Incretin and Islet Hormone Responses to Meals of Increasing Size in Healthy Subjects

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Context: Postprandial glucose homeostasis is regulated through the secretion of glucagon-like peptide 1 (GLP-1) through the stimulation of insulin secretion and inhibition of glucagon secretion. However, how these processes dynamically adapt to demands created by caloric challenges achieved during daily life is not known.

Objective: The objective of the study was to explore the adaptation of incretin and islet hormones after mixed meals of increasing size in healthy subjects.

Design: Twenty-four healthy lean subjects ingested a standard breakfast after an overnight fast followed, after 4 hours, by a lunch of a different size (511, 743, and 1034 kcal) but with identical nutrient composition together with 1.5 g paracetamol. Glucose, insulin, C-peptide, glucagon, intact GLP-1, and glucose-dependent insulinoctropic polypeptide (GIP) and paracetamol were measured after the meals.

Main Outcome Measure: Area under the 180-minute curve (AUC) for insulin, C-peptide, glucagon, GLP-1, and GIP and model-derived β-cell function and paracetamol appearance were calculated.

Results: Glucose profiles were similar after the two larger meals, whereas after the smaller meal, there was a postpeak reduction below baseline to anadir of 3.8 ± 0.1 mmol/L after 75 minutes (P = .001). The AUC for GLP-1, GIP, insulin, and C-peptide were significantly higher by increasing the caloric load as was β-cell sensitivity to glucose. In contrast, the AUC glucagon was the same for all three meals, although there was an increase in glucagon after the postpeak glucose reduction in the smaller meal. The 0- to 20-minute paracetamol appearance was increased by increasing meal size.

Conclusion: Mixed lunch meals of increasing size elicit a caloric-dependent insulin response due to increased β-cell secretion achieved by increased GIP and GLP-1 levels. The adaptation at larger meals results in identical glucose excursions, whereas after a lower caloric lunch, the insulin response is high, resulting in a postpeak suppression of glucose below baseline. (J Clin Endocrinol Metab 100: 561–568, 2015)

It has been shown that the size of the glucose load in an oral glucose tolerance test has only a minor impact on the plasma glucose excursion in healthy subjects (1). The reason for this is that insulin secretion is increased by increasing the glucose load by such a degree that the resulting insulin levels are adequate for effectuating the larger glucose load into a similar glucose excursion (2, 3). Furthermore, Pilichiewicz et al (4) have similarly shown an almost identical glycemia after intraduodenal infusion of glucose at 4 kcal min⁻¹ and 2 kcal min⁻¹ accompanied by higher insulin and glucagon-like peptide-1 (GLP-1) responses for the higher rate of infusion. Thus, a finely tuned

Abbreviations: AUC, area under the curve; E, energy; GIP, glucose-dependent insulinoctropic polypeptide; GLP-1, glucagon-like peptide-1; iGIP, intact GIP; iGLP-1, intact GLP-1.
regulation of GLP-1 and insulin secretion in relation to glucose loads seems to exist, the purpose of which is to assure identical glucose levels, which may be a key factor for glycemic control. A similarly increased incretin hormone and insulin secretion with increased caloric challenges after ingestion of a mixed meal would be important for glucose homeostasis in regular daily life. In one study, Vilsbøll et al (5) demonstrated that the GLP-1, glucose-dependent insulinotropic polypeptide (GIP), and insulin responses were more pronounced after a 520-kcal breakfast meal compared with a 260-kcal breakfast in obese subjects, whereas the glucose profiles were similar after the two meals, indicating an adaptation of insulin and incretin hormones also after mixed meal ingestion.

However, although this study showed increased secretion of incretin hormones and insulin after increased caloric content during a breakfast, whether incretin hormones and the β-cells respond with sufficiently increased secretion after meals ingested at more regular daily life times and of more typical sizes is not known. This is important because 260- and 520-kcal meals are not representative of a normal lunch or dinner, when most subjects ingest their highest caloric meal (6). Therefore, it is still not known whether there is an incretin and islet hormone adaptation to meal ingestion in normal physiology.

