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Intravenous calcitriol normalizes insulin sensitivity in uremic patients

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Intravenous calcitriol normalizes insulin sensitivity in uremic patients. Recent studies suggest that secondary hyperparathyroidism and/or vitamin D deficiency are responsible for the insulin resistance in chronic renal failure. We investigated the effect of a 12-week intravenous treatment with 1,25 dihydroxycholecalciferol on glucose metabolism in 10 hemodialysis patients compared with 10 healthy control subjects by the frequently-sampled intravenous glucose tolerance test, analyzed with the minimal model technique. Compared to control subjects, the uremic patients featured elevated levels of parathyroid hormone (432 ± 60 vs. 41 ± 4 ng/liter, $P < 0.001$), insulin resistance (insulin sensitivity index, S_I: 4.9 ± 0.8 vs. 9.5 ± 0.9 $min^{-1}/(\mu U/ml)$, $P < 0.002$), increased posthepatic insulin delivery (6.48 ± 2.48 vs. 2.73 ± 3.14 nmol/liter in 4 hr, $P < 0.001$) and a reduced C-peptide fractional clearance (0.033 ± 0.004 vs. 0.085 ± 0.009 min^{-1}, $P < 0.0002$). Following treatment with 1,25 dihydroxycholecalciferol, the parathyroid hormone levels decreased significantly to 237 ± 30 ng/liter ($P < 0.05$), the insulin sensitivity index (S_I: 9.6 ± 2.2, $P < 0.05$) reached a value similar to that of control subjects, and posthepatic insulin delivery decreased to 4.63 ± 0.83 nmol/liter in 4 hr ($P < 0.01$), while all the other parameters remained unchanged. In summary, uremic patients with secondary hyperparathyroidism were found to be severely insulin resistant and hyperinsulinemic. Intravenous vitamin D treatment led to a significant reduction of parathyroid hormone levels and to a complete normalization of insulin sensitivity in the hemodialysis patients. Thus, intravenous 1,25 dihydroxycholecalciferol improves insulin resistance in uremic patients, acting *per se* or by reducing secondary hyperparathyroidism.

Impaired insulin secretion and insulin resistance are characteristic features of patients with chronic renal failure [1–4]. The pathogenesis of glucose intolerance in uremia, however, is still unknown. In animal models [5, 6] as well as in studies in humans [7, 8], it has been shown that secondary hyperparathyroidism due to chronic renal failure can inhibit insulin release from the pancreatic beta cells. Correction of hyperparathyroidism by parathyroidectomy is associated with improvement of insulin secretion, but does not affect insulin resistance [7, 8]. Nevertheless, parathyroidectomy can lead to normal glucose tolerance, if increased insulin secretion overcomes the reduced tissue insulin sensitivity in the uremic patients. Recent evidence suggests that vitamin D deficiency might play a major role in the pathogenesis of impaired glucose metabolism in uremia [7]. However, it is still controversial, if repletion of vitamin D deficiency by itself can really improve insulin release [6, 7]. Mak [9] reported that acute intravenous 1,25 dihydroxycholecalciferol (1,25DCC) administration to vitamin-D-withdrawn hemodialysis patients increased insulin secretion and corrected glucose tolerance independent of the unchanged levels of intact parathyroid hormone, calcium or phosphorus. In a different study using the hyperglycemic clamp technique the author also reports a significant increase in insulin sensitivity after one single dose of intravenous vitamin D [10]. However, until now, it is not known if intravenous administration of 1,25DCC for a longer period of time can effectively influence insulin sensitivity and/or insulin secretion. In contrast to oral administration of 1,25 DCC, intravenous treament effectively reduces parathyroid hormone levels in hemodialysis patients by achieving significantly higher 1,25 DCC plasma levels [11–13]. The aim of this study was to obtain a wide metabolic portrait (insulin sensitivity, glucose effectiveness, beta cell insulin release and hepatic extraction of insulin) of hemodialysis patients before and after 12 weeks of intravenous administration of 1,25 dihydroxycholecalciferol, assessed by the frequently sampled intravenous glucose tolerance test analysed with the minimal model technique.

