Reevaluation of Urine C-Peptide as Measure of Insulin Secretion

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Urine C-peptide (UCP) has been proposed as a measure of insulin secretion, because insulin and C-peptide are cosecreted in equimolar concentrations by the pancreatic β-cell. The validity of this approach was tested by comparing insulin secretion rates, calculated by application of a two-compartmental analysis of peripheral C-peptide concentrations, with UCP excretion rates. Insulin secretion and UCP excretion with subjects on a mixed diet were simultaneously measured over a 24-h period in 13 patients with non-insulin-dependent diabetes mellitus and in 14 matched nondiabetic control subjects. The fraction of secreted C-peptide that was excreted in the urine (fractional C-peptide excretion) showed considerable intersubject variability in the diabetic (11.3 ± 1.6%, range 3.9–20.8) and control (8.0 ± 1.7%, range 1.1–27.9, $P = .07$) subjects (means ± SE). UCP clearance demonstrated a similar degree of variability and was not significantly different ($P = .07$) between diabetic (23.8 ± 3.0 ml/min) and control (16.5 ± 2.7 ml/min) subjects. In control subjects, the 24-h insulin secretion rate correlated more closely with the fasting insulin secretion rate ($r = .97$, $P = .0001$), fasting C-peptide ($r = .81$, $P = .0005$), and fasting insulin ($r = .80$, $P = .0005$) concentrations than with the 24-h UCP excretion rate ($r = .62$, $P = .02$). Similar results were obtained in the diabetic patients. The mean coefficient of variation of fractional UCP excretion in 7 nondiabetic control subjects who were studied on a mixed diet over a 24-h period on two occasions was 28.4 ± 10.5%, that of UCP clearance was 28.9 ± 8.6%, and that of simultaneously measured creatinine clearance was 7.8 ± 3.5%. In summary, the fraction of secreted C-peptide that appears in the urine varies considerably between subjects and in the same subject studied repeatedly. UCP excretion does not correlate as well with 24-h insulin secretion as does the fasting insulin secretion rate or the fasting C-peptide or fasting insulin concentration. We conclude that, because the fraction of secreted C-peptide that is excreted in the urine varies considerably between subjects and in the same subject studied on different occasions, UCP is of only limited value as a quantitative measure of endogenous insulin secretion. *Diabetes* 37:1195–201, 1988

Urine C-peptide has been proposed as a measure of endogenous insulin secretion (1–7), because insulin and C-peptide are cosecreted in equimolar concentrations by the pancreatic β-cell (8–11) and a fraction of this peptide is excreted in the urine (12–15). The availability of biosynthetic human C-peptide for experimental use (16–19) enabled us to derive individual pancreatic C-peptide, and therefore insulin secretion rates, from peripheral C-peptide concentrations (18) with a two-compartment model of C-peptide distribution (20,21). The simultaneous measurement of urine C-peptide excretion allowed the accuracy of urine C-peptide as a measure of endogenous insulin secretion to be evaluated in patients with non-insulin-dependent diabetes mellitus (NIDDM) and in nondiabetic subjects.

SUBJECTS AND METHODS

Studies were performed on 13 patients with NIDDM (8 men, 5 women, aged 52.1 ± 2.7 yr) and 14 matched nondiabetic control subjects (7 men, 7 women, aged 46.1 ± 2.5 yr). The duration of diabetes was 6.6 ± 1.7 yr (range 1 mo to 17 yr). Therapy was discontinued ≥3 wk before entry into the study (average fasting blood glucose 215.1 ± 19.2 mg/dl). One patient had been treated with insulin, 6 patients with oral hypoglycemic agents, and the remaining 6 patients with diet alone. The diabetic [body mass index (BMI) 30.7 ± 1.7 kg/m^2; percent ideal body weight (IBW) 136.6 ± 9.7] and

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control (BMI 31.3 ± 2.4 kg/m^2; percent IBW 138.4 ± 10.7) groups were well matched for degree of obesity. Details of the insulin secretion profiles in these patients have recently been published (22). Additional studies were performed on 7 healthy nonobese volunteers (3 men, 4 women, aged 25.4 ± 2.2 yr; BMI 21.7 ± 1.0 kg/m^2, percent IBW 99.0 ± 5.8). Serum creatinine (range 0.4–1.3 mg/dl) and blood urea nitrogen (range 5–21 mg/dl) concentrations were normal in all subjects.

