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Hyperinsulinaemia is not linked with blood pressure elevation in patients with insulinoma

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Summary. We have investigated the hypothesis that insulin is a causal and independent risk factor for blood pressure elevation in humans by comparing pre- and post-operative blood pressure values of 34 consecutive patients with histologically-confirmed diagnosis of insulinoma and 34 age- and sex-matched control patients. In patients with insulinoma hypoglycaemic symptoms were present for 18 (9–36) months. (Values are given as median and 95 % confidence interval or mean and SD). After removal of insulinoma fasting plasma insulin levels decreased from 22 (16–28) mU/l to 11 (6–20) mU/l ($p < 0.003$) and minimal fasting plasma glucose concentrations increased from 2.5 (2.0–3.0) to 4.4 (4.2–5.7) mmol/l ($p < 0.002$) while blood pressure values remained unchanged. Body mass index before operation was comparable between the groups: 25.5 (5.4) kg/m^2 in insulinoma patients and 24.8 (4.7) kg/m^2 in control subjects. Pre-operative and post-operative blood pressure values did not differ between the groups, being (systolic/diastolic) 133 (18)/82 (9) mm Hg in insulinoma patients and 128 (15)/78 (10) mm Hg in control subjects before and 129 (19)/80 (10) mm Hg and 125 (11)/76 (7) after surgery. Chronic hyperinsulinaemia in patients with insulinoma is not associated with a detectable elevation of blood pressure values. Correction of hyperinsulinaemia after surgery for insulinoma does not result in blood pressure changes. These results argue against the hypothesis that insulin is an independent causal factor in the development of essential hypertension in humans.

Key words: Hypertension, hyperinsulinaemia, insulinoma, insulin resistance.

Insulin resistance and hyperinsulinaemia have been linked with elevated blood pressure values in several studies [1–4]. It has been hypothesized that an underlying insulin resistance would lead to compensatory hyperinsulinaemia which, in turn, might result in blood pressure elevation. In fact, insulin has been postulated to stimulate the sympathetic nervous system [5], enhance tubular sodium reabsorption [6, 7], alter membrane ion fluxes [8] and induce changes in vascular structure and function [9]. In obese subjects an interventional decrease of plasma insulin levels is associated with a fall of blood pressure [10]. These findings implicate hyperinsulinaemia as a causal and independent risk factor for hypertension. Indeed, insulin has been repeatedly postulated to be the "missing link" between insulin resistance and essential hypertension [2] and hence a causal factor in the development of elevated blood pressure [11].

On the other hand, insulin can even reduce blood pressure by antagonising vasoconstrictor responses to catecholamines [12] and long-term insulin infusion in dogs failed to increase blood pressure values [13]. In humans hyperinsulinaemia has been studied mostly as a result of insulin resistance. In such settings any evaluation of an independent role of insulin in blood pressure regulation is difficult.

However, patients with insulinoma undergoing surgery represent a unique opportunity to investigate the effect of long-term hyperinsulinaemia on blood pressure in humans where hyperinsulinaemia is not caused by an underlying insulin resistance.

Subjects and methods

From all patients referred to our department between 1975 and 1989 because of suspected hypoglycaemia, in 34 cases a diagnosis of insulinoma was made [14] and later confirmed by surgery and histopathology. All insulinomas were located within the pancreas, 29 cases were of benign histology while five cases histologically revealed islet cell carcinoma, in four cases the insulinoma was associated with metastases of the liver or lymph nodes.

The group consisted of 21 women and 13 men (37 %) age 47 [16] years with a duration of hypoglycaemic symptoms of 18 (9 to 36) months. No patient had a history of hypertension, or blood pressure values persistently above 160/95 mm Hg nor were they taking anti-

hypertensive medication. Neurologic evaluation did not reveal specific additional disorders.

The control group consisted of 34 age- and sex-matched patients who attended the Department of Surgery for minor operations and were otherwise healthy.

