by body mass index and blood pressure status-smoothed curves. Prevalent cases of cardiovascular disease and cancer are excluded. (from Bloom et al, 1986, reference 19)

THE DISTRIBUTION OF BODY FAT

However, there is more to obesity than just the amount of excess weight. Hippocrates classified people into two body builds: habitus apoplecticus and habitus phthisicus (25) but not until after Sheldon and co-workers popularized the idea of categorizing body shape into 3 somatotypes in the 1930s (26) was there mention of a relationship between body build and serum lipids (27) or blood pressure (28), with broad or stocky people having higher levels of both. But the importance of the distribution of body fat was really first clearly stated by Dr. Jean Vague, in 1947 in French (29), in 1956 in English (30). The title of the latter paper was "The degree of masculine differentiation of obesities: a factor determining a predisposition to diabetes, atherosclerosis, gout, and uric calculous disease." 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" which 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. He attributed android obesity and its multiple complications to "overactivity of the pituitary-adrenal axis."

Dr. Vague's 1947 and 1956 observations were pretty much neglected other than for continued reports from Björntorp and co-workers in Gothenberg in the 1970s of metabolic changes in association with greater abdominal fat, which they termed "hypertrophic obesity" (31,32). Only after the papers of Kissebah and co-workers in 1982 (33) and of Krotkiewski et al from Björntorp's lab in 1983 (34) 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 3).

Table 3: Terms for the Two Different Distributions of Body Fat

Android	Gynoid
Upper-body	Lower-body
Apple	Pear
Abdominal	Visceral, gluteal, femoral
Central	Peripheral
Hypertrophic	Hyperplastic
Subscapular skinfold thickness > 25	Subscapular skinfold < 25
Waist-to-hip girth ratio > 0.85	Waist-to-hip < 0.85

Of these, most investigators use one of the two more objective measures, subscapular skinfold (SSF) thickness, determined by calipers, or the waist-to-hip girth ration (WHR), determined by measurement with a tape of the minimum waist circumference and the maximum hip circumference in the standing position. The two measurements may not always coincide but they both are associated with the same metabolic disorders (35). Of the two WHR is preferable since it should be more reliably measured in routine clinical practice. Even more precise assessments can be obtained by computed axial tomography but this hardly seems necessary since an increased WHR is closely correlated with increased amounts of intra-abdominal fat seen by CT scans (36).

Associations With Upper Body Fat

The following have all been shown to be more prevalent with increasing upper-body fat distribution:

- diabetes (37)
- hypertriglyceridemia (38) and low HDL-cholesterol (39)
- hypertension (34,40,41)
- coronary disease (42-44)

In all of these conditions, the relationship is stronger with upper body obesity than with total body obesity, usually defined as body mass index.

The importance of upper body fat predominance can be appreciated by examining the findings among the men in the Honolulu Heart program (44) (Figure 3). Their 12 year incidence of coronary heart disease (CHD) was little influenced by their degree of total body fat, whereas within each tertile of total body fat, the presence of higher upper body fat, measured by subscapular skinfold thickness, was strongly related to the development of CHD. Moreover, the association of upper body fat with increasing blood pressure can be identified even among young children (45).

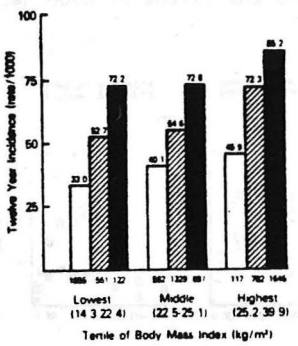

Figure 3: Age-adjusted 12 year incidence of definite CHD in patients divided into tertiles of subscapular skinfold thickness (open bar - lowest; solid bar - highest) within each tertile of body mass index. Figures along x-axis are numbers of subjects. (from Donahue et al, 1987, reference 44)

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 (Figure 4). Much of this is taken from data by Kissebah and Björntorp and their co-workers 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.

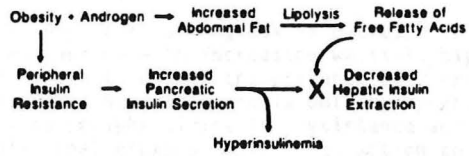

Figure 4: A proposed scheme for the development of hyperinsulinemia with upper body obesity.

