

Kinetics of Human C-peptide in Man

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SUMMARY

A review of studies concerned with the metabolism of human C-peptide showed that the kidney is the major organ in C-peptide removal. The turnover rate of C-peptide was similar to that of proinsulin but considerably slower than that of insulin.

An analysis of corresponding C-peptide and insulin concentrations in normal subjects after the administration of oral glucose or intravenous glucagon was used to define the relationships between the two peptides. These results show that different peripheral vein concentrations of insulin may correspond to identical C-peptide concentrations, depending on sampling conditions. *DIABETES* 27 (Suppl. 1):207-09, 1978.

Insulin is produced in the pancreatic β -cells by cleavage of its single-chain polypeptide precursor, proinsulin, into insulin, the connecting peptide (C-peptide), and two pairs of basic amino acids.^{447,451} Insulin and C-peptide are subsequently secreted into the portal circulation in equimolar quantities^{167,187,389} along with small amounts of proinsulin and its intermediate forms.^{157,386,387}

The position of the liver with respect to pancreatic outflow dictates that precise values for hepatic insulin removal be known in order to estimate insulin secretion from peripheral insulin concentrations. In contrast to insulin, C-peptide is removed only to a minor degree by the liver.^{236,460} For this reason, determination of the C-peptide concentration in peripheral venous plasma yields a more accurate, though indirect, measure of the insulin-secretory activity of pancreatic β -cells.^{167,187,301,393} Provided that the kinetics of C-peptide are known, the insulin secretion rate can be quantitated from peripheral C-peptide concentrations. This also applies to insulin-treated diabetics in whom exogenous insulin and endogenous insulin antibodies interfere with the measurement of endogenous insulin.³⁰¹

The present paper reviews the literature on

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C-peptide kinetics, with special emphasis on human studies. It also contains an analysis of the relationships between C-peptide and insulin in peripheral blood of normal man.

Metabolism of C-peptide

Following the equimolar secretion of insulin and C-peptide from the β -cells into the portal venous bed, the two peptides reach the liver. About 50 per cent of the insulin is removed by the liver,^{115,207,236,306} in contrast to only a minor fraction of the C-peptide,^{236,460} a finding consistent with the apparent lack of metabolic activity of C-peptide.^{160,518} From studies on the metabolism of bovine C-peptide infused into rats, Katz and Rubenstein²¹⁴ concluded that the kidney was the major site of degradation of C-peptide. Studies in human beings with different degrees of renal impairment point to the same conclusion. Thus, elevated concentrations of C-peptide were found in subjects with impaired renal function,^{379,521} and nephrectomized patients had higher C-peptide concentrations than patients with kidneys but without any demonstrable glomerular filtration.³⁷⁹ Since C-peptide is found in the urine,¹⁹⁰ urinary excretion as well as tubular uptake contributes to the renal C-peptide clearance. Peripheral uptake of C-peptide by muscle or adipose tissues does not seem to be significant, but direct experiments to elucidate this point have not been carried out.

Kinetics of C-peptide

Table 1 presents kinetic parameters for the turnover in man of endogenous as well as exogenous beta-cell peptides. The turnover rate of insulin is considerably faster than that of C-peptide or proinsulin.

The metabolic clearance rates of insulin and proinsulin appear to decrease with increasing concentrations of the hormones.⁴⁶⁴ Such an effect has not been demonstrated with C-peptide.

The wide range of values for the immunologic half-life of C-peptide ($T_{1/2,CP}$) in plasma may be due to different experimental conditions. Thus, the $T_{1/2,CP}$

TABLE 1
Kinetic parameters of insulin, C-peptide, and proinsulin in man

Authors	Insulin	C-peptide	Proinsulin
Horwitz et al. ⁸⁶	—	T _{1/2} = 11.1 min.	—
Kuzuya and Matsuda ²⁴⁴	T _{1/2} = 9.8 ± 1.3 min.	T _{1/2} = 20.1 ± 1.6 min.	—
Faber et al.	—	MCR = 4.4 ± 0.2 ml./min./kg. T _{1/2} = 33.5 ± 3.0 min.	—
Starr and Rubenstein ²⁷	T _{1/2} = 4.8 min.	—	T _{1/2} = 17.2 min.
Sönksen et al. ⁴⁶⁴	MCR = 11-34 ml./min./kg. T _{1/2} = 4.3 min.	—	MCR = 2.1-3.7 ml./min./kg. T _{1/2} = 25.6 min.

Human peptides were employed in all studies except that by Sönksen et al.,⁴⁶⁴ who used porcine proinsulin.

