

# Normal Blood Pressure in Patients With Insulinoma Despite Hyperinsulinemia and Insulin Resistance

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## ABSTRACT

This article examines the relationship between blood pressure and serum insulin patients with endogenous hyperinsulinemia due to insulinomas. The hypothesis that hyperinsulinemia is an independent causal factor in the development of essential hypertension in this patient population was investigated. Inappropriately high plasma concentrations of insulin and proinsulin were found in these patients; however, their blood pressure levels did not differ from those of normal control subjects. Moreover, the surgical removal of the insulinomas did not reduce their blood pressure. Therefore, these findings argue against the hypothesis that hyperinsulinemia is an independent causal factor in the development of essential hypertension in humans.

*Key Words:* Hypertension, hyperinsulinemia, insulin resistance, insulinoma

The association of insulin resistance and essential hypertension was first described almost 70 yr ago (1). In this very extensive study, Kylin clearly demonstrated that patients with hypertension had both a diminished glucose tolerance and an increased risk for developing diabetes. He also discovered that hypertension was much more frequent among diabetic patients and proposed a common cause for both diseases. During the last decade, there has been renewed interest in the role of insulin in the regulation of blood pressure and the possible role of hyperinsulinemia in the development of hypertension in humans. Insulin resistance and hyperinsulinemia have

been linked with elevated blood pressure values in several studies and in various settings (2,3). It has been hypothesized that an underlying insulin resistance could lead to compensatory hyperinsulinemia, which in turn, might result in blood pressure elevation through several mechanisms (3). These findings have been interpreted as implicating hyperinsulinemia as an independent risk factor and, possibly, a cause of hypertension. In humans, hyperinsulinemia has been studied where increased insulin concentration was secondary to insulin resistance. In such settings, the evaluation of the independent role of hyperinsulinemia as a risk factor for hypertension is confounded by the presence of an underlying insulin resistance. In contrast, patients with insulinomas who are undergoing surgery present an opportunity to investigate the effect of long-standing hyperinsulinemia on blood pressure because, in these patients, hyperinsulinemia is not secondary to underlying insulin resistance. In this article, we present our findings and those of others on the patterns of insulin secretion and insulin action in patients with insulinomas and summarize available data on blood pressure in these patients.

## INSULIN SECRETION IN PATIENTS WITH INSULINOMAS

Insulinomas are typically solitary, benign tumors (adenomas) of the islets of Langerhans. These consist predominantly of beta cells showing various degrees of dedifferentiation of the ultrastructural apparatus for insulin secretion. Despite the heterogeneity of the histopathology of insulinomas, all patients with these tumors have endogenous hyperinsulinemia and suffer from hypoglycemia. "Endogenous hyperinsulinism" is diagnosed if patients have inappropriately high circulating insulin levels at the time of hypoglycemia (blood glucose below 2 mM). Pathophysiologically, pancreatic insulin secretion is virtually "shut off" when blood glucose concentration falls below 3 mM, as occurs during a prolonged fast. Patients with insulinomas, on the other hand, may show excessive autonomous insulin secretion (an insulin level as high as 700 pM) when the prevailing blood glucose level is around 2 mM.

Twenty-four-hour fasting insulin profiles obtained from 34 patients with insulinomas are compared with corresponding insulin levels in 15 matched normal control subjects in Figure 1. A standardized fast

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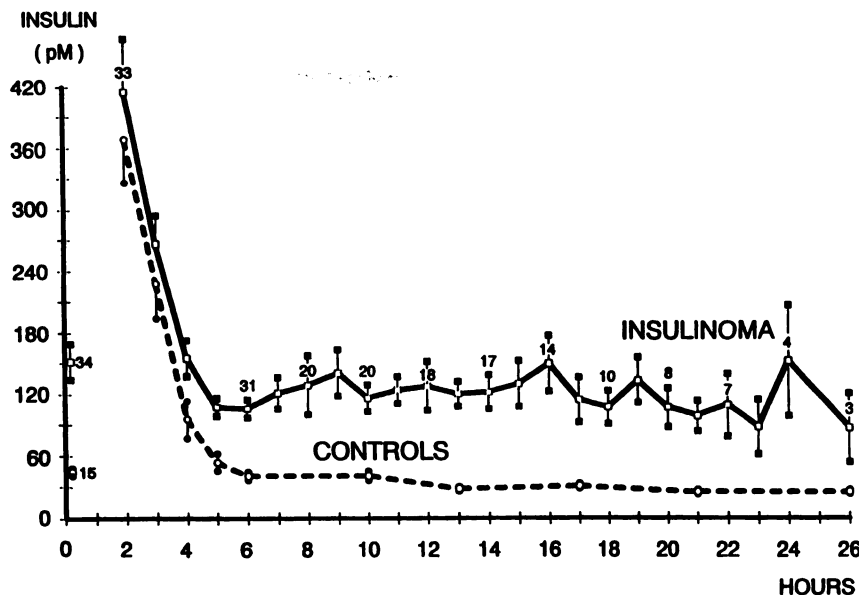


