Diabetologia (1992) 35: 121–128

Diabetologia

The influence of human C-peptide on renal function and glucose utilization in Type 1 (insulin-dependent) diabetic patients

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Summary. The possible influence of C-peptide administration on renal function and whole body glucose utilization was examined in 11 patients (Group 1) with Type 1 (insulin-dependent) diabetes mellitus. They were given an i. v. insulin infusion during the night before the study and were euglycaemic at the time of examination. The glomerular filtration rate and effective renal plasma flow were measured by clearance techniques using constant-rate infusions of inulin and sodium para-aminohippurate. After baseline measurements C-peptide was infused during two periods of 60 min at rates of 5 and 30 pmol · kg^{-1} · min^{-1}. In a control study 0.9% NaCl was infused during two 60 min periods in ten Type 1 diabetic patients (Group 2). Glomerular filtration rate decreased by 7% ($p < 0.001$), effective renal plasma flow increased by 3%, ($p < 0.05$) and whole-body glucose utilization rose by approximately 25% ($p < 0.05$) above basal during low-dose C-peptide infusion. Group 2 showed an unaltered glomerular filtration rate, effective renal plasma flow and glucose utilization during 60 min of NaCl infusion. The differences between Group 1 and Group 2 in glomerular filtration rate and glucose utilization were statistically significant. It is concluded that short-term administration of C-peptide in physiological amounts to patients with Type 1 diabetes may reduce the glomerular filtration rate and increase whole-body glucose utilization. The results suggest the possibility that short-term C-peptide administration may exert a regulatory influence on renal function and stimulate glucose utilization in Type 1 diabetic patients.

Key words: Glomerular filtration rate, filtration fraction, renal blood flow, glomerular permeability.

Insulin is synthesized by the Beta cells in the pancreatic islets as a single-chain precursor, proinsulin. The A and B chains of proinsulin are joined by a connecting peptide (C-peptide). Proinsulin is stored in the Golgi region and it is cleaved by membrane-bound proteases into equimolar amounts of insulin and C-peptide [1]. These products are subsequently transported in secretory granules and released into the circulation by exocytosis [1]. C-peptide is not known to exert biological action in the mammalian organism. Specifically, no circulatory, metabolic or hormonal effects have been ascribed to this peptide [1].

In patients with Type 1 (insulin-dependent) diabetes mellitus secretion of insulin is insuffient or entirely lacking. This is reflected in a reduction or absence of C-peptide levels in the plasma and urine in Type 1 diabetic patients [2]. Since C-peptide is eliminated from the body primarily by the kidney [1], the urinary excretion of C-peptide is fequently used as an index of remaining insulin secretion in Type 1 diabetic patients [3].

An elevated glomerular filtration rate (GFR) [4–10] and glomerular hypertrophy [11, 12] are frequent findings in Type 1 diabetic patients particulary during the early phase of the disease. The rise in GFR may persist for several years – possibly until the development of proteinuria and diabetic nephropathy [7]. Insulin therapy appears to decrease the renal hyperfiltration in untreated newly diagnosed Type 1 diabetic patients but not to the normal levels of GFR seen in non-diabetic subjects [8, 9]. Since the Type 1 diabetic patients with augmented GFR are likely to have low or unmeasurable levels of C-peptide in plasma, and this peptide is mainly handled by the kidney, the possibility that C-peptide exerts a regulatory influence on GFR may be considered. This hypothesis is in line with the fact that Type 2 (non-insulin-dependent) diabetic patients, who retain endogenous insulin and C-peptide production, usually do not develop glomerular hyperfiltration [13] or glomerular hypertrophy [14].

No information is available regarding the possible direct effects of C-peptide on renal function in either Type 1 diabetic patients or healthy subjects. Consequently, the present study examined the influence of C-peptide administration on renal function in a group of Type 1 diabetic

Table 1. Clinical individual data in the two groups studied

	Subject no.	Sex	Age (years)	Duration of diabetes (years)	HbA_{1c} (%)	Insulin dosage ($IU \cdot kg^{-1} \cdot 24\,h^{-1}$)
Group 1 (C-peptide)	1	M	21	9	6.3	0.75
	2	M	30	20	6.2	0.78
	3	M	18	3	7.0	1.24
	4	M	22	10	7.5	0.66
	5	F	20	11	6.5	1.00
	6	F	28	18	7.0	0.64
	7	M	29	10	8.0	0.47
	8	M	25	7	9.0	0.94
	9	M	21	7	6.0	1.00
	10	M	28	16	6.9	0.65
	11	F	20	9	6.6	0.86
Group 2 (0.9% NaCl)	1	M	19	3	6.6	1.06
	2	M	21	7	6.3	0.94
	3	M	29	10	8.0	0.47
	4	M	21	9	6.4	0.78
	5	M	23	10	7.0	0.73
	6	M	30	5	7.7	0.91
	7	M	24	11	7.9	0.59
	8	M	25	8	8.9	0.72
	9	M	27	10	7.6	0.64
	10	M	27	21	7.2	0.80

patients with increased GFR. At the same time the possible effect of C-peptide on whole-body glucose utilization was studied.

