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A pilot study to test the effect of pulsatile insulin infusion on cardiovascular mechanisms that might contribute to attenuation of renal compromise in type 1 diabetes mellitus patients with proteinuria

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Abstract

We hypothesized that correction of insulin deficiency by pulsatile intravenous insulin infusion in type 1 diabetes mellitus patients with nephropathy preserves renal function by mechanisms involving cardiac autonomic function, cardiac mass, or efficiency, or by hemostatic mechanisms. The control group (8 patients) received subcutaneous insulin (3-4 injections per day). The intravenous infusion group (10 patients) received three 1-hour courses of pulsed intravenous insulin infusion on a single day per week in addition to subcutaneous insulin. Laboratory measurements included 2-dimensional Doppler echocardiography, 24-hour ambulatory monitoring with heart rate variation analysis, platelet aggregation and adhesion, plasma fibrinogen, factor VII, von Willebrand factor, fibrinolytic activity, plasminogen activator inhibitor, and viscosity measured at baseline and 12 months. Blood pressure control was maintained preferentially with angiotensin-converting enzyme inhibitors. Ratio of carbon dioxide production to oxygen utilization was measured with each infusion and showed rapid increase from 0.8 to 0.9 ($P = .005$) at weekly treatments through 12 months. We observed an annualized decrease in creatinine clearance of 9.6 mL/min for controls vs 3.0 mL/min for infusion patients. Annualized fall in blood hemoglobin was 1.9 vs 0.8 g/dL, respectively ($P = .013$). There were no differences between the control and infusion group with respect to glycohemoglobin, advanced glycated end products, cholesterol, or triglycerides. No differences between the study groups for hemodynamic or hemostatic factors were evident. Blood pressures were not significantly different at baseline or 12 months. We conclude that although preservation of renal function with attenuation of loss of blood hemoglobin during 12 months of intravenous insulin infusion was associated with improvement in the efficiency of fuel oxidation as measured by respiratory quotient, this occurred without differences in metabolic/hemostatic factors, cardiac autonomic function, cardiac wall, or chamber size. Our hypothesis that preservation of renal function in type 1 diabetes mellitus patients with proteinuria by weekly pulsed insulin infusion involves mechanisms from the autonomic nervous system, cardiac size, and function, or elements of hemostasis was not confirmed.

1. Introduction

Computerized control of glucose/insulin by means of the BioStator GCITS insulin infusion pump (Miles Laboratories, Elkhart, IN) in patients with type 1 diabetes mellitus has been shown to correct hepatic disposal of glucose [1]. Increased efficiency of equimolar amounts of hormones administered in pulsatile fashion when compared with continuous infusion has been demonstrated for insulin [2], glucagon [3], and growth hormone [4,5]. The addition of pulsatile infusion to multiple daily subcutaneous injections has been reported to be of benefit in the prevention of metabolic and microvascular complications in type 1 diabetes mellitus [6,7]. A multicenter, prospective, randomized study has demonstrated preservation of renal function in type 1 diabetes mellitus patients with albuminuria by pulsatile insulin infusion [8]. We hypothesized that correction of insulin deficiency by pulsatile intravenous insulin infusion in patients with type 1 diabetes mellitus preserves renal function by mechanisms

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Table 1
Effect of 12 months of intensive insulin treatment