All studies were carried out in the Clinical Research Center of the University of Chicago after written informed consent had been obtained. The experimental protocol was approved by the institutional review board.

STUDY PROTOCOL

All studies were performed after a 10-h overnight fast. During each experiment, an intravenous sampling catheter was inserted into the dorsum of the hand, and where necessary an infusion catheter was inserted into a vein on the opposite hand. The hand with the sampling catheter was maintained in a heating blanket to ensure arterialization of the venous sample. The individual studies were performed as follows.

Intravenous bolus injection of biosynthetic human C-peptide. All subjects received a bolus injection of 150 μg i.v. biosynthetic human C-peptide (BHCP, Lilly, Indianapolis, IN), and endogenous C-peptide secretion was inhibited by means of a primed constant infusion of somatostatin (500 μg/h, Bachem, Torrance, CA). The details of this protocol have previously been described (18). Analysis of the resulting C-peptide decay curves allowed the kinetic parameters for C-peptide for a two-compartment model of C-peptide distribution to be individually derived in each subject.

Measurement of endogenous insulin secretion and urine C-peptide excretion. Endogenous insulin secretion and urine C-peptide excretion were measured simultaneously under two separate conditions, a mixed meal and an oral glucose load.

Samples for glucose, insulin, and C-peptide were drawn at 15- to 30-min intervals, beginning at 0600, for a total of 24 h. The urine was collected during this 24-h period to measure C-peptide excretion. Creatinine clearance was determined simultaneously. During this time, the subjects consumed a standard diet consisting of 30 kcal/kg comprising 50% carbohydrate, 15% protein, and 35% fat. Twenty percent of total calories were eaten at breakfast and 40% at lunch and dinner. To assess the intraindividual variability or reproducibility of urinary C-peptide handling, seven nondiabetic control subjects were studied on this protocol (including the BHCP injection) on two occasions. An analysis of the 24-h insulin secretory profiles and the meal responses in the diabetic patients and the control subjects has been reported (22).

Seven additional control subjects each ingested 25, 50, and 100 g glucose (Dextol, Sherwood Medical, St. Louis, MO), diluted to 350 ml with water, on three occasions within a 3-wk period. Samples for glucose, insulin, and C-peptide were drawn at 5- to 30-min intervals for 5 h after the glucose administration, and the urine was collected during this period to measure urine C-peptide excretion and creatinine clearance. The responses in plasma glucose and insulin secretory rate have been reported in detail elsewhere (23).

DERIVATION OF PANCREATIC INSULIN SECRETION RATES

The C-peptide decay curves were resolved into the sum of two exponential functions by nonlinear least-squares regression analysis. Metabolic clearance rate (MCR), fractional kinetic rate constants, and distribution volume for C-peptide were derived by application of a two-compartment model of C-peptide distribution and metabolism as proposed by Eaton et al. (20) and Metzler (21). These fractional rate constants and the distribution volume of C-peptide for each individual were then applied to the endogenous plasma C-peptide concentrations measured during the meal or glucose administration studies, and individual insulin secretion rates were derived (18,20). It has been demonstrated by our laboratory that this model allows accurate estimates of insulin secretion rates to be derived under non-steady-state conditions (17,18).

CALCULATION OF URINE C-PEPTIDE PARAMETERS

Urine C-peptide excretion was determined as the product of the urine volume and the concentration of C-peptide in the urine. Urine C-peptide clearance was calculated as previously described (3). The fraction of secreted C-peptide that is excreted in the urine (referred to as fractional C-peptide excretion) was calculated

$$\frac{\text{total urine C-peptide excretion (pmol)}}{\text{total pancreatic C-peptide secretion (pmol)}} \times 100\%$$