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Methods

Subjects

We investigated 10 hemodialysis patients in comparison to 10 sex, age and body weight matched control subjects. The clinical characteristics of all subjects are shown in Table 1. The patients were on regular hemodialysis three times per week for on average 45 months (range, 12 to 144 months). The standard dialysate was containing 1.5 mmol/liter calcium. Dietary calcium intake and the supplementation with phosphate binders (mostly aluminum containing) remained unchanged throughout the study. All patients showed severe secondary hyperparathyroidism with about 10-fold elevated serum levels of parathyroid hormone for at least 12 months (458.7 ± 65 ng/liter, six months before study). Five patients were receiving oral 1,25 dihydroxycholecalciferol before the investigation. These patients discontinued oral vitamin D supplementation four weeks before study. The patients were re-investigated after 12 weeks of intravenous administration of 1,25 dihydroxycholecalciferol. Therapy was started with a dose of 1 μg 1,25DCC after each hemodialysis (Cacijex Abbot, Chicago, Illinois, USA). The subsequent doses were adjusted to the plasma

Table 1. Clinical characteristics of the 10 hemodialysis patients (HD, 5 males and 5 females, age: 40.1 ± 0.4) before and after vitamin D repletion and of 10 healthy control subjects (CS, 6 males and 4 females, age: 38.0 ± 0.3)

	HD before vitamin D	HD after vitamin D	CS	P^a
BMI *kg/m²*	22.6 ± 0.8	22.8 ± 0.8	23.0 ± 0.9	NS
PTH intact *ng/liter*	432 ± 60	237 ± 30[b]	41 ± 4	<0.001
Magnesium *mg/dl*	2.1 ± 0.2	1.9 ± 0.1	1.6 ± 0.1	NS
Potassium *mmol/liter*	5.8 ± 0.4	6.0 ± 0.5	4.2 ± 0.1	<0.01
Calcium *mmol/liter*	2.18 ± 0.03	2.25 ± 0.03	2.35 ± 0.04	<0.01
Phosphorus *mmol/liter*	1.80 ± 0.19	1.94 ± 0.18	1.06 ± 0.04	<0.01
Creatinine *mg/dl*	11.5 ± 1.1	10.7 ± 0.6	0.90 ± 0.01	<0.0001
Urea nitrogen *mg/dl*	71.2 ± 5.0	66.7 ± 4.1	15.4 ± 1.8	<0.0001
Basal glucose *mmol/liter*	4.3 ± 0.15	4.4 ± 0.11	4.6 ± 0.11	NS
Basal insulin *pmol/liter*	90 ± 12	71.4 ± 7.2[b]	36 ± 6	<0.0005
Triglycerides *mg/dl*	197 ± 23	166.8 ± 12.8	163 ± 10.5	NS
Cholesterol *mg/dl*	193.6 ± 10.4	185.5 ± 11.4	188.4 ± 14.3	NS

BMI is body mass index, and PTH is parathyroid hormone.
[a] Testing the difference between CS and HD before vitamin D
[b] $P < 0.05$, comparing HD before vs. after vitamin D treatment

calcium levels. On the average the dose was 0.96 ± 0.08 μg after hemodialysis (median, 1 μg; Q1, 0.85 μg; Q3, 1 μg). Serum 1,25 dihydroxycholecalciferol was measured before starting intravenous calcitriol and at the end of the study (44 hours after the last dose). None of the subjects investigated had any family history of diabetes; no patient was diabetic. All subjects were maintaining their regular diet, none was taking any drug known to affect carbohydrate metabolism and liver function. The Ethical Committee of the Medical Department of the University of Vienna approved the protocol and informed consent was obtained from each subject prior to investigations.

Tests

The subjects underwent a frequently sampled intravenous glucose tolerance test (FSIGT), which started at 8:00 a.m., after an overnight fast. A catheter was inserted into an antecubital vein and basal blood samples were drawn at −20, −10 and −1 minutes. At time zero glucose (300 mg/kg) was injected in 30 seconds. Additional samples were obtained from a contralateral antecubital vein at time 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 25, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 140, 160, 180, 210 and 240 minutes via a three-way stopcock connected with the catheter. Blood was rapidly centrifuged and glucose immediately measured by oxidase method (Beckman Analyzer). The measurement error was ±1.5%. The remaining plasma was stored at −20°C for subsequent insulin and C-peptide determination. Insulin (Pharmacia, Uppsala, Sweden) and C-peptide (Byk Mallinckrodt), as well as serum levels of intact parathyroid hormone (Nichols Institute Diagnostics, San Juan Capistrano, California, USA) were measured by commercially available radioimmunoassays. The interassay coefficient of variation was approximately 10% for the insulin and the C-peptide assay.

