Effect of Insulin Therapy on Blood Pressure in NIDDM Patients With Secondary Failure

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OBJECTIVE — To assess the effect of insulin therapy on blood pressure in NIDDM patients with secondary failure.

RESEARCH DESIGN AND METHODS — The influence of insulin treatment on blood pressure was assessed retrospectively in a group of 80 NIDDM patients with secondary failure to diet and maximum doses of oral hypoglycemic agents. Weight, blood glucose, and blood pressure were recorded over a 3-mo period before and after the initiation of insulin therapy.

RESULTS — There was a significant rise in systolic (131.8 ± 1.7 to 148 ± 1.9 mmHg, $P < 0.05$) and diastolic (80.9 ± 0.9 to 89.2 ± 1.0 mmHg, $P < 0.02$) blood pressures with insulin treatment. Insulin treatment was associated with a significant decrease in blood glucose (18.36 ± 0.28 to 10.4 ± 0.34 mM, $P < 0.01$) and an increase in weight (72.1 ± 1.6 to 78 ± 1.7 kg, $P = 0.01$). A control group of 80 NIDDM patients matched for age, weight, BMI, and duration of diabetes demonstrated no significant change in blood pressure over a matched period of follow-up.

CONCLUSIONS — This study has shown that insulin therapy is associated with significant elevation of both systolic and diastolic blood pressures.

The pathophysiology of essential hypertension involves a complex interplay of several mechanisms that contribute to the initiation and perpetuation of a rise in blood pressure. Once hypertension develops, these mechanisms interact with other physiological variables to sustain the elevated blood pressure. The basic pathophysiological aberration that initiates the process remains an enigma. Several studies conducted on patients with essential hypertension (1–14), obesity (14–21), and NIDDM (7,13,14,17) have demonstrated an association between hypertension and hyperinsulinemia and/or insulin resistance. This study was undertaken to examine retrospectively the effect of insulin therapy on blood pressure in NIDDM patients with secondary failure who had been commenced on insulin.

RESEARCH DESIGN AND METHODS

— This was a retrospective analysis of the clinical records of 80 patients attending a diabetes clinic. All the patients selected had been diagnosed and classified as NIDDM on the basis of the revised World Health Organization criteria. In addition, they had failed to respond to a maximum dose of an oral sulfonylurea agent and/or biguanide. An initial attempt at nonpharmacological measures for control of both diabetes and, where applicable, hypertension had been used in all subjects with respect to diabetes, and in patients with secondary failure, advice was given with respect to weight reduction, adequate diabetic dietary restrictions, and exercise. In hypertensive patients, weight reduction, exercise, and salt restriction was advised before commencement of specific therapy. Age, weight, blood glucose, and blood pressure of these patients were recorded while on oral agents. With respect to the last three parameters, the mean value of at least three recordings in the period before institution of insulin therapy was used in the analysis. Blood glucose was estimated by the glucose oxidase method, and blood pressure was taken in the seated position after at least 5 min of rest with a mercury sphygmomanometer with an appropriate-sized cuff for obese patients and with systolic pressure corresponding to Koratkoff phase 1 and diastolic as Koratkoff phase 5 sounds. Weight was measured with a standard scale and documented to the nearest tenth of a kilogram body weight.

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NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; BMI, BODY MASS INDEX.

Table 1—*Initial clinical and blood glucose profiles of 2 groups*

	Insulin treated (before insulin; $N = 80$)	Control ($N = 80$)
Age (yr)	49.5 ± 1.1 (16–72)	51.5 ± 1.1 (24–74)
Weight (kg)	72.1 ± 1.6 (45–111)	72.7 ± 1.7 (46–139)
BMI (kg/m^2)	29.4 ± 0.7 (20–55)	29.2 ± 0.7 (19–58)
Duration of NIDDM (yr)	11 ± 0.7 (2–28)	10.3 ± 0.2 (6–17)
Blood pressure (mmHg)		
Systolic	131.8 ± 1.7 (103–173)	136.4 ± 2.1 (100–180)
Diastolic	80.9 ± 0.9 (60–102)	82.7 ± 1.1 (60–110)
Blood glucose (mM)	18.36 ± 0.25 (11.1–22.7)	12.2 ± 0.4 (5.8–22.7)

Values are means ± SE with ranges in parentheses.

BMI was then calculated as weight (kg) divided by height (m^2). The mean value for weight, blood glucose, and blood pressure over the 3-mo period was entered as a single value for each patient. Similar parameters described above were recorded over a 3-mo period once a steady insulin dose had achieved glycemic control, i.e., a 2-h postprandial glucose level <12 mM and the mean value calculated for this 3-month period. This group is referred to as the insulin-treated group.