SAMPLE COLLECTION AND ANALYTICAL METHODS

Blood samples for insulin were allowed to clot at room temperature, and the serum was stored at −20°C until assayed. C-peptide samples were drawn into tubes at 4°C containing 500 KIU/ml aprotinin (Trasylol, Bayer, FBA Pharmaceuticals, New York) and 1.2 mg/ml EDTA. Plasma was separated and stored frozen at −20°C until assayed. Plasma glucose was measured immediately with the glucose analyzer (YSI model 23 A, Yellow Springs, OH). Serum insulin was assayed by a double-antibody technique (24). The intra- and interassay coefficients of variation for insulin were 4 and 6%, respectively. Human C-peptide immunoreactivity in plasma (18,25) and urine (3,14) was measured as previously described, with the M1230 antibody. BHCP and ^{125}I-labeled Tyr-BHCP were used as assay standard and tracer, respectively (26). The intra- and interassay coefficients of variation for C-peptide were 4 and 10%, respectively. Urine for the measurement of C-peptide was collected into chilled plastic containers at 4°C, and aliquots were adjusted to pH 7.0 with dilute NaOH. The radioimmunoassay of C-peptide in urine has been validated previously (14). Creatinine in serum and urine was determined by the picric acid colorimetric method.

Statistical analysis. All results are expressed as means ± SE. Nonlinear least-squares regression analysis of the C-peptide decay curves was performed with the BMDP 3R program (BMDP Statistical Software, Los Angeles, CA). The areas under the concentration and secretion rate curves were calculated by the trapezoidal rule. The significance of differences between group means was calculated by the unpaired two-tailed *t* test. Comparisons within groups were made by the paired two-tailed *t* test or by two-way analysis of variance with subsequent Bonferroni (Dunn) *t* tests where appropriate. Pearson correlation coefficients were calcu-

TABLE 1
Integrated insulin secretion and measurements of urine C-peptide and creatinine excretion during the 24-h sampling study in response to mixed meals

	NIDDM subjects	Control subjects	*P*
Integrated plasma C-peptide (nmol · ml^{-1} · min)	1.67 ± 0.22	1.93 ± 0.25	.45
Integrated insulin secretion (nmol/24 h)	359.6 ± 50.6	434.2 ± 75.3	.43
Urine C-peptide (nmol/24 h)	37.8 ± 5.2	34.6 ± 9.0	.76
Urine C-peptide/creatinine (pmol/mg)	26.5 ± 3.7	20.7 ± 4.7	.35
Fractional C-peptide excretion (%)	11.3 ± 1.6 (3.9–20.8)	8.0 ± 1.7 (1.1–27.9)	.07*
Urine C-peptide clearance (ml/min)	23.8 ± 3.0 (8.8–41.9)	16.5 ± 2.7 (2.8–43.2)	.07*
Creatinine clearance (ml/min)	129.2 ± 9.2	136.4 ± 7.1	.54
Urine C-peptide clearance/creatinine clearance	0.19 ± 0.02 (0.08–0.34)	0.13 ± 0.02 (0.02–0.41)	.04*

Values are means ± SE, with ranges in parentheses.
*Value obtained after log transformation of parameter values.

lated to assess the degree of association between variables, and linear regression analysis was used to describe the relationship between variables. Correlation coefficients between groups were compared via Fisher's *Z* transformation and within groups by Williams's modification of Hotelling's *t* statistic (27). The coefficient of variation was calculated to assess the intraindividual reproducibility of measurements. Differences were regarded as being statistically significant at $P \leq .05$. Data analysis was performed with a statistical analysis system (SAS version 6 ed. for personal computers, SAS Institute, Cary, NC).

RESULTS

Kinetics of biosynthetic human C-peptide. The metabolic and kinetic parameters of C-peptide in the three groups of subjects studied are similar to those previously reported from our laboratory (18). In the nondiabetic control subjects the fall in plasma C-peptide concentration after the C-peptide bolus injection demonstrated a fast and slow component with half-disappearance times of 4.7 ± 0.3 and 37.0 ± 0.8 min, respectively. The MCR of C-peptide was 126.5 ± 5.9 ml · min^{-1} · m^{-2}. The fractional kinetic rate constants for C-peptide derived by two-compartmental analysis of C-peptide decay curves were as follows: k_1 = 0.0644 ± 0.0055 min^{-1}, k_2 = 0.0479 ± 0.0019 min^{-1}, k_3 = 0.0600 ± 0.0019 min^{-1}, and volume of distribution 2122.0 ± 94.1 ml/m^2. No significant differences in the parameters were observed between the NIDDM and control groups.