Subjects and methods

Subjects

Two groups were examined. Group 1 consisted of 11 Type 1 diabetic patients (8 male, 3 female) between 18–30 years of age with a history of diabetes mellitus of between 3–20 years (mean, 11 years). Clinical data are given in Table 1. The mean HbA_{1c} was $7.0 \pm 0.3\%$ (normal value at our laboratory is $< 5.0\%$). Nine of the patients had no detectable plasma C-peptide levels in the fasting state (< 0.05 nmol/l) while two retained low concentrations (0.12 and 0.14 nmol/l, respectively). The mean insulin dose was 0.82 ± 0.07 $IU \cdot kg^{-1} \cdot 24\,h^{-1}$. Ten patients were treated with short-acting insulin, three to four doses during the day and one dose of medium-acting insulin at bedtime, and in one patient insulin was given by continuous subcutaneous insulin pump therapy. All patients were normotensive and none of them showed clinical evidence of retinopathy, neuropathy or nephropathy. Only one case of mild background retinopathy was found on eye-ground examination by an experienced ophthalmologist. Nephropathy was excluded on the basis of normal serum creatinine levels and no detectable proteinuria was observed.

Group 2 served as a control group and consisted of ten male Type 1 diabetic patients between 19–30 years of age and with a history of diabetes mellitus of 3–21 years (mean, 9 years). Four of them had participated in the C-peptide infusion study (Group 1) 3–12 months earlier and their insulin regimen was not changed. Their mean HbA_{1c} was $7.1 \pm 0.3\%$ and their mean insulin dose was 0.77 ± 0.06 $IU \cdot kg^{-1} \cdot 24\,h^{-1}$. All were normotensive and they had no detectable C-peptide levels in plasma or urine and did not show clinical evidence of retinopathy, neuropathy or nephropathy. Clinical data are given in Table 1.

All patients were informed of the nature, purpose and possible risks involved in the study prior to giving their consent to participate. The study protocol was reviewed and approved by the Ethics Committee of Karolinska Institute.

Procedure

All subjects came to the laboratory the morning after an overnight fast. During the night they had been given an i.v. infusion of insulin, regulated so that their blood glucose concentrations were close to euglycaemic levels prior to the study.

The investigations were made with the patients in the supine position. Three catheters were inserted percutaneously during local anaesthesia. One was placed in the femoral vein and advanced under fluoroscopic control to a renal vein and the other two were inserted into a brachial artery and an antecubital vein. Effective renal plasma flow (ERPF) and GFR were then measured in the basal state and during infusion of C-peptide at two different dose levels or during infusion of 0.9% NaCl. Water was given orally to ensure an adequate diuresis during the study; approximately 20 ml/kg was ingested during the first hour and approximately $10\ ml \cdot kg^{-1} \cdot h^{-1}$ during the next 5 h. Insulin was given via i.v. infusion ($0.5\ mU \cdot kg^{-1} \cdot min^{-1}$) throughout the investigation and glucose was given i.v. at rates adjusted to maintain blood glucose levels at 5.6 mmol/l ± 10%, as indicated by plasma glucose levels measured at 5 min intervals. Inulin and sodium para-aminohippurate (PAH) infusions were given for 90 min for baseline measurements before the infusion of C-peptide (Group 1) or NaCl (Group 2) was begun. Recombinant human C-peptide, generously supplied by Eli Lilly Co. (Indianapolis, Ind., USA) was used. In Group 1, C-peptide was given i.v. for 1 h (low dose, bolus of $25\ pmol \cdot kg^{-1} \cdot min^{-1}$ for 1.5 min followed by

Table 2. Insulin, glucose and C-peptide levels in arterial blood and glucose utilization within each period (basal, low- and high-dose C-peptide and two 60 min 0.9% NaCl infusion periods) in the groups studied. Mean ± SEM is given

		Insulin (μU/ml)	Glucose (mmol/l)	C-peptide (nmol/l)	Glucose utilization ($mg \cdot min^{-1} \cdot kg^{-1}$)
Group 1	Basal ($n = 11$)	21 ± 1	5.8 ± 0.2	< 0.05	1.86 ± 0.24
	Low-dose C-peptide ($n = 11$)	22 ± 1	5.6 ± 0.1	0.77 ± 0.11	2.38 ± 0.42[a,b]
	High-dose C-peptide ($n = 7$)	21 ± 2	5.5 ± 0.1	2.08 ± 0.32	2.28 ± 0.35[c]
Group 2	Basal ($n = 10$)	21 ± 2	5.5 ± 0.1	< 0.05	1.95 ± 0.22
	60 min 0.9% NaCl ($n = 10$)	22 ± 2	5.6 ± 0.1	< 0.05	2.02 ± 0.21
	120 min 0.9% NaCl ($n = 10$)	22 ± 1	5.3 ± 0.1	< 0.05	2.30 ± 0.23[d]

[a] Indicates significant difference ($p < 0.05$) between basal state and low-dose C-peptide infusion.
[b] Indicates significant difference ($p < 0.01$) between the groups concerning the percental change from basal state to low-dose C-peptide infusion and from basal to 60 min 0.9% NaCl infusion.
[c] Indicates significant difference ($p < 0.02$) between basal state and high-dose C-peptide infusion.
[d] Indicates significant difference ($p < 0.05$) between basal state and 120 min 0.9% NaCl infusion.

