Insulin Resistance Syndrome in Adolescents and Adults

Ikuo Saito, Hiroshi Kawabe, Eiko Takeshita*, Hideki Wainai, Kazuko Murata**, and Takao Saruta**

This study was designed to investigate the possibility of sex and age differences in the insulin-blood pressure relationship in a general Japanese population with a wide age range. Fasting serum insulin, lipids, plasma glucose, blood pressure and anthropometric measurements were made on 1,537 men and 843 women aged 16 to 65 years. Of the 2,380 subjects in the present analysis, 290 (184 men, 106 women) were hypertensive. When divided into four age groups (16 to 17, 21 to 22, 30 to 49 and 50 to 65 years), the male hypertensive subjects were found to have significantly higher fasting insulin levels, triglycerides levels and body mass index and lower glucose/insulin ratios than normotensive male subjects in all age groups. In the women, there was no significant difference in serum insulin levels or glucose/insulin ratios between the hypertensive and normotensive groups in any age group. Simple correlation analysis showed that blood pressure was statistically significantly correlated with serum insulin levels and body mass index in the men in all age groups. In women, the correlation between blood pressure and serum insulin was insignificant in the 21- to 22-year-old age group. In men but not women, multivariate analysis showed that blood pressure was significantly and independently correlated with fasting serum insulin levels. The results of this study suggests the existence of sex and age differences in the insulin-blood pressure relationship in a Japanese population. (*Hypertens Res* 1996; 19 Suppl. I:S19-S22)

Key Words: insulin, hypertension, age, sex

In several population studies hyperinsulinemia has been shown to be correlated with the risk of developing hypertension, as well as lipid abnormalities. A hypothesis has been proposed that hyperinsulinemia may underlie the associations between obesity, hypertension and glucose intolerance (1-3). Although a number of studies have recently examined the association of insulin with blood pressure and serum lipid levels, these studies have been conducted primarily on adults. Few studies have examined a wide age range of individuals extending from young to aged to assess the relationship between insulin and blood pressure (4-6). Falkner *et al.* suggest that there are gender differences in plasma insulin levels in African Americans (7).

In the present school-based study, we investigated age and sex differences in the insulin-blood pressure relationship in a Japanese population.

Methods

Subjects

The study subjects were employees and students of Keio High School and Keio University who came to Keio University Health Center for an annual medical checkup.

Methods

Subjects with diabetes mellitus, endocrine diseases, significant renal or hepatic disease and subjects receiving antihypertensive drugs, systemic corticosteroids or lipid-lowering drugs were excluded from

the analysis. Informed consent was obtained prior to the study. Subjects were instructed to fast for 12 hours before the examination, and compliance was investigated by interview on the morning of the examination.

Blood was drawn by antecubital venipuncture to obtain serum and plasma. Anthropometric measurements included height and weight with the subjects in light clothing without shoes. The body mass index (BMI) was calculated as body weight (kg) divided by the square of body height (m). Blood pressure readings were taken from the right arm by well-trained nurses using an electronic automatic manometer (Nihon Colin BP 103 NiII, Komaki, Japan), previously calibrated against a mercury manometer, with the subjects sitting, after a 5 min rest. "Hypertension" was defined as systolic blood pressure (SBP) of >140 mmHg and diastolic blood pressure (DBP) of >90 mmHg except in female subjects aged 21 to 22 years (SBP >130 mmHg or DBP >85 mmHg). Plasma glucose was determined by the glucose oxidase method. Serum insulin was measured by radioimmunoassay (Shionogi). The intra-assay and inter-assay coefficients of variation were 3.5% and 1.4%, respectively (8). Serum cholesterol and triglycerides were assayed by automated enzymatic methods.

Values are expressed as means $\pm$ SD. A two-tailed *p* value of <0.05 was considered statistically significant. Statistical analysis was performed using Statview 4.1 software.