Relationship between pancreatic insulin secretion rate and urine C-peptide excretion rate. Total daily insulin secretion rates and simultaneously measured urine C-peptide and creatinine excretion rates for both groups are shown in Table 1. Daily insulin secretion rates were not significantly different between the diabetic and control groups (359.6 ± 50.6 vs. 434.2 ± 75.3 nmol, respectively; P = .43). Total daily urine C-peptide excretion was similar in the diabetic and control groups (37.8 ± 5.2 vs. 34.6 ± 9.0 nmol, respectively; P = .76). When urine C-peptide was expressed as a function of urine creatinine, no significant difference between the two groups was found (26.5 ± 3.7 vs. 20.7 ± 4.7 pmol/mg creatinine, P = .35). The fraction of secreted C-peptide that was excreted in the urine tended to be higher in the diabetic patients (11.3 ± 1.6 vs. 8.0 ± 1.7%), but the difference was not statistically significant (P = .07). The individual values of this measurement are represented in Fig. 1 and demonstrate considerable intersubject variability (range 3.9–20.8% in the diabetic group and 1.1–27.9% in the control subjects). Creatinine clearance was similar in the diabetic patients (129.2 ± 9.2 ml/min) and the control subjects (136.4 ± 7.1 ml/min, P = .54). Urine C-peptide clearance was not significantly different between the diabetic and control groups (23.8 ± 3.0 vs. 16.5 ± 2.7 ml/min, respectively; P = .07). Urine C-peptide clearance values also showed a pronounced intersubject variability in the diabetic (range 8.8–41.9 ml/min) and control (range 2.8–43.2 ml/min) groups, comparable to that of fractional C-peptide excretion. Although no significant differences in creatinine and urine C-peptide clearance between the two groups were found, the ratio between urine C-peptide clearance and creatinine clearance was significantly higher in the diabetic group than in the control group (0.19 ± 0.02 vs. 0.13 ± 0.02, respectively; P = .04), but this difference became insignificant after correction for multiple comparisons (28). Thus, no significant differences in the various urine C-peptide measurements were found between the patients with NIDDM and the control subjects, although urine C-peptide clearance and fractional C-peptide excretion tended to be higher in the diabetic patients.

The intraindividual variability (or reproducibility) of fractional urine C-peptide excretion and urine C-peptide clearance was assessed in seven nondiabetic control subjects who were studied on a mixed diet over a 24-h period on two occasions. The mean coefficient of variation of fractional urine C-peptide excretion was 28.4 ± 10.5%, that of urine C-peptide clearance was 28.9 ± 8.6%, and that of simultaneously measured creatinine clearance was 7.8 ± 3.5%.

Correlation between daily insulin secretion and daily urine C-peptide, fasting insulin, C-peptide, and insulin secretion. Figure 2 depicts the relationship between the fasting insulin secretion rate, fasting C-peptide concentration, fasting insulin concentration, and the total daily urine C-peptide excretion and total daily insulin secretion rate for the patients with NIDDM and the matched nondiabetic control subjects. In both groups a significant linear relationship was observed between the total daily insulin secretion rate and the fasting insulin secretion rate, fasting plasma C-pep-