10 pmol·kg^{-1}·min^{-1} for 6.5 min and ending with 5 pmol·kg^{-1}·min^{-1} for 52 min) and then for an additional hour using a bolus and infusion rates six times those of the first infusion period (high dose). Instead of C-peptide, a 0.9% NaCl infusion was given for 2 h in Group 2. Urine (spontaneous voiding) and blood samples were collected at timed intervals throughout the study period for analyses of inulin, PAH and C-peptide.

Renal vein catheterisation was not performed in four patients (two in each group).

GFR and ERPF were measured by the clearances of inulin (Inutest, 25%, Laevosan-Gesellschaft, Linz, Austria) and PAH (Aminohippurate sodium, 20%, Merck Sharp & Dohme, Westpoint, PA, USA) respectively. The inulin and PAH were mixed in a ratio 17:3. After a prime dose of 0.3 ml/kg a continuous infusion (0.375 ml/min) of the mixed solution was given for 3.5 h. Body surface area was calculated according to Haycock et al. [15].

Analyses

The concentration of C-peptide in plasma was measured in duplicate samples by a radioimmunological technique [16] using antibody M1230. The detection limit in the assay is 0.05 nmol/l. The procedure has been described in detail elsewhere [17]. Inulin was analysed in blood by using the anthrone method [18] and PAH by a modified Smith technique [19]. Plasma glucose was measured by a glucose oxidase method (Glucose analyser 2, Beckman, Brea, CA, USA). HbA_{1c} was determined by a specific ion-exchange chromatography technique, using a commercial kit (Mono S HR 5/5, Pharmacia AB, Uppsala, Sweden).

Calculations

Whole-body glucose utilization was calculated as described by De Fronzo et al. [20] during the last 40 min of each period (basal state, low- and high-dose C-peptide and two 60 min NaCl infusion periods). Despite high water intake, most of the subjects had problems with spontaneous voiding of urine in the supine position which resulted in a somewhat unstable diuresis. However, since a constant rate infusion of PAH and inulin was given, resulting in steady-state plasma concentrations of these substances, ERPF and GFR could be determined according to following formulas.

$$1.\ \text{ERPF} = \frac{\text{PAH Infusion Rate}}{\text{A (PAH)} - \text{RV (PAH)}} \times \frac{\text{A (PAH)} - \text{RV (PAH)}}{\text{A (PAH)}};$$

$$2.\ \text{ERPF} = \frac{\text{PAH Infusion Rate}}{\text{A (PAH)}};$$

where A (PAH) and RV (PAH) represent the concentrations of PAH in arterial and renal venous (RV) plasma.

$$3.\ \text{GFR} = \frac{\text{InulinInfusionRate}}{\text{A (IN)} - \text{RV (IN)}} \times \frac{\text{A (IN)} - \text{RV (IN)}}{\text{A (IN)}};$$

$$4.\ \text{GFR} = \frac{\text{Inulin Infusion Rate}}{\text{A (IN)}};$$

where A (IN) and RV (IN) indicate the arterial and renal venous concentrations of inulin. Renal extraction of PAH is calculated as the ratio between the renal venous-arterial concentrations difference of PAH and the arterial concentration of PAH. A (IN and PAH) and RV (IN and PAH) represent the mean value of four determinations taken every 5 min during the last 15 min within each period (basal state, low- and high dose C-peptide and two 60 min NaCl infusion periods).

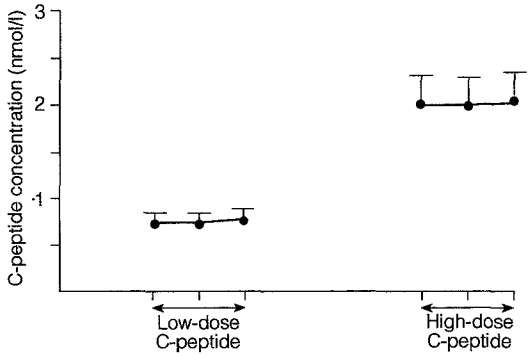

Fig. 1. Steady-state levels of arterial plasma C-peptide concentration during the last 10 min of low- and high-dose C-peptide infusion periods (Mean ± SEM are given)