Data on the duration of the diabetic state before insulin therapy and the period taken to achieve satisfactory glycemic control were also included. A group of 80 patients with NIDDM receiving treatment with oral agents (and matched for age, weight, BMI, and duration of diabetes) served as control subjects. The weight, blood glucose, and blood pressure were recorded initially and subsequent to a matched period of follow-up of blood pressure, as for the insulin-treated group. This group is referred to hereafter as the control group. The diet remained constant during the study period, i.e., no specific restriction of salt was advised, except in hypertensive patients.

Proteinuria was measured at monthly intervals in both groups with a dipstick method (albustix). Clinical characteristics of the insulin-treated and control subjects are shown in Table 1. Of the 80 patients in the study group, there were 22 (28%) blacks and 58 (72%) Indian Asians. The control group demonstrated a similar racial distribution of patients (29 and 71%, respectively). Both groups demonstrated a female preponderance, with the study group comprising 64 (84%) and the control group 57 (72%) women.

Mean BMI of the study group was 29.4 ± 0.7 kg/m^2 (range 20–55 kg/m^2), and that of the control group was 29.2 ± 0.7 kg/m^2 (range 19–58 kg/m^2) (NS). Patients were grouped into three different BMI categories: <25, 25–30, and >30 kg/m^2. There was a similar distribution of patients in each BMI category in the study population and control subjects (BMI <25, 22, and 18%, BMI 25–30, 33 and 46%, and BMI >30 kg/m^2 49 and 36%, respectively).

Twenty of 80 (27%) patients in the insulin-treated group were hypertensive on therapy compared with 24 of 80 (30%) patients in the control group. In both insulin-treated and control groups, >50% of all hypertensive patients were on a diuretic alone or in combination with a β-blocker, vasodilator, α–blocking agent, centrally acting agent, calcium-channel blocker, or an angiotensin converting enzyme inhibitor. The diuretics used were either a thiazide diuretic at a dose ≤25 mg hydrochlorthiazide, a loop diuretic ≤40 mg furosemide, and indapamide at a dose ≤2.5 mg/day. The mean insulin dose needed to achieve glycemic control in the insulin-treated group was 56 ± 2.6 U (range 24–120 U), which reflected a mean insulin dose of 0.81 U/kg body wt (range 0.3–1.7 U/kg). Of the 80 patients, 61 (76%) were on a single daily dose of insulin, whereas, 19 patients (24%) were on a twice-daily insulin regimen.

Comparison between data on oral hypoglycemic and insulin therapy in the insulin-treated group was made with the paired *t* test. Analysis of weight and BMI and its predictive value on subsequent blood pressure rise was made with unpaired *t* test. $P < 0.05$ was statistically significant.

RESULTS

Blood pressure

In the insulin-treated group, there was a significant rise in the systolic blood pressure level from a mean of 131.8 ± 1.7 mmHg before insulin therapy to a mean level of 148.8 ± 1.9 mmHg 8 mo after commencement of insulin ($P < 0.05$). In addition, a more significant rise was seen in the diastolic blood pressure, which rose from a mean level of 80.9 ± 0.9 mmHg to a level of 89.2 ± 1.0 mmHg ($P < 0.02$; Table 2). Of the patients that were initially hypertensive, all showed systolic and diastolic blood pressure elevations similar to the nonhypertensive patients, necessitating additional antihypertensive therapy in their management. The control group showed no significant changes in the systolic or diastolic blood pressure during a matched period of follow-up (Table 2). This was applicable to those that were hypertensive at the onset also.

With patients grouped into weight categories, the initial weight was predictive of the subsequent magnitude in blood pressure elevation, the greatest rise occurring in the group that were most overweight at the onset (Fig. 1). With patients grouped into different BMI categories, the most significant increases in blood pressure on insulin treatment

Table 2—*Blood pressure levels of study population and control subjects over 8-mo follow-up period*

	Before insulin therapy	8-mo Posttherapy	Initial period	8 mo Later
Blood pressure (mmHg)				
Systolic	131.8 ± 1.7 (103–173)	143.8 ± 1.9 (113–193)*	136.4 ± 2.1 (100–180)	136.6 ± 2 (100–170)
Diastolic	80.9 ± 0.9 (60–102)	89.2 ± 1.0 (73–107)†	82.7 ± 1.1 (60–110)	83.4 ± 1.0 (70–100)

Values are means ± SE with ranges in parentheses.
*$P < 0.05$.
†$P < 0.02$.

occurred in the group that was mildly overweight at baseline, i.e., BMI 25–30 kg/m^2, in which the systolic pressure rose from a mean level of 133.9 ± 12 to a level of 140.2 ± 17 mmHg; and the diastolic pressure from a mean level of 81.6 ± 7.8 to 86.2 ± 10.7 mmHg.

