Blood pressure reactions to insulin treatment in patients with type 2 diabetes

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BACKGROUND: The initiation of insulin therapy may be easy and uncomplicated in some patients with type 2 diabetes, but in others, mainly in obese patients, problems often arise (ie, poor compliance, worsening B-cell function and/or insulin resistance).
METHODS: As a substudy of a broader investigation concerning hemorheological effects of insulin treatment in insufficiently controlled type 2 diabetes, blood pressure was recorded in 12 patients at baseline, after two months and after four months on insulin.
RESULTS: After two months on insulin, analyses of triglycerides, high-density lipoprotein cholesterol and total cholesterol indicated metabolic improvement (P<0.05 to 0.001) and a surprisingly uniform increase of blood pressure values (P<0.05 to 0.01) was found. At the same time, the serum sodium concentration increased (P<0.01) and was positively correlated to both systolic and diastolic blood pressure (P<0.01). After four months on insulin, blood pressure returned to pretreatment values or lower (P<0.05 to 0.01). Serum sodium also decreased to pretreatment values. No significant changes of the flow behaviour of blood were seen after the initiation of insulin.
CONCLUSIONS: The number of patients was small and the study was not primarily designed to examine blood pressure. The preliminary conclusion from the present study, however, is that the initiation of insulin treatment in poorly controlled type 2 diabetes causes a temporary and possibly clinically significant elevation of blood pressure. A change in renal treatment of sodium caused by insulin may be one of several possible explanations of the results, but further studies are warranted to confirm the findings.

Key Words: *Blood pressure; Insulin therapy, NIDDM; Sodium excretion*

Patients with type 2 diabetes, especially those who are significantly overweight, are often recommended a change in diet as the first step in treatment. The next step, or in some patients the first step, may be oral hypoglycemic agents – ie, sulphonylureas and/or biguanides. However, in many cases, the need for insulin treatment develops. The initiation of insulin therapy may be uncomplicated in some patients, but in others, mainly in obese patients, problems often arise – ie, poor compliance, worsening B-cell function and/or insulin resistance.

The main theory is that some prediabetic patients may develop resistance to insulin action resulting in compensatory hyperinsulinemia (1). Thus, awareness of insulin resistance appears crucial for understanding the pathophysiology of non-insulin-dependent diabetes mellitus (2). The 'insulin resistance syndrome' has been described as a cluster of risk factors for cardiovascular diseases contributing to the development of hypertension, dyslipidemia, obesity and atherosclerosis (3-7).

The high prevalence of metabolic abnormalities and hypertension in patients with type 2 diabetes increases the risk of the development and progression of both macrovascular and microvascular disease and, thus, also of nephropathy (8,9). In patients with glucose intolerance and hyperinsulinemia, it has been shown that renal sodium retention is increased (6). An underlying defect in intracellular electrolyte handling (calcium, magnesium) or defects in the Na^+/K^+ pump activity may also be factors in the development of insulin resistance and hyperinsulinemia (10-12).

The aim of our original study was to clarify whether patients with type 2 diabetes benefit from insulin treatment with respect to hemorheological variables (whole blood and plasma viscosity). Several investigators have reported that changes in blood rheology and flow properties may be associated with increased risk for cardiovascular damage in diabetic patients. Thus, our intention was to also study other hospital routine parameters (ie, electrolytes, enzymes, lipids, lipoproteins and hematology parameters) that may be altered in type 2 diabetes and thereby may also influence the flow properties of blood. The present report is a substudy based on blood pressure measurements performed in the hemorheological study mentioned above.

METHODS

Twelve patients – six men and six women, all outpatients – were studied. They all had type 2 diabetes for several years and had, as indicated by blood glucose, glycosylated hemoglobin (HbA_{1c}) and plasma triglycerides, a distinct need for a therapy change to insulin to achieve acceptable metabolic control.

The mean age (± SD) was 64.17±7.93 years (range 51 to 73 years) and mean body height was 175.9±4.8 cm (range 169 cm to 185 cm). The mean body weight was 71.8±7.5 kg before insulin treatment and 77.8±9.98 kg after four months of insulin treatment (not significant [NS]). Thus, the patients were only slightly or modestly overweight, and the tendency to gain weight on insulin appeared to confirm, as did other parameters, their need for insulin treatment. At the commencement of insulin treatment they may have been in a catabolic state.

Throughout the study period, six patients were continuously treated with prazosin, atenolol, verapamil, diltiazem or spironolactone for mild hypertension, and with glyceryl trinitrate or alprenolol for angina pectoris. There were no patients with malignancies or other diseases with known hemorheological effects. The patients were assessed before administration of insulin and after two and four months on insulin therapy.