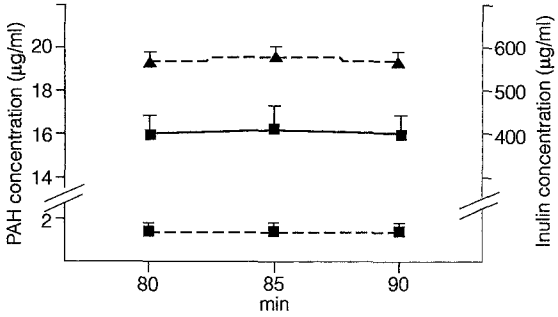

Fig. 2. Steady-state concentrations of inulin (▲---▲) and sodium para-aminohippurate (PAH) (■—■) in the brachial artery and PAH (■---■) in the renal vein during the last 10 min of the 90-min basal study period. Mean ± SEM are given

Statistical analysis

Standard statistical methods were employed using the paired *t*-test, Wilcoxon's signed-rank test, and analyses of variance (repeated measurements) when applicable. Data in the text, tables and figures are presented as mean ± SEM.

Results

None of the patients in Group 1 reported any adverse reactions during the C-peptide infusions. However, in four of the patients the study was discontinued after the first C-peptide infusion because of problems with voiding in the supine position.

Both groups showed stable and unchanged insulin and blood glucose concentrations throughout the study and the levels did not differ between the groups (Table 2).

C-peptide: Steady-state levels of C-peptide were reached during both the low- and high-dose infusion (Fig. 1). As seen from Figure 1 and Table 2 a six-fold increase in the C-peptide infusion rate from low to high dose was accompanied by a three-fold rise in the blood levels of C-peptide [0.77 ± 0.11 nmol/l and 2.08 ± 0.32 nmol/l, respectively]. None of the patients in Group 2 had detectable C-peptide levels in plasma or urine during the study.

Table 3. Mean values ± SEM for glomerular filtration rate (GFR), effective renal plasma flow (ERPF), filtration fraction (FF, GFR/ERPF) and sodium para-aminohippurate (PAH) extraction during basal state and C-peptide infusion (low and high dose) in Group 1 and during basal state and 0.9% NaCl infusion (60 and 120 min) in Group 2

		GFR ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)	ERPF ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)	FF (%)	PAH extraction (%)
Group 1	Basal ($n = 11$)	143 ± 4	741 ± 34	19.3 ± 0.5	90 ± 1
	Low-dose C-peptide ($n = 11$)	133 ± 4[a,c]	760 ± 35[b]	17.6 ± 0.5[a,d]	92 ± 2
	High-dose C-peptide ($n = 7$)	132 ± 4[e,h]	791 ± 34[g]	16.8 ± 0.3[f,i]	91 ± 3
Group 2	Basal ($n = 10$)	132 ± 4	708 ± 22	18.8 ± 0.7	90 ± 1
	60 min 0.9% NaCl ($n = 10$)	130 ± 4	728 ± 23	17.9 ± 0.6[j]	90 ± 1
	120 min 0.9% NaCl ($n = 10$)	127 ± 3[k]	725 ± 28	17.2 ± 0.7[l]	91 ± 1

[a,b] Indicate significant differences ($p < 0.001$ and $p < 0.05$, respectively) between basal and low-dose C-peptide infusion.
[c,d] Indicate significant differences ($p < 0.01$ and $p < 0.05$, respectively) between the groups concerning the percental change from basal state to low-dose C-peptide infusion and from basal to 60 min 0.9% NaCl infusion.
[e,f,g] Indicate significant differences ($p < 0.001$, $p < 0.01$ and $p < 0.05$, respectively) between basal state and high-dose C-peptide infusion.
[h,i] Indicate significant difference ($p < 0.05$ and $p < 0.01$, respectively) between the groups concerning the percental change from basal state to high-dose C-peptide infusion and from basal state to 120 min 0.9% NaCl infusion.
[j] Indicates significant difference ($p < 0.05$) between basal and 60 min 0.9% NaCl infusion.
[k,l] Indicate significant difference ($p < 0.05$ and $p < 0.01$, respectively) between basal state and 120 min 0.9% NaCl infusion

Renal function: Infusion of inulin and PAH resulted in steady-state levels of these substances during each study period (Fig. 2) as is required for the calculation of GFR and ERPF. In Group 1, GFR was 143 ± 3 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ in the basal state and decreased on the average by 7% during the low-dose C-peptide infusion to 133 ± 4 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ ($p < 0.001$). A fall in GFR was seen in each of the 11 patients studied (Fig. 3). GFR tended to decrease further in the seven patients in whom high-dose infusion could be carried out (from 136 ± 4 to 132 ± 4 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$, $p < 0.1$, Table 3, Figure 3). No changes in GFR were found in the control subjects after 1 h of NaCl infusion but a slight decrease (4%, $p < 0.01$) was observed from basal to 2 h infusion of NaCl. The fall in GFR was greater in Group 1 both from basal to low-dose and from basal to high-dose C-peptide than

