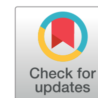

The Measurement of Insulin Clearance

Francesca Piccinini and Richard N. Bergman

Diabetes Care 2020;43:2296–2302 | https://doi.org/10.2337/dc20-0750

Downloaded from http://diabetesjournals.org/care/article-pdf/43/9/2296/630461/dc200750.pdf by guest on 20 August 2022

REVIEW

Insulin clearance has recently been highlighted as a fundamental aspect of glucose metabolism, as it has been hypothesized that its impairment could be related to an increased risk of developing type 2 diabetes. This review focuses on methods used to calculate insulin clearance: from the early surrogate indices employing C-peptide:insulin molar ratio, to direct measurement methods used in animal models, to modeling-based techniques to estimate the components of insulin clearance (hepatic versus extrahepatic). The methods are explored and interpreted by critically highlighting advantages and limitations.

Insulin has a unique pattern of distribution (Fig. 1). Immediately following release from the pancreatic β-cells, insulin enters the abdominal portal vein, and then flows directly into the liver. About half of newly secreted insulin is taken up by hepatocytes on the first pass through the liver before entering extrahepatic circulation. We previously suggested that because the first-pass extraction of insulin is altered by environmental and genetic factors (1), the liver acts as a gateway for insulin, delivering only the appropriate mass of insulin into the organism in proportion to metabolic need. Insulin that survives the first pass through the liver enters the hepatic veins and, thus, the systemic circulation wherein it can act on tissues. Ultimately, it is cleared by insulin sensitive tissues including skeletal muscle, kidneys, and liver (after recirculation) (2). Circulating plasma insulin is thus determined by the balance between insulin release and clearance, which are both important parameters to establish plasma insulin levels.

Even though there are direct arteriovenous methods for measuring insulin secretion and clearance in vivo, they are not directly applicable to humans, as they require portal vein and hepatic artery and vein blood samples, as well as estimation of hepatic blood flow (3). To surmount this inapplicability by still allowing a quantification of insulin secretion and clearance, indirect approaches based on kinetic modeling have become a powerful alternative to calculate insulin release and clearance during oral (meal, oral glucose tolerance test [OGTT]) and intravenous glucose challenges (clamp, frequently sampled intravenous glucose tolerance test [FSIGT]). The importance of modeling insulin clearance, rather than secretion only, was recently emphasized, as we hypothesized that lower insulin clearance might be causal for an increased risk of type 2 diabetes (4): the ability to quantify all of the glucose metabolism parameters through modeling is fundamental to provide a complete clinical overview of the diabetes pathology. Additionally, hyperinsulinemia secondary to reduced clearance may play a role in pathogenesis of cognitive dysfunction including Alzheimer's disease and some forms of cancer (5). Thus, is it possible that insulin clearance may be an important factor in a plethora of important diseases of Western society.

In this work, we review the primary direct and indirect methods to estimate insulin clearance in large animals and in humans. We use the term *insulin clearance* to describe the disappearance of insulin from the bloodstream in the entire organism,

Diabetes and Obesity Research Institute, Cedars-Sinai Medical Center, Los Angeles, CA

Corresponding author: Richard N. Bergman, richard.bergman@cshs.org

Received 5 April 2020 and accepted 14 April 2020

This article contains supplementary material online at https://doi.org/10.2337/figshare.12152271.

© 2020 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at https://www.diabetesjournals.org/content/license.