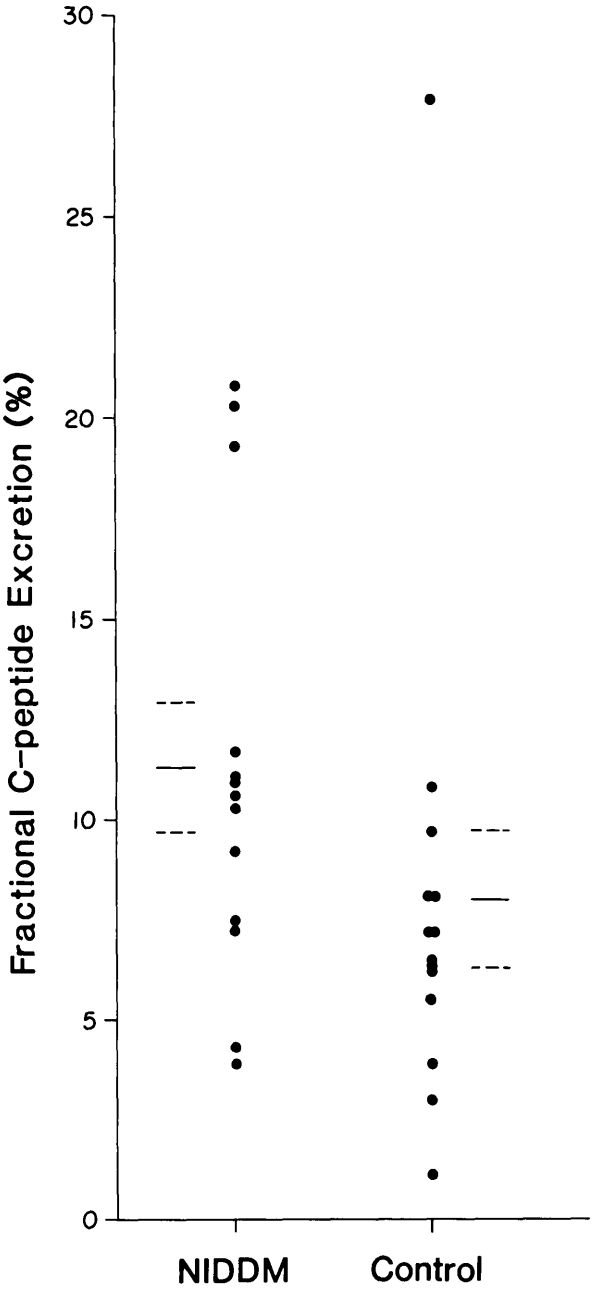

FIG. 1. Individual values of fractional urinary C-peptide excretion (means ± SE) during 24-h meal sampling study in patients with NIDDM and matched nondiabetic control subjects.

tide and insulin concentrations, and daily urine C-peptide excretion. The correlation coefficients for urine C-peptide, fasting insulin, and fasting C-peptide versus 24-h insulin secretory rate were not significantly different between the two groups. A higher correlation between fasting insulin secretion and total daily insulin secretion was found in the control group than in the diabetic group (P = .045), but this difference did not remain significant after correction for multiple comparisons (28). The highest correlation was found between fasting insulin secretion and total daily insulin secretion for the control subjects (r = .97, P = .0001) and the diabetic patients (r = .85, P = .0002). The lowest degree of correlation existed between total daily urine C-peptide excretion and total daily insulin secretion in the diabetic patients (r = .58, P = .04) and the control subjects (r = .62, P = .02). Fasting C-peptide (r = .81, P = .0005) and fasting insulin (r = .80, P = .0005) correlated equally well with daily insulin secretion in the control subjects, and similar correlation coefficients were found in the diabetic group (r = .79, P = .0014 for C-peptide; r = .72, P = .006 for insulin). In both the diabetic and control groups, fasting C-peptide correlated significantly better with total daily insulin secretion than did daily urine C-peptide (P = .025 and P = .0005, respectively). Fasting insulin correlated better with total daily insulin secretion than did urine C-peptide in the control group (P = .005) but not in the diabetic group (P = .15). Daily urine C-peptide excretion was significantly correlated with daily integrated plasma C-peptide concentration in the nondiabetic control subjects (r = .74, P = .003) but not in the patients with NIDDM (r = .50, P = .08).

Effects of different doses of oral glucose on urine C-peptide excretion. Fractional urine C-peptide excretion and urine C-peptide clearance were studied in seven normal subjects who each received oral glucose (25, 50, and 100 g) on three occasions. The results are shown in Table 2. Integrated C-peptide and insulin secretion increased significantly when the dose of glucose was increased from 25 to 50 g and from 50 to 100 g. In contrast, a significant difference in total daily urine C-peptide excretion was only found when the 25- and 100-g doses were compared. Similar to those of the control subjects studied on two occasions, the mean coefficients of variation of fractional urine C-peptide excretion (24.9 ± 5.4%) and urine C-peptide clearance (25.0 ± 5.1%) were high and greater than those of simultaneously measured creatinine clearance (12.6 ± 4.5%).

