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# Relationship between blood pressure and plasma insulin in non-obese and obese non-diabetic subjects

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**Summary.** In this study, we have measured plasma insulin at fasting and following an oral glucose load and blood pressure after glucose load in 367 (247 non-obese, 120 obese) normotensive and untreated mildly hypertensive subjects. Overall, there was no independent association between fasting plasma insulin levels and blood pressure values. After controlling for age and body weight, a significant relationship between postglucose plasma insulin levels and diastolic blood pressure was found. When non-obese and obese subjects were examined separately, significant relationships were identified between postglucose plasma insulin levels and both systolic and diastolic blood pressure values in the former but not in the latter. A comparison of sex-, age-, and weight-matched hyperinsulinaemic vs normoinsulinaemic subjects showed that the former had significantly higher values of blood pressure only if not obese. These results demonstrate that the plasma insulin response to glucose is independently correlated with blood pressure.

**Key words:** Insulin, blood pressure, obesity, healthy man, oral glucose tolerance test.

An association of hypertension and obesity as well as a link between high blood pressure and glucose intolerance have been well established in man [1, 2]. Accordingly, a large survey has recently shown a considerable degree of overlap between obese, glucose intolerant and hypertensive populations suggesting common pathogenetic mechanisms [3]. In this context, hyperinsulinaemia has been indicated as a common physiopathological feature of these three clinical conditions. Nevertheless, hypertension seems to be associated with hyperinsulinaemia independently of the presence of either obesity or glucose intolerance. This conclusion is supported by the finding of higher serum insulin levels in hypertensive versus normotensive subjects even when they are similar for body weight and glucose tolerance [3].

In the present study, we report on the relationship between blood pressure and plasma insulin in a large population of ambulatory volunteers.

## Subjects and methods

A total of 367 subjects were taken into consideration for the study. They were selected from 823 ambulatory volunteers who participated in a survey concerning risk factors of atherosclerosis. Criteria for selection were: (1) no family history of diabetes mellitus; (2) negative history of important diseases; (3) normal physical examination except for obesity and hypertension; (4) blood pressure values not exceeding 160/100 mm Hg; (5) routine laboratory tests within the normal range; (6) normal glucose tolerance according to conventional criteria [4]; (7) no consumption of any drug.

Two hundred and forty-seven subjects were non-obese (body mass index less than 27 kg/m$^2$), and 120 were obese (body mass index equal to or higher than 27 kg/m$^2$).

All subjects underwent a standard oral glucose tolerance test [4], including the measurement of plasma insulin concentration at fasting and 1 and 2 h following the glucose load. Plasma insulin was assayed by a double antibody radioimmunoassay [5].

In all subjects one single blood pressure measurement was obtained 1 to 2 h after the glucose load at a time when they underwent a complete physical examination. Blood pressure was measured by a mercury manometer with standard cuff placed about midpoint of the subject's left arm while the subject was recumbent for at least 10 min. Diastolic blood pressure was recorded at the disappearance of Korotkoff sounds (phase 5).

### *Statistical analysis*

Between groups comparison of mean values was performed using the unpaired Student's t-test. Simple (Pearson's) and partial correlation coefficients as well as standardised regression coefficients were calculated by standard techniques. Data are presented as mean ± standard error.

**Table 1.** Clinical features, plasma glucose and insulin concentrations, and blood pressure values in the whole population as well as in non-obese and obese subpopulations

| | Whole population | Non-obese | Obese |
|---|---|---|---|
| Number of subjects | 367 | 247 | 120 |
| Sex (males/females) | 208/159 | 134/113 | 74 /46 |
| Age (years) | 39.7 ±0.4 | 38.0 ±0.5 | 43.3 ±0.9[a] |
| Body mass index (kg/m$^2$) | 25.5 ±0.2 | 23.6 ±0.1 | 29.3 ±0.2[a] |
| Fasting glucose (mmol/l) | 4.8 ±0.04 | 4.6 ±0.03 | 5.0 ±0.05[a] |
| 1-h glucose (mmol/l) | 5.8 ±0.1 | 5.2 ±0.1 | 6.9 ±0.2[a] |
| 2-h glucose (mmol/l) | 4.3 ±0.1 | 4.1 ±0.1 | 4.6 ±0.1[a] |
| Fasting insulin (pmol/ml) | 0.10±0.002 | 0.09±0.002 | 0.12±0.004[a] |
| 1-h insulin (pmol/ml) | 0.56±0.02 | 0.45±0.01 | 0.74±0.04[a] |
| 2-h insulin (pmol/ml) | 0.30±0.01 | 0.24±0.01 | 0.38±0.03[a] |
| Systolic blood pressure (mmHg) | 125±1 | 123±1 | 131±1[a] |
| Diastolic blood pressure (mmHg) | 82±1 | 80±1 | 86±1[a] |

