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Intravenous Insulin Decreases Urinary Albumin Excretion in Long-term Diabetics with Nephropathy

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Summary. The effect of intravenous injection of insulin on heart rate, plasma noradrenaline and urinary excretion rates of albumin and beta-2-microglobulin was examined in 10 long-term diabetics, 5 of whom had albuminuria. – In patients without albuminuria intravenous injection of insulin resulted in changes similar to but less pronounced than those previously observed in short-term diabetics: albumin excretion, plasma noradrenaline and heart rate increased, creatinine excretion decreased significantly. – Intravenous injection of insulin increased heart rate but not plasma noradrenaline in long-term diabetics with albuminuria. Arterial blood pressure did not change after insulin. Contrary to expectation insulin decreased urinary albumin excretion (from 418 to 312 μg/min, 27 per cent) in these patients. There was a marked decrease in urinary excretion rates of beta-2-microglobulin and creatinine (55 and 17 per cent, respectively) after insulin. – The decrease in albumin excretion after insulin in diabetics with albuminuria is most likely due to renal vasoconstriction. The absence of a rise in albumin excretion after insulin may be due to severe morphological changes in glomeruli in these patients.

Key words: Arterial blood pressure, blood glucose, cardiovascular, heart rate, insulin, long-term diabetes, nephropathy, neuropathy, noradrenaline, proteinuria, urinary albumin excretion.

It is now known that insulin has marked acute effects on sympathetic nervous activity and the cardiovascular system. In short-term diabetic subjects intravenous injection of insulin increases plasma noradrenaline [1, 2, 3] and heart rate [3, 4] and decreases peripheral and renal blood flow as well as glomerular filtration rate [3, 5]. Furthermore, insulin induces hypovolaemia [3, 6] and increases urinary excretion of albumin [5, 7].

The cardiovascular effects of insulin are not due to hypoglycaemia [3]. Except for the changes in renal blood flow and in glomerular filtration rate they occur even in diabetics in whom blood glucose concentration after insulin is maintained at unchanged levels by glucose infusion [7].

The aim of the present study was to examine cardiovascular effects of insulin in long-term diabetics. Patients with normal and elevated albumin excretion, respectively, were selected in order to investigate the influence of glomerular damage on the insulin induced increase in albumin excretion.

Patients

Ten long-term juvenile diabetic patients were studied. From previous studies five of them were known to have elevated urinary excretion rates of albumin (> 25 μg/min). Pertinent clinical data are given in Table 1. Most of the diabetic patients had signs of neuropathy. They were all treated with insulin twice a day, but had their last dose of insulin 24 hours before the investigation. Furthermore, they were asked to eat two pieces of bread beyond their usual diet the evening before the investigation to achieve a somewhat elevated blood glucose level. Informed consent was obtained from all subjects.

Procedure

The patients were examined in the morning after an overnight fast. They rested in the sitting position, standing up only to void. They drank 45 ml of water every 15 min, starting 1 hour before the experiment was initiated and continued during the whole experiment.

After a resting period of half an hour urinary albumin and beta-2-microglobulin excretion were measured in two 30 min periods before and three 45 min periods after insulin. Eight IU of

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Table 1. Clinical data in 10 male juvenile diabetics

Patients	Age (years)	Per cent ideal body weight	Blood pressure mm Hg	Diabetes duration (years)	Retinopathy stage	Neuropathy		Usual daily insulin dose, IU
						Deep tendon[a] reflexes	Biothesiometry volts[b]	
With albuminuria								
1	28	97	115/70	13	Background	Present	21	56
2	31	99	120/80	15	Background	Absent	40	48
3	25	133	125/90	15	Background	Present	28	112
4	34	113	120/80	13	None	Absent	28	72
5	30	93	185/110	16	Background	Present	36	52
Without albuminuria								
6	32	84	100/70	11	Background	Absent	32	40
7	35	104	110/80	27	Prolif.	Present	24	56
8	24	110	115/80	10	None	Present	16	56
9	33	103	120/90	17	Background	Absent	17	96
10	33	106	135/95	20	Background	Present	30	80

Patients with albuminuria had albumin excretion rates greater than 25 μg/min

[a] Patellar and Achilles-tendon reflexes

[b] Normal values are less than 15 volts

insulin (Leo Neutral) was given as a bolus injection during one min, just after termination of the two 30 min periods. Plasma noradrenaline and adrenaline were measured before and 45 min after the injection of insulin. Blood glucose concentration, heart rate and arterial blood pressure were measured at 15 min intervals during the examination.

Methods

Urinary concentration of albumin and beta-2-microglobulin (Phadebas® $beta_2$-microtest) were measured by radioimmunoassays [8, 9]. The interassay coefficients of variation for urinary albumin and beta-2-microglobulin determinations on urine from normal subjects were 6.2 and 9.3 per cent, respectively. Plasma noradrenaline and adrenaline were measured by a double-isotope derivative assay [10]. Arterial blood pressure was measured indirectly by a sphygmomanometer. Plasma glucose was determined by an orthotoluidine method. Creatinine excretion was measured by a standard method. Vibratory perception threshold was measured in the big toe with a biothesiometer. We have previously shown that diabetics with elevated vibratory perception threshold values demonstrate both functional and biochemical signs of sympathetic denervation [11, 12].

Wilcoxon's test for paired samples and Student's t-test for paired samples were used for testing statistical significance [13].

Results

Blood glucose concentration decreased by about 100 mg/100 ml after intravenous injection of insulin, but did not decline below normal fasting levels (Table 2).