T_{1/2} = immunologic half-life.

MCR = metabolic clearance rate.

reported by Horwitz et al.¹⁸⁶ was derived from the serum C-peptide concentrations in two subjects after removal of insulinomas. Kuzuya and Matsuda²⁴⁴ calculated the T_{1/2,CP} from the plasma C-peptide immunoreactivity in six subjects after discontinuation of an infusion of glucagon and glucose. Both authors employed endogenous C-peptide, while we calculated the T_{1/2,CP} from the final part of the multiexponential plasma C-peptide curve obtained after intravenous injection of synthetic human C-peptide into six normal subjects (table 1). Additional studies in man with natural and other preparations of synthetic human C-peptide are needed to resolve these differences.

Studies in animals are of limited value for extrapolating to the human situation. Because many species of C-peptide are still unavailable in adequate amounts, most authors have had to use heterologous C-peptide systems. Oyama et al.³⁴² studied the disappearance curves of labeled tyrosylated natural porcine C-peptide in pigs and reported an average T_{1/2,CP} of 9.9 minutes. This T_{1/2,CP} was calculated from the middle part of a nonlinear curve in a double logarithmic plot. However, if the last part of the curve is used for this calculation, the average T_{1/2,CP} was about 30 minutes.

The metabolic clearance rates of C-peptide, calculated from the C-peptide concentration after injection of synthetic unlabeled C-peptide, were similar in normal and diabetic subjects. This indicates that the insulin-secretory capacity of normal and diabetic subjects can be directly compared from the plasma C-peptide concentrations. It also means that the insulin secretion rate can be calculated from the C-peptide concentration in peripheral blood. The finding by Kühl et al.²³⁶ that the liver does extract the C-peptide to a small extent suggests that the insulin secretion rate thus calculated may be somewhat underestimated because only 85 to 90 per cent of the secreted C-peptide reaches the peripheral vascular compartment.

C-peptide and Insulin in Peripheral Blood

Differences in the hepatic extraction²³⁶ and peripheral kinetics²⁴⁴ of insulin and C-peptide lead to a complex relationship between the concentrations of these peptides in peripheral blood.

The molar ratio of C-peptide and insulin is about 5 in normal fasting individuals^{101,172} and falls to between 2 and 3 after β -cell stimulation.¹⁰¹ This relationship was further studied by comparing the insulin and C-peptide concentrations from the initial and late phases of experiments in which β -cells were stimulated by different secretagogues. For these investigations, 16 normal-weight nondiabetic subjects were studied. Their ages ranged from 18 to 32 years. The plasma concentrations of insulin¹⁶⁶ and C-peptide¹⁷¹ were measured by radioimmunoassay. For the C-peptide determinations, antiserum MI230 was used.⁹⁹

The short stimulus consisted of 1 mg. glucagon administered intravenously as previously described.¹⁰¹ The right panel of figure 1 shows the corresponding values of insulin and C-peptide in the fasting state and two and four minutes as well as 15 and 20 minutes after the injection of glucagon in 10 normal subjects. The longer-lasting β -cell stimulus entailed an oral glucose load of 50 gm. Figure 1 (left panel) shows the corresponding values of insulin and C-peptide in the fasting state and 15 and 30 minutes, as well as 90 and 120 minutes after the glucose load in six normal subjects. Regression lines through the early values (two and four minutes of the glucagon test, 15 and 30 minutes of the oral glucose load) and through the late values (15 and 20 minutes of the glucagon test, 90 and 120 minutes of the oral glucose load) were constructed by the method of least squares. The slopes of the regression lines during the oral glucose load were 3.3 and 4.7 (early and late values, respectively). The corresponding slopes for the glucagon test were 2.3 and 2.6, respectively.