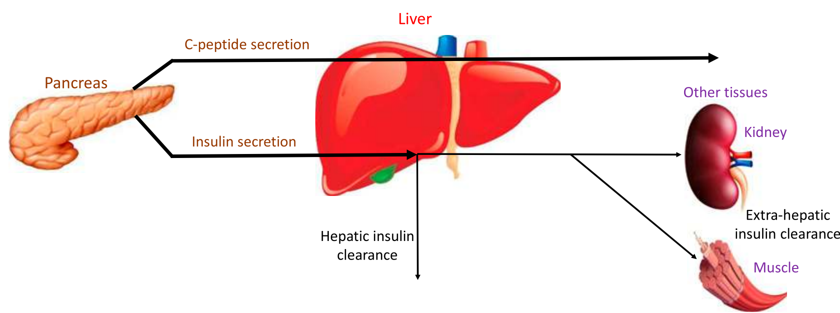

Figure 1—The insulin secretion and clearance rationale. Insulin and C-peptide are equimolarly secreted by the pancreatic β-cells. While C-peptide clearance is considered negligible, insulin undergoes hepatic (by the liver) and extrahepatic (by other tissues such as kidney or muscle) clearance.

which we conceptualize as the sum of two independent processes: hepatic clearance and extrahepatic clearance. Hepatic clearance is the removal of a significant portion of secreted insulin by the liver during the first pass through the hepatic portal circulation, and it also includes the removal of insulin by the liver after recirculation. Extrahepatic clearance is the disappearance of the hormone in other tissues, including skeletal muscle, kidney, and heart. The term *insulin extraction* is the fractional amount (%) of secreted insulin that undergoes removal per unit time, which can be either hepatic or extrahepatic; the calculation of each insulin clearance component is proportional to the corresponding extraction amount (see Table 1 for a glossary of all the terms).

HEPATIC INSULIN EXTRACTION AS C-PEPTIDE TO INSULIN MOLAR RATIO

Plasma C-peptide concentrations were recognized as useful for the calculation of insulin secretion following the discovery of proinsulin and its enzymatic splitting into equimolar concentrations of insulin and C-peptide in the pancreatic β-cells (6). Therefore, given the equimolar secretion of C-peptide and insulin, the generally accepted assumption of the negligible extraction of C-peptide by the liver, and its constant metabolic clearance rate under physiologic conditions, it is possible to estimate insulin secretion rate (ISR) from plasma C-peptide concentrations (7).

An early method to quantify the hepatic insulin fractional extraction (HE) was the C-peptide:insulin molar ratio, as well as the ratio between the incremental areas under the curves (AUC) of the same peptides after nutrient ingestion. These simple calculations have been extensively used both in the fasting state (8) and after oral (9) or intravenous (10) glucose challenges, and they are still employed, for example, see Meier et al. (11) or Heinrich et al. (12). However, the pitfalls of this method were pointed out very early by Polonsky et al. (7) as. If C-peptide and insulin had identical kinetics, the molar ratio would in fact reflect insulin clearance. However, the C-peptide:insulin molar ratio in the blood depends not only on the release rates of these peptides from the pancreatic islets, but also upon their individual disappearance kinetics. Insulin and C-peptide have very different plasma half-lives of 4 vs. 30 min, respectively (7). Additionally, C-peptide kinetics can be described by two compartments (13), whereas insulin has been expressed with one (14) to two (2) or three compartments (15). The different kinetics makes it problematic to simply use the molar ratio as an accurate estimate of disappearance rates. Any changes in either insulin or C-peptide kinetics can alter this C-peptide: insulin molar ratio under fasting conditions and also their AUC ratio after a nutrient glucose stimulus. For example, considering two different subjects analyzed in (16), while the C-peptide:insulin AUC ratio provides a 27% increment of HE from subject 1 to subject 2, modeling techniques, described below (2), reveal a 200% difference of HE between them.

For all the reasons above, the C-peptide: insulin molar ratio depends on several independent factors, and thus, the molar ratio cannot be considered an accurate calculation of HE. Furthermore, with this method, no information about the extrahepatic component of insulin clearance is provided. Alternative approaches must be used.