The blood pressure rise was similar in blacks and Indian Asians, except for a racial difference in the percentage increase of systolic and diastolic pressures over baseline being 4.9 and 1.2% compared with 2.1 and 4.6% for systolic and diastolic blood pressures for blacks and Indian Asians, respectively. There were no differences in the blood pressure changes in men compared to women. With Spearman link correlations, the mean insulin dose (U/kg body wt) was strongly correlated with the increase in both systolic and diastolic blood pressures after insulin treatment.

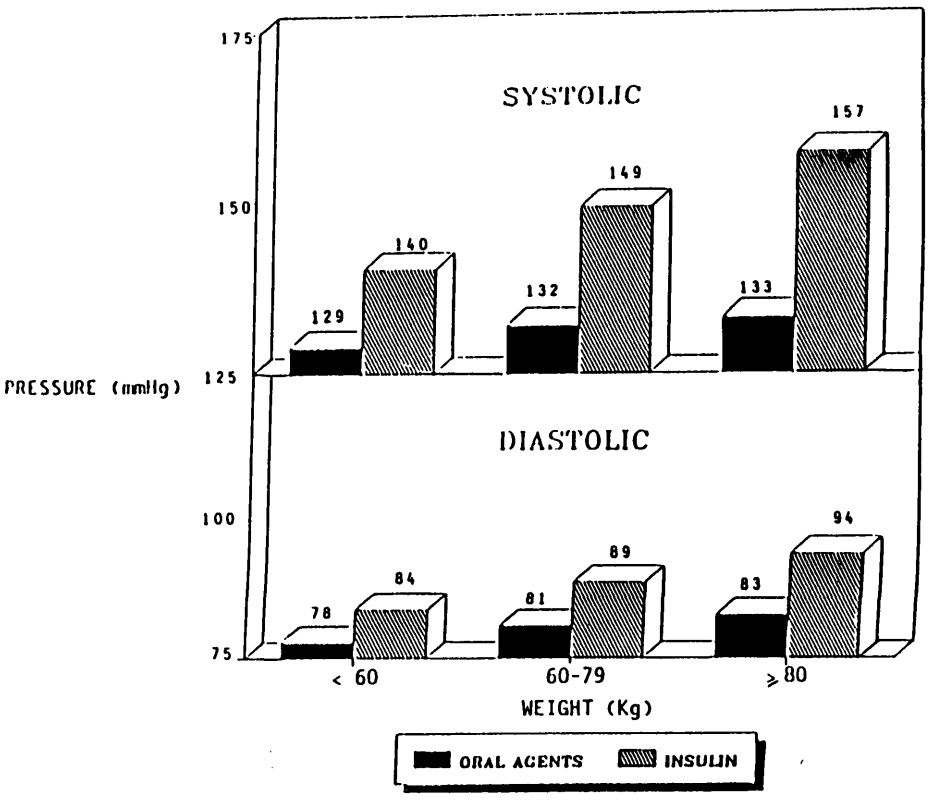

Figure 1—*Blood pressure changes in different weight categories before and after insulin therapy.*

Weight

Insulin therapy was associated with significant weight gain; the mean weight in this group rising from 72 ± 1.6 kg before insulin therapy to 78 ± 1.7 kg while on insulin therapy ($P = 0.01$). There was no significant change in weight in the control group (72.1 ± 1.7 and 72.8 ± 1.7 kg, respectively) during the corresponding period.

Blood glucose

There was a significant fall in the mean blood glucose level on insulin therapy, from 18.4 ± 0.3 mM on oral agents to 10.4 ± 0.3 mM on insulin treatment ($P < 0.01$). Glycemic control remained unchanged in the control group (12.2 ± 0.4 and 12.4 ± 0.4 mM, respectively). Proteinuria >300 mg/24 h (Albustix positive) was not observed in either the insulin-treated or control group during the study.

CONCLUSIONS— The association of hyperinsulinemia and/or insulin resistance with hypertension has been shown in numerous studies on obesity (14–21), glucose intolerance (7,13,14,17), and essential hypertension (1–14). Although this association may not necessarily be causal, it appears that hyperinsulinemia with or without insulin resistance is central to these three conditions. However, there is virtually no data on the influence of insulin treatment on blood pressure. Saudek et al. (24) showed that insulin

treatment resulted in sodium retention in six patients with poorly controlled diabetes, but at least three of these patients were ketotic. The effect on blood pressure was not documented in the latter study.