The patients were assessed in the fasting state before the morning dose of insulin was administered.

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TABLE 1
Laboratory results in patients with type 2 diabetes at baseline and after 2 and 4 months on insulin treatment, compared with healthy controls

Laboratory test	Healthy controls, n=10	Before insulin, n=12	After 2 months on insulin, n=12	After 4 months on insulin, n=12
Blood glucose, mmol/L	4.46±0.15	11.89±4.00***	10.78±3.67***	9.61±3.13*** †
Glycosylated hemoglobin, %	4.26±0.07	9.35±1.73***	8.59±1.44***	8.14±1.47*** †††
Mean corpuscular volume, fL	89.36±0.96	92.99±3.10	92.09±3.00†	90.98±3.32††
Erythrocyte sedimentation rate, mm/h	5.50±1.04	19.69±21.85*	19.88±17.92**	15.44±9.78**
Leukocyte count, $\times 10^9$/L	6.36±0.44	7.56±1.10*	8.17±1.88*	7.73±1.34*
Monocyte count, $\times 10^9$/L	0.31±0.03	0.68±0.34***	0.70±0.45*	0.51±0.21* †
Plasma fibrinogen, g/L	2.75±0.16	3.77±0.90**	3.96±1.02**	3.71±0.69**
S-potassium, mmol/L	3.99±0.05	4.38±0.34**	4.38±0.27**	4.38±0.28**
S-sodium, mmol/L	139.40±0.78	137.82±0.61	140.20±0.74††	138.44±0.82
S-ALP, µkat/L	2.29±0.13	3.31±0.64***	3.45±0.93***	3.48±0.67***
S-ALT, µkat/L	0.28±0.02	0.38±0.15*	0.33±0.10	0.34±0.16
Plasma triglycerides, mmol/L	0.67±0.07	1.82±0.90***	1.33±0.89* ††	1.43±0.98* ††
High-density lipoprotein cholesterol, mmol/L	1.28±0.10	1.06±0.23*	1.17±0.26†††	1.15±0.26†
S-total cholesterol, mmol/L	5.27±0.42	5.79±0.65	5.41±0.89†	5.51±0.99
S-glutamyltransferase, µkat/L	0.41±0.06	1.02±0.42	1.08±0.52†	1.05±0.51
S-bilirubin, µmol/L	10.80±0.83	11.61±1.91	10.93±2.99	10.31±1.89†

*Data for patients with type 2 diabetes presented as mean ± SD; data for healthy controls presented as mean ± SEM. *P<0.05; **P<0.01; ***P<0.001 versus controls. †P<0.05; ††P<0.01; †††P<0.001 treatment values versus pretreatment values. ALT Alanine aminotransferase; ALP Alkaline phosphatase; S Serum*

Blood pressure
Blood pressure was measured before administration of insulin and after two and four months on insulin. Blood pressure was recorded in the left arm with the patient in the supine position after 10 min rest, using a cuff of appropriate size. The Korotkoff method was used. The mean of two measurements was recorded. Antihypertensive therapy was not changed when a moderate change of blood pressure was registered on only one occasion.

Routine blood samples
Laboratory parameters were determined by routine hospital methods.

Statistics
The data are expressed as means ± SDs. The SDs between the control and the diabetic groups were evaluated with the Student's *t* test for unpaired data. Differences between pretreatment and treatment values in the patient group were analyzed with a *t* test for paired observations. Pearson's coefficients were computed for correlation analysis between blood pressure and sodium concentration in plasma or body weight. Two-sided values of P<0.05 were considered to be statistically significant.

RESULTS

Routine blood samples
Before insulin treatment: Compared with healthy subjects, the diabetic group showed increased values for blood glucose, HbA_{1c}, mean corpuscular volume, erythrocyte sedimentation rate, leukocyte count, monocyte count, plasma fibrinogen, serum (S)-potassium, S-alkaline phosphatase, S-alanine aminotransferase, plasma triglycerides and high-density lipoprotein (HDL) cholesterol (P<0.05 to 0.001) (Table 1).

Pretreatment values versus values after two months of insulin treatment: The metabolic state of the patients improved, as indicated by blood glucose (NS), HbA_{1c} (NS), plasma triglycerides (P<0.01), HDL cholesterol (P<0.001) and total cholesterol (P<0.05); S-sodium increased (P<0.01) (Table 1).

After four months of insulin treatment, the pattern of the metabolic state remained and was more evident. Compared with pretreatment values, decreased values were found for blood glucose, HbA_{1c}, mean corpuscular volume and S-bilirubin (P<0.05 to 0.001). HDL cholesterol levels were still increased compared with pretreatment values (P<0.05). S-sodium decreased to pretreatment values (Table 1).

