Insulin Secretion, Sensitivity, and Metabolic Profile of Young Healthy Offspring of Hypertensive Parents

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Hyperinsulinemia and insulin resistance are commonly observed in essential hypertension, which is part of the metabolic syndrome. The aim of this study was to examine whether insulin secretion abnormalities or alterations in insulin sensitivity and glucose tolerance are also present in healthy men, offspring of patients with essential hypertension. Twelve young (27 ± 3.6 years), lean normotensive offspring were compared with 14 age-, sex-, and body mass index (BMI)-matched controls without a family history of hypertension, diabetes mellitus, and coronary heart disease. We studied glucose tolerance, insulin secretion, and sensitivity using 10-hour hyperglycemic and 10-hour hyperinsulinemic-euglycemic clamps (HIC). Glucose tolerance was comparable in the offspring and controls. However, the offspring had higher insulin and C-peptide levels during the hyperglycemic clamp (HGC) compared with controls ($P < .05$). There was no difference in the early phase of insulin secretion between the groups. The insulin sensitivity index (glucose infusion rate/serum insulin) was significantly lower in the offspring during both clamps. Moreover, the offspring had higher systolic ($P < .001$) and diastolic ($P < .001$) blood pressure and had higher serum cholesterol ($P < .01$) and triglyceride ($P < .05$) levels. Apparently healthy, young, lean individuals with a genetic predisposition to essential hypertension and with normal glucose tolerance had higher insulin secretion and lower insulin sensitivity than controls. These abnormalities, together with higher blood pressure and altered lipid metabolism, may play a role in the development of hypertension and an increased risk of cardiovascular morbidity and mortality in these individuals.

HYPERTENSION and hyperinsulinemia are 2 established major risk factors of cardiovascular disease in most countries. Essential hypertension is now considered to be an insulin-resistant state, in which genetic and acquired factors play an important role. Subjects at risk of developing hypertension are also relatively insensitive to insulin.[1-3] suggesting that insulin resistance precedes the development of increased blood pressure. On the other hand, it has been hypothesized that insulin resistance in hypertensive persons may be the result of elevated blood pressure.[4]

Healthy, young adults with a positive family history of hypertension are at an increased risk of developing hypertension,[5] and they may be at an increased risk of developing cardiovascular disease irrespective of their blood pressure.[6] This hereditary tendency of hypertension probably involves a multigenic system.[7] Many investigators have proposed that the genetic risk may include metabolic traits, such as insulin resistance and compensatory hyperinsulinemia,[8] which may promote hypertension.[9,10]

The pathogenesis of hypertension is a complex multifactorial process, and the mechanisms mediating its clinical characteristics are not well understood. Neither the underlying mechanism nor direct causality between hypertension and insulin resistance has been identified to date.

Clinical hypertension comprises more than elevated blood pressure. Previous studies have shown that markers of insulin and lipid metabolism,[11] hemocoagulation, sympathoadrenal system[12] can be altered early in the course of hypertension or even in the prehypertensive stages.[13,14]

No study published to date has reported, in essential hypertension-prone subjects, the first and second phases of insulin secretion along with insulin sensitivity and the extent of glucose tolerance using a combination of 10-hour hyperglycemic clamp (HGC) and hyperinsulinemic-euglycemic clamp (HIC).

We studied a group of young, lean, clinically asymptomatic offspring of hypertensive parents (OHP) and compared them with age-, sex-, and body mass index (BMI)-matched individuals without a family history of hypertension, diabetes mellitus, and ischemic heart disease. The aim of our study was to assess the first and second phases of insulin secretion, insulin sensitivity, and glucose tolerance using a combination of the 2 clamp methods and to determine whether some of the clinical characteristics might precede a manifestation of hypertension.

