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Insulin Resistance, Hyperinsulinemia, and Dyslipidemia in Nonobese Individuals With a Family History of Hypertension

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Various facets of glucose, insulin, and lipid metabolism were compared in 76 normal volunteers—38 with and 38 without a family history of hypertension. The two groups were comparable in terms of age, gender distribution, and degree of obesity (both generalized and abdominal). Although the plasma glucose response to oral glucose was similar in both groups, glucose-stimulated insulin concentrations were significantly greater in volunteers with a family history of hypertension ($P < .001$). Furthermore, the steady state plasma glucose concentration during a constant infusion of glucose, insulin and somatostatin was significantly greater in subjects with a family history of hypertension (8.1 ± 0.6 *v* 6.2 ± 0.6 mmol/L, $P < .001$). Since the steady-state plasma insulin levels during the infusion were similar, these results indicate that normotensive individuals with a family history of hypertension are relatively insulin resistant. Finally, plasma very low density lipoprotein (VLDL) triglyceride and VLDL cholesterol were higher in those with a family history of hypertension, as was the ratio of total to high density lipoprotein cholesterol. Thus, normotensive individuals with a family history of high blood pressure are insulin resistant, hyperinsulinemic and dyslipidemic when compared to a matched group of healthy volunteers without a family history of hypertension. Am Hypertens 1992;5:694–699

KEY WORDS: **Family history of hypertension, insulin resistance, hyperinsulinemia, dyslipidemia.**

Although antihypertensive treatment has been very effective in reducing morbidity and mortality from stroke, the impact of lowering blood pressure on coronary heart disease (CHD) has been less than might have been expected.[1,2] At the present time, there is no consensus as to why this might be the case. For example, it could be argued that the clinical trials aimed at addressing these issues were not carried out long enough to result in unequivocal answers. Another possibility is that the antihypertensive treatment program used in most trials was associated with metabolic changes that increase risk of CHD.[3–6] More recently, it has become apparent that patients with high blood pressure, in general, have associated defects of glucose, insulin, and lipid metabolism[7–14] that can be discerned before the initiation of antihypertensive treatment. Since all of these changes have been shown to increase risk of CHD,[15–19] it could be speculated that many patients with high blood pressure share a cluster of metabolic abnormalities, in addition to the increase in blood pressure, which contribute to the increased risk of CHD associated with this syndrome. If this is the case, it might be possible to demonstrate the presence of these metabolic changes in

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TABLE 1. BASELINE CHARACTERISTICS (MEAN ± SD)

Variable	Positive Family History	Negative Family History
Age (years)	38 ± 9	36 ± 11
Gender (Women:men)	27:11	27:11
Body mass index (kg/m^2)	23.7 ± 3.4	23.5 ± 3.2
Waist-to-hip ratio	0.85 ± 0.01	0.83 ± 0.01
Physical activity (kcal/day)	1603 ± 46	1574 ± 51
Systolic blood pressure (mm Hg)	111 ± 13	110 ± 12
Diastolic blood pressure (mm Hg)	74 ± 9	71 ± 8

normotensive subjects, with a positive family history of high blood pressure. The present study was initiated to address this issue.

METHODS

This study was performed in 76 healthy, normotensive volunteers, divided into two groups of 38 each on the basis of whether or not there was at least one first-degree relative with a history of high blood pressure. Subjects stating that either a parent or sibling was treated with antihypertensive medication were classified as having a positive family history, whereas those without such a history were designated as having a negative family history. Subjects were recruited in an effort to match them carefully in terms of age, gender, and body mass index. All subjects were in good general health, without any known disease, and taking no medication known to affect carbohydrate or lipid metabolism. In addition, physical examination, hemogram, urinalysis, chemical screening battery, and electrocardiogram were normal. Fifteen of the individuals with a family history of hypertension had a positive family history of non–insulin-dependent diabetes mellitus (NIDDM) whereas 12 subjects without a family history of hypertension had a positive family history of NIDDM. Degree of obesity was estimated by determining both body mass index and the ratio of waist-to-hip circumference. Level of habitual physical activity was estimated by a modified version of a self-reporting questionnaire,[20] in which subjects describe the time spent during the previous week performing various activities. Empirical constants are used to calculate the amount of energy used per day, and the data have been expressed as kcal/m^2. Arterial blood pressure was measured with a mercury sphygmomanometer, using the disappearance of Korotkoff sounds (phase V) as criterion for the determination of the diastolic blood pressure. The reported blood pressures are the arithmetic means of measurements made on two separate days, before venipuncture, and after subjects sat for at least 5 min in a quiet environment. The baseline characteristics of the two groups are presented in Table 1, showing that the two groups were matched for age, gender, and obesity. Furthermore, there was no difference in either level of physical activity or blood pressure between the two groups.