FSIGT data analysis

FSIGT data were submitted to the computer programs which calculate the characteristic metabolic parameters by fitting glucose, insulin and C-peptide data to the minimal models which describe the time courses of glucose, insulin, and C-peptide concentration. The models, originally developed in dogs [14, 15] have found a wide application in human studies [reviewed in 16, 17]. The minimal models have previously been described in detail [18, 19] and here we briefly present what is useful to the understanding of their application in this study. The glucose disappearance model [14, 18, 20–22] accounts for the effect of insulin and glucose on glucose disappearance following the exogenous glucose injection. It provides parameter S_I ($min^{-1}/(\mu U/ml)$), the insulin sensitivity index, defined as the ability of insulin to enhance glucose disappearance and to inhibit hepatic glucose production; and parameter S_G (min^{-1}), the glucose effectiveness, defined as the ability of glucose *per se* to enhance its own disappearance and to inhibit glucose production independent of any dynamic change of insulin. The two-compartment C-peptide minimal model [19, 23] accounts for the effect of glucose on the changes of C-peptide concentration during an FSIGT by quantifying the ability of the beta-cells to secrete the peptide in response to the glycemic stimulus and C-peptide kinetics after its entry into the peripheral circulation. The model provides parameter k_{01} (min^{-1}), which is the C-peptide fractional clearance rate, that is, the peptide disappearance in unit time per unit volume, the C-peptide secretion per unit volume CPS(t), the sensitivity to the glucose stimulation of the first (Φ_1, min^{-1} pM/(mg/dl)) and second (Φ_2, min^{-2} pM/(mg/dl)) phase of the dynamic (prehepatic, suprabasal) insulin release. Basal insulin and C-peptide secretion rate, per unit volume, BSR (pM/min), may be computed by multiplying the clearance rate k_{01} by the basal C-peptide concentration. The minimal model of insulin FSIGT data [15], by analyzing peripheral hormone concentration provides quantitative figures of posthepatic insulin delivery per unit volume, that is, IDR(t), the time course of insulin appearance into the systemic circulation, (BDR) (pM/min), the basal delivery rate, and the total amount of hormone reaching the peripheral circulation.

Calculations

The estimation of the parameters of the models was carried out using a non-linear least squares estimation technique by the computer program MINMOD [20], which was modified to account also for C-peptide data [23]. A constant variance structure was assumed for the measurement error. Accuracy and precision of the estimates were evaluated according to the validation

criteria of model identification [24]. Because insulin and C-peptide are secreted in equimolar fashion, CPS(t) also represents the beta-cell insulin release. The total amount of prehepatically secreted (TIS, 10^3 pM in 4 hr) and posthepatically delivered insulin (TID, 10^3 pM in 4 hr) were computed by the integral, between zero and 240 minutes, of CPS(t) and IDR(t), respectively. Hepatic insulin extraction, HE(t), as a percent of the secreted hormone, may be computed as the difference between CPS(t) and IDR(t), normalized to CPS(t) [19]. The total areas under the insulin and C-peptide concentration curves were calculated by using the trapezoidal integration. Initial glucose distribution volume VD (liter) was computed as the ratio between the administered glucose dose and the extrapolated concentration at time zero.

Statistical analysis

Differences in mean values between the haemodialysis patients with vitamin D deficiency and the control subjects were tested for significance by means of the analysis of variance. The significance of the differences between the patients before and after vitamin D repletion were calculated by paired Student's *t*-test. All data and results are given as means ± SE unless otherwise designated. Converting factors are: glucose 1 mg/dl = 0.056 mmol/liter; insulin 1 μU/ml = 6 pmol/liter; C-peptide 1 ng/ml = 0.331 nmol/liter.