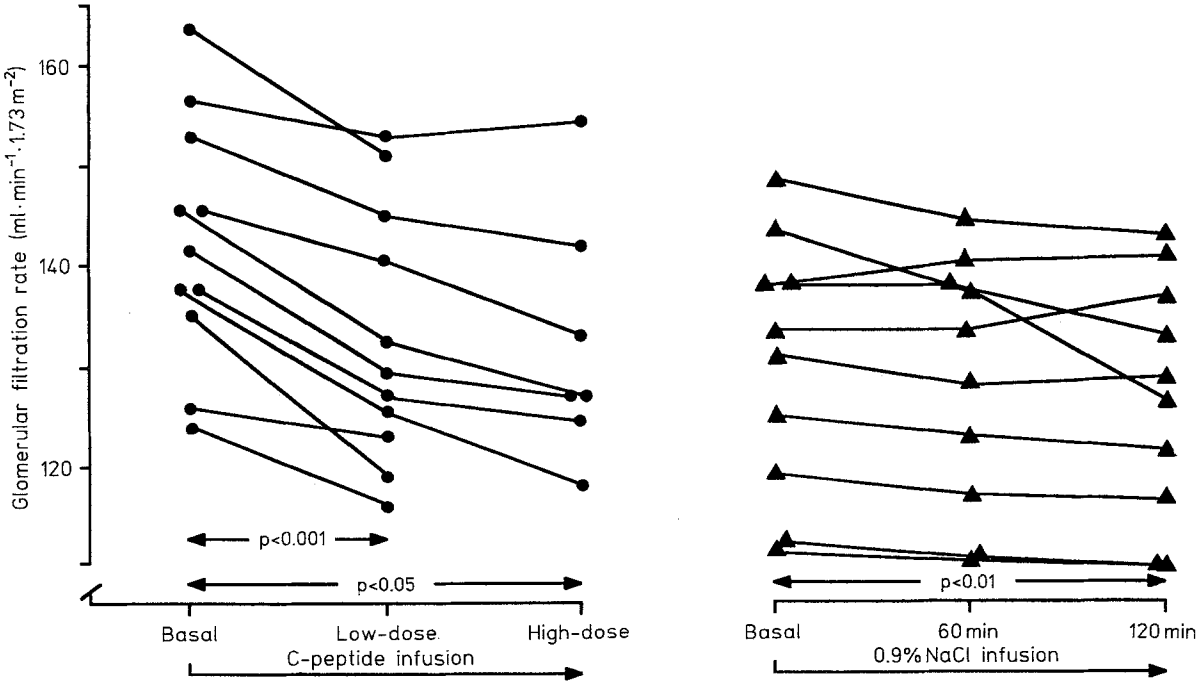

Fig. 3. Individual values for glomerular filtration rate in the basal state and during low- and high-dose C-peptide infusion in Group 1 (*left panel*) and in basal state and during 60- and 120-min infusions of 0.9% NaCl in Group 2 (*right panel*)

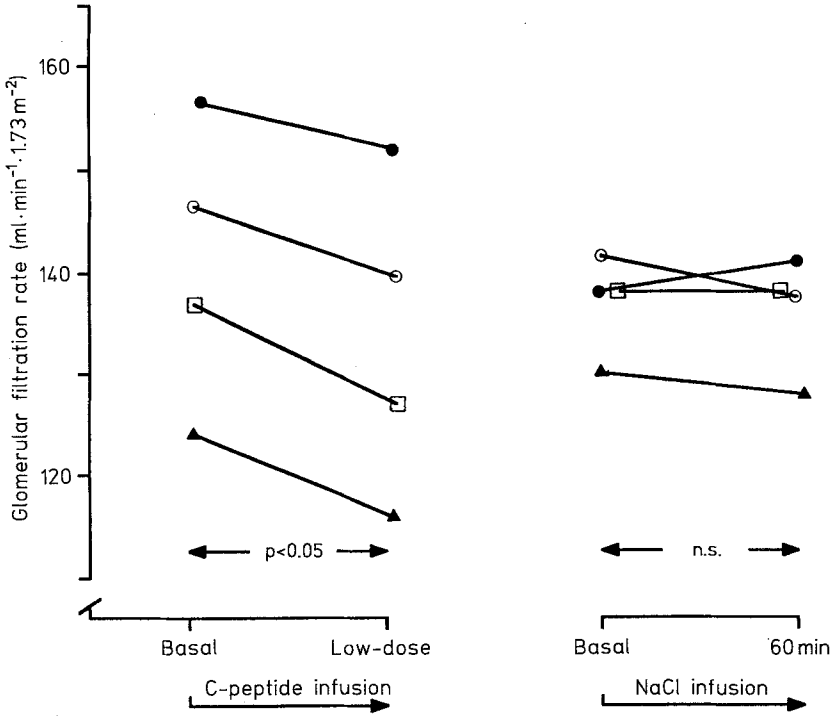

Fig. 4. Individual values for glomerular filtration rate in the four patients who participated in both Group 1 and Group 2. *Left panel* represents the values received at the basal state and during low-dose C-peptide infusion (Group 1) and *right panel* represents the values received at basal state and during 60-min infusions of 0.9% NaCl (Group 2)

during corresponding periods in Group 2 ($7.1 \pm 1.0\%$ vs $1.9 \pm 0.6\%$, $p < 0.001$ and $8.8 \pm 1.5\%$ vs $4.0 \pm 1.4\%$, $p < 0.05$). In addition, the four patients who participated in both Group 1 and Group 2 (Fig. 4) all had a greater fall in GFR from basal to low-dose C-peptide infusion than from basal to 60 min NaCl administration ($4.8 \pm 0.9\%$ vs $0.7 \pm 1.2\%$, $p < 0.05$).