Parameter	Control		Infusion	
	Baseline	1 y	Baseline	1 y
Glycohemoglobin A_{1c} (%)	9.8 ± 0.5	8.0 ± 0.3	9.1 ± 0.6	8.5 ± 0.6
AGE products (U)	13.0 ± 1.8 (8)	7.2 ± 1.9 (7)	12.5 ± 3.5 (8)	8.3 ± 1.5 (9)
Insulin dose (U/d)	48.6 ± 4.5	39.5 ± 2.2	40.1 ± 4.2	42.4 ± 4.9
Assisted hypoglycemia (no. per patient/y)	5 (range, 0-32)	0	35 (0-303)	0
Assisted hypoglycemia during study (no. per patient/y)		0		1
Self-treated hypoglycemia (no. per patient/y)	7 (range, 0-14)	17 (2-55)	9 (0-20)	21 (7-109)
Weight (kg)	77.8 ± 4.0	76.7 ± 4.5	73.3 ± 3.7	73.2 ± 4.2
Edema (% present)		83		17 *
MAP (mm Hg)	103.8 ± 3.4	104.3 ± 2.6	96.2 ± 2.7	98.0 ± 2.6
24-Hour urine protein (mg)	3754 ± 935	2024 ± 645	3692 ± 998	2203 ± 729
Hemoglobin (g/dL)	13.7 ± 0.5	11.8 ± 0.5	13.5 ± 0.7	12.7 ± 0.7 **
Serum creatinine (mg/dL)	1.74 ± 0.14	2.19 ± 0.28	1.78 ± 0.23	1.86 ± 0.25 ***
Creatinine clearance (mL/min)	55.4 ± 7.0	45.8 ± 7.0	58.4 ± 7.0	55.4 ± 8.7
Loss of clearance (mL/[min y])		9.6		3.0
No decrease in clearance during study (%)		0		55 ****

AGE indicates advanced glycated end-products.
* $P = .043$, 2-tailed Fisher exact test.
** $P = .013$.
*** $P = .001$.
**** $P = .029$, 2-tailed Fisher exact test.

involving cardiac autonomic function, cardiac mass, or efficiency, or by hemostatic mechanisms.

2. Patients and methods

Patients (n = 71) participated in a 12- to 18-month randomized protocol at 7 centers that demonstrated a slowing of loss of renal function in diabetic individuals with proteinuria treated with a weekly pulsatile insulin infusion. Description of the full protocol was previously published [8]. In brief, the control group received 3 to 4 subcutaneous insulin injections per day; the infusion group received, in addition, three 1-hour infusions in a pulsatile fashion over one 8-hour period each week. Both groups were seen weekly by investigators with the goal of optimizing glycemic and blood pressure (preferentially treated with angiotensin-converting enzyme inhibitors) control. On infusion days, by means of the metabolic cart, oxygen utilization and carbon dioxide production were simultaneously measured at the beginning and at the end of the infusion hour. Mean results for the 3 infusion hours included 9 determinations preinfusion and 9 at the end of infusion.

The group at the Joslin Clinic enrolled 18 patients (8 randomized to control and 10 to insulin infusion) who underwent an extensive cardiovascular evaluation in addition to the multicenter protocol as part of a pilot study attempting to identify intermediate mechanisms that might contribute to the preservation of renal function. This subgroup underwent 2-dimensional Doppler echocardiography at baseline and 12 months, and 24-hour ambulatory monitoring with heart rate variation analysis every 6 months. Study group designation was concealed from readers of the individual tests.

Plasma samples taken at baseline and at 6 and 12 months were analyzed in duplicate for fibrinogen, factor VII, von Willebrand factor, fibrinolytic activity, plasminogen activator inhibitor, and viscosity. Platelet aggregation after stimulation with adenosine diphosphate, collagen, and epinephrine was performed in a platelet aggregometer at baseline and 12 months. Platelet adhesion was also determined using a modified Hele-Shaw flow system at baseline and 12 months.

Because of the risk of hypoglycemia in patients with multiple cardiac risk factors from tight diabetes control, a detailed diary of hypoglycemic reactions was kept and analyzed with respect to total insulin dose.

The study was designed to run for 12 months, with an option for the investigators to extend it to 18 months in the event that the treatment seemed effective but had not yet reached statistical significance at 12 months. Patients were offered the opportunity to extend participation for up to 6 months, at which time the study was terminated.