Upper Body Fat and Insulin

Obesity is 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 (46). However, the degree of hyperinsulinemia is more striking in those with a predominance of upper body fat (47) (Figure 5). This has been shown both in adults and children with upper body fat predominance (48).

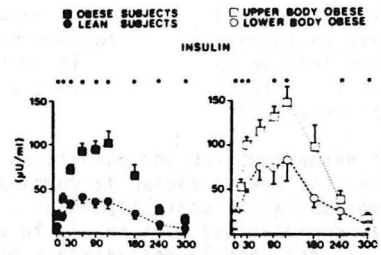

Figure 5: Plasma insulin concentration during oral glucose tolerance testing. Left: Comparison between the non-obese (n=6) and the obese (n=16) groups; Right: Comparison between the age- and weight-matched upper (n=6) and lower (n=7) body obese subgroups. *P<0.05 or less. (from Peiris et al, 1986, reference 47)

Peiris et al (47) sought 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 post-hepatic delivery of insulin because of a decrease in its hepatic extraction. As numerous investigators have done, they took advantage of the fact that, whereas the first-pass extraction of insulin from the portal circulation by the liver can be extensive, the connecting peptide (C-peptide) that is secreted on an equimolar basis with insulin is negligibly extracted. They measured the peripheral turnover kinetics of C-peptide for an estimate of prehepatic (total pancreatic) insulin production and subtracted from that estimate the amount of peripheral insulin turnover or the posthepatic insulin delivery rate. The difference between total insulin production and posthepatic insulin delivery was taken as an estimate of the percentage of hepatic insulin extraction during the first portal passage.

Peiris et al (47) found a progressive decrease in the percent of hepatic insulin extraction with increasing waist-to-hip ratio in 16 obese women (Figure 6), 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. Similar results had previously been noted in patients with obesity not characterized as to its distribution (49).

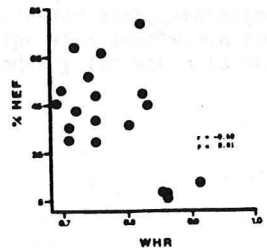

Figure 6: Correlation between waist to-hip girth ratio (WHR) and percent of hepatic extraction fraction of insulin (HEF). (from Peiris et al, 1987, reference 49)

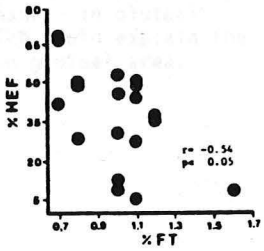

Figure 7: Relationship of plasma percent of free testosterone (% FT) to hepatic extraction (HEF) of insulin. (from Peiris et al, 1987, reference 49)

In addition to confirming the dual mechanism for hyperinsulinemia in obesity, the Milwaukee investigators 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 (Figure 7) (50). 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 (51).

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 (52). As shown by in vitro study of fragments of adipose tissue obtained from abdominal and gluteal subcutaneous depots from obese subjects, the rate of lipolysis after exposure to the beta$_1$-adrenergic agonist isoproterenol was higher in abdominal fat than in gluteal fat obtained both from men and women (53) (Figure 8 left). This could then explain the various metabolic defects seen with increased abdominal fat, in keeping with the report by Björntorp (32) 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. Strömblad and Björntorp have observed a similar decrease in hepatic insulin clearance in rats with increased abdominal fat secondary to caloric-induced obesity (54).

The study by Leibel and Hirsch (53) also demonstrated that exposure to the mixed alpha/beta adrenergic agonist norepinephrine induced a lesser rate of lipolysis in the abdominal fat from obese men than from obese women (Figure 8, right). The authors interpreted this as a reflection of greater abdominal alpha$_2$-receptor function in men, which is known to exert an antilipolytic effect. The greater antilipolytic effect of abdominal alpha$_2$-receptors in men could then explain the greater tendency for men to accumulate fat within the abdomen. Conversely, increased alpha$_2$-receptor activity has been measured in gluteal adipocytes from women compared to men (55), which could explain the tendency for women to accumulate more fat in the gluteal area.