ERPF in Group 1 was in the basal state 741 ± 34 ml·min^{-1}·1.73 m^{-2} with a slight increase (3%, $p < 0.05$) to 760 ± 35 ml·min^{-1}·1.73 m^{-2} during low-dose C-peptide infusion. At the end of the high-dose infusion ERPF had risen by 6% in relation to the basal value ($p < 0.05$). No significant change in ERPF was found between low- and high-dose administration (Table 3, Fig. 5).

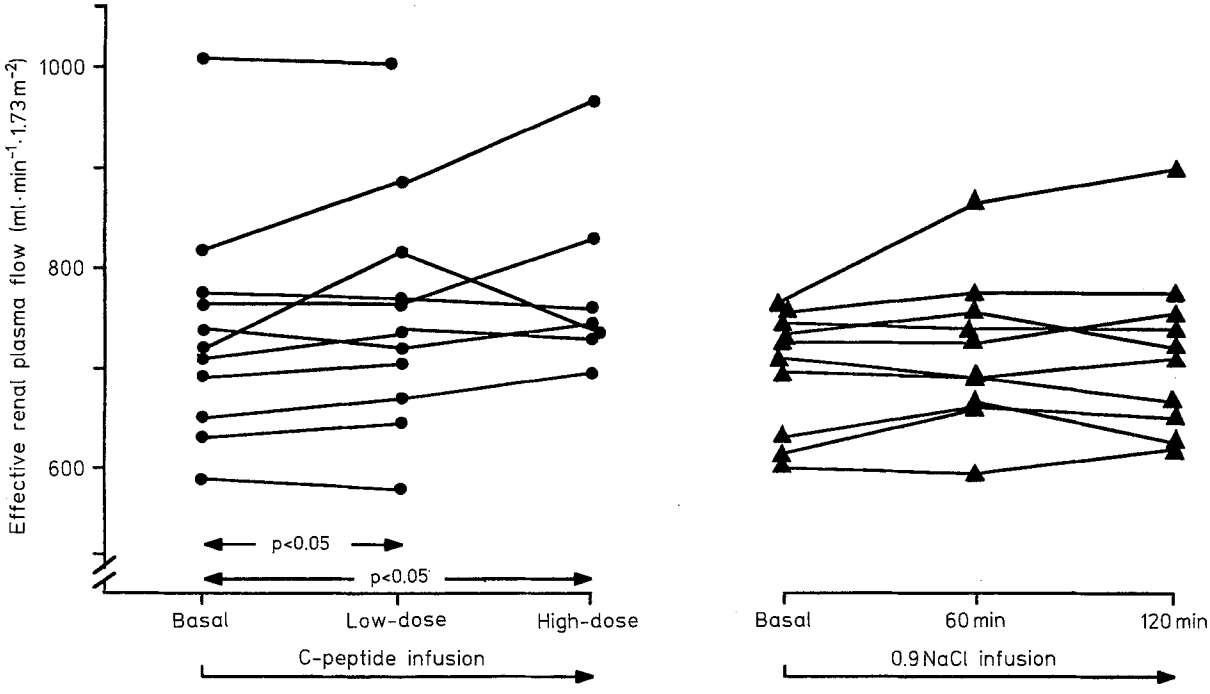

Fig. 5. Individual values for effective renal plasma flow in the basal state and during low- and high-dose C-peptide infusion in Group 1 (*left panel*) and in basal state and during 60 and 120-min infusions of 0.9% NaCl in Group 2 (*right panel*)