Results

FSIGT

The time course of the average glucose, insulin and C-peptide concentrations are shown in Figure 1. Basal glucose and insulin levels are reported in Table 1. Despite similar basal and stimulated glucose levels in the hemodialysis patients (HD) and in the control subjects (CS), HD featured more than doubled basal and stimulated (peak: 888 ± 102 vs. 390 ± 30 pmol/liter, $P < 0.0006$) insulin concentrations. The basal (3.84 ± 0.50 vs. 0.51 ± 0.06 nmol/liter, $P < 0.0005$; HD vs. CS) as well as the supra-basal C-peptide concentrations (peak 6.59 ± 0.69 vs. 2.63 ± 0.19 nmol/liter, $P < 0.0005$) were also markedly elevated in the uremic patients compared to the control subjects. The total area under the curve of insulin resulted 35.4 ± 3.6 nmol/liter in 240 minutes in the hemodialysis patients compared to 12 ± 0.6 ($P < 0.01$) in the control subjects and that of C-peptide was also markedly elevated in the uremic patients compared to the control subjects (1.32 ± 0.13 vs. 0.215 ± 0.049 μmol/liter in 240 min; $P < 0.0001$; HD vs. CS). In addition, the C-peptide value of the last sample at 240 minutes (4.72 ± 0.49 nmol/liter) remained elevated in the patients and different from the pre-injection level ($P < 0.005$).

Model parameters

The metabolic parameters obtained by the model analysis are shown in Table 2. The tissue insulin sensitivity index, S_I, was markedly decreased in HD, while the glucose effectiveness, S_G, was not different in both groups. Initial glucose distribution space was slightly, although insignificantly, elevated in the patients. The C-peptide fractional clearance rate (k_{01}) was decreased in HD, as expected in patients with overt renal failure. The basal prehepatic insulin secretion rate (BSR) and total insulin secretion (TIS = 46.3 ± 7.5 vs. 22.5 ± 3.4 nmol/liter in 240 min, $P < 0.01$, HD vs. C, respectively) were significantly elevated in HD. Sensitivities of the first and second phase responsiveness, the parameters Φ_1 and

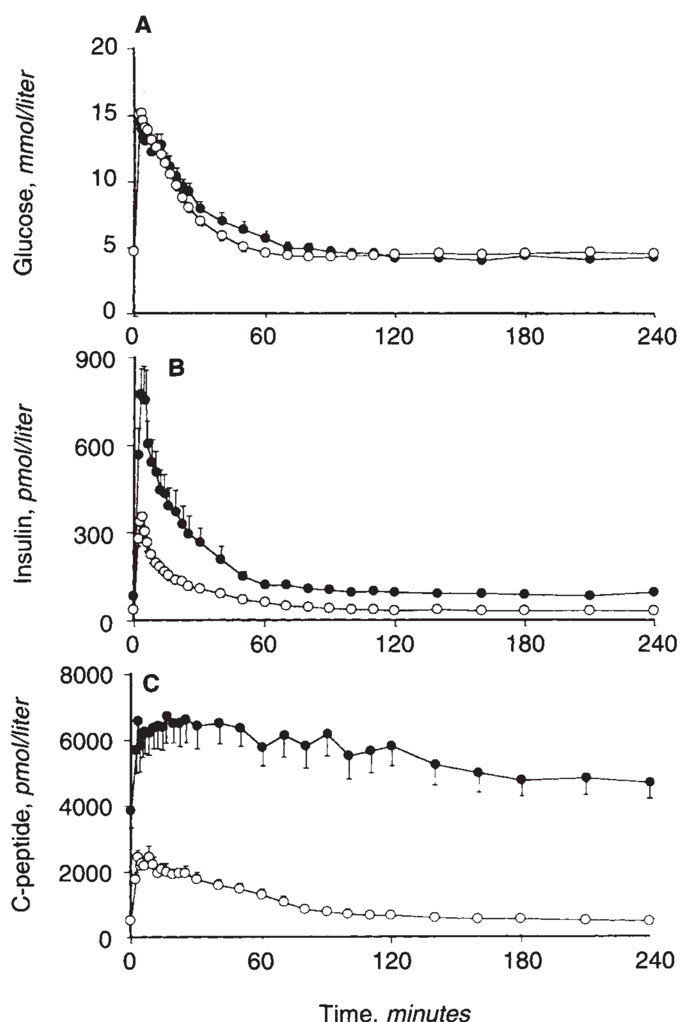

Fig. 1. *Average FSIGT time course of glucose, insulin and C-peptide concentrations in control subjects (open circles) and in patients before vitamin D treatment (closed circles).* Glucose (0.33 g/kg) was injected at time zero.

