Increased Waist/Hip Ratio, Metabolic Disturbances, and Family History of Hypertension

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To test whether nonhypertensive subjects with a two-generation positive family history of hypertension (PFH) are characterized by disturbed glucose metabolism, 16 men (38 ± 6 years old) with PFH and 25 subjects matched for age and with negative family histories of hypertension (NFH) were recruited. Blood pressure; serum lipids; erythrocyte transmembrane sodium transport; and the glucose, plasma insulin, and C-peptide responses to an oral glucose tolerance test were investigated. Subjects with PFH had higher blood pressure, body weight, body mass index (BMI), waist/hip ratio (WHR), and abdominal sagittal diameter than subjects with NFH. Baseline blood glucose, plasma insulin, serum lipids, and transmembrane sodium transport did not differ between the two groups. Blood glucose levels at 90 and 120 minutes after oral glucose were significantly higher in subjects with PFH than in controls. Blood glucose adjusted for BMI and WHR at 90 minutes was significantly related to a PFH. Plasma insulin level at 90 minutes during the glucose load was significantly higher in subjects with PFH. In multivariate analysis, WHR was significantly related to baseline blood pressure, insulin, and cholesterol, whereas BMI was significantly associated with the insulin response to the oral glucose tolerance test. Transmembrane sodium transport was significantly related to blood pressure only. In conclusion, subjects with PFH are characterized by increased body weight and BMI, increased visceral fat accumulation, and an altered blood glucose response to an oral glucose load. It was also shown that WHR was related to blood pressure and that BMI was more related to cholesterol and response to glucose loading than a PFH was. (Hypertension 1992;20:563-568)

KEY WORDS • hypertension, genetic • body mass index • glucose • insulin • sodium

The association between primary hypertension, impaired glucose tolerance, insulin resistance, and obesity has suggested a common pathogenetic mechanism. The relation between primary hypertension and overweight has long been recognized. Whether it is overweight per se or other associated factors that are primarily responsible for the elevated blood pressure observed in the overweight subject has not been clarified. However, it has been suggested that impaired glucose tolerance, independent of overweight, is significantly associated with primary hypertension. Epidemiological studies have also demonstrated a close relation between hypertension, diabetes, and overweight. Recent data from several studies have suggested that insulin resistance is the common feature shared by primary hypertension, overweight, and diabetes. A study by Pollare et al emphasized the importance of blood pressure on glucose metabolism, although it was obvious that obesity further impaired the glucose tolerance and increased the insulin resistance among hypertensive patients.

Despite the large body of epidemiologically data potentially linking insulin and glucose metabolism to primary hypertension, a number of major questions still need to be addressed. Does insulin resistance precede primary hypertension, or is it a consequence of it? Does weight gain precede both insulin resistance and hypertension, and is insulin resistance linked to the heredity of primary hypertension?

Because obesity, impaired glucose tolerance, diabetes, and hypertension so often coexist, it is tempting to hypothesize that these features are different expressions of related genetic dispositions or the result of lifestyle influence in certain families. If there is a genetic background for insulin resistance in primary hypertension, normotensive subjects with positive family histories of hypertension should have metabolic profiles similar to those of hypertensive subjects at least during a provocative test.

The present study was designed to clarify whether nonhypertensive men with positive family histories of hypertension for two generations had altered glucose tolerance.

Methods

Study Groups

This study was approved by the Ethics Committee of the Medical Faculty, University of Göteborg, and in-
formed consent was obtained from the subjects before the investigation. All subjects included in the present study were investigated at the Wallenberg Laboratory for Cardiovascular Research, Sahlgrenska Hospital, Göteborg. They were instructed to continue their ordinary lifestyle but to avoid heavy exercise and alcohol consumption the week before the experimental procedure. All subjects arrived at the laboratory at 8 AM after 10 hours of overnight fasting and were investigated between 8:30 and 11 AM in a sound-protected room with a laboratory temperature of 22–24°C.

Two groups of nonhypertensive men matched for age were investigated (mean age, 38±6 years). One group consisted of subjects with positive family histories of hypertension for two generations (n=16), and the control group had negative family histories of hypertension for two generations (n=25).