Fasting plasma insulin levels were measured by radioimmunoassay before and 1 to 3 weeks after surgery as described previously [14]. A 100 g oral glucose load was administered to all 34 insulinoma patients. They remained fasting until blood glucose had decreased to 1.5 mmol/l with subsequent hourly measurements of serum insulin. Three patients fasted for 6 h, 13 for 12 h, 8 for 18 h and 10 for 24 h. Fifteen age-, sex- and body weight-matched healthy control subjects underwent the same procedure with insulin measurements every 4 h after completion of a 6-h oral glucose tolerance test. From the early and late phase after the glucose load insulin concentrations were calculated as area under the curve per hour. In 11 patients serum proinsulin-like component was determined by column chromatography and expressed as a percentage of immunoreactive insulin [14]. All methods were unchanged throughout the entire study period.

In patients with insulinoma and in control subjects all blood pressure values recorded up to 3 weeks before and 3 weeks after surgery were evaluated. Blood pressure recordings on the day of surgery were excluded as were blood pressure values associated with blood glucose levels below 2.5 mmol/l. In most cases, blood pressure was measured in the morning with a sphygmomanometer with the patient in the recumbent position, Korotkoff phase 5 was used as the diastolic blood pressure value. In patients with insulinoma eight (range 2–12) measurements were performed before and five (2–9) after the operation. In control subjects blood pressure was measured three (3–4) times before and four (3–6) times after operation. Mean blood pressure was calculated as one-third of systolic plus two-thirds of diastolic blood pressure values.

Statistical analysis

Normally distributed values are presented as mean and SD, otherwise median and 95% confidence intervals (95% CI) are given. Comparison of data was done by a parametric test (Student's *t*-test) or non-parametric two-tailed test (Mann-Whitney test) where appropriate. Significance was registered at the 5% level.

The study had a power of 80% to detect minimum differences of 11 mm Hg systolic and 6 mm Hg diastolic between insulinoma patients and control subjects and 14 mm Hg systolic and 7 mm Hg diastolic in insulinoma patients before and after operation in a two-tailed test [15].

Results

After surgery and removal of insulinoma, fasting plasma insulin concentrations decreased from 22 (16–28) mU/l to 11 (6–20) mU/l ($p < 0.003$) and minimal fasting plasma glucose concentrations increased from 2.5 (2.0–3.0) mmol/l to 4.4 (4.2–5.7) mmol/l ($p < 0.002$). The median of the area under the diurnal insulin curve in insulinoma patients was 2860 $mU/l \cdot min^{-1} \cdot h^{-1}$ (range 914–8459) as compared to 1557 $mU/l \cdot min^{-1} \cdot h^{-1}$ in control subjects ($p < 0.001$; Mann-Whitney test). Before surgery the mean value of the proinsulin-like component was 29% of total immunoreactive insulin with a range from 7% to 63%.

No significant changes in blood pressure values were noticed after surgery in either insulinoma patients or control subjects (Table 1). The difference in mean blood pressure values before and after surgery was 2 (−4–9) mm Hg in insulinoma patients and 3 (−1–8) mm Hg in control subjects ($p = 0.8$). Systolic, diastolic and mean blood pressure values were not significantly different between the groups at any time (Table 1). No significant correlations between plasma insulin concentrations or duration of hypoglycaemic symptoms and blood pressure values were noticed. Body mass index was comparable between insulinoma patients and control subjects 25.5 (5.4) kg/m^2 vs 24.8 (4.7) kg/m^2 ($p = 0.6$).

Discussion

Patients with insulinoma usually present with a symptomatic hyperinsulinaemia and a moderate insulin resistance [14, 16]. In this study the substantial elevation of plasma insulin concentrations in patients with insulinoma was not associated with significantly higher blood pressure values when compared to a control group. In addition, blood pressure readings remained unaffected by the removal of the insulinoma and subsequent reduction in insulinaemia.

A previously uncontrolled study reported that correction of hyperinsulinaemia by surgery in patients with insulinoma does not result in a fall of blood pressure values [17]. However, this study has not been accepted as convincing since it was uncontrolled and reported values of only seven patients. Our study had a power of 80% to detect minimal differences of 11 mm Hg systolic and 6 mm Hg diastolic values between the groups, therefore, we may have overlooked smaller differences. It is, however, questionable whether such differences would be sufficient to produce clinically relevant blood pressure elevations. In our study hyperinsulinaemia in insulinoma patients was present for a mean period of at least 18 months and reduced by 50% after insulinoma surgery. The mean percentage of serum proinsulin-like component of total immunoreactive insulin was about 30%. This and the disappearance of hypoglycaemic symptoms after surgery indicates that prior to their operation the patients were in a substantially hyperinsulinaemic state. However, our findings do not exclude the possibility that higher plasma insulin concentrations, different patterns of insulin secretion or a longer exposure to high insulin levels might have had an effect on blood pressure.