This fundamental question was explored in this study in which we analyzed the postlunch response of GLP-1, GIP, and β-cell function to three lunch meals with identical nutritional composition but with different size (511, 743, and 1034 kcal), being representative of the recommended range of normal lunch calories (7). Meals were ingested at the same time of the day (noon) after a standardized breakfast at 8:00 AM (ie, standardized lunch time and prelunch the same time of the day (noon) after a standardized break).

Subjects and Methods

Subjects

This was a single-center study involving 24 healthy lean subjects, 12 men and 12 women, being 20–28 years old [mean age 25 ± 2 y (SD)]. They had no personal history of diabetes or gastrointestinal diseases. Body mass index was 20–25 kg/m² (mean 22 ± 1.4 kg/m²). Six of the female subjects had combined contraceptive pills, two had progesterone-only pill, two had a single contraceptive implant, and two did not use hormone contraception. No other drugs were taken.

Ethics and good clinical practice

The study was approved by the Ethics Committee of the Lund University. All the subjects gave their written informed consent before entry into the study. The study was registered at www.clinicaltrials.gov (identification number NCT01366781). The study was conducted using good clinical practice and was in accordance with the Declaration of Helsinki.

Study protocol

All subjects ingested the three lunches of different size after a standardized breakfast, which was the same on all occasions. Thus, on three occasions in randomized order, separated by at least 3 weeks and maximally 6 weeks, and after an overnight fast, the subjects were served a standardized breakfast at 8:00 AM, consisting of 524 kcal (19% protein, 18% fat, 63% carbohydrate) as rye and white whole-meal bread (60 g), margarine (40% enriched Becel; 10 g), ham from smoked pork (fat 3%; 15 g), cheese (fat 17%; 15 g), juice (285 g), green paprika (40 g), light sour milk fat 0.5% enriched (200 g) and cereals mix-muesli with fruit (40 g). After the breakfast, the subjects had no food or drink until 12:00 PM, when they were served a lunch meal based on sirloin steak with the composition according to Supplemental Table 1, containing 511 kcal, 743 kcal, or 1034 kcal on three different occasions. Meals were consumed within 10–20 minutes. A tablet of paracetamol (1.5g; GlaxoSmithKline) dissolved in water was administered together with the lunch meals for analyses of paracetamol kinetics (10, 11). All three meals had identical nutrient compositions [protein energy (E) 18%, fat E32%, and carbohydrates E50%]. The females did the challenge on the same day of the menstrual period. Blood samples were taken throughout a 300-minute period after lunch intake at time point t = −5, −2, 5, 10, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240, and 300 minutes.

Analysis

Blood samples for the assay of glucose, insulin, C-peptide, glucagon, and paracetamol were collected into chilled tubes containing EDTA (7.4 mmol/L) and aprotinin (500 KIU/mL; Novo Nordisk) and were immediately centrifuged at 4°C; plasma was frozen at −20°C until analysis. Glucose was measured using the glucose oxidase method. Insulin levels were analyzed using an ELISA (Mercodia Corp). Glucagon and C-peptide were analyzed using a double-antibody RIA (Linco Research). Blood samples for the determination of intact GLP-1 (iGLP-1) and intact GIP (iGIP) were collected into chilled tubes containing EDTA and aprotinin with the addition of the dipeptidyl peptidase-4 inhibitor diprotin A (0.1 mmol/L; Bachem). iGLP-1 and iGIP concentrations were determined with ELISA (Millipore Corp and De-
following formula (17):

$$\frac{I(t) + ISR(t)/hPF}{Glg(t)(1 + MCRGlg/hPF)}$$

where ISR(t) is insulin secretion at time t, hPF is hepatic plasma flow, I(t) and Glg(t) are the measured peripheral plasma concentrations of insulin and glucagon at time t, and MCRGlg is the metabolic clearance rate of glucagon. hPF was estimated by multiplying the cardiac index (3.2 L-min⁻¹m⁻²)(18) by a plasma to blood ratio of 0.6 and by assuming that the hepatic blood flow is 30% of the cardiac index (0.576 L-min⁻¹m⁻²) (19). MCRGlg was taken to be 0.537 L-min⁻¹m⁻² (20). Paracetamol appearance (in micromoles per minute) was calculated by deconvolution, using the two-exponential model of paracetamol kinetics proposed by Rawlins et al. (11).