Figure 1. Mean values (bars indicate SD) of immunoreactive insulin concentrations in insulinoma patients and healthy subjects. Graphs demonstrate diurnal insulin profiles of insulinoma patients ( $N = 34$ ) and of healthy control subjects ( $N = 15$ ). At time 0, a 100-g oral glucose load was administered; the early insulin response is not shown. All healthy subjects completed the fast. The numbers of insulinoma patients completing the fasting period are indicated.

was initiated after a 100 g of oral glucose load. The average serum insulin levels in insulinoma patients leveled off around 120 pM versus less than 30 pM in control subjects. Only a minority of patients with insulinoma could fast for more than 12 h.

Endogenous hyperinsulinemia, regardless of its histopathologic origin, is associated with the increased secretion of proinsulin (4,5). Proinsulin or proinsulin-like molecules were found in hyperplastic islet cells obtained from insulinomas (6). Insulinoma cells also showed diminished conversion of proinsulin to insulin (4). The inability of exogenous insulin to suppress proinsulin secretion in insulinoma patients indicates a loss of negative feedback control between these two hormones (5).

It has been recently found that proinsulin and split-products of the proinsulin molecule may be recognized by standard insulin RIA (7). Thus, "insulin" overproduction, as is seen with insulinoma, may actually be a mixture of proinsulin and insulin (6,8). Clarification of this issue awaits the availability of more-specific proinsulin assay.

Despite the endogenous hypersecretion of insulin, fasting serum insulin levels in some patients may be only moderately elevated because of the significant uptake of insulin by the liver (9). It is important to recognize that serum insulin levels of 50 to 70 pM are still clearly inappropriate when blood glucose levels are below 2 mM.

## INSULIN RESISTANCE IN INSULINOMA PATIENTS

By euglycemic glucose clamp techniques, Nankervis *et al.* have demonstrated that insulinoma patients have diminished glucose disposal in comparison with healthy individuals (10). These findings have recently been confirmed by Pontiroli *et al.* (11). It is unclear whether this is due to relative or absolute hyperinsulinemia and subsequent down-regulation of insulin receptors or to the induction of postreceptor defects in glucose metabolism. Because many insulinoma patients become obese because of excess food intake, impaired glucose disposal may be related to obesity. However, these patients do not show the postprandial hyperinsulinemia that is typically seen in subjects with obesity-related insulin resistance.

## INSULINOMA AND GLUCOSE HOMEOSTASIS

When insulin secretion in insulinoma patients does not decline appropriately in the postabsorptive state, the relatively high insulin level interferes with glucose homeostasis as glucose output from the liver is suppressed while glucose uptake by insulin sensitive tissues continues at a rate inappropriate for the declining glucose concentration (9,10). The flow of gluconeogenic substrates to the liver is decreased, as is evidenced by the reduced mobilization of amino acids and glycerol and decreased hepatic uptake of these precursors.

Insulin levels found in insulinoma patients after glucose challenge or ingestion of carbohydrate-rich meals are often not as high as those found in patients with obesity and early stages of type 2 diabetes. Hyperinsulinemia in the latter group compensates for primary insulin resistance and persisting hyperglycemia. However, glycemia clears rapidly in insulinoma patients and the insufficiently suppressed secretion of endogenous insulin is excessive relative to the concurrent glycemia. When compared with insulin secretion in healthy subjects, this elevation is only moderate.

### INSULINOMA AND BLOOD PRESSURE

The largest study of blood pressure values in insulinoma patients was reported from the Mayo Clinic (12). Preoperative records of 250 insulinoma patients seen between 1921 and 1991 were reviewed. The median duration of hypoglycemic symptoms was 2 yr. The median age for the patients studied was 41 yr, with 12% having blood pressure values above 140/90 mm Hg and 3.6% with histories of past treatment for hypertension. This study seems to indicate a particularly low prevalence rate of hypertension

**TABLE 1. Characteristics of insulinoma patients and control group<sup>a</sup>**

	Insulinoma Patients	Control Patients
Male/Female	13/21	13/21
Age (yr)	47	47
BMI (kg/m <sup>2</sup> )	25.5	24.8

<sup>a</sup> Mean values are given. BMI, body mass index.