Table 1—Glossary

Term	Definition
Insulin clearance	Hepatic and extrahepatic removal of insulin
Hepatic insulin clearance	Removal of a portion of secreted insulin by the liver during the first pass across portal circulation and later on during recirculation
Extrahepatic insulin clearance	Removal of a portion of secreted insulin by organs and tissues other than the liver
Insulin extraction	The fractional amount (%) of secreted insulin that undergoes removal, which can be either hepatic (HE) or extrahepatic; the corresponding clearance component is proportional to it

IN VIVO MEASURE OF INSULIN CLEARANCE

In contrast to the C-peptide:insulin molar ratio, accurate and direct methods exist for estimating insulin clearance in vivo. Asare-Bediako et al. (17) compared two indirect estimates of insulin clearance in dogs with direct arteriovenous measurement. The first indirect method was proposed based on the euglycemic-hyperinsulinemic clamp (EGC): this allowed the authors to estimate the metabolic clearance rate (MCR) in vivo (17) as the ratio between exogenous insulin infusion rate and the resulting steady-state plasma insulin concentration (17,18). The increase in insulin during a clamp is not simply due to the exogenous insulin infusion rate, as the endogenous secretion is often suppressed, and the increment of insulin must correct for suppression of endogenous insulin appearance. Also, while this method is widely used (19,20), it does not distinguish hepatic from extrahepatic clearance.

A second indirect method (17) is the calculation of the fractional clearance rate of insulin (FCR) during the FSIGT (that includes an intravenous insulin injection). Often, investigators have assumed a single exponential decline in insulin after injection (21,22). This monoexponential

Downloaded from http://diabetesjournals.org/care/article-pdf/43/9/2296/630461/dc200750.pdf by guest on 20 August 2022

assumption of insulin disappearance does not account for changes in the endogenous insulin release. In fact, there are temporal changes in endogenous insulin release during the FSIGT (23), which make a monoexponential assumption of insulin disappearance result into an incorrect estimate of insulin clearance. Despite its limitations, the monoexponential assumption has been employed to estimate clearance in several large clinical studies (24).

A novel approach to direct measurement of HE was used in the canine model (17,25). The method requires intraportal as well as peripheral insulin infusion (PPII) during the use of an EGC (see Fig. 2*A*). In this approach, two separate clamp experiments are performed on two different days in the same animal: on day one, insulin is infused via the abdominal portal vein, and on a different day, the hormone is infused via a peripheral vein (17,25). Because of first-pass degradation by the liver, the intraportal infusion rates are chosen at twice those of the peripheral infusion to attempt to achieve similar systemic plasma insulin values in both infusion experiments (17,25). This procedure allows calculation of the insulin clearance rate (CL) from the slope (m) of the best-fit line of insulin infusion rates to steady-state plasma insulin concentrations, both intraportally (CL_{po}) and peripherally (CL_{pe}):

$$CL_{po} = \frac{1}{m_{po}}, \quad (1)$$

$$CL_{pe} = \frac{1}{m_{pe}}, \quad (2)$$

where CL_{po} is the intraportal insulin clearance rate, CL_{pe} is the peripheral insulin clearance rate, and m_{po} and m_{pe} are the slopes of the intraportal and peripheral insulin infusion rates, respectively, versus the resulting plasma insulin levels from the two protocols (see Fig. 2*B*). Assuming that insulin kinetics are linear because of the studied range of insulin concentrations (22) and that the hepatic insulin clearances after the first pass are the same in both the experiments (26), HE is calculated as the following:

$$HE(\%) = \left(\frac{CL_{po} - CL_{pe}}{CL_{po}}\right) \cdot 100. \quad (3)$$

Thus, from Eqs. 2 and 3:

$$HE(\%) = \left[1 - \frac{m_{po}}{m_{pe}}\right] \cdot 100. \quad (4)$$

As shown in (16), FCR, rather than MCR, is the indirect method that provides the best correlation with the direct measurement of HE. This suggests that FCR could be considered a surrogate of insulin clearance, while MCR could be related to the extrahepatic component. It is of particular interest that, with this accurate method, a considerable range in HE was observed within a population of normal animals (22–72% first-pass degradation). As insulin clearance is variable among animals, the portal method suggests that insulin clearance by the liver could be an important metabolic variable subject to genetic and environmental influences.