Table 1. Anthropometric Measurements and Blood Pressure

	Male				Female		
	16-17 yr	21-22 yr	30-49 yr	50-65 yr	21-22 yr	30-49 yr	50-65 yr
Height(cm)							
Normotensive	171±6	172±6	170±6	166±6	159±5	157±5	154±5
Hypertensive	171±5	172±5	169±5	165±7	161±5	156±6	152±5
Weight(kg)							
Normotensive	60±7	63±8	65±8	62±9	50±5	51±6	51±7
Hypertensive	63±10***	69±11***	69±7***	64±11	54±7*	53±6	54±8**
Body Mass Index(kg/m ²)							
Normotensive	20.5±2.1	21.3±2.2	22.6±2.6	22.5±2.9	19.7±1.7	20.7±2.3	21.5±2.6
Hypertensive	21.5±2.9*	23.4±3.2*	24.3±2.6***	23.4±2.8*	20.6±2.6	21.8±2.5*	23.4±3.3***
Systolic Blood Pressure(mmHg)							
Normotensive	123±10	122±10	121±12	122±12	108±10	115±12	119±13
Hypertensive	147±7	145±4	149±14	152±11	133±2	146±5	151±12
Diastolic Blood Pressure(mmHg)							
Normotensive	66±7	67±6	77±9	85±9	61±6	69±8	70±9
Hypertensive	77±8	78±6	90±10	90±8	73±4	87±8	85±8

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. Normotensive.

Fig. 1. Serum insulin levels in hypertensive and normotensive subjects. Values are means. * $p < 0.05$ vs. Hypertensive subjects.

Results

Characteristics of the Subjects

Of the 2380 subjects in the present analysis, 290 (184 men, 106 women) were defined as hypertensive. The hypertensive men had significantly higher BMI and fasting insulin levels in all age groups (Table 1 and Fig. 1). Fasting plasma glucose, total cholesterol and triglyceride levels were higher and glucose/insulin (G/I) ratios were lower in the hypertensive male subjects than in the normotensive

male subjects except in the 50- to 65-year-old age group (Table 2). The hypertensive women had a significantly higher BMI than the normotensives in the 30- to 49-year-old and 50- to 65-year-old age groups. There was no significant difference in serum insulin or serum cholesterol levels between the hypertensive and normotensive groups in any age group. The plasma glucose and serum triglycerides levels were significantly higher in the hypertensives than in the normotensives in the age 30- to 49-year group. The G/I ratios in the two groups were not significantly different.

Table 2. Plasma Glucose, Glucose/Insulin Ratio and Serum Lipids Levels

	Male				Female		
	16-17 yr	21-22 yr	30-49 yr	50-65 yr	21-22 yr	30-49 yr	50-65 yr
Glucose(mg/dl)							
Normotensive	86±5	84±6	93±12	99±16	81±6	87±7	90±10
Hypertensive	89±7**	86±4	97±11**	100±14	82±7	96±9***	93±8
Glucose/Insulin ratio							
Normotensive	14.1±5.6	17.6±7.3	11.6±5.4	13.7±6.1	11.8±5.0	11.7±4.8	13.5±6.6
Hypertensive	12.2±5.1*	9.9±3.3*	9.5±4.2*	12.1±5.9	12.3±5.2	11.6±5.5	14.4±7.3
Total Cholesterol(mg/dl)							
Normotensive	170±26	169±27	193±33	206±33	185±29	187±31	217±32
Hypertensive	182±38***	182±30*	206±36**	203±29	197±35	196±37	215±32
Triglycerides(mg/dl)							
Normotensive	67±36	77±34	122±83	131±103	66±28	68±42	83±59
Hypertensive	83±53*	107±68*	143±80**	136±77	61±29	94±90**	84±42
HDL Cholesterol(mg/dl)							
Normotensive	60.9±11.1	64.6±13.7	54.6±12.8	55.8±14.6	68.8±13.0	66.9±14.3	68.2±15.2
Hypertensive	56.6±11.7**	59.8±16.2	55.8±12.0	59.3±15.8	74.7±11.6	61.8±11.2	68.0±21.1

* $p < 0.05$, ** $p < 0.01$ vs. Normotensive.