The experimental protocol was approved by the Institutional Review Board of Stanford University Medical Center, and informed consent was obtained before ini-

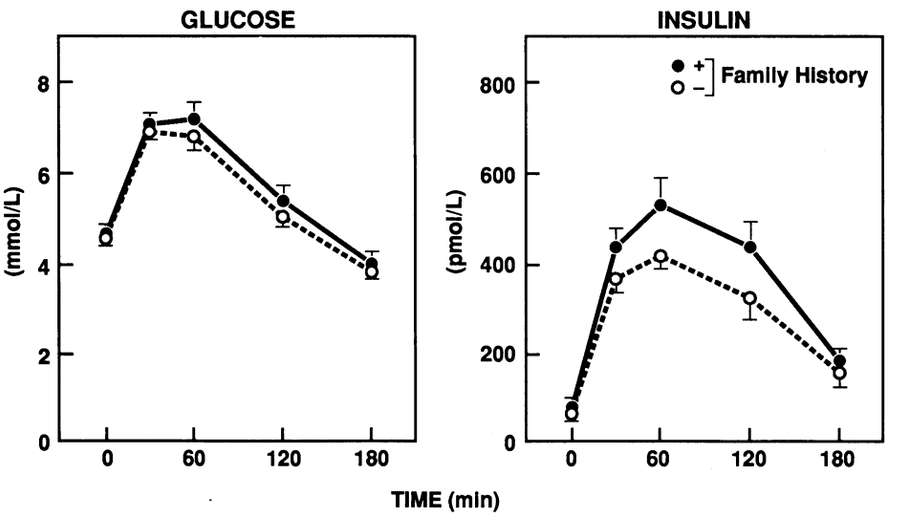

FIGURE 1. *Plasma glucose and insulin responses concentration in response to a 75 g oral glucose challenge in volunteers with* (+, ●——●) *and without* (−, ○——○) *a family history of hypertension.*

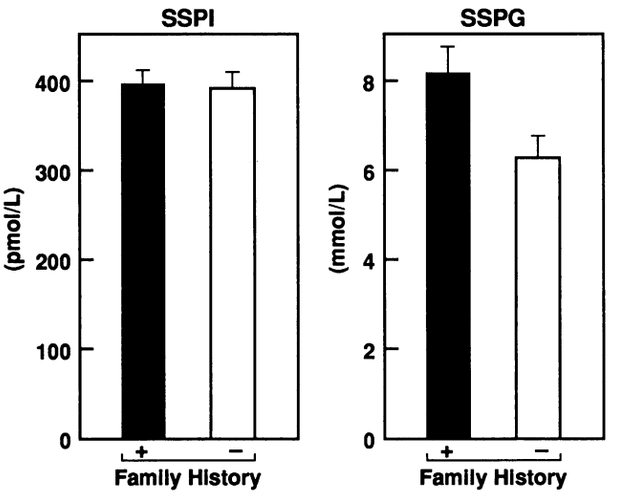

FIGURE 2. *Steady-state plasma insulin (SSPI) and glucose (SSPG) concentrations during the insulin suppression test in volunteers with (+,■) and without (−,□) a family history of hypertension.*