Φ_2, were 465.8 ± 61.7 min^{-1} pM/(mg/dl)) and 0.091 ± 0.02 min^{-2} pM/(mg/dl) in HD compared to 137.9 ± 21.8 and 0.083 ± 0.017 in the control subjects (Φ_1, $P < 0.0005$, HD vs. C). Basal (BDR) as well as total (TID) posthepatic insulin delivery were also found to be significantly higher in the hemodialysis patients than in control subjects. Mean hepatic insulin extraction was not significantly different between both groups (86 ± 2.5 vs. 84 ± 3%, HD vs. C).

Effect of the repletion of vitamin D in hemodialysis patients

Twelve weeks after intravenous administration of 1,25 dihydroxycholecalciferol the plasma levels of parathyroid hormone decreased significantly (Table 1), whereas calcium and phosphorus levels remained unchanged. Serum 1,25 dihydroxycholecalciferol levels increased from 17.1 ± 7.1 to 39.5 ± 7.3 pg/ml ($P < 0.01$). The lipid metabolism was not altered by intravenous vitamin D treatment (Table 1).

The insulin sensitivity parameter increased significantly and reached the level similar to that of the healthy control subjects (Table 2), whereas glucose effectiveness was not affected by

Table 2. Model estimated and calculated parameters from the FSIGT for 10 controls (CS) and 10 patients on hemodialysis (HD) before and after vitamin D repletion

	CS	HD before vitamin D	HD after vitamin D	P^a
Glucose				
S_I	9.34 ± 0.97	4.95 ± 0.76	9.95 ± 2.10[b]	< 0.002
S_G	0.031 ± 0.005	0.025 ± 0.006	0.021 ± 0.004	NS
V_D	16.8 ± 0.8	18.5 ± 1.0	18.3 ± 1.1	NS
Insulin delivery				
BDR	6.3 ± 1.0	14.1 ± 2.5	12.0 ± 1.9	< 0.001
TID	2.7 ± 3.1	6.7 ± 1.08	4.6 ± 0.8[b]	< 0.001
C-peptide kinetics				
k_{01}	0.085 ± 0.009	0.033 ± 0.004	0.031 ± 0.002	< 0.0002
BSR	42 ± 8	145 ± 36	137 ± 18	< 0.006

Parameter meanings and units are: S_I (insulin sensitivity) 10^{-4} min^{-1}/(μU/ml); S_G (glucose effectiveness) min^{-1}; V_D (volume of distribution of glucose) percent of body weight; BDR (basal posthepatic insulin delivery rate) pM/min; TID (total posthepatic insulin delivery) nM in 4 hrs; k_{01} (C-peptide fractional clearance rate) min^{-1}; BSR (basal insulin secretion rate) pM/min.

[a] Testing the difference between the hemodialysis patients (HD) before vitamin D repletion and the control subjects (CS)

[b] $P < 0.02$ testing the difference between the hemodialysis patients before and after vitamin D repletion

vitamin D treatment. FSIGT patterns before and after 1,25 dihydroxycholecalciferol administration are shown in Figure 2. The basal and stimulated glucose concentrations did not really change after treatment. C-peptide concentrations were also not statistically different from those before treatment (area under the curve: 1.63 ± 0.14 μmol/liter in 240 min). However, the basal (71.4 ± 7.2 pmol/liter, $P < 0.01$) and stimulated (peak 636 ± 144 pmol/liter, $P < 0.005$) insulin levels showed a significant decrease after vitamin D administration. The total area under the curve for insulin was also lower (27.6 ± 3 nmol/liter in 240 min, $P < 0.02$), reflecting a lower post-hepatic insulin delivery (TID). The time course of the hepatic insulin extraction during the FSIGT before and after treatment is shown in Figure 3. Dynamic suprabasal hepatic insulin extraction increased significantly (86.4 ± 0.4 vs. 90.8 ± 0.5%; $P < 0.001$, before vs. after vitamin D treatment, respectively), while all the other model calculated parameters did not change significantly after vitamin D treatment.