MATERIALS AND METHODS

Subjects

The OHP consisted of 12 young non-obese men with a positive family history of hypertension (1 or both parents) and a negative family history of diabetes mellitus, morbid obesity, and ischemic heart disease. They were not taking any drugs. One or both parents had to be hypertensive (ie, receiving antihypertensive medication). The OHP were matched according to age, sex, and BMI to a group of 14 healthy controls without a family history of hypertension, diabetes mellitus, and ischemic heart disease, who were not taking medication that could affect glucose metabolism. No subject had known cardiac, renal, or hepatic disease. Both groups consisted of men; women were excluded from insulin sensitivity testing to eliminate potential variations in glucose disposal related to ovarian function. A family history of hypertension was determined by personal interview. Using the criteria recently defined by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, all subjects had a normal oral glucose test (OGTT).[15] Physical health was assessed by routine clinical examination. Written informed consent was obtained from each participant

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Table 1. Characteristics of the OHP and Control Groups

	OHP (n = 12)	CON (n = 14)	*P*
Age (yr)	27.5 ± 3.6	26.3 ± 4.6	NS
BMI (kg/m^2)	25.6 ± 3.4	24.5 ± 1.5	NS
WHR	0.89 ± 0.07	0.84 ± 0.06	NS
Waist (cm)	89.9 ± 8.5	85.2 ± 7.5	NS
Hip (cm)	102.4 ± 7.0	99.8 ± 4.9	NS
BP_s (mm Hg)	129.5 ± 6.03	115.5 ± 3.9	‡
BP_d (mm Hg)	79.6 ± 4.9	67.9 ± 4.8	‡
TG (mmol/L)	2.53 ± 2.27	1.26 ± 0.5	*
CHOL (mmol/L)	5.11 ± 0.9	3.87 ± 0.7	†
HDL-C (mmol/L)	1.12 ± 0.3	1.01 ± 0.1	NS
LDL-C (mmol/L)	2.68 ± 0.9	2.08 ± 0.56	NS
HbA_{1c} (%)	5.12 ± 0.2	5.08 ± 0.2	NS

NOTE. Data are means ± SD.

Abbreviations: BP_s, BP_d, systolic and diastolic blood pressure; BMI, body mass index; WHR, waist-to-hip ratio; TG, serum triglycerides; CHOL, total serum cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA_{1C}, glycosylated hemoglobin; OHP, offspring of hypertensive parents; CON, controls; NS, not significant.

*$P < .05$, †$P < .01$, ‡$P < .001$.

in this study after the purpose, nature, and potential risks of the study had been explained. Clinical characteristics of the subjects are summarized in Table 1.

Study Protocol

The subjects were examined on 2 separate occasions: a HGC was performed as the first (1), and a HIC as the second (2) test within the next month. All subjects underwent all tests.

The OHP and controls were admitted to a research laboratory of the Institute of Clinical and Experimental Medicine after a 12-hour fast; the subjects underwent a physical examination including their weight, height, BMI, waist-to-hip ratio (WHR) determination, and their basal biochemistry with glycosylated hemoglobin (HbA_{1c}).

Systolic and diastolic blood pressure was measured in triplicate after at least 10 minutes in the supine position. On the clamp day, a cannula was inserted into the deep antecubital vein of one arm for all infusions, and another cannula was placed retrogradely in a heated (60°C) dorsal hand vein of the same arm for arterialized blood sampling. After needle placement, 30 minutes of rest were allowed to re-establish basal conditions. Then, basal (fasting) blood samples for determination of plasma glucose, immunoreactive serum insulin (IRI), C-peptide, serum total lipids, and lipoprotein fractions were collected.

HGC

Glucose tolerance and insulin secretion were assessed by the HGC.[16] The subjects underwent a 10-hour HGC starting at 7:30 AM. Plasma glucose was acutely raised above the basal level by a manually given initial dose of 40% glucose solution and maintained at the desired hyperglycemic level (12 mmol/L) by infusing 15% glucose at varying rates according to blood glucose levels, measured at 5- to 15-minute intervals. Plasma samples were obtained at 0, 4, 6, 10, 30, 60, 90, 100, 110, 120, 180, 190, 200, 280, 290, 300, 360, 370, 380, 480, 490, 500, 580, 590, and 600 minutes and analyzed for IRI and C-peptide concentrations. During the HGC, urine samples were collected to measure glucosuria.