MODELING C-PEPTIDE AND INSULIN KINETICS TO CALCULATE INSULIN CLEARANCE

Because of the limitations of the C-peptide: insulin ratio and considering the impracticality to perform the PPII method in humans, mathematical models have emerged as a requisite tool to noninvasively estimate insulin clearance in vivo.

The Eaton Model: Three-Compartment Insulin Kinetics and Calculation of Secretion With Deconvolution of C-Peptide Data

Eaton et al. (27), in 1983, used the kinetic model initially proposed by Sherwin et al. (15) to calculate insulin clearance. In the model, insulin kinetics is represented by three compartments: plasma, extrahepatic space, and extravascular dilutional space (Fig. 3). Endogenous insulin appearance was assumed to be equal to the C-peptide release rate from the pancreatic islets. Therefore, secretion could be calculated from deconvolution of plasma C-peptide concentrations (13). HE was estimated after oral glucose ingestion, meal ingestion, and arginine infusion (27). Of note, the Eaton model calculated both the hepatic and extrahepatic insulin clearance. To do this, it was necessary to assume (i.e., not to individually estimate) 12 of the 13 model parameters as mean values from earlier dog experiments (28,29). To the extent that these model parameters may be different in humans, the consequent individual estimation of the single constant value of HE for each subject may be questioned.

Cobelli et al. (3). proposed a simpler mathematical model consisting of two-compartments for C-peptide kinetics (13), used with a previous linear, single-compartment insulin kinetic model (14) (see the rationale of the model, Fig. 4). The basic assumption underlying this method is the equimolar secretion of the two peptides, with only insulin undergoing significant hepatic clearance. Therefore, the individual calculation of ISR was possible through parameter estimation from the C-peptide kinetics. Consequently, HE reconstruction from the ISR and posthepatic insulin delivery rate (IDR) was performed, without the need to assume any parameter a priori. The downside of this approach consists of the simultaneous assessment of both insulin secretion and kinetics, which might be responsible for undesired compensation in the parameter estimates (see the Toffolo approach discussed below).

The Tura Model: Single Compartment Kinetics for C-Peptide and Insulin During OGTT

Tura et al. (30) proposed a model of C-peptide and insulin kinetics, allowing the estimation of ISR and insulin degradation during the OGTT. This approach has a singular advantage: the estimation of both hepatic and extrahepatic insulin fractional clearance. However, in this model, both C-peptide and insulin were described with single-compartment distribution kinetics, even though C-peptide kinetics had been shown to be described with two compartments (13), possibly limiting the accuracy of the approach of Tura et al. Furthermore, the model assumes a constant HE during the experiment, even if this process is time-varying, for several reasons: the relationship with hepatic plasma flow (31), glucose administration (3), and saturable receptor-mediated mechanisms (32). Ultimately, ISR is estimated individually with piecewise polynomials, including several unknown parameters (30).

The Toffolo Approach: Two-Compartment C-Peptide Kinetics and Single-Compartment Insulin Kinetics During FSIGT

In 2005, Toffolo et al. (33) introduced a new model of insulin secretion and kinetics to assess HE during the insulin-modified

Downloaded from http://diabetesjournals.org/care/article-pdf/43/9/2296/630461/dc200750.pdf by guest on 20 August 2022