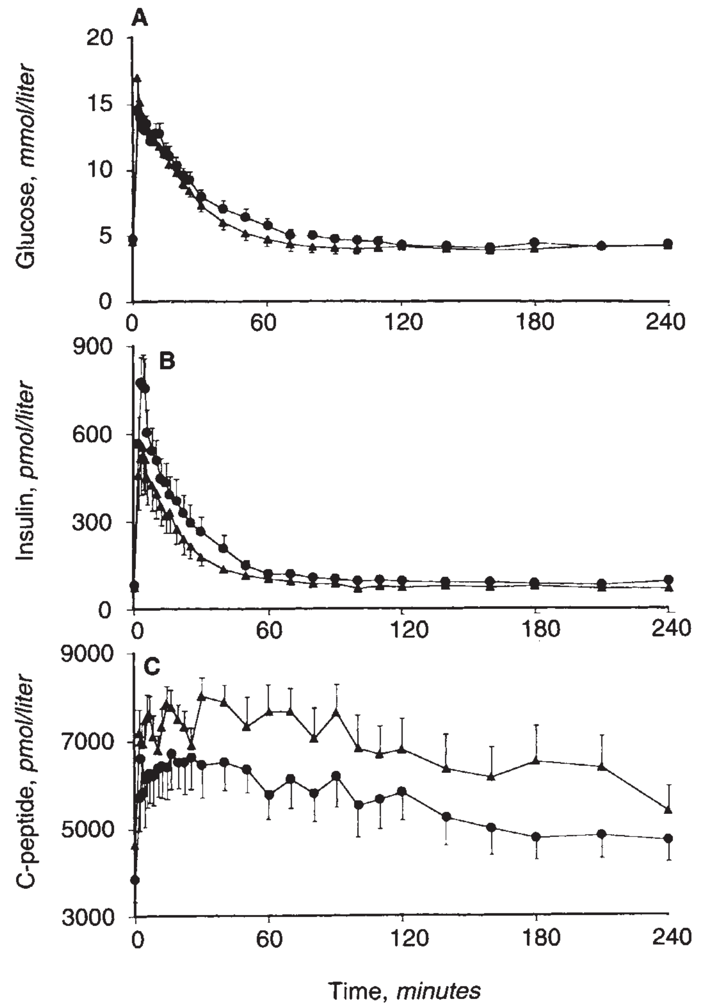

Fig. 2. *Average FSIGT time course of glucose, insulin and C-peptide concentrations in patients before (closed circles) and after (closed triangles) vitamin D treatment.* Glucose (0.33 g/kg) was injected at time zero. Note the different C-peptide scale, compared to Fig. 1.

Discussion

It is well established that uremic patients feature abnormalities in insulin secretion, insulin metabolism and tissue insulin sensitivity [1–4]. Apart from changes in the electrolytes, the secondary hyperparathyroidism and/or vitamin D deficiency are supposed to play a major role in the pathogenesis of uremic glucose intolerance and insulin resistance [5–12]. However, the underlying mechanisms are not yet fully understood and the role of elevated parathyroid hormone levels on insulin secretion is controversial. Several studies reported that patients with primary hyperparathyroidism are insulin resistant and hyperinsulinemic [5, 25–27]. However, two studies in dogs could not confirm a direct effect of parathyroid hormone *per se* on hyperinsulinemia and insulin resistance [5, 25]. Akmal et al [5], using an uremic parathyroidectomized dog model, reported that elevated PTH levels caused glucose intolerance due to a reduction in insulin secretion. Fadda et al [6] studied the effects of chronic renal failure and secondary hyperparathyroidism on insulin release and reported that acute exposure of the beta cells to parathyroid hormone stimulates glucose-induced insulin secretion modulated by an increase in cytosolic calcium, whereas chronic exposure to high parathyroid hormone concentrations led to inhibition of insulin release from the pancreas [28]. Mak et al [7] studied uremic patients on hemodialysis with uncontrollable hyperparathyroidism, characterized by glucose intolerance and insulin resistance, before and after surgery, and reported that an increase in insulin secretion could normalize glucose tolerance despite unchanged insulin-resistance. In a subsequent study in pre-dialysis uremic children, Mak et al [29] demonstrated that medical correction of hyperparathyroidism by high dose phosphate binders and vitamin D supplementation can lead to a significant improvement in glucose metabolism. Thus, it was suggested that either the high parathyroid hormone levels or low concentrations of plasma 1,25DCC might inhibit insulin secretion and cause glucose intolerance in insulin-resistant uremic patients [30]. These conflicting results concerning the role of secondary hyperparathyroidism and/or vitamin D deficiency in uremia stimulated the present study. In particular, no data about the long term effects of intravenous vitamin D treatment on