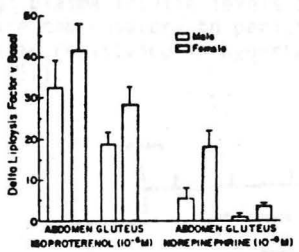

Figure 8: Effects of sex and anatomical site on mean ($\pm$ SEM) lipolytic responses to isoproterenol (10^{-6} M) and norepinephrine (10^{-6} M). The DLF is the increment in lipolysis rate above that in unstimulated tissue. (from Leibel and Hirsch, 1987, reference 53)

These data suggest that 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 response to beta$_1$-adrenergic agonists which stimulate lipolysis, resulting in greater release of free fatty acids into the portal circulation. These fatty acids or other accompaniments to lipolysis may in some manner inhibit the extraction of insulin by the liver, shunting more into the periphery (54). Whether this construct is correct or not, there is no question that 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 non-defined. The presence of higher plasma insulin levels in non-obese hypertensive patients was first described in 1966 (56), confirmed by Björntorp's group in 1976 (57) and highlighted in a large survey from Israel in 1985 (16). In the last few years, multiple papers and reviews have documented the association (58,59).

In addition to high insulin levels, and perhaps responsible for them, a significant degree of peripheral resistance to insulin has been described in non-obese hypertensive patients (Figure 9) (60). With various measures of hepatic and peripheral actions of insulin, these investigators demonstrated a 40 percent reduction of whole-body glucose uptake that was accounted for by a decrease in nonoxidative disposal involving impaired 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 hepatic glucose release, fatty acids and potassium transport. The authors, therefore, assume the high plasma insulin levels after glucose loading in non-obese hypertensives are compensatory to peripheral insulin resistance. Similar insulin resistance in hypertension has been reported by Reavan and co-workers (61).

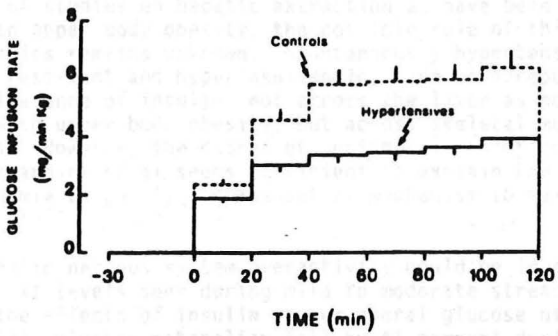

Figure 9: The amount of glucose that had to be infused to maintain a steady plasma glucose concentration during the insulin clamp period (from Time zero on). (from Ferrannini et al, 1987, reference 60)

Ferrannini et al (60) reviewed the evidence that similar resistance to insulin's peripheral effect on glucose utilization as noted in their hypertensives has been seen in obesity and non-insulin dependent diabetes mellitus (Table 4). However, these latter two conditions also display other defects in insulin action that are not seen in hypertension.

Table 4: Characteristics of Insulin Resistance in Obesity, Non-Insulin-Dependent Diabetes Mellitus (NIDDM), and Essential Hypertension

Effect of Insulin	Obesity	NIDDM	Hypertension
Whole-body glucose uptake	↓	↓	↓
Suppression of glucose output	↓	±	±
Glucose oxidation	↓	↓	±
Lipid oxidation	↑	±	±
Nonoxidative glucose disposal	↓	↓	↓
Suppression of lipolysis	±	↓	±
Promotion of potassium uptake	↓	±	±

* ↓ Denotes reduced, ↑ increased, and ± more or less unchanged.

(From Ferrannini et al. N Engl J Med 1987;317:350-7)

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. In the absence of studies on hepatic extraction as have been performed in subjects with upper body obesity, the possible role of this component of insulin dynamics remains unknown. Spontaneously hypertensive rats, which are insulin resistant and hyperinsulinemic, have been reported to have a decreased clearance of insulin, not across the liver as noted in animals and people with upper body obesity, but across skeletal muscle and the kidneys (62). However, the degree of peripheral resistance to insulin noted by Ferrannini et al seems sufficient to explain the hyperinsulinemia as purely a compensatory mechanism to maintain euglycemia.