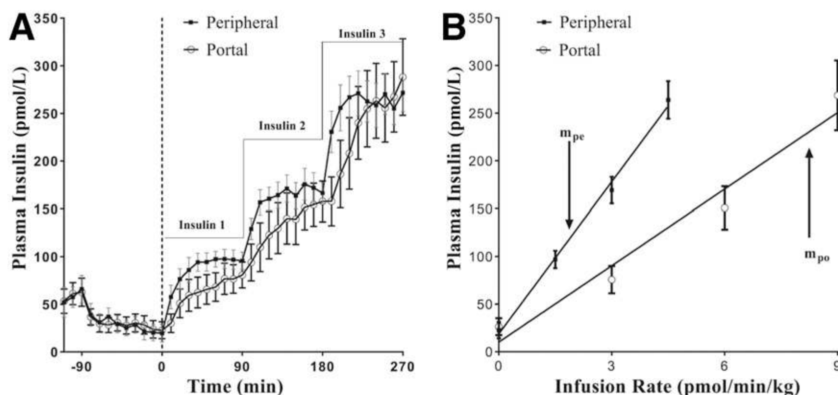

Figure 2—PPII clamp for measuring first-pass hepatic insulin extraction. *A*: The insulin profile during the PPII experiments. For portal infusion protocol (white circles), insulin 1 = 3.0 pmol·kg^{-1}·min^{-1}, insulin 2 = 6.0 pmol·kg^{-1}·min^{-1}, and insulin 3 = 9.0 pmol·kg^{-1}·min^{-1}. For peripheral infusion protocol (black squares), insulin 1 = 1.5 pmol·kg^{-1}·min^{-1}, insulin 2 = 3.0 pmol·kg^{-1}·min^{-1}, and insulin 3 = 4.5 pmol·kg^{-1}·min^{-1}. One-half of the portal infusion rates were used in the peripheral protocol for matching systemic concentrations. *B*: The infusion rate versus steady-state plasma insulin concentrations. The correlation coefficient *r* for peripheral infusion versus steady-state concentrations (black squares) was 0.99, and slope, m_{pe}, was 53.1 kg·min^{-1}·L^{-1}. For portal infusion versus steady-state concentrations (white circles), r = 0.98 and slope, m_{po}, was 26.7 kg·min^{-1}·L^{-1}. First-pass hepatic insulin extraction (%) = $[1 - (m_{po}/m_{pe})]\cdot 100$ = 50%. Each data point is a mean ± SE of n = 9. Adapted with permission from Asare-Bediako et al. (17).

FSIGT (i.e., the one also including an insulin infusion/injection administered 20 min after the initial glucose bolus). Toffolo et al. (33) overcame some disadvantages included in previous models. They employed two-compartment C-peptide kinetics (13) by including standard population values (34), allowing for reliable estimates of β-cell secretion (ISR), unbiased by undesired kinetic-secretion compensations (see the rationale represented in Fig. 4). Concerning insulin, the authors (33) exploited the peculiarity of the insulin-modified FSIGT, where the decay of insulin concentrations after the exogenous insulin input allows the estimation of insulin kinetics, still avoiding unreliable interactions with the secretion. In this case, insulin was described with a linear single compartment that included a functional description of glucose on IDR (33). By combining the ISR obtained from the C-peptide model and IDR calculated with the insulin one, the HE over time, given as $HE(t)$, was obtained, as well as an index quantifying the insulin extraction at basal level (HE_b) and during the insulin-modified FSIGT (HE_{tot}) (32) (see Supplementary Material for the detailed equations). Because this model did not include extrahepatic insulin clearance, the same authors proposed an alternative in the appendix of the same work (33), describing insulin clearance as the sum of the hepatic component, proportional to $HE(t)$, and an extrahepatic one. Because HE_b and HE_{tot} correlated among both the model options, the authors supported the robustness of the original model, i.e., the one that did not include the extrahepatic clearance. Therefore, the main limitation in this case relied on the extrahepatic insulin clearance, which was not considered in the first and currently used version of this model and which was assumed to be constant over the experiment, in the appendix model. In addition, $HE(t)$ was reconstructed only considering newly secreted insulin and not the recirculation through the liver.