Table 3. Simple Correlation

	Male				Female		
	16-17 yr	21-22 yr	30-49 yr	50-65 yr	21-22 yr	30-49 yr	50-65 yr
Systolic Blood Pressure vs.							
Insulin	0.214***	0.136**	0.219***	0.216***	0.07	0.122**	0.141*
BMI	0.265***	0.227***	0.290***	0.205***	0.137*	0.271***	0.317***
Diastolic Blood Pressure vs.							
Insulin	0.237***	0.163**	0.171**	0.255**	0.077	0.018	0.107
BMI	0.191***	0.188***	0.251***	0.243***	0.109	0.239***	0.250**

BMI: body mass index; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Relationship between Serum Insulin and Blood Pressure

Simple correlation analysis showed that systolic and diastolic blood pressure were statistically significantly related to serum insulin levels in the men (Table 3). The correlation between systolic blood pressure and serum insulin levels was insignificant in 21- to 22-year-old women, and the correlation between diastolic blood pressure and serum insulin was insignificant in 21- to 22-year-old and in 50- to 65-year-old women. Systolic and diastolic blood pressure values were correlated with BMI in men and women of all age groups except women aged 21 to 22 years. In men, but not in women, multivariate analysis showed that blood pressure was significantly and independently correlated with the fasting serum insulin levels (Table 4).

Discussion

The present study demonstrates that hyperinsulinemia/insulin resistance is independently associated with elevated blood pressure in young and old adults. This association was found mainly in men,

and not in young or old women.

A high serum insulin concentration in the presence of a normal plasma glucose level may indicate insulin resistance or a relative lack of insulin degradation (9). Although the euglycemic hyperinsulinemic clamp method may be more sensitive in detecting abnormal insulin sensitivity, it is impractical for use in a school-based study.

There are several epidemiological studies showing a positive correlation between serum insulin and blood pressure (1-3), but no such relationship has been found in some studies (10, 11). Ohmori *et al.* showed that both fasting and 2-h post-glucose-load insulin levels were significantly correlated with blood pressure in Japanese men and women (12). Bonora *et al.* found a significant correlation between plasma insulin after glucose loading and blood pressure in Italian men and women (13). Consistent with the results of our study, a study in Hong Kong Chinese showed that fasting insulin levels are an independent predictor of blood pressure in men but not in women (14). Haffner *et al.* found that plasma insulin levels and blood pressure were correlated in Mexican-American men but not

Table 4. Results of Multiple Regression Analysis

		Regression coefficient	t value	p value
Systolic Blood Pressure vs.				
Male 16-17 yr	Insulin	0.143	3.13	0.0019
	BMI	0.219	4.79	0.0001
Male 21-22 yr	Insulin	0.096	2	0.045
	BMI	0.203	4.22	0.001
Male 30-49 yr	Insulin	0.133	2.43	0.016
	BMI	0.217	3.95	0.001
Male 50-65 yr	Insulin	0.132	1.74	0.080
	BMI	0.185	2.45	0.020
Female 21-22 yr	Insulin	0.056	0.86	0.387
	BMI	0.126	1.94	0.06
Female 30-49 yr	Insulin	0.099	1.82	0.069
	BMI	0.244	4.48	0.001
Female 50-65 yr	Insulin	0.008	0.10	0.916
	BMI	0.328	4.19	0.001
Diastolic Blood Pressure vs.				
Male 16-17 yr	Insulin	0.195	4.22	0.001
	BMI	0.129	2.77	0.006
Male 21-22 yr	Insulin	0.096	2	0.045
	BMI	0.203	4.22	0.001
Male 30-49 yr	Insulin	0.090	1.65	0.010
	BMI	0.199	3.58	0.0004
Male 50-65 yr	Insulin	0.161	0.21	0.030
	BMI	0.208	2.79	0.006
Female 21-22 yr	Insulin	0.068	1.05	0.294
	BMI	0.100	1.54	0.126
Female 30-49 yr	Insulin	0.103	1.88	0.062
	BMI	0.204	3.71	0.0002
Female 50-65 yr	Insulin	0.015	0.19	0.847
	BMI	0.203	3.29	0.001

