PREVENTIVE MEDICINE 14, 428–435 (1985)

Pathophysiological Interrelations of Obesity, Impaired Glucose Tolerance, and Arterial Hypertension[1]

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There is a large amount of epidemiological and clinical evidence for associations among obesity, impaired glucose tolerance, and arterial hypertension; nevertheless, the pathophysiological mechanisms underlying these associations have not yet been elucidated. In this article, some working hypotheses are discussed, and original data are presented from two studies focusing on these pathophysiological interrelations. A case–control study of obese normotensive and hypertensive patients, matched for sex, age, and degree of overweight, has shown that obese patients with associated arterial hypertension have higher fasting serum insulin levels and reduced glucose tolerance compared with their normotensive peers. A second study compared subjects with impaired glucose tolerance with a control group of clinically healthy individuals of comparable sex, age, and body mass index, and it revealed that impaired glucose tolerance is associated with significantly higher blood pressure levels, independent of body weight. The results of the two studies together suggest that the association between hypertension and impaired glucose tolerance is independent of overweight; they also give some support to the hypothesis that hyperinsulinemia may contribute to the development of high blood pressure in obese patients.

INTRODUCTION

Modern medicine in industrialized countries is faced most often with the association among obesity, diabetes, and hypertension, a triad with a very high risk of cardiovascular mortality. Although genetic factors undoubtedly play an important role in the etiology of these conditions, environmental factors may not only precipitate each of them but may also contribute to the reciprocal and adverse influence among them.

The purpose of this article is to report on preliminary data from two case–control studies focusing on the relationships among blood pressure, overweight, and impaired glucose tolerance (IGT).

There is convincing evidence from epidemiological studies, both cross-sectional and longitudinal, that (a) blood pressure is significantly related to body mass in all age groups (3, 5, 13, 15, 16, 24, 29), (b) weight gain increases the likelihood of developing hypertension at some point in life (5, 15, 29), and (c) the correction of overweight improves blood pressure control (7, 9, 23, 26, 30).

[1] Presented at the symposium, "Epidemiology and Prevention of Hypertension and Its Cardiovascular Complications," June 16–17, 1984, Saanen-Gstaad, Switzerland.

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0091-7435/85 $3.00

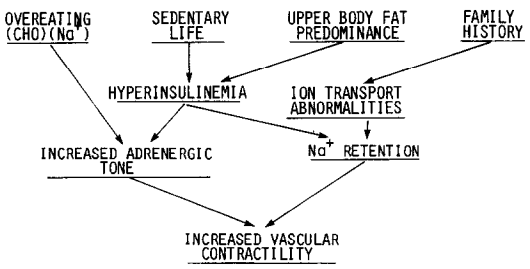

FIG. 1. Possible pathophysiological interrelations of obesity and arterial hypertension.

In our study of 1,631 men employed at the Olivetti factory in Naples and who participated in a survey of cardiovascular risk factors in the Neapolitan area, age-adjusted systolic and diastolic blood pressure levels increased gradually with increasing body weight or body mass index (BMI) (26). A similar finding has been obtained from the examination of 276 sixth-grade students in Marano, a suburb of Naples: children in the upper quintile of the BMI distribution had significantly higher systolic pressure than those in the lowest quintile (27). The statistical association between blood pressure and body mass can thus be detected very early in life. Moreover, there also exists epidemiological and clinical evidence of an even stronger correlation between changes in body weight and concomitant changes in blood pressure over time (7, 9, 15, 23, 26, 29, 30).

From our previous experience with prolonged observation of 160 massively obese patients followed up to 3 years after a substantial weight reduction, it appears that those who maintained a weight loss greater than 10% ($n = 70$) had average systolic and diastolic pressure values, respectively, 10 and 6 mm Hg lower than their initial values (19).