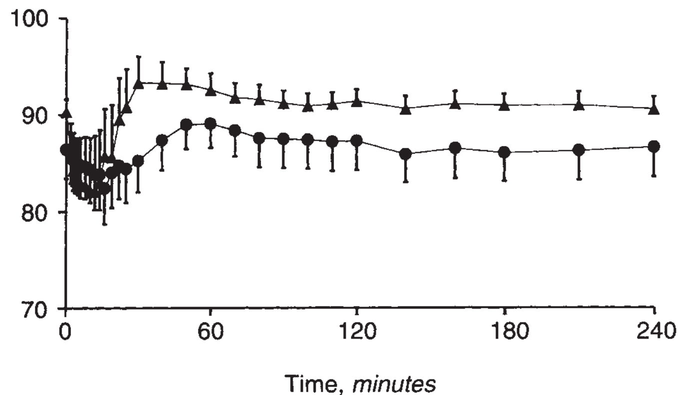

Fig. 3. *Time course of the hepatic insulin extraction expressed in percent of the hormone released by the beta-cell after vitamin D treatment (closed triangles), compared with that of pre-treatment (closed circles).*

glucose metabolism are available. We therefore evaluated glucose and insulin metabolism before and after 12 weeks of intravenous 1,25DCC supplementation in uremic patients with secondary hyperparathyroidism.

Our results confirmed severe insulin resistance in hemodialysis patients, the insulin sensitivity index being 47% lower in the uremic patients compared with controls. In fact several studies have demonstrated tissue insensitivity to insulin to be the dominant carbohydrate defect in uremia [1, 2, 4]. The glucose effectiveness [22] did not differ between the patients and controls, thus the glucose disappearance, induced by glucose *per se*, was apparently not affected by the uremia.

We infer on beta cell activity and hyperinsulinemia before and after 1,25 dihydroxycholecalciferol treatment, both analyzing the areas under the curves (qualitative analysis, but model independent), and with modeling analysis (quantitative, but under the assumption that some hypotheses hold). The former shows an unequivocally marked elevated and sustained insulin and C-peptide concentration both at basal (pre-injection and at the end of the test) and in dynamic conditions. Of course, the causes of this may be either increased secretion or decreased clearance or both. The modeling analysis demonstrated a reduced C-peptide clearance, as expected for a compound mostly degraded in the kidneys. In addition, the C-peptide model indicates that insulin secretion is significantly increased in uremics compared to normal subjects. A reason for the augmented insulin secretion may be a compensatory mechanism to overcome peripheral insulin resistance [31]. Since tissue insensitivity to insulin is uniformly present among uremic patients, normal glucose tolerance will be maintained only if the beta cells can augment their insulin secretion sufficiently to compensate for the insulin resistance. With this respect, an increase of B-cell sensitivity to glucose (mostly first phase) was detected. In fact, our patients showed similar basal and stimulated glucose concentrations as the healthy control subjects indicating normal glucose tolerance.

The peripheral insulin concentration was also found to be markedly higher in the patients than in control subjects. Also the corresponding model derived parameters, the basal as well as total posthepatic insulin delivery, were more than doubled in the patients compared to controls. This finding was reflected in the observation that hepatic insulin extraction did not differ between patients and control subjects. Thus, hepatic extraction of insulin does not seem to be affected by uremia. In fact, insulin is almost totally degraded by the liver and since our patients had no signs of impaired liver function, they should be expected to normally extract insulin, as also confirmed by the modeling analysis. Mondon, Dolkas and Reaven [32], measuring the extraction of porcine insulin during recycling perfusion of isolated liver from nephrectomized rats, have also shown that insulin removal by the liver was not affected by uremia, and that hepatic insulin extraction did not differ between normal and uremic rat liver.