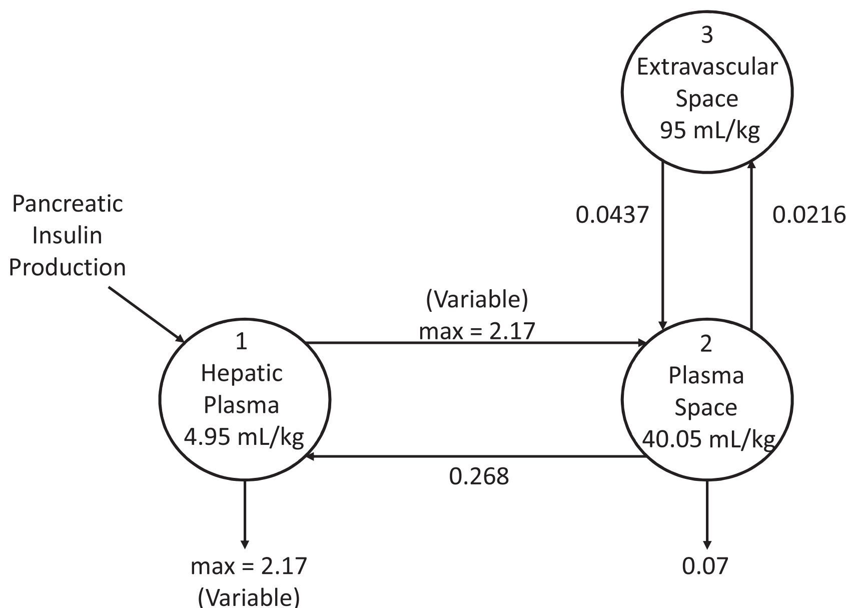

Figure 3—The three-compartment model (hepatic, vascular, and extravascular pools) used to describe insulin kinetics. Adapted with permission from Eaton et al. (27).

The Campioni Approach: Two-Compartment C-Peptide Kinetics and Single-Compartment Insulin Kinetics During Oral Tests

A further advance was introduced by Campioni et al. (35), in which a model of HE was proposed during an oral test (see the rationale in Fig. 4). The authors used the same two- compartment C-peptide kinetics previously employed (13,33), with assumed values of C-peptide kinetics (34), to estimate ISR (36). Concerning insulin kinetics, the single compartment model (33) had to be edited to estimate IDR without having the peculiarities of the insulin-modified FSIGT. To do so, IDR was derived from Eq. 1 of Supplementary Material, and $HE(t)$ was expressed as a piecewise linear function with a fixed number of breaking points as (see the Supplementary Material for details). The authors developed standard parameters of insulin kinetics depending on anthropometric characteristics, and validated them by comparison with the insulin-modified FSIGT in the same subjects. By fixing the insulin kinetics parameters to these values, the breaking points of $HE(t)$ were the only ones to be estimated. However, in this model, several disadvantages can be considered. First, the parametric $HE(t)$ description, i.e.,

Downloaded from http://diabetesjournals.org/care/article-pdf/43/9/2296/630461/dc200750.pdf by guest on 20 August 2022