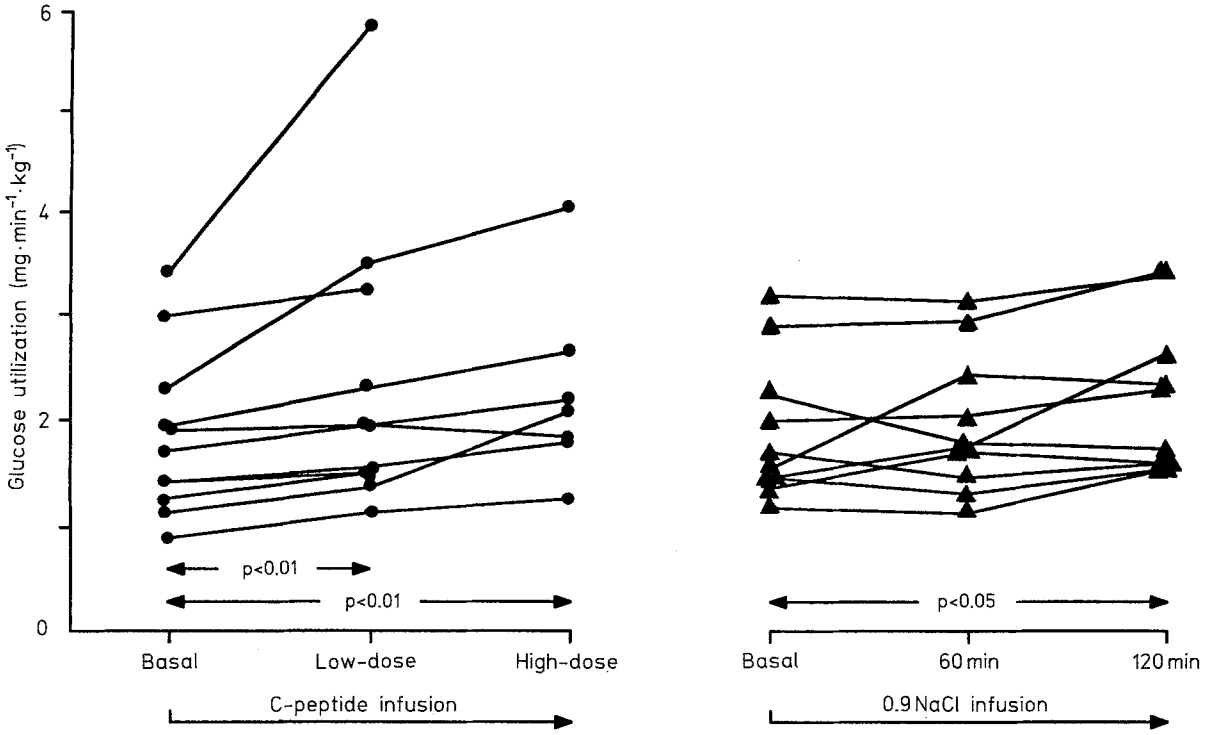

Fig. 6. Individual values for glucose utilization in the basal state and during low- and high-dose C-peptide infusion in Group 1 (*left panel*) and in basal state and during 60- and 120-min infusions of 0.9% NaCl in Group 2 (*right panel*)

In the control subjects ERPF did not change from the basal to 60 or 120 min infusion of NaCl (Table 3, Fig. 5).

Filtration fraction calculated as the ratio between GFR and ERPF decreased from 19.3 ± 0.5% in the basal state to 17.6 ± 0.5% ($p < 0.001$) during low-dose C-peptide in Group 1 with a further reduction from low- to high-dose infusion (to 16.8 ± 0.3%, $p < 0.05$, Table 3). Filtration fraction was also reduced in Group 2 during 60 min ($p < 0.05$) and 120 min ($p < 0.01$) NaCl infusion in comparison with basal value. However, Group 1 showed a more marked reduction than did Group 2 during corresponding periods ($p < 0.01$, both from basal to low or basal to high-dose).

The renal PAH extraction was stable and constant (90–92%) in both groups throughout the study (Table 3).

Glucose utilization: Whole-body glucose utilization was 1.86 ± 0.24 mg·min^{-1}·kg^{-1} in the basal state and increased by approximately 25% from the basal level to low-dose C-peptide infusion ($p < 0.01$, Table 2, Fig. 6). A further increase from 1.98 ± 0.3 to 2.28 ± 0.35 mg·min^{-1}·kg^{-1} (15%, $p < 0.05$) was observed during the high-dose infusion in the seven patients who participated in both low- and high-dose C-peptide administration. There was a significant difference in the glucose utilization change from basal to low-dose (25 ± 6%) and from basal to 60 min NaCl infusion (6 ± 7%) between the two groups ($p < 0.02$). In Group 2 no significant change in glucose utilization was seen during the first 60 min of NaCl infusion but a small rise was observed after 120 min ($p < 0.05$, Table 2, Fig. 6).

Discussion

The present study group was made up of young Type 1 diabetes patients without signs of clinical late diabetic complications and in a state of good metabolic control, as indicated by HbA_{1c} values close to the normal range. Most of the patients had an increased GFR in the basal state (138 ± 3 for Group 1 and 2 as compared to 120 ± 2 ml·min^{-1}·1.73 m^{-2}, $p < 0.001$, found in 16 healthy subjects, aged 18 ± 1 years, studied at this department) and no significant residual C-peptide production at the time of the study. Previous work has suggested that hyperglycaemia per se might induce renal hyperfiltration [10]. Consequently, all patients were studied in the euglycaemic state in order to minimize the possible influence of hyperglycaemia on renal function.