All subjects included in the present study were healthy sons of normotensive and hypertensive fathers who had participated in the Primary Preventive Trial in Göteborg, in which a random third (n=9,996) of the male population 47–54 years old were examined for cardiovascular risk factors.11 All hypertensive men (n=686) with two consecutive recordings of blood pressure above 175 mm Hg systolic or 115 mm Hg diastolic or treatment for hypertension were referred to and followed up at our Hypertension Unit, Sahlgrenska Hospital, Göteborg. Of these subjects, 49 hypertensive men who had themselves given a positive history of parental hypertension or stroke before the age of 65 in both parents were asked if they had a son living in or near Göteborg. These men (n=49) had a total of 24 sons, all of whom were contacted and invited to participate. Sixteen subjects with positive family histories were examined in the present study. Of the remaining eight individuals, one was excluded because of current medication for hypertension, one because of alcoholism, two were traveling salesmen, and one was in military service and could not participate. Three subjects declined to participate.

Subjects in the control group were recruited among the sons of 65 normotensive randomly selected men (blood pressure below 130 mm Hg systolic, 90 mm Hg diastolic) who had themselves given a negative history of parental hypertension or stroke in the same screening examination.11 These normotensive men had 33 sons living near Göteborg. In the present study, 25 of these control subjects with negative family histories of hypertension for two generations participated. One was excluded because of diabetes mellitus and one because of malignant melanoma. Two were living abroad at the time of investigation, and four subjects were not willing to participate.

All parents, including those selected at follow-up and living near Göteborg, still alive and willing to participate at the time of follow-up were examined regarding current blood pressure, body weight and height, and medication. All hypertensive fathers were on antihypertensive treatment. Nevertheless, systolic and diastolic blood pressures were significantly higher among fathers on treatment for primary hypertension (149±12/87±6 mm Hg; p<0.05, p<0.01, n=13) than among normotensive fathers (134±11/78±5 mm Hg, n=23). Among hypertensive fathers, body mass index was also significantly higher (28.4±3.2 kg/height²) than in normotensive fathers (25.5±2.9 kg/height², p<0.05). Only four of the spouses of the hypertensive fathers were on antihypertensive therapy, and no spouses of the normotensive men were on antihypertensive therapy. In spouses of the hypertensive men (n=12), blood pressure was 148±18/83±6 mm Hg and body mass index 26.6±3.7 kg/m², and they did not differ significantly in regard to blood pressure (142±22/79±8 mm Hg) and body mass index (26.2±4.5 kg/m²) from the spouses (n=24) in the normotensive families. Selection procedure of the investigated subjects and parental data have been described previously.12,13

**Blood Pressure and Heart Rate**

Blood pressure was measured phonographically after 30 minutes’ rest, with the subjects in a semirecumbent position, with a method validated against intra-arterial blood pressure (unpublished observations from our laboratory). The mean value of three consecutive measurements was calculated. A standard cuff, 12×35 cm, was used. The cuff was automatically inflated and deflated. Signals indicating cuff pressure and Korotkoff sounds were registered simultaneously on paper on a minograph (Siemens-Elema, Stockholm). Diastolic blood pressure was recorded when the Korotkoff sounds disappeared (phase V). Mean arterial blood pressure was calculated as one third of the pulse pressure plus diastolic blood pressure. Heart rate was calculated from simultaneously recorded electrocardiograms.

**Anthropometric Measurement**

Body weight and height were measured with subjects in undershorts and without shoes to the nearest 0.5 kg of weight and to the nearest 0.5 cm of height. Body mass index was calculated as body weight (kg)/body height (m)². Body surface area was calculated as:

\[
\text{body weight (kg)}+\frac{[\text{body height (cm)}−160]}{100}+1
\]

Hip (at the trochanter) and waist (at the umbilicus) circumferences were measured to the nearest 0.5 cm while the subject was standing, and abdominal sagittal diameter was measured to the nearest 0.5 cm with the subject in the supine position.