tiating any studies. Volunteers were admitted to the Stanford General Clinical Research Center, and the following measurements made. Venous blood was obtained after an overnight fast on two occasions for determination of fasting plasma glucose,[21] insulin,[22] triglyceride (TG),[23] and cholesterol concentrations.[24] The assay variance of normal and elevated levels for glucose, insulin, TG, and cholesterol concentrations are 2.1 and 1.8%, 4.2 and 6.1%, 3.4 and 2.1%, 1.8 and 1.5%, respectively. In addition, plasma was separated by ultracentrifugation[25] for measurement of lipoprotein cholesterol and TG concentration. The data reported represent the average of these two measurements. On one morning, after an overnight fast, plasma glucose and insulin concentrations were determined before and 30, 60, 120, and 180 min after the administration of a 75 g oral glucose challenge. Finally, insulin-mediated glucose uptake was estimated by a modification of the insulin suppression test originally described by our research group.[12,13] This study was also performed after an overnight fast, and involved the continuous intravenous infusion of somatostatin (5 μg/min) for 180 min, insulin (25 mU/m^2/min) and glucose (240 mg/m^2/min) into an indwelling Teflon catheter in a superficial antecubital vein. Venous blood samples were obtained from a similar catheter inserted in a contralateral antecubital vein, kept patent by a slow infusion of 0.9% sodium chloride. Blood was obtained every 10 min during the last half hour for measurement of plasma glucose and insulin concentrations, and the mean value of these four measurements used to calculate the steady state plasma insulin (SSPI) and steady state plasma glucose (SSPG) concentrations. To assess the stability of SSPG and SSPI during the infusion test in each individual, coefficient of variance (CV) of the four values was calculated: the mean ± SD of these CV values for the group with a family history versus those without was 6.4 ± 4.3% *v* 6.9 ± 5.2% for SSPG and 3 ± 1% *v* 2 ± 1% for SSPI, respectively. Since the SSPI is similar in all individuals, the SSPG concentration provides a measure of insulin-mediated glucose disposal; the higher the SSPG, the more insulin-resistant the individual.

Statistical Analysis Values for continuous variables are expressed a mean ± standard error (SEM). Since the continuous variables were continuously distributed in the two study populations, statistical analysis was performed with standard methods for two tailed, unpaired Student's *t* tests. Differences between the plasma glucose and insulin responses of the two groups to the oral glucose challenge were compared by two-way analyses of variance.

RESULTS

Plasma glucose and insulin responses before and after the oral glucose challenge are illustrated in Figure 1. The results in the left panel show that plasma glucose concentration of the two groups were not significantly different. However, plasma insulin concentrations were significantly higher in individuals with a family history of hypertension ($P < .001$).

Figure 2 shows the steady state plasma insulin (SSPI) and glucose (SSPG) concentrations of the two groups during the insulin suppression tests. The SSPI concentrations were similarly in subjects with (397 ± 14 pmol/L) and without a family history of hypertension (391 ± 12 pmol/L). Despite the almost identical SSPI levels, SSPG concentrations were significantly ($P <$ .001) higher in the group with a family history of high blood pressure (8.1 ± 0.6 *v* 6.2 ± 0.6 mmol/L).

Plasma lipid and lipoprotein concentrations of the two groups can be seen in Table 2. These data demonstrate that total plasma cholesterol concentration was marginally higher (4.80 ± 0.15 *v* 4.44 ± 0.12 mmol/L, $P < .07$) in those with a family history of hypertension. It can be seen that this overall change was due to an increase in VLDL cholesterol (0.50 ± 0.06 *v* 0.23 ± 0.03 mmol/L, $P < .001$), without any significant difference in LDL cholesterol (2.65 ± 0.12 *v* 2.54 ± 0.1 mmol/L, P = NS). In addition, HDL cholesterol concentration was somewhat lower (1.34 ± 0.06 *v* 1.47 ± 0.05 mmol/L, $P < .1$) and the sum of VLDL + IDL + LDL significantly higher (3.47 ± 0.14 *v* 3.0 ± 0.11 mmol/L, $P < .003$) in those with a family history of high blood pressure. In addition, the ratio of total cholesterol to HDL cholesterol was significantly higher in the group with a positive family history (3.84 ± 0.18 *v* 3.09 ± 0.11, $P < .001$).