Blood pressure
The systolic and diastolic blood pressure increased significantly when insulin treatment was started, but later it decreased; after four months on insulin, the blood pressure values decreased until they were lower than pretreatment values. The mean systolic blood pressure before the initiation of insulin treatment was 159.58±13.05 mmHg, and after two months on insulin it was 162.2±12.52 mmHg (P<0.05) (Table 2). The mean diastolic blood pressure before the initiation of insulin was 86.25±4.83 mmHg, and after two months on insulin it was 89.17±5.97 mmHg (P<0.05) (Table 2). The mean blood pressure ([systolic + diastolic]/2) before the initiation of insulin was 123.08±4.43 mmHg and after two months on insulin it was 126.17±7.84 mmHg (P<0.01) (Table 2).

After four months on insulin treatment, mean systolic blood pressure, mean diastolic blood pressure and mean blood pressure decreased to 156.67±11.93 mmHg, 84.17±4.69 mmHg and 120.67±6.53 mmHg, respectively, corresponding to P<0.05, P<0.01 and P<0.05, respectively, compared with the pretreatment blood pressure values (Table 2).

TABLE 2
Blood pressure (BP) in patients with type 2 diabetes at baseline, and after 2 and 4 months of insulin treatment

		Before insulin			After 2 months on insulin			After 4 months on insulin		
Patient	Age, years	SBP	DBP	Mean BP	SBP	DBP	Mean BP	SBP	DBP	Mean BP
1	73	165	90	128	170	95	133	160	85	123
2	61	170	80	125	165	80	123	165	75	120
3	51	150	85	118	155	90	123	150	80	115
4	70	140	80	110	140	85	113	140	80	110
5	51	170	90	130	175	95	135	165	85	125
6	62	160	85	123	165	85	125	150	85	118
7	61	170	90	130	175	95	135	160	90	125
8	65	160	80	120	165	80	123	160	80	120
9	70	155	95	125	155	95	125	145	90	118
10	60	135	85	110	140	85	113	140	85	113
11	73	180	85	133	175	90	133	180	85	133
12	73	160	90	125	170	95	133	165	90	128
Mean	64.17	159.58	86.25	123.08	162.2*	89.17*	126.17**	156.67*	84.17**	120.67*
SD	7.93	13.05	4.83	4.43	12.52	5.97	7.84	11.93	4.69	6.53

**P<0.05, **P<0.01 treatment values versus pretreatment values. D Diastolic; S Systolic*

Correlation between blood pressure and S-sodium concentration, and blood pressure and body weight

After two months on insulin, both systolic and diastolic blood pressures were positively correlated to S-sodium concentration (P<0.01). No significant correlation was found between body weight and blood pressure values.

DISCUSSION

The present report is a result of a subanalysis of a larger study concerning the possible relations between the initiation of insulin treatment, fatty acid composition of phospholipids in the erythrocyte membrane measured by gas chromatography and blood rheology parameters (13). The blood pressure changes reported were found in a computerized check-up of study data and clinical registrations compiled during the main study, but were analyzed some years later. Thus, it should be observed that the main study was not designed for investigations of blood pressure reactions to insulin administration and the number of patients was not very significant.

The actual role of insulin in the pathogenesis of hypertension in humans remains obscure. Earlier reports (14) mainly describe experimental work in dogs, but its relevance to human hypertension is not obvious. Insulin, however, appears to have vasodilating properties (15), and it is also known to stimulate the sympathetic nervous system and promote renal sodium reabsorption (16). An increase in plasma insulin markedly reduces sodium excretion (17,18). Studies (19) have shown that during euglycemic hyperinsulinemia, urinary sodium excretion may fall by as much as 50%. In the present study, S-sodium followed the same pattern as values for blood pressure. Thus, S-sodium increased significantly (P<0.01) after two months on insulin. At four months on insulin, S-sodium values decreased to the same values as measured before insulin initiation.

Singh et al (20) found that non-insulin-dependent diabetes mellitus patients have a tendency to retain sodium under the influence of insulin. Institution of insulin should then lead to decreased sodium excretion, increased levels of S-sodium and increased blood pressure. This study showed that the increased blood pressure values are not caused by an increased body weight and that increased values of sodium in plasma are positively correlated to blood pressure at two months on insulin.

In the present study, statistically significant elevations of systolic, diastolic and mean blood pressure were seen (P<0.05 to 0.01) after two months on insulin. After four months on insulin, blood pressure levels decreased to preinsulin blood pressure levels or lower (P<0.05 to 0.01). These findings lead to the preliminary conclusion that initiation of insulin treatment in patients with insufficiently controlled type 2 diabetes may cause a temporary elevation of blood pressure.