**Blood Glucose, Plasma Insulin, C-Peptide, and Serum Lipids**

An oral glucose tolerance test was performed in all subjects in the morning after 10 hours of overnight fasting. The examined subjects were resting in the semirecumbent position and took 100 g glucose orally. Blood was drawn from a peripheral catheter after the subjects had rested for 45 minutes in a semirecumbent position at zero time and every 30 minutes throughout the test. Blood glucose was determined with a glucose oxidase method using a commercially available reagent (Glox, Kabi, Stockholm) and with glycerin-buffered perchloric acid as the protein-precipitating agent. Plasma insulin was analyzed by a double-antibody method with a commercial radioimmunoassay kit (Phadebas, Pharmacia, Uppsala, Sweden) as was the connecting peptide (C-peptide, Novo, Copenhagen). Serum lipids were analyzed according to previously described methods.15
Determinations of Intraerythrocyte Sodium and Transmembrane Sodium Fluxes

Intraerythrocyte sodium content was determined by flame photometry after dissolution of the blood sample in concentrated nitric acid as previously reported. Sodium influx and the rate constant of sodium efflux were calculated from uptake values of $^{22}$Na erythrocytes at steady-state conditions by use of a modified Keynes's formula, as previously described in detail. The washed erythrocytes were incubated for 15, 60, 120, and 240 minutes in the presence of $^{22}$Na, and the uptake could be described as a monoeponential function. This monoeponential uptake ($Y$) can be written as $Y = E + (m/k)(1-e^{-kt})$, where $m$ denotes influx (mmol • l$^{-1}$ • h$^{-1}$), $k$ is the rate constant of cellular efflux (hr$^{-1}$), and $E$ is the rapid initial uptake of $^{22}$Na (mmol • l$^{-1}$), which is close to zero in erythrocytes. Estimates for $m$, $k$, and $E$ that make this formula best describe the observed uptake values for $^{22}$Na were calculated according to the least-squares method.

Statistics

Standard methods were used for calculation of mean±SD. To test the hypothesis of no differences in means between the two groups, Student's $t$ test was used. Differences within groups at different times were assessed by Student's paired $t$ test. Only two-tailed tests were used, and values of $p<0.05$ were regarded as statistically significant. Multivariate analysis was handled by STAT VIEW 512+ package (Brain Power Inc., Calabasas, Calif.) implemented on an Apple Macintosh SE/30 personal computer (Apple Computer Inc., Cupertino, Calif.). Mantel's test was used to test the relation between continuous and noncontinuous variables.

Results

Baseline Characteristics of the Groups

Systolic and diastolic blood pressures were found to be significantly higher in subjects with positive family histories of hypertension than in control subjects (Table 1). Body weight, body mass index, waist/hip ratio, and abdominal sagittal diameter were significantly higher in subjects with positive family histories of hypertension than in subjects with negative family histories of hypertension (Table 1). In Mantel's test, a positive family history of hypertension was significantly related to both body mass index ($p<0.05$) and waist/hip ratio ($p<0.05$).

Mantel's test showed also that body mass index was more important for the blood pressure than a positive family history of hypertension was. When waist/hip ratio was included in the analysis, waist/hip ratio was found to be more strongly related to the blood pressure than body mass index was.

Glucose Metabolism and Serum Lipids

Fasting blood glucose, plasma insulin, C-peptide, and serum lipids did not differ between the two groups at baseline (Table 2). The blood glucose level was significantly higher at 90 minutes ($p<0.01$) and at 120 minutes ($p=0.02$) in subjects with positive family histories of hypertension (Figure 1). The blood glucose response (i.e., change from baseline) to oral glucose load was significantly increased at 90 minutes ($p<0.05$) in subjects with positive family histories of hypertension compared to controls (Figure 1).