DISCUSSION

The accurate measurement of the pancreatic secretion rate of insulin is important not only for studies into the pathogenesis of diabetes mellitus but also in the evaluation of the efficacy of new approaches to the therapy of this condition. We have recently demonstrated that insulin secretion rates can be derived by deconvolution analysis of peripheral C-peptide concentrations utilizing a two-compartment pharmacokinetic model (17,18). Although this approach provides an accurate measure of β-cell function, it is difficult to apply and cumbersome for large-scale studies in which repeated measurements of insulin secretion are needed. The measurement of the urinary concentrations of several hormones has been used as a means of assessing their production rates and the same approach has been suggested for the evaluation of insulin secretion by measuring urine C-peptide excretion (12–14). Thus, urine C-peptide has been used as a measure of endogenous insulin secretion under varying conditions in several studies that have recently been summarized (11). Meistas et al. (1,2) and Kruszynska et al. (19) reported a significant correlation between total daily insulin secretion and urine C-peptide excretion. In addition, Meistas et al. (2) found that the fractional C-peptide excretion during a 24-h period varied between 0.4 and 4.2% (~10-fold range) in patients with NIDDM, demonstrating a high intersubject variability of this measure. However, these authors did not derive the MCR or kinetic parameters for C-peptide in each subject as was done in our study and by Kruszynska et al.