This study has shown that insulin treatment is associated with a significant increase in both systolic and diastolic blood pressures. There are several possible mechanisms that could account for this observation. At least part of the rise could be due to weight gain because the relationship of obesity and hypertension is a well-recognized association. However, previous studies on the subject do not provide a formula linking increments in weight with increments in blood pressure. From the Framingham study, it was observed that a 10% increase in weight correlated with a rise in systolic blood pressure of 6.6 mmHg in men and 4.5 mmHg in women (46). No such data exist for diastolic pressure. With such comparisons, albeit unsatisfactory, the magnitude of pressure changes occurring in our group of patients is in excess of that accountable for by weight gain alone. In addition, the blood pressure rise in our study was noted to occur before any increase in weight in 10% of the study population, indicating that insulin in itself rather than weight gain was the likely explanation for the observed rise in blood pressure. Furthermore, the mean insulin dose (U/kg body wt) was strongly correlated with the increase in both systolic and diastolic blood pressures. A second possibility is the development or worsening of nephropathy. In this study, renal function before and after treatment with insulin was not measured; however, no patient developed gross proteinuria >300 mg/24 h during this period. Renal function is unlikely to be a source of any significant contribution because the same conditions would be applicable to the control group who were matched in several respects, and clearly, there was no change in the latter group with respect to blood pressure.

Other possible mechanisms that could explain the rise in blood pressure seen with insulin therapy relate to the influence insulin has on sodium retention and sympathetic stimulation. Insulin causes sodium retention in the distal nephron, i.e., distal convoluted tubule and thick ascending loop of Henle, even at physiological concentrations. Studies on the isolated toad bladder (25), which possesses electrolyte transporting characteristics similar to mammalian distal tubule (dogs [26] and humans [27]), show this as a consistent property; in addition, insulin stimulates volume resorption in the rabbit proximal convoluted tubule (28). Such sodium-retaining properties appear to be independent of renal hemodynamic factors, such as the glomerular filtration rate or the filtered load of glucose, or alterations in hormonal factors such as glucagon and aldosterone. Moreover, experimental evidence suggests that the presence of hypertension does not modulate the antinatriuretic activity of insulin (29). The resultant sodium retention causes an increased extracellular fluid volume resulting in volume-related hypertension (45). In addition, salt overload can produce hypertension by increasing peripheral vascular resistance irrespective of the cardiac output level (30), possibly by altering vascular reactivity (31,32), increasing norepinephrine turnover, or via central neural effects.

Studies with the euglycemic clamp technique have shown that insulin stimulates the sympathetic nervous system in the absence of changes in blood glucose and in a dose-response fashion (33). Similarly, sucrose feeding in rats produces hyperinsulinemia and increased sympathetic nervous system activity, resulting in an increase of blood pressure (34). Reports on the role of catecholamines on blood pressure are conflicting (11,35,36); however, a review of 78 comparative studies on plasma catecholamines in patients with essential hypertension (37) showed an association between hypertension and high catecholamines in most of them. The exact mechanism by which insulin stimulates the sympathetic nervous system is not known. Notwithstanding, the elevation in norepinephrine by insulin could have effects on the cardiovascular system both directly via an increase in heart rate and peripheral vasoconstriction and indirectly via increased intracellular calcium and increased responsiveness to vasoconstrictors. Carbohydrate ingestion in older individuals may also increase catecholamines via noninsulin mechanisms and be a link to the sympathetic nervous system stimulation in these patients. Furthermore, insulin stimulates cardiac muscle contractility (38). These factors together with the renal sodium-retaining properties of norepinephrine could produce an elevated blood pressure.

A further explanation for the rise in blood pressure with insulin therapy relates to changes in various cations that have an influence on vascular contractility. Previous experimental studies have correlated an elevated sodium content and a decreased potassium content of vessels with increased vascular resistance (39). Similarly, Blaustein (40) suggests a central role for an increase in intracellular calcium, stimulating smooth muscle contraction and increasing responsiveness to vasoconstrictors. Although such changes are not a consistent finding in all hypertensive patients (41–44), they could provide an explanation for the relationship between insulin on the one hand and vascular resistance and blood pressure on the other.

Of interest in this study was the predictive value of the weight before insulin therapy in determining the magnitude of blood pressure elevation. In fact, the greatest blood pressure elevation occurred in those with the highest body weight. Therefore, we postulate that those most overweight, possibly being most insulin resistant, underwent a further exacerbation of their insulin resistance beyond a critical limit, after which blood pressure rose significantly; the process could have been accelerated by exogenous insulin itself.

In conclusion, although this

study serves to highlight the rise in blood pressure accompanying insulin treatment in patients with secondary oral hypoglycemic failure, the mechanisms involved need further elucidation. It may be prudent in these patients to persevere with a greater attention directed at adherance to diet, weight reduction, and exercise as an alternative to insulin therapy in an attempt to achieve adequate glycemic control. It remains of great concern that, although the blood glucose may improve with insulin treatment, the resultant increase risk in weight and blood pressure could further aggravate the increased risk diabetic patients have of developing coronary artery disease.

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