From the rate of paracetamol appearance, the following three parameters were calculated: 1) the amount of paracetamol that appeared during the first 20 minutes (early paracetamol appearance) as a fraction of the recovered dose; 2) the amount of paracetamol appeared between 20 and 60 minutes (late paracetamol appearance) as a fraction of the recovered dose; and 3) the mean time of paracetamol appearance as the integral of the product of time and paracetamol appearance, divided by the recovered dose. These calculations were performed over a time period of 120 minutes because the rate of the paracetamol appearance was virtually zero after 2 hours. The models give estimates every 5 minutes, ie, more often than the blood samples were taken. Reported values are mean ± SEM unless otherwise stated. A paired t test and a one-way Bonferroni compression test were used to test the significance between the meals test. Relationships between variables were assessed using the Spearman correlation coefficient ($\rho$).

**Results**

**Glucose**

Plasma glucose rose from a baseline of approximately 4.5 mmol/L after all three meals to reach a peak after 30 minutes. For the two larger meals, the peak glucose levels were exactly the same (5.7 ± 0.2 mmol/L), and after the peak, the values returned to baseline after 90 minutes (Figure 1). In contrast, after the smaller meal, the glucose peak was somewhat lower (5.3 ± 0.1 mmol/L), and, more importantly, there was a postpeak reduction below baseline to a nadir of 3.8 ± 0.1 mmol/L after 75 minutes ($P < .001$) before the levels reached baseline. There were no differences in AUCglucose among the meals (Table 1).

**Insulin, C-peptide, and $\beta$-cell function**

Plasma insulin and C-peptide concentrations increased after all three meals, with peaks at 30 minutes for insulin and at 45 minutes for C-peptide levels (Figure 1). After the peak, insulin levels went down but were elevated in a calorie-dependent manner above baseline throughout study period ($P < .001$). The insulinogenic index, AUCinsulin, and AUCC-peptide were significantly increased by increas-

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**Figure 1.** Plasma levels of glucose, insulin, and C-peptide, and insulinogenic index after ingestion of 511 kcal (●●), 743 kcal (○○), and 1034 kcal (△△) mixed meal in healthy subjects (n = 24). Means ± SE are shown. (Published online: 2014-2865; doi: 10.1210/jc.2014-2865 jcem.endojournals.org)
ing meal size (Figure 1 and Table 1). Increasing the meal size produced also an increase in insulin secretory rate and β-cell glucose sensitivity, whereas the differences in the rate sensitivity did not reach statistical significance (Figure 2). β-Cell glucose sensitivity was significantly higher after 1034 kcal (92 ± 10 pmol·min⁻¹·m⁻²·mmol L⁻¹) than after 511 kcal (64 ± 8 pmol·min⁻¹·m⁻²·mmol L⁻¹; P < .001) but not different between 743 and 511 kcal. The β-cell potentiation factor showed the typical initial increase followed by a gradual return to baseline; with the higher caloric intake, the increase was progressively more sustained, and the 150- to 50-minute potentiation ratio was progressively increased (Figure 2). Insulin clearance decreased with meal size (Table 1) and was inversely related to total insulin secretion across all meals (ρ = −0.50, P < .0001).

**Incretin hormones**

Intact GLP-1 concentrations increased after all three meals in a calorie-dependent manner (Figure 3). The 30-minute peak levels were 8.9 ± 0.8 pmol/L after 511 kcal, 11.4 ± 0.9 pmol/L after 743 kcal, and 16.0 ± 1.5 pmol/L after 1034 kcal (P < .001). After the 30-minute peak, the levels of iGLP-1 decreased after all meals, although the levels remained above the baseline during the length of the study. The AUCiGLP-1 was significantly higher by increasing the caloric load in the meal (P = .004; Table 1). iGIP concentrations increased from the baseline after meal ingestion with a peak at 60 minutes, ie, slightly later than the iGLP-1 peak. The peak iGIP levels were 71.1 ± 5.0 pmol/L after 511 kcal, 82.0 ± 5.4 pmol/L after 743 kcal, and 93.1 ± 4.6 pmol/L after 1034 kcal (P = .01). The AUCiGIP was significantly increased by increasing caloric load (Table 1). In the whole data set, the 180-minute incremental GLP-1 AUC was positively related to all model-derived β-cell function parameters, in a similar way (ρ = approximately 0.25, P < .05). The relationships with GIP were not significant, with the exception of the potentiation ratio (ρ = 0.35, P < .005).