Besides the correlation of blood pressure with body mass, there is now some evidence from epidemiological studies of a statistically significant association between hypertension and IGT, even in the absence of overweight or after correction for body weight (4, 20). These and other studies (12) indicate, in addition, that hypertension may be associated with elevated serum insulin levels, also commonly found in overweight subjects. This observation has been the basis for a working hypothesis suggesting that hyperinsulinemia could be the common denominator in the triple association of overweight, IGT, and arterial hypertension (11, 25). Figure 1 is a schematic drawing of the interrelations of these three abnormal conditions and of the possible role played by hyperinsulinemia.

There are currently several clinical and experimental observations that support this hypothesis, although the evidence available is largely circumstantial. The intravenous infusion of insulin with maintenance of normal blood glucose levels by euglycemic clamp is followed by a significant increase in tubular sodium reabsorption and thus by sodium retention (8, 21).

The intravenous injection of insulin also induces, in animals (14), in normal subjects, and in insulin-dependent diabetics (22), a sustained increase in heart rate and in plasma noradrenaline concentration, indicating activation of the sympathetic nervous system (6, 33). It has been proposed, therefore, that a state of

TABLE 1
CHARACTERISTICS OF TWO GROUPS OF OBESE NORMOTENSIVE AND OBESE HYPERTENSIVE PATIENTS

	Normotensive (n = 21)	Hypertensive (n = 21)
Sex		
Male	12	12
Female	9	9
Age (years)	39 ± 2[a]	42 ± 2[a]
Height (cm)	163 ± 2	162 ± 2
Weight (kg)	108 ± 5	106 ± 5
BMI (kg/m^2)	40.5 ± 1.5	40.3 ± 1.6
SBP (mm Hg)	124 ± 3	171 ± 4*
DBP (mm Hg)	82 ± 1	109 ± 2*
Blood glucose (mg/dl)	77.2 ± 4.3	80.8 ± 3.6
Serum insulin (log μU/ml)	1.29 ± 0.03	1.42 ± 0.04*
I/G ratio	0.26 ± 0.02	0.32 ± 0.02
Urinary C-peptide (nmol/24 hr)	27.1 ± 2.0	32.8 ± 3.1

Note. BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure.
[a] Mean ± SE.
* $P < 0.01$.

chronic volume expansion and/or an increase in the adrenergic tone could be the pathogenetic link between hyperinsulinemia and hypertension (11, 25). Although this hypothesis may be attractive, it remains to be determined whether the association of hyperinsulinemia and hypertension is an independent association or is secondary to the effects of overweight. Our personal experience in this regard is based on the results of two recent studies, one on obese patients and one on subjects with IGT. The main findings of these studies are summarized in the next sections.

CASE–CONTROL STUDY OF OBESE NORMOTENSIVE AND OBESE HYPERTENSIVE PATIENTS

One group of obese normotensive (blood pressure below 140/85 mm Hg on two separate occasions) and one of obese hypertensive patients (blood pressure consistently above 150/100 mm Hg) participated in this study (28). The patients were recruited from those referred to the Obesity Outpatient Clinic: they were ages 20–55 years, had a BMI above 31 and a fasting blood glucose level below 120 mg/dl, were free of any other significant pathological condition, and were under no dietary or pharmacological treatment. The two groups were carefully matched for sex, age, and BMI (Table 1).

After the screening stage, the patients were invited to come back for a standard oral glucose tolerance test (OGTT), while on a normal diet with liberal carbohydrate intake. On the day before the OGTT, they collected a 24-hr urine sample for the determination of C-peptide excretion, an indicator of daily insulin production.