in Mexican-American women (15). The reason for the sex difference in the relationship between hyperinsulinemia and blood pressure is unclear. The difference may be explained in part by the influence of endogenous sex hormones (7). The majority of women aged <49 years old are premenopausal and women aged >50 years old are postmenopausal. Our failure to find a correlation between plasma insulin and diastolic blood pressure in women aged >50 years suggests that a mechanism other than endogenous sex hormone may be responsible. Further studies are needed to determine the various factors involved in the insulin-blood pressure relationship in Asian women. The Bogalusa Heart Study showed that fasting insulin was significantly and positively associated with systolic and diastolic blood pressure in children and young adults, but not in the 13- to 16-year-old group (16). The different tendency in the insulin-blood pressure association may be due to the influence of the growth spurt and the complex hormonal effects that occur during puberty. The present data seem to confirm these findings in the Asian population.

In summary, we have shown that blood pressure is significantly and independently related to fasting insulin levels in Japanese men in all age groups, including 16- to 17-year-old subjects, but not in women. This finding could be important for devising strategies to prevent hypertension and cardiovascular disease.

References

1. Modan M, Halkin H, Almog S, *et al*: Hyperinsulinemia: a link between hypertension, obesity and glucose intolerance. *J Clin Invest* 1985; **75**: 809-817.
2. Ferrannini E, Buzzigoli G, Bonadonna R, *et al*: Insulin resistance in essential hypertension. *N Engl J Med* 1987; **317**: 350-357.
3. Reaven GM: Role of insulin resistance in human disease. *Diabetes* 1988; **37**: 1595-1607.
4. Saito I, Nishino M, Kawabe H, *et al*: Leisure time physical activity and insulin resistance in young obese students with hypertension. *Am J Hypertens* 1992; **5**: 915-918.
5. Kawabe H, Saito I, Nishino M, Wainai H, Nagano S, Saruta T: Hyperinsulinemia in obese and non-obese young Japanese hypertensive men. *Hypertens Res* 1994; **17**: 133-136.
6. Bao W, Srinivasan SR, Wattigney WA, Berenson GS: Persistence of multiple cardiovascular risk clustering related to syndrome X from childhood to young adulthood. *Arch Intern Med* 1994; **154**: 1842-1847.
7. Falkner B, Hulman S, Kushner H: Gender differences insulin-stimulated glucose utilization among African-Americans. *Am J Hypertens* 1994; **7**: 948-952.
8. Oguchi S, Takeshita E, Uchida T, Kikuchi H, Iri H: Fundamental evaluation of insulin radioimmunoassay kit "Shionoria". *Igaku to Yakugaku* 1991; **26**: 561-567 (in Japanese).
9. Caro JF: Insulin resistance in obese and nonobese man. *J Clin Endocrinol Metab* 1991; **73**: 691-695.
10. Mbanya JN, Thomas TH, Wilkinson R, Alberti KGMM, Taylor R: Hypertension and hyperinsulinemia: a relation in diabetes but not essential hypertension. *Lancet* 1988; **1**: 733-734.
11. Muller DS, Elahi D, Pratley RE, Tobin JD, Andres R: An epidemiological test of the hyperinsulinemia-hypertension hypothesis. *J Clin Endocrinol Metab* 1993; **76**: 544-548.
12. Ohmori S, Kiyohara Y, Kato I, *et al*: Hyperinsulinemia and blood pressure in a general Japanese population: the Hisayama study. *J Hypertens* 1994; **12**: 1191-1197.
13. Bonora E, Zavaroni I, Alpi O, *et al*: Relationship between blood pressure and plasma insulin in non-obese subjects. *Diabetologia* 1987; **30**: 719-723.
14. Woo J, Cockram CS, Lau E, Chan A, Swaminathan R: Association between insulin and blood pressure in a community population with normal glucose tolerance. *J Hum Hypertens* 1992; **6**: 343-347.
15. Haffner SM, Fong D, Hazuda HP, Pugh JA, Patterson JK: Hyperinsulinemia, upper body adiposity, and cardiovascular factors in non-diabetics. *Metabolism* 1988; **37**: 338-345.
16. Jiang X, Srinivasan SR, Bao W, Berenson GS: Association of fasting insulin with blood pressure in young individuals. The Bogalusa heart study. *Arch Intern Med* 1993; **153**: 323-328.