**Glucagon and prehepatic insulin to glucagon ratio**

Plasma glucagon concentrations increased after meal ingestion with a peak level after 30 minutes, with no significant difference between meals (Figure 4). After the peak, glucagon reached baseline after 60 minutes. After the 511-kcal meal, the glucagon levels increased between 60 and 75 minutes, ie, when glucose levels had fallen below baseline (by 28.5 ± 1.5 pmol/L; P = .02). The AUCGluca gon did not differ between the meals (Table 1). We also modeled the prehepatic insulin to glucagon molar ratio, a variable quantifying the influence of islet hormones on hepatic glucose production. The ratio increased after meal ingestion to a peak at 30 minutes (Figure 4); the AUC increased by increasing the caloric loads (Table 1).

**Paracetamol**

The average recovery of paracetamol in all studies was approximately 1.4 g, with no difference in paracetamol bioavailability between meals. However, as the meal size increased, the paracetamol appearance curve

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**Table 1.** AUC for Insulin, Glucose, C-Peptide, Glucagon, Prehepatic Insulin to Glucagon Ratio, iGLP-1, iGIP, and Paracetamol, and Insulinogenic Index, Prehepatic Insulin to Glucagon Ratio, Paracetamol Appearance and Insulin Clearance After Ingestion of 511-kcal, 743-kcal, and 1034-kcal Mixed Meal in Healthy Subjects (n = 24)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>511 kcal</th>
<th>743 kcal</th>
<th>1034 kcal</th>
<th>P (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mmol/L-min</td>
<td>803 ± 24</td>
<td>861 ± 25</td>
<td>867 ± 28</td>
<td>.26</td>
</tr>
<tr>
<td>Insulin, pmol/L-min</td>
<td>16.367 ± 1880</td>
<td>22.365 ± 2330</td>
<td>30.147 ± 3774</td>
<td>.0001</td>
</tr>
<tr>
<td>C-peptide, nmol/L-min</td>
<td>0.41 ± 0.03</td>
<td>0.57 ± 0.03</td>
<td>0.79 ± 0.05</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Glucagon, pmol/L-min</td>
<td>5228 ± 194</td>
<td>5583 ± 235</td>
<td>5128 ± 245</td>
<td>.34</td>
</tr>
<tr>
<td>iGLP-1, pmol/L-min</td>
<td>1172 ± 145</td>
<td>1342 ± 153</td>
<td>1684 ± 163</td>
<td>.004</td>
</tr>
<tr>
<td>iGIP, pmol/L-min</td>
<td>8889 ± 528</td>
<td>11.094 ± 479</td>
<td>13.152 ± 596</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Insulinogenic index, nmol/mmol</td>
<td>0.15 ± 0.01</td>
<td>0.17 ± 0.01</td>
<td>0.20 ± 0.01</td>
<td>.01</td>
</tr>
<tr>
<td>Prehepatic insulin to glucagon ratio, pmol/pmol-min</td>
<td>760 ± 63</td>
<td>972 ± 94</td>
<td>1363 ± 163</td>
<td>.0016</td>
</tr>
<tr>
<td>Paracetamol appearance 0–20 min, % of total</td>
<td>58 ± 4</td>
<td>72 ± 4</td>
<td>81 ± 5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Paracetamol appearance 20–60 min, % of total</td>
<td>31 ± 3</td>
<td>21 ± 4</td>
<td>8 ± 4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Paracetamol mean appearance time, min</td>
<td>28.2 ± 1.9</td>
<td>22.4 ± 1.4</td>
<td>21.2 ± 1.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Insulin clearance, L/min/m²</td>
<td>1.30 ± 0.11</td>
<td>1.18 ± 0.08</td>
<td>0.96 ± 0.05</td>
<td>.005</td>
</tr>
</tbody>
</table>