| TABLE 1. Baseline Data in Subjects With Positive Family Histories of Hypertension and Subjects With Negative Family Histories of Hypertension |
|-------------------------------------------------|-------------------------------------------------|-----------------|-------------|
| Baseline data                                   | PFH (n=16)                                      | NFH (n=25)      | $p$         |
| Systolic blood pressure (mm Hg)                 | Mean 131 ± 13                                  | Mean 120 ± 9    | <0.01       |
| Diastolic blood pressure (mm Hg)                | Mean 85 ± 9                                   | Mean 76 ± 7     | <0.01       |
| Heart rate (bpm)                                | Mean 65 ± 8                                   | Mean 62 ± 5     | NS          |
| Body weight (kg)                                | 90.2 ± 13                                     | 79.2 ± 11       | <0.01       |
| Body mass index (kg/m$^2$)                      | 27.6 ± 3.6                                     | 24.5 ± 3.0      | <0.01       |
| Waist circumference (cm)                        | 97.4 ± 10.8                                    | 89.2 ± 9.8      | <0.01       |
| Hip circumference (cm)                          | 101 ± 8.5                                     | 97 ± 6.1        | NS          |
| Waist/hip ratio                                 | 0.96 ± 0.05                                   | 0.92 ± 0.05     | <0.05       |
| Abdominal sagittal diameter (cm)                | 22.1 ± 3.3                                     | 20.0 ± 2.7      | <0.05       |

PFH, positive family history of hypertension; NFH, negative family history of hypertension; bpm, beats per minute.

| TABLE 2. Baseline Metabolic Data in Subjects With Positive Family Histories of Hypertension and Subjects With Negative Family Histories of Hypertension |
|-------------------------------------------------|-------------------------------------------------|-------------|-------------|
| Laboratory data                                | PFH (n=16)                                      | NFH (n=25) | $p$         |
| Fasting blood glucose (mmol/l)                  | Mean 4.8 ± 0.4                                  | Mean 4.7 ± 0.5 | NS          |
| Fasting serum insulin (microunits/ml)           | 8.9 ± 5.6                                      | 8.9 ± 5.2     | NS          |
| C-peptide (nmol/l)                              | 0.61 ± 0.25                                    | 0.56 ± 0.17   | NS          |
| Serum cholesterol (mmol/l)                      | 5.67 ± 1.0                                     | 5.34 ± 1.0    | NS          |
| Serum triglycerides (mmol/l)                    | 1.41 ± 0.7                                     | 1.54 ± 0.7    | NS          |

PFH, positive family history of hypertension; NFH, negative family history of hypertension.
Comparisons were made of plasma insulin and serum cholesterol levels between the subjects with positive family history of hypertension and the subjects with negative family history of hypertension. Results are given as mean±SEM. *p<0.05; **p<0.01.

In the present study, we recruited nonhypertensive men with positive or negative family history of primary hypertension for two generations, selected from the whole population and defined as previously suggested by Watt.22

It would be anticipated that metabolic and hemodynamic abnormalities related to primary hypertension should be found in subjects with positive family history of hypertension for two generations who are consequently at high risk of developing primary hypertension. In previous studies, normotensive subjects with hypertensive parents have rather well-characterized prehypertensive abnormalities such as weight gain,12 increased systemic and renal vascular response to angiotensin II,19 and blunted renal sodium excretion in response to acute sodium loading.20 Such sodium sensitivity in young normotensive subjects has recently been shown to be related to a hyperinsulinemic response to oral glucose loading.21

In the present study, subjects with positive family histories of hypertension for two generations had higher blood pressure, body weight, waist/hip ratio, and abdominal fat accumulation than did subjects with negative family histories of hypertension. During the oral glucose tolerance test, the late blood glucose and plasma insulin levels were higher in subjects with positive family histories of hypertension than in subjects with negative family histories of hypertension. Adjusted for body mass index and waist/hip ratio, the late increase in blood glucose was still significantly related to a positive family history of hypertension. It was also shown that blood pressure and baseline insulin level were linked to increased waist/hip ratio type of overweight, as suggested by higher levels in heavier subjects. An increased body mass index was related to the response to an oral glucose load, because heavier subjects showed an increased plasma insulin response during the oral glucose tolerance test. A relation between visceral fat accumulation and glucose metabolism has previously been reported in healthy young men.18 Serum cholesterol, a well-known risk factor for cardiovascular diseases, was also related to the degree of overweight and fat distribution in the present study.