TG concentrations are also shown in Table 2, and total

TABLE 2. PLASMA LIPID AND LIPOPROTEIN CONCENTRATIONS

Variable (mmol/L)	Positive Family History	Negative Family History	P
Cholesterol (CHOL)	4.80 ± 0.15	4.44 ± 0.12	< .07
VLDL-CHOL	0.50 ± 0.06	0.23 ± 0.03	< .001
IDL-CHOL	0.34 ± 0.07	0.21 ± 0.02	< .08
LDL-CHOL	2.65 ± 0.12	2.54 ± 0.10	NS
HDL-CHOL	1.34 ± 0.06	1.47 ± 0.05	< .10
VLD + IDL + LDL-CHOL	3.47 ± 0.14	3.00 ± 0.11	< .003
Ratio of CHOL/HDL-CHOL	3.84 ± 0.18	3.09 ± 0.11	< .001
Triglyceride (TG)	1.15 ± 0.07	0.76 ± 0.05	< .001
VLDL-TG	0.71 ± 0.07	0.40 ± 0.04	< .001
IDL-TG	0.14 ± 0.02	0.10 ± 0.01	NS
LDL-TG	0.19 ± 0.01	0.16 ± 0.01	< .05
HDL-TG	0.11 ± 0.01	0.09 ± 0.01	< .06

plasma concentration (1.15 ± 0.07 *v* 0.76 ± 0.005 mmol/L, $P < .001$) was almost twice as high in individuals with a family history of hypertension. Although this change was primarily due to an increase in VLDL-TG (0.71 ± 0.07 *v* 0.40 ± 0.04 mmol/L, $P < .001$), there were also increases in LDL-TG (0.19 ± 0.01 *v* 0.16 ± 0.01 mmol/L, $P < .05$) and HDL-TG (0.11 ± 0.001 *v* 0.09 ± 0.01 mmol/L, $P < .06$).

DISCUSSION

When compared to normotensive volunteers, patients with high blood pressure have been shown to be insulin resistant, hyperinsulinemic, and dyslipidemic.[7–14] The present results show that similar differences were seen when first-degree relatives of patients with hypertension were compared to individuals without a family history of high blood pressure. Essentially similar results have recently been reported by Ferrari and associates.[26] It is of interest to note that Ferrari et al estimated in vivo insulin action in men, whereas 70% of the patients in the current study were women. Thus, insulin resistance is present in first-degree normotensive relatives of patients with high blood pressure, irrespective of gender. Our results, and those of Ferrari and colleagues, provide support for the view that abnormalities of insulin and lipid metabolism can be demonstrated in individuals at risk to develop hypertension before a discernible increase in blood pressure. At the same time, it should be noted that neither hyperinsulinemia nor dyslipidemia occur in association with renal vascular hypertension in human beings or rats.[27–31] Given these considerations, it seems reasonable to conclude that the presence of resistance to insulin-mediated glucose uptake, hyperinsulinemia, and dyslipidemia in patients with hypertension antedates the increase in blood pressure and does not appear to be a consequence of hypertension per se.

Demonstration in the present study that differences in insulin action, insulin secretion, and lipid metabolism were observed in normotensive individuals divided into groups on the basis of a family history of high blood pressure provides evidence that the association between high blood pressure and the metabolic changes noted has a genetic basis. This conclusion is consistent with the previous findings of Ferrari et al,[26] as well as with the recent demonstration by Selby and associates[32] that monozygotic twins were three times as likely as dizygotic twins to have dyslipidemic hypertension if the cotwin was also affected. Although plasma insulin concentration were not measured in the study by Selby et al, glucose intolerance and frank diabetes were more frequent in twin pairs concordant for dyslipidemic hypertension. However, the view that the metabolic changes seen in patients with high blood pressure are genetically determined does not mean that the phenotypic expression of these abnormalities cannot be modified by environmental influences. For example, weight loss and exercise training have been shown to lower blood pressure and both plasma insulin and TG concentrations in obese individuals.[33–35] On the other hand, the fact that weight loss and/or physical activity can modulate blood pressure and insulin and lipid metabolism should not obscure the fact that genetic factors are involved in the metabolic changes noted in a substantial number of patients with high blood pressure.

Finally, the observation that metabolic observations can be detected in normotensive individuals with a family history of hypertension emphasizes the potential importance that these changes play in the development of CHD in patients with high blood pressure. The clinical importance of these issues is strongly supported by the report of Selby et al,[32] in which it was shown that the mortality from twins with dyslipidemic hypertension was greater than twins who had either hypertension or dyslipidemia alone. Thus, although we may not fully understand why high blood pressure and a cluster of metabolic abnormalities occur in some patients with hypertension, there appears to be little

doubt as to the gravity of this phenomenon when it is present.

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