**Figure 2.** Insulin secretory rate, the β-cell potentiation factor, and the β-cell dose response after ingestion of 511 kcal (●-●), 743 kcal (○-○), and 1034 kcal (△-△) mixed meal in healthy subjects (n = 24). Means ± SE are shown.
was shifted to the left (Figure 4); thus, with larger meals, the mean appearance times were shorter, the early appearance was higher, and the late appearance was lower (Table 1). The mean appearance time was strongly inversely related to early appearance (\( \rho = -0.8, P < .0001 \)). Across all meals, the pattern of paracetamol appearance was related to the GLP-1 response and to a lesser extent to the GIP response, as assessed by the 180-minute incremental hormone AUC. In particular, the GLP-1 response was directly related to early paracetamol appearance (\( \rho = 0.48, P < .0001 \)) and inversely to the mean appearance time (\( \rho = -0.46, P < .0001 \)). Thus, a higher early paracetamol appearance and shorter appearance time produced a stronger GLP-1 response. The results for GIP were similar but with weaker correlations (\( \rho = -0.38, P < .001 \), and \( \rho = 0.19, P = .1 \), for the early appearance and the mean appearance time, respectively).

**Discussion**

Metabolic adaptation to changing demands is required for normal homeostasis, and this is particularly so for glucose homeostasis because increasing caloric loads require higher insulin responses to avoid hyperglycemia. This has been shown after breakfast ingestion after an overnight fast when meals with different caloric loads were found to have very similar glucose responses but clearly different insulin responses, with higher insulin response after higher caloric intake being required to prevent hyperglycemia (5, 21, 22). In the present study, we explored the responses of glucose, incretin hormones, and islet hormones after normal lunches of different caloric content but with exactly the same composition to establish the changes in glucose, incretin hormone, and islet hormone secretion after caloric demands created by different caloric loads as seen in daily life. The meals had a caloric content of 511 kcal, 743 kcal, and 1034 kcal with 60% of the energy from carbohydrates, 32% from fat, and 18% from protein. Meals were ingested at the same time of the day (noon) after a fixed fast of 4 hours after a standardized breakfast taken at 8:00 AM in the morning. Accounting for these factors is important because the \( \beta \)-cells have a memory effect after the preceding stimulation (8), which has to be controlled for, and because secretion of incretin hormones shows a diurnal pattern (9).

The main findings of the study are as follows: 1) there is a clear augmentation of the responses of the incretin hormones after increased caloric ingestion at lunch; 2) for the two largest meals, this is translated into an adaptive increase in \( \beta \)-cell function and circulating insulin, which perfectly adapts to the caloric demand, resulting in identical glucose excurs-
sions; and 3) the smaller mixed meal (511 kcal) resulted in a postpeak glucose reduction below baseline, which was restored in association with an increase in glucagon to prevent hypoglycemia.

The augmentation in insulin secretion and β-cell function after meal ingestions could be explained by the dynamics of the incretin hormones because both GLP-1 and GIP increased in a caloric-dependent manner and because both GLP-1 and GIP are known to glucose dependently stimulate insulin secretion (23, 24). The increase in incretin hormones by increased meal size might be explained by an increased nutrient exposure of K cells and L cells in the intestinal mucosa because both cells have been shown to respond to luminal carbohydrate, fat, and protein (23, 25). Although the K cells are predominantly located in the proximal part of the intestinal tract, whereas L cells are primarily located in the distal part (26), GLP-1 levels increased at the same time as GIP and the peak of GLP-1 was seen earlier than the peak GIP in all three meals. This would suggest a complex intergut mechanisms that may involve neural factors (27) but may also be explained by the occurrence of L cells also more proximally (26). Therefore, although the study shows a clear physiological incretin hormone and insulin secretion adaptation to increasing caloric load after a normal lunch ingestion, which are also related to gastric emptying, the precise mechanism underlying this adaptation needs to be explored in future studies.