The OGTT was performed by giving 75 g of glucose as a 33% solution. Blood samples for blood glucose and serum insulin measurement were obtained at 0,

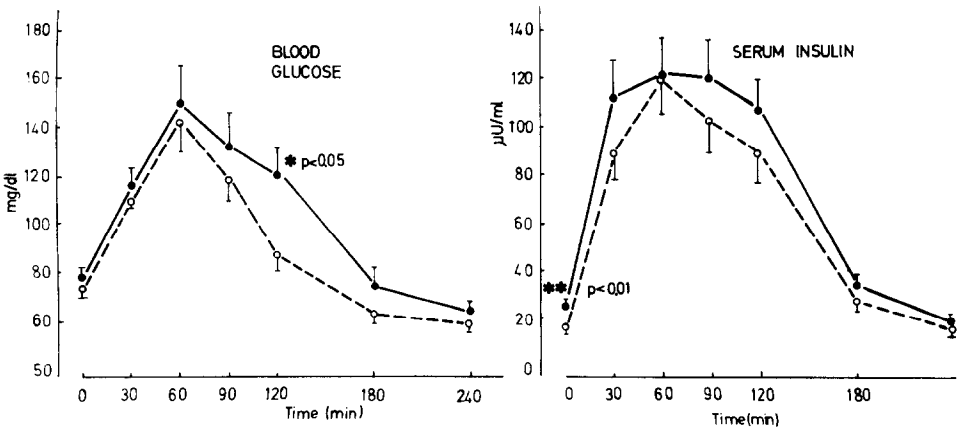

FIG. 2. Blood glucose and serum insulin (M ± SE) during standard OGTT in obese normotensive (open circles) and obese hypertensive patients (closed circles).

30, 60, 90, 120, 180, and 240 min. The results of this study are summarized in Table 1.

While average blood glucose was similar in the two groups, obese hypertensive patients had significantly higher fasting serum insulin levels (as the distribution of the individual values deviated markedly from normality, a logarithmic transformation was applied to the row data to allow statistical comparison). The 24-hr C-peptide excretion was also slightly higher in the hypertensives, although not significantly so. The areas under the curve of blood glucose and serum insulin concentration during the OGTT were not significantly different in the two groups; however, IGT, defined by the WHO Expert Committee criteria (32), was significantly more common in the hypertensive group (Fig. 2). At 120 min after the oral load, nine obese hypertensive subjects had a blood glucose level above 140 mg/dl compared with four subjects in the normotensive group.

To summarize, this study indicated that, in obese patients, high blood pressure was independently associated with IGT and higher fasting serum insulin levels.

THE SIP TELEPHONE COMPANY STUDY

This study was another case–control study specifically aimed at clarifying the relationships among IGT, hypertension, and obesity.

Sixty-five individuals with IGT and 125 euglycemic controls matched for sex, age (±4 years), and BMI (±2) participated in this study. The subjects were recruited from among 1,376 middle-aged (40–59 years) employees of the Naples Telephone Company participating in a health survey (SIP survey 1980). Hypertensives under treatment were excluded.

Glucose tolerance status was assessed by an OGTT according to the diagnostic criteria proposed by the European Association for the Study of Diabetes (17). Blood pressure, measured on two different occasions according to the WHO recommendations, was found to be significantly higher in individuals with IGT

TABLE 2
BLOOD GLUCOSE, BLOOD PRESSURE, AND MATCHED VARIABLES OF THE TWO GROUPS PARTICIPATING IN THE STUDY (SIP SURVEY)

	Age (years)	Sex (M/F)	BMI (kg/m^2)	Blood glucose (mg/dl) 0 min	Blood glucose (mg/dl) 120 min	SBP (mm Hg)	DBP (mm Hg)
IGT (n = 65)	47.9 ± 5.1[a]	38/27	28.8 ± 3.5	93.0 ± 18.1***	150.5 ± 32.2***	134.2 ± 17.7**	87.7 ± 11.9*
Controls (n = 125)	47.3 ± 5.3	75/50	28.5 ± 3.1	75.9 ± 12.4	74.8 ± 16.8	125.7 ± 16.7	83.4 ± 9.1

Note. BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure.
[a] Mean ± SD.
* $P < 0.05$.
** $P > 0.02$.
*** $P > 0.001$.

(Table 2). This association was independent of the confounding influences of age and body weight, which have often been indicated as possible explanatory factors (31). No significant difference in personal characteristics could be found that might account for the observed differences in blood pressure.