After 12 weeks of intravenous treatment with 1,25DCC the insulin sensitivity index, S_I, rose to the value of the healthy controls. The suprabasal, dynamic insulin concentration as well as the concentration of parathyroid hormone markedly decreased after intravenous vitamin D supplementation. As there were no real changes in the electrolytes (calcium, phosphorus, potassium or magnesium) in the patients before and after the intravenous 1,25DCC, they cannot be involved in the change of insulin metabolism after vitamin D treatment. Abnormalities in lipid metabolism are commonly found in patients with chronic renal failure [33, 34] and hypertriglyceridemia can cause insulin insensitivity. It has recently been reported [35] that oral calcitriol therapy has been associated with a positive effect on triglyceride levels in hemodialysis patients. However, the triglyceride and cholesterol levels in the patients were not significantly elevated compared to the control subjects and also did not change significantly after 12 weeks of intravenous calcitriol treatment. Lind et al [36] also found no alterations in lipid metabolism following calcitriol treatment in uremic patients. Impaired lipid metabolism does not seem to play an important role in the insulin resistance syndrome of chronic uremia [37], and alterations in lipid metabolism are not involved in the improvement of insulin sensitivity after intravenous vitamin D therapy. Thus, intravenous calcitriol treatment by itself or by a decrease in parathyroid hormone levels leads to a normalization in glucose and insulin metabolism. Several studies have shown that intravenous vitamin D supplementation leads to about fourfold higher plasma peak responses compared to the oral preparation. Intravenous treatment yields a more efficient suppression of parathormone secretion and allows a greater delivery to peripheral tissues, which might increase important biological effects of the vitamin [11–13]. Various animal studies showed that the endocrine pancreas is a target for 1,25DCC, the active metabolite of vitamin D [38, 39] and that this metabolite seems to play a major role in the modulation of insulin secretion [40, 41]. In a vitamin D depleted rat model it has been shown that dietary vitamin D repletion significantly increased insulin secretion [40] and vitamin D deficiency was associated with an inhibition of pancreatic insulin release [41]. Mak [9] reported that hemodialysis patients regained close-to-normal glucose tolerance by becoming hyperinsulinemic after a single intravenous dose of 1,25DCC at 2 $\mu g/m^2$ given two hours before the conventional intravenous glucose tolerance test or the clamp study. Since the patients studied featured normal glucose tolerance and compensatory insulin hypersecretion, a vitamin D induced increase in insulin secretion would be of little therapeutic benefit. Indeed, we observed no significant change in insulin secretion and a decrease in posthepatic insulin delivery after 12 weeks of intravenous vitamin D treatment. We therefore have to assume a direct effect of intravenous vitamin D administration on insulin sensitivity. In this context a recent study of Mak [10] is of considerable interest

investigating the effect of a single dose of intravenous vitamin D on insulin sensitivity by means of the euglycemic clamp technique in children with chronic renal insufficiency. He clearly showed an increase in insulin sensitivity induced by vitamin D combined with an increase in insulin secretion. Since serum concentrations of intact parathyroid hormone, calcium, magnesium, potassium, urea nitrogen and creatinine were not significantly changed in this study, the authors concluded that vitamin deficiency independent of parathyroid hormone and calcium levels contributes to the disturbances in glucose metabolism and insulin secretion.

In accordance to the acute effect of one single dose of intravenous vitamin D, chronic treatment over 12 weeks with intravenous 1,25DCC led to a significant increase in insulin sensitivity in uremic patients. However, in contrast to the acute effect of vitamin D we did not find a modulating effect of vitamin D on insulin secretion. This might be due to the fact that the patients studied had no defect in insulin secretion and showed compensatory beta cell hypersecretion in response to insulin resistance. In addition, after chronic intravenous 1,25DCC treatment we observed a significant amelioration of secondary hyperparathyroidism, which might also contribute to the improvement in insulin sensitivity. However, since an improvement of insulin sensitivity was already observed after one single dose of intravenous vitamin D [10], a direct effect of 1,25DCC on insulin sensitivity is more likely. The mechanism by which vitamin D affects insulin sensitivity remains unclear. In this context, a recent *in vitro* study showing that vitamin D increases insulin receptor mRNA levels is of considerable interest [42]. Finally, our analysis showed an increase in hepatic insulin extraction after vitamin D treatment. We do not have an explanation of this, but we can hypothesize that a sort of compensatory mechanism occurs which tries to avoid excessive hyperinsulinemia in a situation of relatively normal insulin sensitivity. However, further studies, ad hoc performed, are necessary to clarify the effect of calcitriol on the liver action on insulin degradation.

In summary, the patients with renal insufficiency featured insulin resistance, which was normalized after vitamin D repletion, and secondary hyperparathyroidism, which was significantly reduced after treatment. We cannot differentiate if the secondary hyperparathyroidism or vitamin D deficiency were responsible for the low insulin sensitivity. Nevertheless, we can conclude that intravenous 1,25DCC treatment by itself or by reduction of secondary hyperparathyroidism could be useful to improve or even reverse insulin resistance commonly found in uremic patients.

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