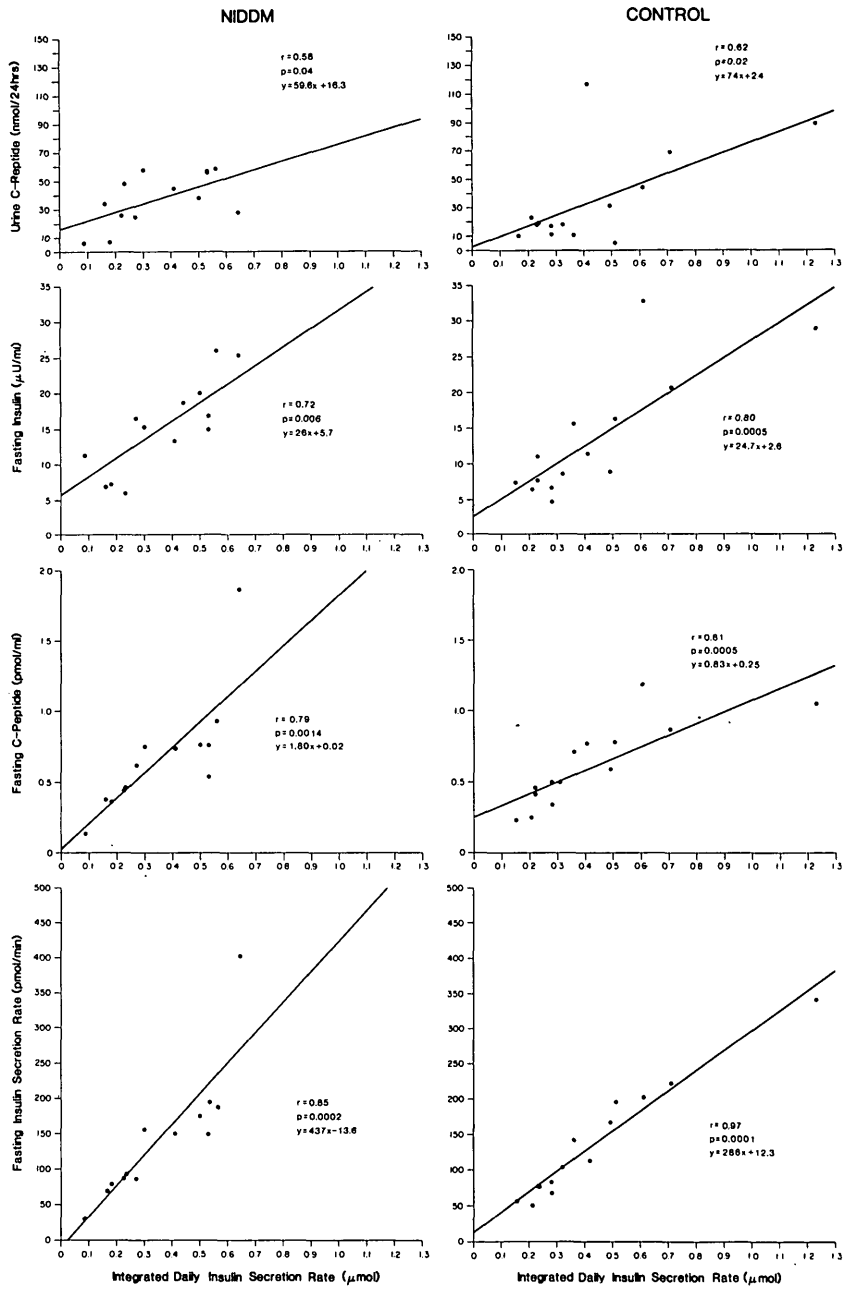

FIG. 2. Relationship between total daily insulin secretion and total daily urine C-peptide excretion, fasting insulin, fasting C-peptide, and fasting insulin secretion in patients with NIDDM (*left*) and matched nondiabetic control subjects (*right*).

(19); instead, they used a mean value for the C-peptide MCR reported by Faber et al. (16).

The accuracy of urine C-peptide in the evaluation of β-cell function is not known. Previous studies have demonstrated a significant correlation between urinary and plasma concentrations of C-peptide (3,4,12,13,29). However, because urine C-peptide is derived by glomerular filtration of plasma C-peptide, a correlation between these two variables may be expected to exist but alone does not prove that urine C-peptide accurately reflects insulin secretion. Thus, if urine C-peptide were to be an ideal marker of insulin secretion, the fraction of secreted C-peptide that appears in the urine should vary within a narrow range between subjects and should remain constant in the same subject when studied on different occasions (2,11). In addition, it would be advantageous if the fractional C-peptide excretion rate were unchanged under different physiological circumstances and in various disease states.

The availability of simultaneous measurements of the insulin secretion rate and urine C-peptide excretion in this study enabled us to examine the extent to which these assumptions on urine C-peptide kinetics are valid. The results demonstrated considerable between-subject variability of fractional urine C-peptide excretion and urine C-peptide clearance, both in patients with NIDDM and nondiabetic subjects. When seven of the nondiabetic control subjects were restudied under the same conditions over a 24-h period on mixed meals, the coefficient of variation of fractional urine C-peptide excretion was 28.4% and that of urine C-peptide clearance was 28.9%. Similar variability was seen when the same subjects received three increasing doses of oral glucose. Furthermore, in normal subjects, the 24-h insulin se-

TABLE 2
Parameters of insulin secretion and of urine C-peptide and creatinine excretion during 5 h after oral glucose administration in 7 nondiabetic subjects

	Glucose dose (g)		
	25	50	100
Integrated plasma C-peptide (pmol · ml^{-1} · min)	213.5 ± 19.8*	297.9 ± 67.4*	498.6 ± 27.1*
Integrated insulin secretion (nmol/5 h)	46.8 ± 6.5*	65.3 ± 4.5*	106.7 ± 4.8*
Urine C-peptide (nmol/5 h)	3.0 ± 0.6*	3.3 ± 0.5	5.1 ± 0.6*
Urine C-peptide/creatinine (pmol/mg)	8.8 ± 2.0*	11.0 ± 3.0†	16.6 ± 3.3*†
Fractional C-peptide excretion (%)	6.1 ± 0.8 (2.8–9.0)	5.1 ± 0.8 (2.2–8.6)	4.9 ± 0.8 (2.9–8.5)
Creatinine clearance (ml/min)	163.9 ± 46.9	148.3 ± 33.7	134.6 ± 11.4
Urine C-peptide clearance (ml/min)	14.1 ± 2.5 (4.6–22.8)	11.5 ± 1.7 (3.5–16.4)	10.5 ± 1.5 (5.3–17.5)
Urine C-peptide clearance/creatinine clearance	0.10 ± 0.02 (0.04–0.20)	0.09 ± 0.01 (0.03–0.13)	0.08 ± 0.01 (0.04–0.15)