Serum insulin, both fasting and during OGTT, was very similar in the two groups. Renal function, estimated by the measurement of glomerular filtration rate corrected for body surface area (GFR/m^2), was within the normal range in both the IGT and control groups, and the mean values of GFR/m^2 were not significantly different between the two groups.

Dietary habits, established by means of a 7-day food record, were not different between the two groups. Total caloric, carbohydrate, and fiber intake were very similar in the IGT and control groups, as was alcohol consumption (unpublished data). The only detectable difference between the two groups was the more sedentary lifestyle of those with IGT, as indicated by significantly lower habitual physical activity, as established by questionnaire (Table 3) (2). Better physical fitness in the euglycemic group was confirmed by the evidence of a significantly

TABLE 3
PHYSICAL ACTIVITY AND BEAT-TO-BEAT VARIATION (BTBV) IN INDIVIDUALS WITH IGT AND CONTROLS (SIP SURVEY)

	Physically active (%)	Basal hr (beats/min)	Postexercise hr (beats/min)	BTBV (beats/min)
IGT (n = 62)	8* (n = 5)	74.5 ± 12.8[a,*]	113.4 ± 15.8**	16.7 ± 7.0
Controls (n = 117)	20 (n = 23)	70.9 ± 10.7	105.7 ± 17.8	15.8 ± 6.3

[a] Mean ± SD.
* $P < 0.05$.
** $P < 0.005$.

lower heart rate at rest and postexercise. Possible impairment of the autonomic nervous system in individuals with IGT was excluded by the beat-to-beat variation test (1).

CONCLUSIONS

The results of the two studies reported here together strongly suggest that the association between hypertension and IGT is independent of overweight. They support the findings of some previous studies published by other authors (4, 20). Berglund *et al.* reported results from the Goteborg Study, carried out on a random sample of men ages 40–59 years, of increased fasting serum insulin levels and reduced glucose tolerance in normal weight and moderately overweight hypertensives compared with normotensives of similar body weight (4). More recently, evidence has been presented by Modan *et al.* in favor of an association between hypertension and IGT, independent of age, sex, obesity, and medical treatment, in a random population sample of 2,475 subjects of both sexes (20). These authors have also found higher fasting and postload serum insulin levels in a subgroup of this same population.

The role of hyperinsulinemia in the triple association of IGT, overweight, and hypertension still remains to be fully clarified. The previous reports mentioned above suggest that circulating insulin is increased, at least in the fasting state, in hypertensives compared with normotensives, independently of body weight. This is also the conclusion from our case–control study in obese patients. Hyperinsulinemia could be seen as being either the cause or the effect of the relationship between obesity and high blood pressure. The increased insulin production very common in obese patients could bring about an increase in blood pressure through its effects on kidney function and/or on the sympathetic nervous system. IGT could be the result of an increased adrenergic drive secondary to hyperinsulinemia.

Alternatively, hyperinsulinemia could be regarded as a product of a primarily enhanced adrenergic tone in patients with arterial hypertension. The overproduction of insulin could be compensatory for an increased insulin resistance induced by elevated levels of circulating catecholamines, often found in essential hypertension.

Physical exercise, by reducing the adrenergic nervous system activity and insulin production, could help to prevent the development of hypertension in obese patients. It is worth mentioning in this regard the study of Krotkiewski *et al.*, which shows that the blood pressure decline attained by obese hypertensive patients by a program of regular physical exercise was associated with a reduction in elevated serum insulin concentration rather than with changes in body fat (18). These hypotheses remain largely speculative: further investigations are needed in order to elucidate the pathophysiological links among such associations.

To summarize, there is a large body of epidemiological and clinical evidence of a triple association among obesity, IGT, and arterial hypertension. It appears from published information as well as from our own data that the statistical association between IGT and high blood pressure is independent of overweight, although the latter may contribute to the development of both. The possible role

of hyperinsulinemia in these multiple interrelations is still largely speculative and remains to be further clarified. It seems likely that regular physical exercise may be beneficial to prevent and control high blood pressure in obese patients as well as in those with IGT.

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