HIC

The degree of insulin resistance was evaluated using the 10-hour HIC.[16] A priming dose of insulin infusion (Actrapid HM 100 U/mL, Novo Nordisk, Copenhagen, Denmark) was rapidly given during the initial 10 minutes to raise plasma insulin to the desired concentration, followed by a 1-step hyperinsulinemic (insulin infusion 1 mU/kg · min, maintaining serum insulin levels at approximately 75 μU/mL)-euglycemic (plasma glucose clamped at 5 mmol/L) clamp starting at 7:30 AM (time zero). During constant-rate insulin infusion, euglycemia was maintained by a variable rate of infusion of 15% glucose solution. IRI and C-peptide levels were measured at 0, 100, 120, 180, 200, 280, 300, 380, 480, 500, 580, and 600 minutes, and plasma glucose was determined every 5 to 15 minutes during the clamp.

After completing insulin infusion, the patients consumed a meal, and glucose infusion was continued for another 20 minutes. The individuals remained in our research department until their blood glucose had returned to normal.

Calculations

Glucose tolerance was calculated as the mean glucose infusion rate (M, mg/kg · min) during HGC in 6 steady-state periods (1 = 100 to 120 minutes, 2 = 180 to 200 minutes, 3 = 280 to 300 minutes, 4 = 360 to 380 minutes, 5 = 480 to 500 minutes, 6 = 580 to 600 minutes) and assessed as blood glucose levels during OGTT and HbA_{1c}.

Insulin sensitivity was assessed as M, glucose metabolic clearance rate (MCR, mL/kg · min) and as the insulin sensitivity index (M/I) during HIC. M/I was calculated by dividing M (as the average of 3 measurements during 6 steady-state periods of HIC) by the average of 2 IRI concentrations during the same intervals.

Insulin secretion was calculated as the area under the curve (AUC) for IRI and C-peptide during HGC by the trapezoidal rule. The incremental AUC of IRI and C-peptide concentrations during the HGC were calculated by trapezoidal method. The first-phase and the late-phase IRI and C-peptide secretory responses were estimated by calculating the incremental AUC during the first 10 minutes and between 10 and 600 minutes, respectively. Log-transformed IRI and C-peptide levels from 0 to 10 minutes were used (in analysis of variance [ANOVA] for repeated measures) to calculate first-phase insulin and C-peptide release and log-transformed IRI and C-peptide levels from 10 to 600 minutes for second-phase release.

We assumed that hepatic glucose production was completely suppressed during euglycemic hyperinsulinemia at the achieved level of plasma insulin.[17,18] The glucose infusion rate then reflects total insulin-stimulated glucose metabolism during steady-state hyperinsulinemia.

Laboratory Measurements

Blood glucose was determined immediately using glucose oxidase method (Beckman Glucose Analyzer; Beckman Instruments, Fullerton, CA). IRI was measured by an immunoradioassay using an IMMUNOTECH Insulin IRMA kit (IMMUNOTECH, Prague, Czech Republic). C-peptide was determined by an IMMUNOTECH C-peptide IRMA kit (IMMUNOTECH). Total serum cholesterol (CHOL), high-density lipoprotein cholesterol (HDL-C), and serum triglycerides (TG) were measured by an enzymatic method using CHOD-PAP tests (Hoffmann La Roche, Basel, Switzerland). HbA_{1c} concentrations in blood were measured by ion exchange high-performance liquid chromatography (HPLC) using a Bio-Rad Hemoglobin A_{1c} Column Test (BIO-Rad Laboratories GmbH, Munich, Germany).

Statistical Analyses

Data in the text and figures are presented as the mean ± SD. Student's 2-tailed *t* test for unpaired data was used to compare data between OHP and controls. When the data were not normally distributed, the Mann-Whitney rank-sum test for unpaired data was used. The AUC for insulin and C-peptide levels were calculated as total AUC during the 10-hour HGC and HIC using the trapezoidal rule. Relation-

Table 2. Plasma Glucose and Insulin Levels During OGTT in OHP and Control Groups

	OHP (n = 12)	CON (n = 14)	*P*
Gly 0 min (mmol/L)	4.98 ± 0.49	5.01 ± 0.27	NS
Gly 30 min (mmol/L)	7.59 ± 1.08	7.23 ± 1.19	NS
Gly 60 min (mmol/L)	6.25 ± 1.36	5.89 ± 1.44	NS
Gly 120 min (mmol/L)	4.75 ± 1.92	4.4 ± 0.93	NS
IRI 0 min (μmol/mL)	10.9 ± 4.53	8.9 ± 2.7	*
IRI 30 min (μmol/mL)	95.7 − 54.4	53.2 ± 19.2	*
IRI 60 min (μmol/mL)	87.1 ± 54.2	48.4 ± 16.3	*
IRI 120 min (μmol/mL)	29.5 − 19.2	22.7 ± 10.9	*

NOTE. Data are means ± SD.