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In the present study, we recruited nonhypertensive men with positive or negative family histories of primary hypertension for two generations, selected from the whole population and defined as previously suggested by Watt.22 It has been suggested that patients with primary hypertension share certain metabolic abnormalities such as resistance to insulin-stimulated glucose uptake, hyperinsulinemia, and hypertriglyceridemia, and in treated or untreated hypertension, an abnormal plasma insulin response to an oral glucose load has been demonstrated. The association between hyperinsulinemia and primary hypertension suggests a causal relation, but such observations do not prove that insulin resistance and hyperinsulinemia are involved in the development of primary hypertension or even the long-term regulation of blood pressure. For example, there is evidence that plasma insulin concentrations are associated with activity in the sympathetic nervous system.

**Figure 1.** Line graph shows blood glucose during oral glucose tolerance test in subjects with positive family histories of hypertension (PFH) and control subjects with negative family histories of hypertension (NFH). Values are mean±SEM. *p<0.05; **p<0.01.

**Figure 2.** Line graph shows plasma insulin during oral glucose tolerance test in subjects with positive family histories of hypertension (PFH) and control subjects with negative family histories of hypertension (NFH). Values are mean±SEM. *p<0.05.
probably related to the hemodynamic effects, with vasodilatation recently reported in normal humans. Another site of action for plasma insulin is the kidney, in which insulin can promote renal tubular sodium reabsorption. It is also well known that insulin influences cell membrane ion transport, and a link between hyperinsulinemia, obesity, glucose intolerance, and cation imbalance with increased erythrocyte sodium content has been suggested.

Several potential risk factors for the development of hypertension have been described. In a study by Skarfors et al, in which middle-aged men were investigated and followed up for 10 years, baseline blood pressure was the most important factor for the development of primary hypertension, followed by body mass index and fasting plasma insulin and response during an intravenous glucose tolerance test. In a previous study it was reported that fat cell size and waist circumference are related to blood pressure level in middle-aged men. Waist/hip ratio has previously been described to be related to cardiovascular morbidity and an increased risk for diabetes mellitus.

The influence of heredity on body weight has been demonstrated and seems to depend on the degree of overweight in the family. An increase in body weight is among the environmental factors that have been demonstrated as being related to this family aggregation of increased blood pressure. As in the present study, however, the significance of this association is con-founded by the fact that the familial resemblance of body weight appeared to be as genetically determined as that of blood pressure. In a study by Stamler et al, both a positive family history of hypertension and overweight were found to be independently and cumulatively associated with a higher incidence of primary hypertension. It has also been demonstrated that non-diabetic subjects with positive family histories of non-insulin-dependent diabetes mellitus have a cardiovascular and metabolic pattern similar to those with positive family histories of hypertension.

The present study found that higher blood pressure, waist/hip ratio, and body mass index increased cardiovascular risk and that nonhypertensive subjects with positive family histories of hypertension are characterized by metabolic abnormalities previously known to be related to primary hypertension.

We also found that waist/hip ratio and the degree of overweight were more important for the blood pressure than a positive family history of primary hypertension, whereas the fat distribution with an increased waist/hip ratio and sagittal abdominal diameter was significantly related to a positive family history of hypertension. The relation between the degree of overweight, abdominal fat distribution, and signs of insulin resistance as in the present study has previously been reported to be a result of an inhibition of hepatic clearance of insulin, providing a mechanism whereby lipolytically sensitive visceral fat may influence peripheral insulin concentration, insulin sensitivity, and a propensity to decrease glucose tolerance. The present study further confirms the linkage between primary hypertension, overweight, fat distribution, and alteration in glucose metabolism in nonhypertensive subjects with positive family histories of hypertension.

In addition, these findings indicate that consideration should be given to behavioral modifications that can reduce body weight; lifestyle modifications might also include increased physical activity to reduce body weight and improve insulin sensitivity in subjects at high risk of both primary hypertension and overweight.

In conclusion, in the present study we demonstrated that subjects with positive family histories of hypertension for two generations are characterized by higher blood pressure, body mass index, waist/hip ratio, and an altered response to an oral glucose load. Blood pressure and metabolic disturbances were strongly related to the degree of overweight and fat distribution. These and previous findings indicate that overweight, increased waist/hip ratio, and metabolic disturbances occur in nonhypertensive subjects predisposed to primary hypertension.

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