**TABLE 2. Mean systolic and diastolic blood pressure values in patients with insulinoma and in control subjects before and after surgery<sup>a</sup>**

	Insulinoma Patients	Control Patients	Mean Difference (95% CI)/ P Value
<b>Systolic Blood Pressure</b>			
Before surgery	133 (18)	128 (15)	5 (-3 to 13)/0.21
After surgery	129 (19)	125 (11)	4 (-4 to 12)/0.30
<b>Diastolic Blood Pressure</b>			
Before surgery	82 (9)	78 (10)	3 (-2 to 8)/0.17
After surgery	80 (10)	76 (7)	3 (-1 to 8)/0.11
<b>Mean Blood Pressure</b>			
Before surgery	98 (12)	95 (11)	4 (-2 to 9)/0.20
After surgery	96 (11)	92 (9)	4 (-1 to 10)/0.10

<sup>a</sup> Values are in mm Hg; mean (SD) and mean differences (95% confidence interval [CI] and P values between both groups).

when compared with data from the age-comparable subset of the Framingham study population (13).

We investigated 34 consecutive patients with insulinoma with long-standing duration of hypoglycemic symptoms (14). Patients were compared before and after surgery with a control group of normotensive patients undergoing minor surgery. Patients were matched for age, sex, and body weight (Table 1). Before surgery, no insulinoma patients had hypertensive blood pressure values or were treated with antihypertensive medication. Mean blood pressure values were comparable in insulinoma patients and in controls both before and after surgery (Table 2). After the removal of the insulinoma, elevated fasting plasma insulin levels (Figure 1) decreased significantly by 50% and blood pressure values remained unchanged (Table 3).

Two recent studies from Japan also reported that the surgical correction of hyperinsulinemia in patients with insulinoma does not result in a decrease in blood pressure (15,16). All patients had normal blood pressure values (mean, 127/74 mm Hg) and had not been treated for hypertension. No correlation between systolic or diastolic blood pressure values and plasma insulin concentrations was found (15).

A recent study from Italy reported blood pressure values of 13 patients with insulinoma and of 6 patients with nontumoral hypoglycemia (11). Only 3 of these 19 patients were hypertensive, and 2 of them had a genetic predisposition to essential hypertension.

### DISCUSSION

Elevated blood pressure values for patients with insulinoma have not been reported to date in the literature. However, there are indications of a particularly low prevalence of elevated blood pressure

**TABLE 3. Characteristics of insulinoma patients before and after surgery<sup>a</sup>**

	Insulinoma Patients Before Surgery	Insulinoma Patients After Surgery
Fasting Plasma Insulin (mU/L)	22 (16–28)	11 (6–20) <sup>b</sup>
Fasting Plasma Glucose	2.5 (2.0–3.0)	4.4 (4.2–5.7) <sup>b</sup>
Duration of Hypoglycemic Symptoms	18 (9–36)	
Blood Pressure—Systolic/Diastolic (mm Hg)	133/82	129/80

<sup>a</sup> Mean values or median and range are given.

<sup>b</sup>  $P < 0.003$ .

(>140/90 mm Hg) or treated hypertension in these patients (12,14). About 10% of the patients with insulinoma have blood pressure values above the normal range, whereas in the general population aged 18 to 74 yr, the prevalence of blood pressure values above normal reaches about 30% (17). These rather low prevalences of hypertension for insulinoma patients and the lack of blood pressure change after correction of hyperinsulinemia argue strongly against the hypothesis that insulin is a causal and independent factor for the development of essential hypertension.

These findings appear to challenge reports of an association between hyperinsulinemia and hypertension (2,3). However, hyperinsulinemia has not been unequivocally associated with essential hypertension in all studies (18). Furthermore, associations that are peculiar to specific populations indicate that unknown genetic factors seem to be of crucial importance in this context (19,20).

An alternative explanation for these findings is that epidemiologic studies, which discovered an association of hyperinsulinemia and hypertension, might have been confounded by additional factors that are more common in hypertensive than in normotensive patients. For example, in hypertensive patients, a higher prevalence of heart failure (21), impaired renal function (22), and more pronounced atherosclerotic lesions (23) may be causative factors for elevated serum insulin concentrations. Insulin sensitivity, and hence serum insulin concentrations, can also be influenced by altered eating habits (24), decreased habitual physical activity (25), and a different body fat distribution (26). In fact, in a recently published large European epidemiologic study, blood pressure was not related to serum insulin concentrations after adjustment for these confounding factors (27).

These findings and studies on patients with insulinoma invite speculations that insulin resistance might be linked to hypertension, not through insulin, but through the as yet unknown factors that cause both insulin resistance and blood pressure elevation (28).

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