3. Results

3.1. Glycemic control

For our study group (n = 18), as in the multicenter study, glycemia control as measured by glycohemoglobin ($P = .006$) and advanced glycated end products ($P = .01$) decreased. No significant differences in measures of diabetic

Table 2
Effect of 12 months of intensive insulin treatment on autonomic (24-hour ambulatory electrocardiographic) and standard echocardiographic measurements

Parameter	Control		Infusion	
	Baseline	1 y	Baseline	1 y
Day-night MAP ratio	1.01 ± 0.03 (7)	1.07 ± 0.03	0.98 ± 0.36	1.04 ± 0.03
SDNN (ms)	68.9 ± 7.7 (6)	73.0 ± 7.3	96.2 ± 16.2 (9)	86.7 ± 14.1
PNN50 (%)	0.51 ± 0.22 (6)	0.35 ± 0.25	2.16 ± 1.48 (9)	3.76 ± 2.36
RMSSD (ms)	10.8 ± 0.8 (6)	10.2 ± 1.4	14.0 ± 4.6 (9)	17.1 ± 5.6
CVNN	10.4 ± 1.0 (6)	10.8 ± 1.1	14.0 ± 1.9 (9)	12.8 ± 1.8
HF (ms^2)	33.7 ± 4.34 (7)	35.5 ± 5.3	258.2 ± 181.4 (9)	189.6 ± 146.2
LF (ms^2)	142.2 ± 31.2 (7)	83.9 ± 25.3	901.3 ± 682.6 (9)	637.6 ± 493.1
LV mass (g)	217.7 ± 33.8 (6)	194.8 ± 30.8	207.0 ± 10.9	184.5 ± 15.9
LV septum (mm)	10.3 ± 0.3 (6)	9.8 ± 0.5	10.0 ± 0.5	9.4 ± 0.6
Fiber shortening (%)	36.8 ± 1.7 (6)	39.3 ± 2.4	38.6 ± 1.7	39.4 ± 2.5
Ejection fraction (%)	56.7 ± 5.4 (6)	57.5 ± 5.6	62.0 ± 1.1	61.5 ± 1.1
E/A ratio	1.10 ± 0.08 (6)	1.09 ± 0.12	1.32 ± 0.16	1.42 ± 0.7

SDNN indicates standard deviation of RR intervals; PNN50, percent of NN intervals with variation of greater than 50 months; RMSSD, square root of the mean squared of successive RR intervals; CVNN, coefficient of variation of RR intervals; HF, high frequency; LF, low frequency; LV, left ventricular.

control between the control and infusion groups were demonstrated. As noted in Table 1, in the 2 years before entry into the study, the control patients (n = 8) had 7 episodes of hypoglycemic coma and an additional 57 hypoglycemic episodes that required assistance. Patients in the infusion group (n = 10) had 13 episodes of coma and an additional 347 episodes necessitating assistance.

During the 12-month period studied, control group patients (n = 8) had 132 hypoglycemic events (average, 22 per patient per year), of which none resulted in either coma or required assistance. Mean daily insulin dose decreased significantly from 49 to 40 U ($P = .014$). Infusion patients (n = 10) had 272 hypoglycemic events (average, 30 per patient per year), of which 1 was associated with a minor motor vehicle accident. Mean daily insulin dose increased slightly from 40 to 42 U. The 12-month change in insulin dose was significantly different between the study groups (−13.8 ± 3.7 vs 2.3 ± 3.5, $P = .009$). Both groups had decreases in weight (control, 77.8 to 76.7 kg; infusion, 73.3 to 73.2 kg). Despite a fall in insulin dose by 12 months, the control group had a higher incidence of edema ($P = .043$) than the infusion group, in which the insulin dose rose slightly. Infusion patients demonstrated respiratory quotient (RQ) (V_{CO_2}/V_{O_2}) increase from 0.854 ± 0.003 to 0.954 ± 0.050 ($P = .005$) in the initial few weeks of infusion therapy. At the end of 1 year of weekly treatments, RQ increased from 0.826 ± 0.002 to 0.915 ± 0.001 ($P = .005$).