Sympathetic nervous system overactivity could be involved. Epinephrine, at levels seen during mild to moderate stress, will antagonize the effects of insulin on peripheral glucose utilization. In one study (63), glucose metabolism fell by 41 percent during the infusion of epinephrine, the same decrement as noted by Ferrannini et al in their study of patients with hypertension (60). 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. Nonetheless, plasma norepinephrine levels are increased in older (64) and obese (65) subjects so that sympathetic activity may be involved in the high incidence of hypertension seen in those populations.

As logical as is a role for increased sympathetic activity in the causation of both hypertension and insulin resistance, one study has failed to find evidence for increased sympathetic activity in a group of obese hypertensives compared to a group of obese normotensive subjects (66).

HYPERTENSIVE EFFECTS OF HYPERINSULINEMIA

However it arises, hyperinsulinemia may elevate the blood pressure in at least three possible ways. In addition insulin has effects on transport across cell membranes that also may serve to raise the blood pressure.

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 (67). Insulin also increase sodium chloride reabsorption in proximal tubules *in vitro* (68) 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 (69) or obesity (70) 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 (71). 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 (72). Moreover, insulin increases cardiac rate and contractility in a manner that may not be entirely mediated by increased plasma catecholamines (73).

Sympathetic nervous activation and hypertension may be induced in rats by overfeeding carbohydrates or fats (58), 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. As reviewed by Lever (74), the persistence of hypertension, however it is initiated, likely involves hypertrophy of resistance vessels, a process which could be induced by numerous humoral or neural

stimuli. Insulin has been clearly shown *in vitro* (75,76) (Figure 10) and possibly *in vivo* (77) to be a potent stimulus for the growth of vascular endothelial and smooth muscle cells and there are receptors for insulin and insulin-like growth factor I on blood vessels (78). The greater stimulation by insulin of the *in vitro* growth of endothelial cells obtained from retinal capillaries than on those obtained from aorta (Figure 11) (78) 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.

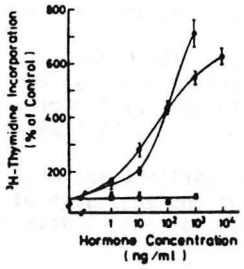

Figure 10: Stimulation of [^{3}H]thymidine incorporation into smooth muscle cells exposed to insulin (O--O), insulin like growth factor (IGF) I (●--●), human growth hormone (▲--▲) for 24 h. (from Kaiser et al, 1985, reference 76)

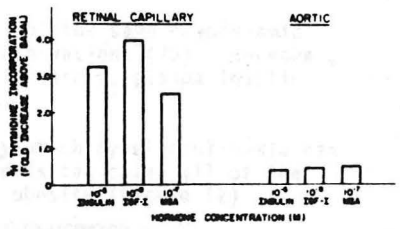

Figure 11: Comparison of the stimulating effect of insulin, IGF-I, and MSA on ^{3}H-thymidine incorporation in endothelial cells from bovine retinal capillaries (left) and aorta (right). (from King et al, 1985, reference 78)

Increased Sodium Pump Activity

Yet another way in which insulin could be involved in the pathogenesis of hypertension is by its effects on cell membrane transport mechanisms. Insulin incubated with leucocytes stimulates ouabain-sensitive sodium efflux, a measure of sodium pump activity (79). An increase in sodium pump activity could explain the sodium-retaining and hypokalemic effects of insulin. The role of the sodium pump in the pathogenesis of primary hypertension remains uncertain, some believing it is inhibited by a circulating inhibitor, others that it is stimulated to compensate for an increase in intracellular sodium that arises from a defect in membrane transport. Therefore, the possible role of insulin-induced stimulation of the sodium pump (assuming that what has been shown with leucocytes is a reflection of what happens in vascular tissue), remains uncertain although the apparent result would be a reduction in intracellular sodium concentration, not an effect that would be expected to be responsible for a rise in 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 (80). In 9 animals fed enough beef fat to cause a 20 percent 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 (70). Moreover, when weight loss accomplishes a fall in blood pressure, plasma insulin levels fall (81,82).