Mean±SEM; [a] $p<0.001$ obese vs non-obese subjects

**Table 2.** Simple correlations between blood pressure and plasma insulin in the whole population as well as in non-obese and obese subpopulations

| | Fasting insulin | 1-h insulin | 2-h insulin | 1+2 h insulin |
|---|---|---|---|---|
| *Whole population* | | | | |
| Systolic blood pressure | 0.14[b] | 0.26[c] | 0.17[b] | 0.26[c] |
| Diastolic blood pressure | 0.19[c] | 0.29[c] | 0.22[c] | 0.31[c] |
| *Non-obese subpopulation* | | | | |
| Systolic blood pressure | 0.02 | 0.22[c] | 0.07 | 0.20[c] |
| Diastolic blood pressure | 0.11[a] | 0.26[c] | 0.11[a] | 0.25[c] |
| *Obese subpopulation* | | | | |
| Systolic blood pressure | 0.10 | 0.14 | 0.15 | 0.17 |
| Diastolic blood pressure | 0.05 | 0.15 | 0.22[a] | 0.21[a] |

[a] $p<0.05$; [b] $p<0.01$; [c] $p<0.001$

**Table 3.** Partial correlation coefficients between blood pressure and plasma insulin after controlling for age and body mass index in the whole population as well as in non-obese and obese subpopulations

| | Fasting insulin | 1-h insulin | 2-h insulin | 1+2 h insulin |
|---|---|---|---|---|
| *Whole population* | | | | |
| Systolic blood pressure | 0.0008 | 0.09 | 0.04 | 0.09 |
| Diastolic blood pressure | 0.064 | 0.14[b] | 0.12[a] | 0.16[b] |
| *Non-obese subpopulation* | | | | |
| Systolic blood pressure | 0.0001 | 0.16[b] | 0.08 | 0.16[b] |
| Diastolic blood pressure | 0.10 | 0.21[c] | 0.12[a] | 0.21[c] |
| *Obese subpopulation* | | | | |
| Systolic blood pressure | 0.024 | 0.022 | -0.020 | 0.08 |
| Diastolic blood pressure | 0.004 | 0.048 | 0.10 | 0.08 |

[a] $p<0.05$; [b] $p<0.01$; [c] $p<0.001$

**Table 4.** Standardised regression coefficients between blood pressure and plasma insulin after controlling for age and body mass index in the whole population as well as in non-obese and obese subpopulations

| | Fasting insulin | 1-h insulin | 2-h insulin | 1+2 h insulin |
|---|---|---|---|---|
| *Whole population* | | | | |
| Systolic blood pressure | 0.042 | 0.097 | 0.023 | 0.11 |
| Diastolic blood pressure | 0.004 | 0.11 | 0.068 | 0.15 |
| *Non-obese subpopulation* | | | | |
| Systolic blood pressure | 0.083 | 0.18 | 0.031 | 0.19 |
| Diastolic blood pressure | 0.008 | 0.19 | 0.029 | 0.20 |
| *Obese subpopulation* | | | | |
| Systolic blood pressure | 0.023 | 0.022 | -0.32 | -0.001 |
| Diastolic blood pressure | 0.037 | 0.023 | 0.10 | 0.091 |

**Table 5.** Standardised regression coefficients between blood pressure and either age or body mass index (BMI) after controlling for BMI and age, respectively, in the whole population as well as in non-obese and obese subpopulations

| | Age | BMI |
|---|---|---|
| *Whole population* | | |
| Systolic blood pressure | 0.265 | 0.699 |
| Diastolic blood pressure | 0.200 | 0.924 |
| *Non-obese subpopulation* | | |
| Systolic blood pressure | 0.160 | 0.568 |
| Diastolic blood pressure | 0.176 | 0.568 |
| *Obese subpopulation* | | |
| Systolic blood pressure | 0.443 | 0.414 |
| Diastolic blood pressure | 0.249 | 0.825 |

## Results

Table 1 reports clinical data of the whole population and of non-obese and obese subpopulations. Obese subjects were significantly older than non-obese subjects, and had significantly higher values of blood pressure, plasma glucose and insulin concentrations.

Table 2 reports simple correlation coefficients between plasma insulin levels and blood pressure values in the whole population, and in non-obese and obese subpopulations. In the whole population significant relationships were found between either systolic or diastolic blood pressure and both fasting and postglucose plasma insulin. In non-obese subjects 1-h plasma insulin significantly correlated with systolic blood pressure ($p<0.001$), and fasting, 1-h and 2-h plasma insulin significantly correlated with diastolic blood pressure ($p<0.05$, 0.001 and 0.05, respectively). In obese subjects the only significant relationship was that between 2-h plasma insulin and diastolic blood pressure ($p<0.05$).