Insulin secretion was augmented by increasing caloric intake, as evident by the enhanced levels of insulin and C-peptide. Our results suggest that this is achieved by the higher incretin hormones, resulting in increased β-cell function (insulinogenic index) because the increase in glucose levels after meal ingestion was similar in the three meals and could not explain the difference. In addition to the direct measure (ie, insulinogenic index), this is also supported by the model analyses of insulin secretion, which showed increased β-cell glucose sensitivity after ingestion of the larger meal compared with the smaller meals. We also found that insulin clearance was reduced by increasing the meal size, which further adds to the hyperinsulinemia. The reduced insulin clearance may be explained by the augmented insulin secretion that yielded elevated C-peptide and insulin concentrations at the liver level. Stimulated insulin secretion with hyperinsulinemia has been shown to reduce hepatic insulin extraction (28–30) and thus insulin clearance (31). This is important because it has previously been shown that a reduction of insulin clearance contributes to the strong insulin response associated with the incretin effect in humans (32). The incretin hormones may therefore indirectly contribute to reduced insulin clearance, which is supported by results in an experimental mouse model that GLP-1 reduces insulin clearance (33).

Glucagon secretion was stimulated by all three meals, which may be explained by the protein in the meal and activation of the autonomic nervous system (34, 35). However, there was no difference between the meals, suggesting that the α-cells are not subject to dynamic adaptation to the meal caloric content similar to that of the β-cells. Collectively, this resulted in turn in a higher estimated prehepatic insulin to glucagon ratio by increasing the caloric load, which is a reflection of a stronger islet signal to the liver to restrain the hepatic glucose release, which may be a major mechanism protecting from hyperglycemia after the largest meal. An interesting observation in the present study was that glucagon levels increased after a postpeak reduction of glucose below baseline at 60–75 minutes after meal ingestion of the small meal. This would thus serve as a protection from hypoglycemia after a mixed meal of smaller size. The increase in glucagon at this stage after meal ingestion may be achieved by GIP because GIP has been shown to stimulate glucagon secretion at low glucose (36) and euglycemia (37). The result thus demonstrated a finely tuned balance of insulin and glucagon to regulate glucose homeostasis in healthy subjects.

It is known that the rate of gastric emptying contributes to postprandial glucose control in healthy subjects (38). In this study we evaluated gastric emptying after all meals by using the indirect paracetamol test. Although easy to perform and noninvasive, we acknowledge that this technique is not the best test for estimating gastric emptying (39); nonetheless, it has been validated by observing paracetamol appearance in the larger meals may be a sign of a rapid increase in early gastric emptying by increasing the size of a solid meal. This confirms previous results that increasing meal size increases gastric emptying (40, 41); this may be due to increased antral motility that results from activated gastric wall stretch and volume receptors (38, 41). This rapid gastric emptying might have contributed to the higher incretin levels and the subsequent reduction in paracetamol appearance in the larger meals may be a sign of the GLP-1 induced inhibition of gastric emptying, the ileal brake (42).

In conclusion, we demonstrate that increasing meal size elicits a caloric-dependent insulin response due to increased β-cell secretion achieved by increased GIP and GLP-1 levels to which an initial rapid gastric emptying contributes in combination with educed insulin clearance. The increased insulinemia at the two larger meals perfectly adapts to the caloric demand with higher insulin after
larger than medium meal size, resulting in identical glucose excursions. In contrast, after a lower caloric lunch (511 kcal), the insulin response seems to be inappropriately high, resulting in postpeak suppression of glucose below baseline. Based on these findings, we suggest that there is an almost perfect adapting insulin response to caloric demands after mixed lunch meals of medium or large size in healthy humans, whereas a lower caloric meal may need extra carbohydrate content to prevent eliciting a counterregulatory response.

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Author contributions include the following: W.A. and B.A. designed and performed the study and wrote the manuscript. G.P., A.M., and R.B. performed the modeling of the data. W.A., B.O., G.P., R.B., A.M., and B.A. researched the data and contributed to the interpretation of the data and discussion, review, and editing of the manuscript. B.A. is the guarantor of the work and takes responsibility for the contents of the article.

This study had a trial registry number of NCT01366781.

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References

C-peptide secretion and kinetics in humans: direct and model-based measurements during OGTT. Am J Physiol Endocrinol Metab. 2001;E966–E674.