Values are means ± SE, with ranges in parentheses. Values sharing symbols in the same row are significantly different ($P < .05$).

cretion rate was found to correlate more closely with the fasting insulin secretion rate ($r = .97$, $P = .0001$) and fasting C-peptide ($r = .81$, $P = .0005$) and fasting insulin concentrations ($r = .62$, $P = .02$). The practical implication of these findings is that because the fractional urine C-peptide excretion in individual subjects is not known, comparisons of insulin secretion rates, based purely on urine C-peptide concentrations, are subject to considerable error. This is particularly true in situations where accurate quantitation of β-cell function is necessary, such as in the evaluation of the efficacy of immunosuppressive agents in the treatment of insulin-dependent diabetes (IDDM; 30). Although disappointing, this conclusion is hardly surprising considering that C-peptide appears in the urine only after secretion into the portal system, passage through the liver, appearance in the peripheral circulation, filtration by the glomerulus, and after tubular reabsorption of most of the filtered C-peptide (11,31,32). Thus, many factors (i.e., variations in the renal plasma flow, glomerular filtration rate, and the tubular reabsorption and degradation rate of C-peptide) may affect the excretion of C-peptide in urine, and differences in these factors between subjects may explain the weak correlation between urine C-peptide and insulin secretion, as well as the high intersubject variability of fractional C-peptide excretion that was found in our study. Variations from day to day in these factors may also explain the low intraindividual reproducibility of fractional C-peptide excretion and urine C-peptide clearance. Because only a small fraction of secreted C-peptide (~5%) appears in the urine (12–15), a small change in tubular reabsorption will result in a large change in the quantity of C-peptide excreted. Thus, if the percentage of secreted C-peptide excreted in the urine increases from, for example, 5 to 6%, the absolute amount of C-peptide in the urine will increase by 20%. This emphasizes the importance of our evaluation of the excretion of C-peptide in the urine in relation to its secretion rate or plasma concentration (3), in contrast to studying changes in absolute urine C-peptide excretion alone (4,33,34).

Thus, the most accurate method of quantitating insulin secretion rates seems to be to apply a two-compartmental analysis of peripheral C-peptide concentrations with individual C-peptide kinetic parameters. This method is particularly valuable when short-term changes in the pattern of insulin secretion are being studied or when accurate quantitation of insulin secretion is required. However, if this method is not available, measurement of both the fasting C-peptide and insulin concentrations correlate well with the 24-h insulin secretion rate and, although not fully quantitative, provide valuable insight into β-cell function. This is particularly true of the fasting C-peptide, which is not affected by changes in hepatic extraction such as may occur with insulin in obesity (11). Because we have previously demonstrated that the clearance of C-peptide from plasma is consistent from day to day in the same subject (18), the daily variability in plasma C-peptide can be assumed to accurately reflect changes in insulin secretion. In general, the results of our study suggest that urine C-peptide is a less accurate marker of insulin secretion than either the fasting C-peptide or insulin concentrations, and because it is more cumbersome and associated with uncertainties regarding the completeness of urine collection, this measure would appear not to yield additional useful information concerning β-cell function. In contrast to plasma C-peptide, these data demonstrate that the fraction of secreted C-peptide that is excreted in the urine may vary in the same individual. Thus, changes in urinary C-peptide may not necessarily reflect changes in β-cell secretion but may merely be due to variability in the urinary handling of the peptide. One advantage of urine C-peptide may be in the detection of small amounts of residual β-cell function in IDDM, when the fasting plasma C-peptide is below the detection limit of the assay, and the measurement of 24-h urine C-peptide, which provides an integrated measure of insulin secretion, may permit the detection of residual β-cell function (35,36).

In conclusion, we have clearly demonstrated in this study that the fraction of secreted C-peptide that is excreted in the urine varies considerably between subjects and in the same subject studied repeatedly. Although daily urine C-peptide excretion correlates significantly with total daily insulin secretion, the high inter- and intrasubject variability of fractional C-peptide excretion limits the value of urine C-peptide as an accurate quantitative measure of insulin secretion.

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