Table 3 reports partial correlation coefficients between plasma insulin and blood pressure after controlling for age and body mass index. In the whole population a significant correlation between diastolic blood pressure and both 1-h and 2-h plasma insulin was

**Table 6.** Clinical features, plasma glucose and insulin levels at fasting and after a 75 g OGTT, and blood pressure values in hyperinsulinaemic and normoinsulinaemic non-obese subjects

| | Hyper-insulinaemic | Normo-insulinaemic |
|---|---|---|
| Number of subjects | 32 | 32 |
| Sex | 22 M/10 F | 22 M/10 F |
| Age (years) | 39.2 ±1.3 | 39.4 ±1.0 |
| Body mass index (kg/m$^2$) | 24.7 ±0.3 | 24.7 ±0.3 |
| Fasting glucose (mmol/l) | 4.7 ±0.1 | 4.7 ±0.1 |
| 1-h glucose (mmol/l) | 6.0 ±0.29[a] | 5.2 ±0.25 |
| 2-h glucose (mmol/l) | 4.2 ±0.21 | 4.1 ±0.8 |
| Fasting insulin (pmol/ml) | 0.14±0.01[c] | 0.08±0.01 |
| 1-h insulin (pmol/ml) | 0.94±0.06[c] | 0.35±0.02 |
| 2-h insulin (pmol/ml) | 0.42±0.04[c] | 0.20±0.01 |
| Systolic blood pressure (mmHg) | 126±2[a] | 120±2 |
| Diastolic blood pressure (mmHg) | 8±1[b] | 79±2 |

Mean ± SEM. [a] $p<0.05$; [b] $p<0.01$; [c] $p<0.001$

**Table 7.** Clinical features, plasma glucose and insulin levels at fasting and after a 75 g OGTT, and blood pressure values in hyperinsulinaemic and normoinsulinaemic obese subjects

| | Hyper-insulinaemic | Normo-insulinaemic |
|---|---|---|
| Number of subjects | 27 | 27 |
| Sex | 21 M/6 F | 21 M/6 F |
| Age (years) | 41.5 ±1.5 | 42.1 ±1.2 |
| Body mass index (kg/m$^2$) | 29.5 ±0.3 | 29.5 ±0.3 |
| Fasting glucose (mmol/l) | 5.03±0.09 | 4.87±0.09 |
| 1-h glucose (mmol/l) | 7.80±0.39[a] | 5.84±0.30 |
| 2-h glucose (mmol/l) | 5.13±0.19[a] | 4.10±0.14 |
| Fasting insulin (pmol/ml) | 0.14±0.01[a] | 0.09±0.01 |
| 1-h insulin (pmol/ml) | 1.01±0.07[a] | 0.44±0.03 |
| 2-h insulin (pmol/ml) | 0.57±0.04[a] | 0.19±0.01 |
| Systolic blood pressure (mmHg) | 133±3 | 132±2 |
| Diastolic blood pressure (mmHg) | 87±1 | 87±2 |

Mean ± SEM. [a] $p<0.001$

found ($p<0.05$ and 0.01, respectively). In the non-obese subpopulation 1-h plasma insulin significantly correlated with either systolic or diastolic blood pressure ($p<0.01$ and 0.001, respectively), and 2-h plasma insulin significantly correlated with diastolic blood pressure ($p<0.05$). In the obese subpopulation no significant relationship between plasma insulin and blood pressure was found.

Table 4 reports standardised regression coefficients between plasma insulin and blood pressure after controlling for age and body mass index. The higher coefficients were those between post-glucose insulin and both systolic and diastolic blood pressure in the non-obese population. These coefficients were of the same order of magnitude of those between blood pressure and age, but consistently lower of those between blood pressure and body mass index (Table 5).

Table 6 reports clinical features, plasma glucose and insulin concentrations, and blood pressure values from two subgroups consisting of 32 hyperinsulinaemic and 32 sex-, age-, and weight-matched normoinsulinaemic non-obese subjects, while Table 7 reports the same data from 27 hyperinsulinaemic and 27 sex-, age-, and weight-matched normoinsulinaemic obese subjects. Hyperinsulinaemic non-obese and obese subjects had fasting and/or postglucose plasma insulin concentrations higher than the mean+2 SD of 247 non-obese subjects. Normoinsulinaemic non-obese and obese subjects had fasting and/or postglucose plasma insulin levels within the mean±1 SD of 247 non-obese subjects. In non-obese, but not in obese subgroups, both systolic and diastolic blood pressure was significantly higher in the presence of hyperinsulinaemia ($p<0.05$ and 0.01, respectively).