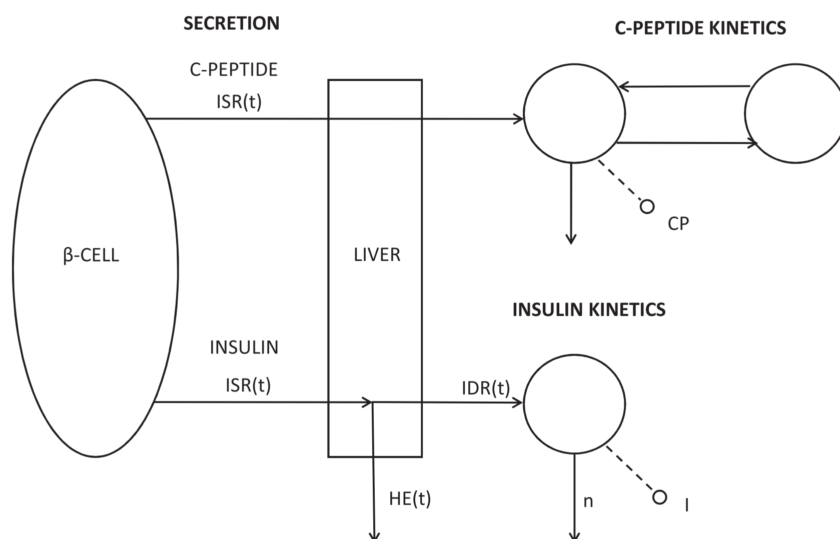

Figure 4—The rationale for assessing insulin hepatic extraction from modeling insulin and C-peptide data. Adapted with permission from Campioni et al. (35). CP (pmol/L), C-peptide concentration in the accessible compartment; HE (%), hepatic insulin extraction; I (pmol/L), plasma insulin concentration, accessible to measurement; IDR (pmol/min), post-hepatic insulin delivery rate; ISR (pmol/min), insulin secretion rate.

a piecewise linear function with breaking points rather than a continuous profile, may introduce some error. Second, the calculation of $HE(t)$ is based only on newly secreted insulin and not on the recirculation of plasma insulin through the liver. Moreover, the model does not include the extrahepatic clearance component. Fractional extrahepatic extraction is assumed to be constant during the experiment and equal to 40%. This assumption of constancy does not reflect actual data, as individual values of hepatic and extrahepatic insulin clearance have been shown to vary over a wide range (2,37,38).

C-Peptide Kinetics and Three-Compartment Insulin Kinetics During Oral Tests

In 2013, Piccinini et al. (39) proposed a model to estimate HE during an oral test. This includes the same C-peptide kinetics and secretion description used in a previous model (34), but it used three compartments for insulin kinetics (15). The peculiarity of this model, overcoming the merely mathematical representation of HE by Campioni et al. (35), is the physiological representation of $HE(t)$ that is selected here to be linearly dependent on plasma glucose concentrations (39):

$$HE(t) = -a_G \cdot G(t) + a_{0G}, \qquad (5)$$

where a_G represents the control of plasma glucose on HE, and a_{0G} is obtained from the steady-state constraints; HE_b and HE_{tot} are still derived from Eq. 2 and 3 of the Supplementary Material. The relationship in Eq. 5 is based on the evidence that, during an oral test, the reconstructed profiles of HE decrease, while insulin and glucose concentrations rise (35).

Several models were tested in (39), with increasing complexity of insulin kinetics, as well as a different physiological derivation of HE that was dependent on plasma glucose and/or insulin concentrations. In fact, previous observations suggested that nutrient intake modifies HE (40,41) and that the insulin-degrading enzyme is inhibited by hyperglycemia and hyperinsulinemia (42). Besides providing HE_b and HE_{tot}, this more physiologic model allows the estimation of HE sensitivity to plasma glucose concentrations. However, the extrahepatic component of insulin clearance was not considered. In addition, this model estimates HE while only considering the newly secreted insulin and not the recirculation of plasma insulin through the hepatic vein and artery (2).

The Polidori Model: C-Peptide Deconvolution for the Calculation of Secretion and Two- Compartment Model Insulin Kinetics during FSIGT

To overcome some of the limitations of previous models, Polidori et al. (2) recently proposed a model estimating both hepatic and extrahepatic contributions to insulin clearance from the insulin-modified FSIGT. Insulin is described as existing in both a peripheral and a hepatic compartment (see Fig. 5). The following are model assumptions: *1*) the endogenously secreted insulin enters the portal circulation first, and then proceeds to the systemic circulation; *2*) IDR is calculated from plasma insulin concentrations and fixed value (i.e., not individually estimated) of hepatic plasma flow; *3*) the extrahepatic insulin clearance rate is proportional to plasma insulin concentrations; and *4*) hepatic insulin clearance can be described as linear or with saturation kinetics. With these assumptions, calculating ISR with deconvolution and exploiting the peculiarity of the insulin-modified FSIGT, i.e., an exogenous insulin infusion in 20–25 min, the model estimates the relative contributions of hepatic and extrahepatic insulin clearance, over the FSIGT duration. To relate the insulin clearance values obtained through this model with other experimental methods and to enable a similar clinical evaluation, Polidori et al. (2) derived an index of clearance for intravenous infusion (CL_{IV}), to be compared with the hyperinsulinemic clamp, as well as an index of clearance for portal infusion (CL_{portal}), to be related with endogenous secretion. The model parameters CL_{IV} and CL_{portal} were obtained by dividing the intravenous or portal insulin infusion rates by the steady-state insulin concentrations for both the linear and the saturable versions of the model (2).