*$P < .05$, gly, IRI 0 min, 30 min, 60 min, 120 min ± glycemia, immunoreactive insulin levels during oGTT.

Table 3. Glucose Tolerance in Six Steady-State Periods During 10 Hours Hyperglycemic Clamp

M (mg/kg · min)	OHP (n = 12)	CON (n = 14)	*P*
M1	18.8 ± 5.1	18.9 ± 5.2	NS
M2	24.1 ± 5.1	23.2 ± 4.8	NS
M3	25.1 ± 4.0	24.9 ± 4.1	NS
M4	25.2 ± 4.4	25.7 ± 4.0	NS
M5	22.7 ± 5.7	23.9 ± 3.9	NS
M6	21.0 ± 4.4	22.2 ± 3.2	NS

NOTE. Data are means ± SD. Glucose infusion rate (M) in 6 steady-state periods during hyperglycemic clamp, 6 periods: 1 = 100 to 120 min, 2 = 180 to 200 min, 3 = 280 to 300 min, 4 = 360 to 380 min, 5 = 480 to 500 min, 6 = 580 to 600 min.

ships between measures were tested by correlation analyses (Pearson's correlation or Spearman's correlation). Significant differences between basal and insulin clamp periods within each group were tested by 1-way ANOVA for repeated measures. Standard equations were used to calculate correlation coefficients.

RESULTS

The clinical and biochemical characteristics of the 2 groups are presented in Table 1. There were no differences in age, sex, and BMI. Systolic and diastolic blood pressure was within the normal range, but significantly higher in OHP ($P < .001$). CHOL and TG were significantly elevated in OHP. There were no differences in HDL-C levels. Low-density lipoprotein cholesterol (LDL-C) levels were slightly, but not significantly, higher in subjects with a family history of hypertension. The levels of HbA_{1c} were similar in both groups.

As demonstrated in Table 2, glycemias during the OGTT tended to be slightly, but not significantly, higher in OHP. However, the fasting and postload plasma insulin concentrations were higher in OHP versus controls ($P < .05$).

HGC

Fasting plasma glucose levels were comparable in controls and OHP and were increased to 12 mmol/L during the first 120 minutes in both groups (mean coefficient of variations of blood glucose was < 4.8%). During the 6 steady-state periods of HGC, the amount of glucose infused (M) to maintain the plasma glucose levels at 12 mmol/L was similar in both groups (Table 3). Figures 1 and 2 illustrate the plasma IRI and C-peptide levels during HGC. In OHP, the first-phase IRI and C-peptide responses (0 to 10 minutes) did not differ from those in the control group. The late-phase IRI and C-peptide secretory responses (10 to 600 minutes, log-transformed AUC for IRI and C-peptide) were elevated in OHP compared with controls ($P < .05$).

HIC

During the 1-step 10-hour HIC, similar steady-state plasma insulin levels were maintained in OHP (75.6 ± 3.1 μU/mL) and the control group (73.15 ± 5.76 μU/mL). From the first to the fourth steady-state periods, no differences in insulin-mediated glucose disposal (M) were observed between OHP and controls. However, M was significantly lower ($P < .05$) in OHP versus controls in the last 2 clamp periods. OHP also showed decreased glucose MCR in the second and third clamp periods ($P < .05$); significantly higher differences were noted in the fifth to sixth steady-state clamp periods ($P < .01$). While there were no differences in the first HIC period between the groups in insulin sensitivity index, insulin sensitivity was lower in OHP from the second to the fifth periods ($P < .05$), with the lowest insulin sensitivity noted in the last, sixth HIC period ($P < .01$), as shown in Table 4. Negative correlations between M/I and BMI, blood pressure, CHOL, and LDL-C levels were demonstrated in OHP only (Table 5).

DISCUSSION

Using clamp methods over the longest periods known to us from studies to date, we have demonstrated, in OHP compared with controls, normal glucose tolerance, but elevated insulin secretion and insulin resistance.