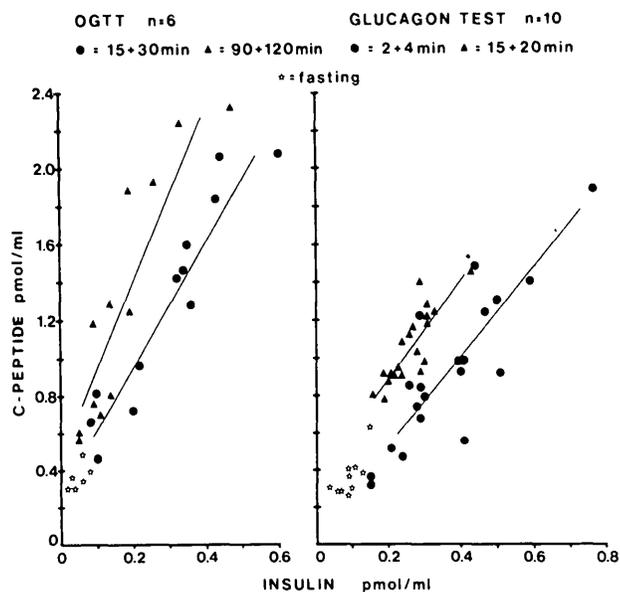


FIG. 1. Corresponding concentrations of insulin and C-peptide in the fasting state together with initial and late values during an oral glucose load (OGTT) and intravenous glucagon test in normal subjects.

As can be seen from figure 1, the early values from both tests cover an area clearly to the right of the area covered by the late values. This indicates that the insulin concentration corresponding to a given C-peptide concentration is higher during the early phase of β -cell stimulation than during the late phase.

The higher slopes observed after oral glucose than after the glucagon test indicate that lower insulin concentrations coexist with the same C-peptide concentrations after prolonged stimulation of the β -cell.

These observations are the basis for developing the schematic diagram illustrating the relationships between insulin and C-peptide (figure 2). In the fasting state, the C-peptide concentration is five to seven times higher than the insulin concentration, owing to the slower turnover of C-peptide. After stimulation, the concentrations of both peptides increase, but the increase is relatively greater for insulin, because of its lower basal concentration. The curve describing the relationship between insulin and C-peptide during rapid secretion therefore deviates to the right. When the clearance rates of the peptides exceed their post-hepatic delivery rate, their peripheral concentrations decline. Because of the higher clearance rate of insulin, lower concentrations of insulin than of C-peptide are found. The curve representing the relationship between the two peptides during decreasing secretion, therefore, deviates to the left.

With short-term stimulation, the relationship be-

tween C-peptide and insulin is mostly determined by their relative rates of secretion and their corresponding posthepatic molar ratio. During the glucagon test, therefore, a shift to the right takes place for both curves, as indicated by the lower slopes of the regression lines. On the other hand, the shift to the left of both curves during an oral glucose load shows that the difference in their metabolic clearance rates is the decisive factor in the relationship between the two peptides during prolonged stimulation.

These results demonstrate that the relationships between C-peptide and insulin are complex and that different concentrations of insulin may correspond to the same C-peptide concentration, depending on the conditions of sampling.

ACKNOWLEDGMENT

The dedicated technical assistance of Miss Bodil Mathiasen and Miss Jane Falk as well as the excellent secretarial help of Mrs. Lotte Rosentoft and Miss Helle Espersen are gratefully acknowledged.

The English version of this article was revised by I. Munck.

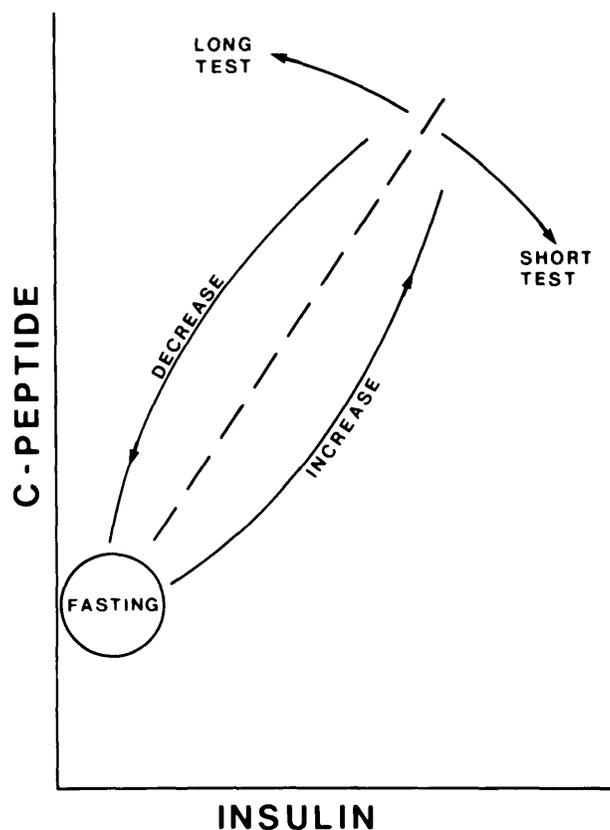


FIG. 2. Schematic drawing of the relationships between insulin and C-peptide in peripheral blood of normal subjects. Detailed information is given in the text.