With the addition of the possible ways by which hyperinsulinemia can lead to hypertension, the pathogenetic hypothesis can cover all of the major risk factors associated with upper body obesity (Figure 12).

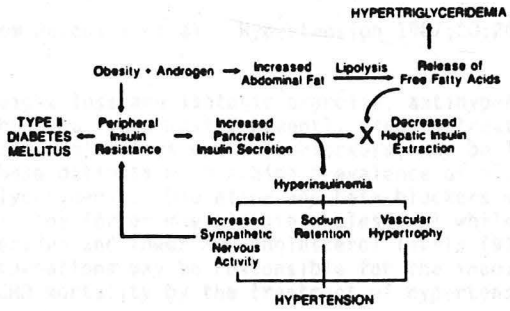

Figure 12: A proposed scheme for the development of hyperinsulinemia with the mechanisms for induction of the major complications.

MANAGEMENT OF THE DEADLY QUADRANGLE

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 (83), greater benefit in correction of the metabolic abnormalities might be achieved than would be assumed from the degree of weight loss. There may be a special place for omega3 fatty acids found in fish oils in that they prevented the insulin resistance which developed in rats fed a high linoleic fatty acid diet (84). However, these fatty acids may accentuate hypercholesterolemia (85), so their value remains uncertain.

Exercise may be especially beneficial, both in helping to lose weight and in reducing hyperinsulinemia even without weight loss. As shown first by Björntorp and associates (86,87), repetitive isotonic exercise is associated with falls in plasma insulin and increased insulin sensitivity, even if body weight does not fall. Others have also noted improved glucose utilization and lower plasma insulin levels after regular exercise both in rats (88) and in humans (89) (Table 5).

Table 5: Anthropomorphic, Hemodynamic, and Biochemical Data for 50 Obese Adolescents Before and After a 20-Week Weight Loss Program

	Obese control (n=17)		Diet group (n=15)		Diet + exercise group (n=18)	
	Before	After	Before	After	Before	After
Weight (kg)	72.6	76.4	72	69.1	71.2	68.4
Blood pressure (mm Hg)						
Systolic	126	131	125	115	128	114
Diastolic	73	77	79	69	78	69
Sum insulins (μU/ml)	305	342	282	204	255	149

(From Rocchini et al. Hypertension 1987;20:267-73.)

Beyond weight loss and isotonic exercise, antihypertensive drugs may be needed. The two types 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 (90); the former may elevate cholesterol while the latter may raise triglycerides and lower HDL-cholesterol levels (91). These metabolic perturbations may be responsible for the inability to show a reduction in CHD mortality by the treatment of hypertension with these 2 agents (92).

Of the other 4 major classes of antihypertensive drugs, there is little that either favors or discredits the use of central $alpha_2$-agonists, angiotensin converting enzyme (ACE) inhibitors or calcium entry blockers. All 3 of these groups seem to have no deleterious effects on appetite regulation, glucose tolerance or lipid levels. ACE 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 (93). The fourth class, $alpha_1$-antagonists, have two favorable characteristics: they may lower plasma cholesterol levels (91) and, in a report presented in October 1987, 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 (94).

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 not present before the gain of weight (95) and they appear in parallel with the increase in weight (96). What needs greatest emphasis is the alarming rate of development of these risk factors even in very young children who gain excess weight and become even minimally obese (97,98). Moreover, those children whose parents are obese, hypertensive, or diabetic have a greater likelihood of following in their footsteps (99), either because of genetic or environmental sharing (100).

The need to advise mothers against overfeeding their babies and to prevent excess weight gain during infancy seems particularly critical in view of the evidence that increased feeding during infancy leads to a greater likelihood of obesity after puberty and beyond, even though the manner by which infant overnutrition leads to later obesity remains uncertain (101). Clearly, there is a growing problem of increasing childhood obesity, related both to excess feeding and reduced exercise (18). Rather than spending billions of dollars and hours in spas, health clubs, and fat clinics as adults trying, usually with little success, to correct the problem, a major campaign should be directed at what should be a relatively easy goal: maintain normal body weight during infancy and childhood. Thereby, much of the danger posed by the quadrangle of upper body obesity, hyperinsulinemia, hyperlipidemia, and hypertension should be avoidable.

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