The blood pressure changes were small, but it was still noticeable that the majority of the patients had increased systolic and diastolic blood pressures.

The findings also indicate that the initial elevation of blood pressure is replaced by a moderate decrease. From a clinical point of view, a rather rapid and unobserved increase in blood pressure at the initiation of insulin treatment may be a problem. Erythrocytes have a fixed age of approximately 120 days and then they are eliminated by the spleen. Thus, at four months, all erythrocytes have been replaced by new ones. Therefore, the patients were studied before taking insulin, and after two and four months on insulin to monitor the effects of insulin on erythrocytes throughout the cells' life cycle. It may be advisable, especially in those patients with retinopathy, nephropathy and cerebrovascular disease, to intensify blood pressure controls at frequent intervals after initiating insulin therapy to better define when and if an increase in blood pressure begins, reaches its maximum and decreases. It was also recommended to monitor blood pressure with 24 h ambulatory readings to improve both accuracy and precision of the measurements. Further studies, with a larger number of patients and a more specific design, are warranted to confirm our results.

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REFERENCES

1. Reaven GM. Insulin resistance, the insulin resistance syndrome and cardiovascular disease. Panminerva Med 2005;47:201-10.
2. Hollenbeck C, Reaven G. Variations in insulin-stimulated glucose uptake in healthy individuals with normal glucose tolerance. J Clin Endocrinol Metab 1987;64:1169-73.
3. Rader DJ. Effect of resistance, dyslipidemia and intra-abdominal adiposity on the development of cardiovascular disease and diabetes mellitus. Am J Med 2007;120(3 Suppl 1):12-8.
4. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37:1595-607.
5. Sowers JR, Standley PR, Ram JL, Jacober S, Simpson L, Rose K. Hyperinsulinaemia, insulin resistance and hyperglycaemia: Contributing factors in the pathogenesis ofs hypertension and atherosclerosis. Am J Hypertens 1988;6:260-70.
6. DeFronzo RA, Ferranninni E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidaemia and atherosclerotic cardiovascular disease. Diabetes Care 1991;14:173-94.
7. Persson SU, Larsson H, Odeberg H. Reduced number of circulating monocytes after institution of insulin therapy – relevance for development atherosclerosis in diabetics? Angiology 1988;49:423-33.
8. Kannel WB, Wilson MD, Zhang T-J. The epidemiology of impaired glucose tolerance and hypertension. Am Heart J 1991;121:1268-73.
9. Peralta CA, Kurella M, Lo JC, Chertow GM. The metabolic syndrome and chronic kidney disease. Curr Opin Nephrol Hypertens 2006;15:361-5.
10. Modan M, Halkin H, Fuchs Z, et al. Hyperinsulinaemia – a link between glucose intolerance, obesity, hypertension, dyslipoproteinaemia, elevated serum uric acid and internal cation imbalance. Diabetes Metab 1987;13:375-80.
11. Sechi LA, Melis A, Pala A, Marigliano A, Schi G, Tedde R. Serum insulin, insulin sensitivity and erythrocyte sodium metabolism in normotensive and essential hypertensive subjects with and without overweight. Clin Exp Hypertens A 1991;13:261-76.
12. Nagase N. Hypertension and serum Mg in the patients with diabetes and coronary heart disease. Hypertens Res 1999;19(Suppl):65-8.
13. Persson SU, Wohlfart G, Larsson H, Gustafson A. Correlations between fatty acid composition of the erythrocyte membrane and blood rheology data. Scand J Clin Lab Invest 1996;56:183-90.
14. Brands MW, Mizelle HL, Gaillard DA, Hildebrandt DA, Hall JE. The haemodynamic response to chronic hyperinsulinaemia in conscious dogs. Am J Hypertens 1991;4:164-8.
15. Creager MA, Liang CS, Coffman JD. Beta adrenergic-mediated vasodilator response to insulin in the human forearm. J Pharmacol Exp Ther 1985;235:709-14.
16. Gupta AK, Clark RV, Kirchner KA. Effects of insulin on renal sodium excretion. Hypertension 1992;19(Suppl 1):167-71.
17. Baum M. Insulin stimulates volume absorption in the proximal convoluted tubule. J Clin Invest 1987;56:335-40.
18. De Fronzo RA. The effects of insulin on renal sodium metabolism. Diabetologia 1981;21:165-71.
19. De Fronzo RA, Cooke CR, Andres R, et al. The effects of insulin on renal handling of sodium, potassium, calcium and phosphate in man. J Clin Invest 1975;55:845-55.
20. Singh SK, Sarkar D, Agrawal JK. Insulin resistance and urinary excretion of sodium in hypertensive patients with non-insulin dependent diabetes mellitus. J Assoc Physicians India 1999;47:709-11.