The advantage of 10-hour HGC was that it allowed evaluating both the first and second phases of insulin secretion and

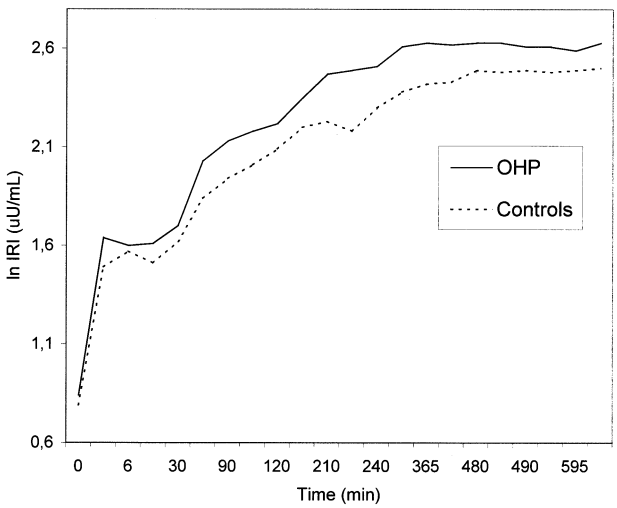

Fig 1. Course of plasma IRI levels during 10-hour HGC. IRI, log-transformed data for immunoreactive insulin levels during 10-hour HGC. AUC was significantly increased in OHP compared with controls, *$P < .05$; OHP, offspring of hypertensive parents.

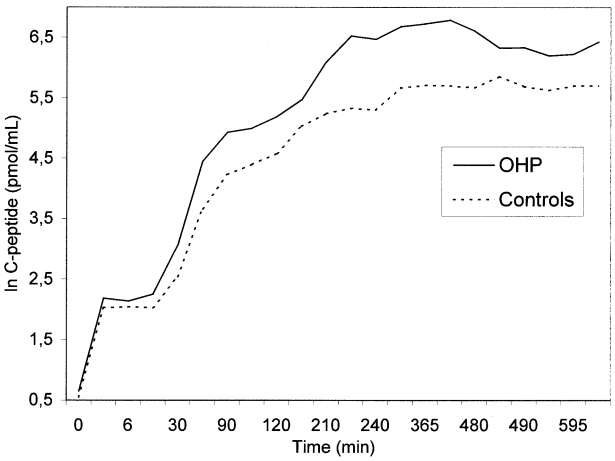

Fig 2. Course of plasma C-peptide levels during 10-hour HGC. C-peptide, log-transformed data for C-peptide levels during 10-hour HGC. AUC was significantly increased in OHP compared with controls, *$P < .05$.

the dynamics of insulin action, because little is known about these conditions in hypertensive patients or their offspring.

Impaired insulin secretion during the first 10 minutes was associated, irrespective of other cardiovascular risk factors, with high blood pressure.[19] A positive correlation between insulinemia and blood pressure has been demonstrated in 1,1001 participants of the Heureka study.[20]

In OHP, no differences in first-phase insulin secretory response were found compared with controls. However, the second phase was increased in OHP. No associations between parameters of insulin secretion and blood pressure were demonstrated in our study, but a negative correlation between insulin sensitivity index (M/I) and blood pressure was seen in the OHP group only.

The increase in islet β-cell efficiency, seen during HGC, appears to be an adaptive response to insulin resistance and decreased insulin sensitivity in these healthy young persons.[21-23] Subsequently, OHP need higher fasting and poststimulation plasma insulin levels to maintain normal glucose tolerance compared with control subjects.

Our results are in agreement with the study of Sánches and Margalet[24] in which young offspring of insulin-resistant, nonobese, essential hypertensive patients were shown to have increased postglucose insulin levels, although their glucose clearance was normal, suggesting an early alteration in insulin sensitivity.