In the five diabetics with albuminuria insulin decreased albumin excretion from a mean pre-insulin value of 418 μg/min to a mean post-insulin value of 312 μg/min (Table 3, a mean decrease of 27 per cent, 2P = 0.013). Urinary excretion of creatinine decreased 17 per cent in the same period (2P = 0.0077). There was a marked decrease in urinary excretion rates of beta-2-microglobulin (mean 55 per cent, 2P = 0.0023).

In the five long-term diabetics without albuminuria the changes observed after insulin were similar, but less pronounced, than those found in short-term diabetics. Urinary albumin excretion increased from a mean value of 11.4 μg/min before to a mean value of 14.2 μg/min after insulin (2P = 0.047). Urinary excretion of beta-2-microglobulin did not change significantly after insulin in these patients. Creatinine excretion decreased from a mean preinsulin value of 1.43 mg/min to 1.13 and 1.23 mg/min in the first and second period after insulin (21 and 14 per cent, respectively, 2P = 0.0032 and 0.013). The corresponding values in the group of patients with albuminuria were 23 and 16 per cent, respectively.

There were no changes in plasma noradrenaline (mean 0.37 ng/ml in the sitting position both before and 45 min after insulin) and plasma adrenaline and in arterial blood pressure after insulin in the five diabetics with albuminuria, while heart rate increased significantly in the first 45 min period after insulin (from a mean value of 76 ± 12 (SE) to 83 ± 16 beats/min, 2P = 0.038). Mean heart rate and mean plasma noradrenaline increased in patients without albuminuria from 75 to 84 beats/min and from 0.29

Table 2. Mean blood glucose concentrations ± SE (mg/100 ml) obtained in 10 long-term diabetics with and without albuminuria at 15 min intervals in two 30 min periods before and three 45 min periods after intravenous injection of insulin. Results are mean values for each period except in the first post-insulin period

Patients	Pre-insulin values		Post-insulin values				
	0–30	30–60	0–15	15–30	30–45	45–90	90–135
	min						
With albuminuria							
Mean	324	322	334	291	265	233	226
SE ±	100	97	99	98	93	89	89
Without albuminuria							
Mean	309	307	288	258	210	179	170
SE ±	112	109	102	117	118	98	87

Table 3. Urinary excretion rates of albumin (μg/min), beta-2-microglobulin (ng/ml) and of creatinine (mg/min) obtained in 5 long-term diabetics with albuminuria in two 30 min periods before and three 45 min periods after intravenous injections of insulin

Nos.		Pre-insulin values		Post-insulin values		
		0–30	30–60	0–45	45–90	90–135
		min				
	Albumin	200	209	171	158	133
1	β-2-microglobulin	66	66	51	44	37
	Creatinine	1.45	1.57	1.34	1.31	1.44
	Albumin	420	420	64	270	286
2	β-2-microglobulin	67	56	16	18	12
	Creatinine	2.23	1.92	0.68	1.55	1.41
	Albumin	122	120	88	89	86
3	β-2-microglobulin	123	151	88	78	60
	Creatinine	1.49	1.35	1.04	1.14	1.32
	Albumin	140	141	116	113	128
4	β-2-microglobulin	66	84	48	33	15
	Creatinine	1.34	1.32	1.27	1.14	1.23
	Albumin	1296	1105	959	1040	981
5	β-2-microglobulin	57	91	68	7	7
	Creatinine	1.00	1.14	1.00	0.96	1.01
Mean	Albumin	436	399	280	334	323
	β-2-microglobulin	76	90	54	36	26
	Creatinine	1.50	1.46	1.07	1.22	1.28

to 0.39 ng/ml at 45 min after insulin, respectively (2P = 0.022 and 0.031).

Discussion

The present study shows that urinary albumin excretion decreases after intravenous injection of insulin in long-term diabetics with albuminuria in contrast to the findings in short-term diabetics [5, 7] and in long-term diabetics without signs of nephropathy.

Renal blood flow and glomerular filtration rate were not measured in the present study, but, judged by the pronounced decrease in creatinine excretion, they were in all probability decreased after insulin in both groups of patients examined. In a previous study in which blood glucose was allowed to decline after insulin renal blood flow and glomerular filtration rate decreased markedly [5]. A decrease in renal blood flow and in glomerular filtration rate is the most likely explanation for the decrease in renal excretion rates of albumin after insulin in diabetics with albuminuria. In short-term diabetics vasoconstriction may tend to decrease albumin excretion, but other factors predominate, with the net effect that albumin excretion is increased. As discussed elsewhere [5, 7]

the increase in albumin excretion after insulin is most likely of glomerular origin. It is possible that the absence of increase in renal albumin excretion in diabetics with albuminuria is due to morphological changes in glomeruli or in afferent and efferent vessels present in these patients.

The decrease in creatinine excretion in long-term diabetics was considerably more pronounced than previously observed in a group of short-term diabetics (19 versus 5 per cent, respectively (unpublished results). However, the experimental designs were not identical, particularly with respect to the position of the subjects and water intake.

In short-term diabetics arterial blood pressure either does not change after insulin or may even increase slightly [3, 5, 7]. Arterial blood pressure may decrease after insulin in patients with autonomic neuropathy [14, 15, 16]. In the present study there was no change in arterial blood pressure in diabetics with nephropathy even though there was no increase in plasma noradrenaline.

The normal rise in heart rate observed after insulin in diabetics with nephropathy and no change in plasma noradrenaline is not surprising because, in a previous study in rabbits, we showed that this action of insulin occurs independently of the autonomic nervous system [17].

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