3.2. Renal function

Creatinine clearance decreased during the study period from 55 to 46 mL/min in the control group and from 58 to 55 mL/min in the infusion group (Table 1). These differences were not significant for either group. The change in serum creatinine over 12 months was 0.45 ± 0.16 in the control group and 0.08 ± 0.06 in the infusion group ($P = .056$). The change in hemoglobin was significantly different between the 2 study groups (control, −1.9 ± 0.32; infusion, −0.77 ± 0.25; $P = .013$). Between the control and weekly infusion groups, there was no difference in mean arterial pressure (MAP) at baseline or at 12 months. The change from baseline to 12 months in MAP was also not significantly different between the control and infusion groups. There was a significant increase in the presence of edema in the control group without significant difference in degree of proteinuria when compared with the insulin infusion group.

3.3. Cardiac autonomic function and echocardiographic measurements

Details of the relationship between time and frequency domain measures of heart rate variation (cardiac autonomic function) and echocardiographic measurements of left

Table 3
Effect of 12 months of intensive insulin treatment on hemostatic parameters

Parameter	Control		Infusion	
	Baseline	1 y	Baseline	1 y
Fibrinogen (mg/dL)	391 ± 31	338 ± 41	428 ± 51	357 ± 41
Factor VII (%)	126.1 ± 5.8	105.9 ± 5.2	139 ± 5.7	100.3 ± 9.8
Von Willebrand factor (%)	163 ± 15	110 ± 22	163 ± 19	157 ± 17
Fibrinolytic activity (mm^2)	173.9 ± 14.6	75.1 ± 12.2	138.6 ± 22.4	90.2 ± 20.0
Plasminogen activator inhibitor 1 (ng/mL)	10.22 ± 3.00	9.41 ± 1.77	5.46 ± 0.76	12.9 ± 1.45
Platelet adhesion (no. of platelets)	135 ± 24	184 ± 27	161 ± 35	
Platelet aggregation				
ADP (mmol/L)	1.73 ± 0.34	2.44 ± 0.42	1.99 ± 0.76	2.50 ± 0.84
Collagen (s)	92.8 ± 8.3	84.4 ± 7.8	105.3 ± 15.0	86.0 ± 12.6
Epinephrine (mmol/L)	0.13 ± 0.08	1.20 ± 0.90	1.47 ± 0.81	1.12 ± 0.37

ADP indicates adenosine diphosphate.

ventricular mass and function in control and insulin therapy study groups are shown in Table 2. There were no significant differences demonstrated between study groups at baseline and 12 months, or in changes over the course of the study period with respect to measures of parasympathetic, sympathetic, or left ventricular function. Likewise, no differences with respect to left ventricular geometry or mass were found.

3.4. Hemostatic function

There were no significant differences between study groups with regard to baseline and 12 months, or in changes in hematocrit, albumin, fibrinogen, factor VII, fibrinolytic activity, plasminogen activator inhibitor, von Willebrand factor, viscosity, and tests of platelet aggregation or adhesion (Table 3).

4. Discussion

4.1. Glycemic control

The study groups experienced similar levels of improvement in glycohemoglobin and advanced glycated end products. Weekly infusion therapy was associated with no change in mean daily insulin dose, in contradistinction to the control group in which mean daily insulin decreased significantly. We could not therefore attribute the high incidence of edema in the control group to insulin excess.

In the 2 years before randomization, our patient population had demonstrated a considerable requirement for assistance to treat hypoglycemia. Because of a protocol that involved careful weekly monitoring of all patients by health care personnel, a marked reduction in episodes of hypoglycemia that required assistance or hospitalization was observed in both groups.

The renal medulla and the retina require an RQ of 1.0, suggesting that energy production is highly dependent upon glucose utilization [9]. An RQ of less than 0.80 is most likely associated with some risk to these vital target tissues [1,10,11]. More important may be the capacity to respond to therapy with an increase to greater than 0.80 [1,10,11]. Patients with type 2 diabetes mellitus treated with sulfonylurea [12] and normal adults have been documented at 0.90 [10,11]. A significant increase in carbohydrate/fat oxidation was routinely noted in each infusion patient throughout the duration of the study. The pulsed infusions in this study increased RQ significantly. Uncontrolled diabetes has been demonstrated to increase energy demands generated from the oxidation of glucose in the renal medulla [9]. Increased efficiency of fuel utilization may result in preservation of function.