There is increasing evidence to suggest that elevated insulin levels precede the increases in blood pressure in these patients and contribute to the development of hypertension,[25,26] thus hyperinsulinemia and insulin resistance seem to be associated with genetic factors for hypertension.[8]

Lower insulin action was marked on M and MCR during HIC in OHP compared with controls. Furthermore, reduced insulin sensitivity was noted in OHP, when assessed as an insulin sensitivity index (M/I). Our findings are consistent with earlier reports of hyperinsulinemia and insulin resistance in hypertensive patients and in those with borderline hypertension[4,18,27] and with conclusions of several investigators using the HIC technique who observed impaired insulin sensitivity and increased blood pressure in subjects with genetic predisposition to hypertension.[1,3,28] Despite the fact that young OHP were not obese, only in this group have we found negative correlations between the insulin sensitivity indexes, BMI, and the other markers of metabolic syndrome, usually present in obese or insulin-resistant persons. We supposed the genetic disposition might be one cause of those relationships in these persons. However, findings of other studies were in contrast with these observations.[29,30]

Reduced insulin sensitivity and increased blood pressure have been reported in young adults (mean age, 25 years), with a positive family history of hypertension using minimal-model method.[25,31] Using the glucose tolerance test and an insulin suppression test, Facchini et al[11] also demonstrated insulin resistance in individuals with a positive family history of hypertension. In healthy men, insulin resistance as measured by minimal model method, was associated with blood pressure.[32] Diastolic blood pressure correlated negatively with insulin sensitivity in 20 healthy prepubertal children.[33]

In some studies, insulin resistance has been proposed to be a pathogenic factor in essential hypertension.[9,10] Clinical manifestation of hypertension can be a function of time over which arterial hypertrophy and an increment of vascular reactivity

Table 4. Glucose Infusion Rate, Clearance, and Insulin Sensitivity Index in Six Steady-State Periods During 10 Hours Hyperinsulinemic-Euglycemic Clamp in OHP and Controls

	M (mg/kg · min)			MCR (mL/kg · min)			M/I		
Period	OHP (n = 12)	CON (n = 14)	*P*	OHP (n = 12)	CON (n = 14)	*P*	OHP (n = 12)	CON (n = 14)	*P*
1	8.68 ± 2.86	10.36 ± 3.76	NS	10.02 ± 3.92	12.40-4.58	NS	0.17 ± 0.17	0.35 ± 0.45	NS
2	10.13 ± 2.96	12.37 ± 2.90	NS	11.32 ± 3.34	14.77-3.54	*	0.11 ± 0.08	0.19 ± 0.09	*
3	10.44 ± 2.52	12.69 ± 3.10	NS	11.49 ± 2.85	14.32-3.60	*	0.12 ± 0.07	0.20 ± 0.09	*
4	10.61 ± 2.22	12.16 ± 2.87	NS	11.74 ± 2.73	13.79-3.55	NS	0.13 ± 0.08	0.25 ± 0.08	*
5	10.11 ± 2.10	12.24 ± 2.08	*	10.41 ± 2.1	13.43-2.06	†	0.10 ± 0.07	0.18 ± 0.07	*
6	10.03 ± 2.11	12.50 ± 2.82	*	10.72 ± 2.09	13.25-2.39	†	0.11 ± 0.07	0.23 ± 0.11	†

NOTE. Data are means ± SD. Glucose infusion rate (M), clearance (MCR) and log-transformed insulin sensitivity index (M/I) in 6 steady-state periods during HIC, periods: 1 = 100 to 120 min, 2 = 180 to 200 min, 3 = 280 to 300 min, 4 = 360 to 380 min, 5 = 480 to 500 min, 6 = 580 to 600 min.

*$P < .05$, †$P < .01$.

Table 5. Correlation Coefficients Between Insulin Sensitivity Index M/I in Six Steady-State Periods During Hyperglycemic Clamp and Selected Variables in OHP

	BMI	WHR	BP_s	BP_d	CHOL	LDL-C
M/I 1	−0.6983†	−0.3253	−0.2706	−0.3702	−0.4801*	−0.4654*
M/I 2	−0.6465†	−0.3982*	−0.3149	−0.4814*	−0.5228†	−0.5344†
M/I 3	−0.4964*	−0.3140	−0.4437*	−0.5008*	−0.3890	−0.2968
M/I 4	−0.4246*	−0.3483	−0.4231*	−0.4548*	−0.3422	−0.2747
M/I 5	−0.4128*	−0.3416	−0.3158	−0.4548*	−0.3700	−0.3279
M/I 6	−0.5108†	−0.2643	−0.2701	−0.4914*	−0.3861	−0.3845

NOTE. Insulin sensitivity index M/I in 6 steady-state periods during hyperglycemic clamp, periods: 1 = 100 to 120 min, 2 = 180 to 200 min, 3 = 280 to 300 min, 4 = 360 to 380 min, 5 = 480 to 500 min, 6 = 580 to 600 min.