Hyperinsulinaemia and insulin resistance is more pronounced in obese subjects than in insulinoma patients. However, lean hypertensive patients show serum insulin values very similar to those measured in patients with insulinoma [18].

We have put great emphasis on the unbiased evaluation of blood pressure values. No recorded value was excluded except for those measured on the day of operation and those associated with very low blood glucose concentrations. In addition, most measurements were carried out at the same time of the day with the patient in the recumbent position. However, blood pressure values in hospitalised patients awaiting surgery may be different from those of a normal population. We have therefore chosen a control group of patients who underwent minor operations. In both hospitalised patient groups blood pressure was measured by nurses and it is unlikely that a recording bias has contributed to the measurements.

Table 1. Mean systolic and diastolic blood pressure values (mm Hg) in patients with insulinoma and in control subjects before and after surgery (mean (SD) and mean differences (95 % confidence interval (CI)) and *p* values between both groups

	Insulinoma patients	Control patients	Mean difference (95 % CI)/*p* value
Systolic blood pressure			
Before surgery	133 (18)	128 (15)	5 (−3 to 13)/0.21
After surgery	129 (19)	125 (11)	4 (−4 to 12)/0.30
Diastolic blood pressure			
Before surgery	82 (9)	78 (10)	3 (−2 to 8)/0.17
After surgery	80 (10)	76 (7)	3 (−1 to 8)/0.11
Mean blood pressure			
Before surgery	98 (12)	95 (11)	4 (−2 to 9)/0.20
After surgery	96 (11)	92 (9)	4 (−1 to 10)/0.10

However, smaller or short-term blood pressure elevations could have been missed by multiple standard blood pressure recordings. Multiple measurements over several years were evaluated in our study and therefore no fully standardized blood pressure recordings could be carried out. On the other hand, blood pressure values recorded by trained nurses, as done in our study, may be more accurate than those measured by physicians [19].

Acute hyperinsulinaemia may increase blood pressure and catecholamine secretion. However, chronic hyperinsulinaemia does not substantially change catecholamine concentrations [20] and we do not think that these hormones have influenced blood pressure values in insulinoma patients. However, even though we have excluded blood pressure values associated with hypoglycaemic blood glucose levels, a hypoglycaemia-associated elevation of counter-regulatory hormones and their impact on blood pressure values cannot be totally excluded in our study. In such cases we might have overestimated (rather than underestimated) the real blood pressure in insulinoma patients.

Our findings contribute to the discussion on whether insulin resistance is causally linked through hyperinsulinaemia with essential hypertension [1–4]. The lack of significant differences in blood pressure both between the groups and after removal of insulinoma indicate that there is probably no pronounced effect of insulin on blood pressure regulation in human subjects. In fact hyperinsulinaemia is not unequivocally associated with essential hypertension [21] and unknown genetic factors seem to be of crucial importance in this context [22, 23]. In patients with chronic autonomic failure acute administration of insulin may even lower blood pressure [24] and decrease vascular reactivity to catecholamines [12]. In addition, some experimental findings indicate that insulin resistance and hence deficiency of insulin at the cellular level, rather than hyperinsulinaemia per se, may lead to hypertension [25].

Epidemiological findings confirming an association between hyperinsulinaemia and hypertension might have been confounded by additional factors which are more common in hypertensive patients than in normotensive subjects. In hypertensive patients more frequent congestive heart failure [26], impaired renal function [27] and more pronounced atherosclerotic lesions [28] could have contributed to elevated insulin concentrations. Insulin sensitivity and hence serum insulin concentrations can also be influenced by altered eating habits [29] lesser physical activity [30] and a different body fat distribution [31]. In fact, in a recently published large European epidemiological study blood pressure was no longer related to serum insulin concentrations after adjustment for waist circumference [32].

These findings and our study invite speculation as to whether insulin resistance might be linked with hypertension, not through insulin but an unknown factor which may cause both insulin resistance and blood pressure elevation, as recently proposed [33].

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