Diminished production of advanced glycated end products would be associated with decreased direct deposition in the glomerular mesangium and decreased adherence to the glomerular epithelial podocyte by means of a specific receptor [13]. Mesangial deposition resulting in scarring would account for decreased filtration of nitrogen waste products. Podocyte adherence via the receptor for advanced glycated end product would result in albuminuria [14].

4.2. Renal function

It is possible that partial correction of total body RQ may have been reflected in that part of the kidney most sensitive to increased demand for energy production from glucose oxidation associated with type 1 diabetes mellitus.

In the multicenter study that included a larger group of patients [8], creatinine clearance in the control group decreased by 7.69 mL/(min y) compared with 2.21 mL/(min y) in the infusion group. The duration of that study was only 18 months. If continuation of therapy beyond 12 months were to demonstrate durable and linear effects, the projected time to reach a creatinine clearance of 10 mL/min with a probable need for renal replacement therapy would be 6 years for the control group and 22 years for those on insulin infusion therapy. For the 18 patients in our substudy, rate of loss of creatinine clearance was 9.6 mL/(min y) for the control group and 3 mL/(min y) for the infusion group, which would predict a need for renal replacement therapy in 5 years for the control group and 16 years for the infusion group.

A rise in serum creatinine with a fall in creatinine clearance has been described in patients with type 1 diabetes mellitus followed for 3 years after islet cell transplantation due to the effects of the immunosuppressive drugs [15]. The mean creatinine clearance at baseline was about 92 mL/min, with a fall of about 7 mL/(min y) over 3 years in patients without significant proteinuria. The study population with significant albuminuria and a mean creatinine clearance of 56 mL/min could not safely be offered islet cell transplantation instead of pulsed insulin because of the likelihood of accelerated renal deterioration.

4.3. Cardiac and autonomic function

Improvements in glycemic control have been demonstrated to be associated with improvement of autonomic reflex responses [16,17], cardiac function [18,19], and outcome [20]. In this study, we postulated that weekly pulsatile insulin infusion would also be associated with autonomic functional, cardiac structural, and functional changes. The absence of any significant differences in blood pressure, autonomic, cardiac structural, or functional measurements when the control group was compared with the infusion group led us to conclude that the preservation of renal function was independent of autonomic and hemodynamic causes.

4.4. Hemostatic function

We have previously shown a significant fall in elevated levels of fibrinogen and factor VII in patients with type 1 diabetes mellitus whose glycohemoglobin and advanced glycated product levels simultaneously improved [21,22]. In these same patients, there was evidence of both accelerated platelet adhesion and accelerated fibrinolysis at baseline. There were no significant decreases in platelet aggregation over

12 months, but fibrinolytic activity fell toward the reference range, whereas levels of plasminogen activator inhibitor rose toward the reference range. None of these findings reached statistically significant differences between the study groups in the present report, suggesting that preservation of renal function was independent of hemostatic cause.

5. Limitations

This is a small single-center study of limited duration. If the reduction in the slope of creatinine clearance loss is also associated with a decrease in major adverse cardiac events and an increase in the duration of time to renal replacement therapy, then the benefits that we attribute to weekly insulin infusion therapy may be understated. Instability of renal function is a predictor of major adverse cardiovascular events in patients with diabetes and heart disease. Because renal dysfunction is associated with truncated survival, the excess cost of major adverse cardiovascular events must be incorporated into future studies. A larger study in type 1 or 2 diabetes mellitus patients with any level of renal dysfunction should be undertaken to determine whether metabolic manipulation is associated with a lessening of major adverse cardiovascular events.

6. Conclusions

Our hypothesis that preservation of renal function in type 1 diabetes mellitus patients with proteinuria by weekly pulsed insulin infusion involves mechanisms from the autonomic nervous system, cardiac size, and function, or elements of hemostasis was not confirmed. It seems therefore that the improvements of cardiac structure and function and the changes in hemostatic balance seen with improvement in glycemic control are independent of the method of insulin administration.

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