Abbreviations: BMI, body mass index; WHR, waist to hip ratio; $BP_{s,d}$, systolic, diastolic blood pressure; CHOL, total cholesterol level; LDL-C, low-density lipoprotein cholesterol.

*$P < .05$, †$P < .01$.

continue. The possible mechanism involves both acute insulin action, impairment of the vasodilator effect and changes in skeletal blood flow,[34] stimulation of the sympathetic nervous system,[12] salt sensitivity,[35] sodium retention in the kidneys,[36] and the long-term effect of insulin on structural vascular and cardiac changes capable of producing hypertension.[37]

In our study, young lean hypertension-prone subjects had significantly higher systolic and diastolic blood pressure compared with controls. Previous reports have indicated a tendency even for the children or young OHP to develop hypertension by themselves.[4]

The importance of blood pressure was documented by Klumbiene et al[38] in a 20-year longitudinal study showing that the best predictors of adult blood pressure were the initial childhood pressure levels and change in BMI, with other factors being less predictive.

CHOL and TG levels were significantly higher in our group of insulin-resistant OHP. Moreover, in OHP, we found negative correlations between insulin sensitivity index (M/I) and CHOL, LDL-C, blood pressure, and BMI. Although there are reasons to believe that insulin resistance is a consequence of lipoprotein abnormalities, findings from the San Antonio Heart Study demonstrated that high fasting plasma insulin preceded the development of hypertriglyceridemia and high blood pressure.[39] Our data also confirm the results of the Honolulu Heart Program[40] and the recent study of Misra et al[41] in which hyperinsulinemia and dyslipidemia were found in non-obese normotensive OHP. Insulin resistance is persistently associated with these adverse, unfavorable metabolic changes, which are already present at about 30 years of age.[19] Some studies conducted in the OHP and prospective studies have shown that hyperinsulinemia or insulin resistance preceded the manifestations of some features of the metabolic syndrome, ie, increased total CHOL and TG levels together with lower HDL-C concentrations.[25,42]

Laakso et al[43] demonstrated that insulin resistance, as measured by euglycemic clamp techniques, was associated with adverse lipid and lipoprotein changes favoring atherosclerosis not only in subjects with varying degrees of glucose tolerance but, also, in nondiabetic individuals. The association of high insulin levels with adverse lipid and lipoprotein changes indirectly reflected the association of insulin resistance with lipid and lipoprotein levels.

Much attention has focused on the effect of a positive family history of hypertension, which seems to be an even more important risk factor than any of the other 4 factors, obesity, diabetes mellitus, hypercholesterolemia, and hypertriglyceridemia.[44] Young, normotensive individuals with a positive family history of hypertension have a significantly elevated body weight. Widgren et al[45] speculated that, through obesity, genetic factors might influence the progression of insulin resistance. However, our study group was BMI-matched with controls, and these individuals were not obese. It is very important that the matching process in this study excluded the effect of obesity, body fat distribution, age, and sex, which are associated with insulin resistance.[46] We selected our subjects very strictly in terms of their BMI, and they did not differ even in WHR.

Thus, our results really indicate that, when comparing "crude" clinical methodology to highly sophisticated, metabolic methodology, mild abnormalities were coexistent in the OHP both for blood pressure on one hand and glucose and insulin dynamics on the other.

Conclusions

Compared with a control group, lean young healthy OHP showed increased insulin secretion during the second phase of secretion, insulin resistance, elevated blood pressure, and lipid alterations. The mechanisms explaining the relationship between decreased insulin sensitivity, hyperinsulinemia, elevated blood pressure, and lipid disturbances remain unclear. However, these results have implications in the understanding of an increased risk of atherosclerosis developing in these individuals, in whom clinical manifestations of high blood pressure may be a late symptom of the insulin resistance syndrome with characteristic genetic and metabolic features marked even in young, clinically asymptomatic subjects.[14,38,44]

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