During low-dose C-peptide infusion the patients showed a small but significant decrease in GFR (−7%) a finding which is supported by the fact that all patients showed a similar response. An influence of C-peptide on ERPF was also observed during this period but in the opposite direction and of lesser magnitude (3%), leading to a more marked reduction in filtration fraction than in GFR. It is noteworthy that the influence of C-peptide on renal function occurred already with the low-dose infusion, which had been estimated to restore basal physiological concentrations of C-peptide. Only a small further decrease in GFR took place when the C-peptide infusion rate was increased six-fold. Thus, a dose-response relationship could not be established between GFR and plasma C-peptide concentrations.

The possibility should be considered that the experimental procedure itself, by virtue of the prolonged

study period (5 h) during which the subjects rested in the supine position without ingestion of food, and/or the slow rate insulin infusion ($0.5\ mU \cdot kg^{-1} \cdot min^{-1}$) may have influenced renal function. However, in the ten patients who received 0.9% NaCl rather than C-peptide under otherwise identical conditions, no change in GFR could be observed during the first 60 min. In addition, all four patients who participated in both study groups had a greater fall in GFR during low-dose C-peptide infusion compared with 60 min 0.9% NaCl infusion ($p < 0.05$). These observations support the hypothesis that C-peptide does in fact exert a direct effect on renal function in Type 1 diabetic patients.

A dose-response relationship could not be seen for C-peptide infusion rate and steady-state plasma levels of C-peptide. A six-fold increase of C-peptide infusion resulted in no more than a three-fold increase in plasma C-peptide levels. Thus, our findings suggest that whole body metabolism of C-peptide increases with augmented rates of C-peptide infusion. This finding contrasts with that of Polonsky et al. [21], who observed that the metabolic clearance rate for C-peptide remained unchanged in Type 1 diabetic patients regardless of the rate of C-peptide administration. The differences may be due to variations in study design. In the present study constant insulin and variable glucose infusions were adjusted so as to maintain plasma glucose in the normoglycaemic range. This resulted in a steady-state insulin plasma level of 21 μU/ml. In the studies by Polonsky et al. [21] a variable insulin infusion was given, adjusted to maintain the plasma glucose levels in the euglycaemic range. The plasma insulin levels found in their healthy control subjects were 6–7 μU/ml. The plasma insulin levels found in the Type 1 diabetic patients were not reported but we assume that they had levels similar to those of the healthy control subjects. In that case, our Type 1 diabetic patients had insulin levels at least twice as high as the patients in the study by Polonsky et al. [21].

In order to maintain an unchanged blood glucose level during C-peptide infusion the rate of glucose infusion had to be increased by about 25% during low-dose C-peptide infusion but could be kept unchanged during the corresponding time period with NaCl infusion. High-dose infusion resulted in a further small rise in glucose utilization as is evident from the data in the seven patients who received both high- and low-dose infusion. In the latter patients the rise amounted to 43% above basal after high-dose infusion as compared to no more than 18% in NaCl control subjects. In view of these findings and the fact that arterial insulin levels remained unchanged during this period, it is unlikely that the observed rise in glucose utilization was an effect of insulin. This finding suggests that C-peptide exerts a stimulatory effect on glucose utilization in Type 1 diabetic patients although the possibility of an inhibition of hepatic glucose production by C-peptide cannot be excluded. There is, as far as we know, only one human study, presented in abstract form, in which the effect of C-peptide on carbohydrate metabolism in Type 1 diabetic patients has been evaluated [22]. No significant changes in the concentrations of glucose, lactate, alanine, β-hydroxybuturate, glycerol or non-esterified fatty acids during 2 h observation after an i.v. C-peptide injection (24–36 nmol) in either diabetic ($n = 7$) or healthy control subjects ($n = 4$) could be found. However, Wallberg-Henriksson et al. [23] have recently reported that human C-peptide in physiological amounts increases glucose uptake in incubated skeletal muscle under in vitro conditions in healthy persons. Another study by Wallberg-Henriksson et al. [24] demonstrates that glucose uptake in skeletal muscle from Type 1 diabetic patients is stimulated by C-peptide to almost 100% of the effect obtained by equimolar amounts of insulin. Hoogwerf et al. [25] found in a recent study that C-peptide infusion in physiological amounts to healthy persons might exert a suppresive effect on insulin and glucagon release. Wojcikowski et al. [26] found that infusion of rat C-peptide in unphysiologically high doses increases and prolongs the hypoglycaemic effect of exogenous insulin in alloxan-diabetic rats. Thus, the above studies support the notion that C-peptide may stimulate glucose utilization.

In conclusion, the present study does not confirm earlier suggestions that C-peptide is a biologically inactive substance [1]. Instead, the results suggest the possibility that short-term administration of C-peptide may exert a regulatory influence on renal function as well stimulate glucose utilization in Type 1 diabetic patients.

Acknowledgements. This study was supported by grants from the Karolinska Institute and the Swedish Medical Research Council (no. 3108).

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Received: 11 March 1991
and in revised form: 16 September 1991

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