## Discussion

It has been suggested that insulin plays a role in the regulation of blood pressure. A hypertensive effect of the hormone could possibly occur through the stimulation of sodium reabsorption by the distal nephron segment of the kidney [6], and the increase in the release of norepinephrine from the sympathetic nerves [7].

The involvement of insulin in the mechanisms responsible for hypertension is supported by the finding that high plasma insulin concentrations are a feature of patients with essential hypertension [3, 8–12]. However, the higher plasma insulin values of hypertensive subjects could have been generated by the concomitant presence of obesity and/or impaired glucose tolerance, which are both associated with hyperinsulinaemia [13] and high values of blood pressure [1, 2]. Moreover, the age of the subjects under study could have affected the association of hypertension and hyperinsulinaemia since aging is characterised by both hyperinsulinaemia [14] and high values of blood pressure [15]. Indeed, only a recent large survey of the adult Jewish population of Israel has clearly demonstrated an association between hypertension and hyperinsulinaemia independent of obesity, glucose intolerance and age [3].

As to the relationship between plasma insulin and blood pressure in non-hypertensive subjects or in populations where hypertensive are combined with normotensive subjects, the matter is still controversial. A significant association between the two variables has been found in childhood by Voors et al. [16] but not by Floorey et al. [17]. Berglund and Andersson [9] did not find any relationship between blood pressure and fasting insulin in a population of 164 hypertensive and normotensive men. After controlling for age, body weight and glucose tolerance, Lucas et al. [18] observed that both systolic and diastolic blood pressure significantly correlated with fasting plasma insulin in 33 very obese normotensive to mildly hypertensive women. Manicardi et al. [12] were able to find a significant relationship between systolic blood pressure and 2-h plasma insulin in 18 hypertensive but not in 17 normoten-

sive obese, non-diabetic subjects. After controlling for age, body weight and measures of body composition, Weinsier et al. [19] did not observe any correlation between fasting insulin and mean arterial pressure in 204 obese subjects unselected for glucose tolerance. Finally, Fournier et al. [20] found significant relationships between fasting plasma insulin and both systolic and diastolic blood pressure in 248 non-diabetic subjects unselected for obesity or hypertension, although these relationships were remarkably diminished after controlling for age and adiposity. The discrepancies reported in above mentioned publications might depend on differences in the selection of subjects under study.

The present study involved a large group of subjects in apparent good health, the only abnormalities accepted for inclusion being obesity (120/367 subjects) and mild untreated hypertension (66/367 subjects). The independent association between plasma insulin and blood pressure was explored by two approaches: (1) calculating the correlation coefficients between blood pressure and either fasting or postglucose plasma insulin levels after controlling for age and body weight; (2) comparing blood pressure in hyperinsulinaemic and normoinsulinaemic subjects which were matched for sex, age and body weight, and similar for physical activity, dietary habits, alcohol intake and cigarette smoking. In addition, the relationship between blood pressure and plasma insulin was investigated separately in non-obese and obese subjects. As in many epidemiological studies, only a single blood pressure value was obtained; but a peculiar feature of our study is that blood pressure was measured after an oral glucose load.

Our data show that in a population of subjects with apparent good health, including obese and untreated mildly hypertensive subjects, diastolic blood pressure was significantly correlated with postglucose plasma insulin levels. This relationship was independent of age and body weight. However, when obese and non-obese subjects were examined separately, no significant relationship was found between blood pressure and plasma insulin in the obese, while a significant relationship was found between postglucose plasma insulin and both systolic and diastolic blood pressure in the non-obese. Thus, the post-glucose plasma insulin response seems to be independently associated with blood pressure in non-obese subjects only, while the association between plasma insulin and blood pressure in obesity seems to be mainly mediated by factors such as age and body weight. The latter conclusion is substantiated by the observation that hyperinsulinaemic non-obese but not hyperinsulinaemic obese subjects had values of both systolic and diastolic blood pressure significantly higher than those of sex-, age-, and weight-matched normoinsulinaemic subjects. Interestingly, in non-obese subjects the variation of blood pressure when the independent variable was plasma insulin was similar to that observed when the independent variable was age, i.e. a factor closely related to blood pressure [15].

As previously reported [1, 15, 21, 22], obese subjects showed significantly higher blood pressure values and plasma insulin levels than non-obese subjects. However, in the presence of obesity the increase in plasma insulin concentrations was not associated with an increase in blood pressure, as observed in non-obese subjects. This might be due to the fact that in the presence of obesity a hypothetical "hypertensive" effect of insulin is being confounded by other factors. Whilst such factors remain to be identified, they may possibly include sodium-retaining steroids, the renin-angiotensin-aldosterone system, serum triiodothyronine levels, or sympathetic nervous activity [22].

In conclusion, our data are compatible with the hypothesis that insulin may play a role in the regulation of blood pressure in non-obese man.

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