Further Application of the Polidori et al. Approach With Combined Clamp and OGTT Data

Besides the insulin-modified FSIGT, the model by Polidori et al. (2) was later applied to OGTT data combined with EGC on the same subjects (43): ISR was calculated during both tests with deconvolution, and it was used together with the known insulin infusion rate from the clamp to fit the measured plasma insulin concentrations from the OGTT and the clamp (43). Hepatic and extrahepatic insulin clearance were then estimated, assuming them to be the same during both tests. Moreover, in a recent work (44), the model by Polidori et al. (2) was simplified into two linear equations, obtained from the original ones in steady state, for the hyperglycemic clamp: one related to the preinfusion basal state

Downloaded from http://diabetesjournals.org/care/article-pdf/43/9/2296/630461/dc200750.pdf by guest on 20 August 2022

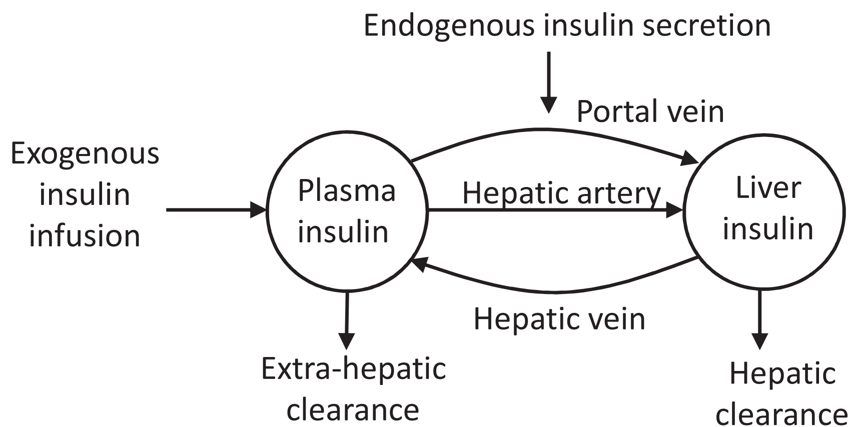

Figure 5—A graphical representation of the mathematical model used to estimate hepatic and extrahepatic insulin clearance. Adapted with permission from Polidori et al. (2).

(between −20 and 0 min), and the other one during the last 30 min of high insulin infusion. This led to the calculation of both hepatic and extrahepatic insulin clearance in obese youths, with simple linear algebra.

The approach by Polidori et al. (2) provided both hepatic and extrahepatic insulin clearance, with a quantification of the relative contribution of each component during the experiment. However, it has some limitations: the ISR used in the model was obtained with deconvolution, based on standard population parameters as in Van Cauter et al. (34), and ISR was treated as a model input, as well as the exogenous insulin. Moreover, the hepatic plasma flow value was fixed, similarly to the work of Ferrannini and Cobelli (26). These latter assumptions might not apply under pathological conditions, such as renal or hepatic disease. However, this model (2) has so far been applied to the insulin-modified FSIGT and not to oral tests (meal, OGTT) performed without a clamp on the same subjects. Meals and OGTTs are indeed characterized by the oral administration of nutrients, which do not have such separable periods of exogenous and endogenous insulin appearance. Efforts to apply this method to pure oral tests are in progress, which would significantly ease the evaluation of the whole metabolic pattern in clinical human studies.

Summary

While insulin clearance can be measured directly in animals, the difficulty of accessing the portal and hepatic veins limit such assessments to animal models. To overcome this limitation, modeling techniques have long been applied to noninvasively estimate insulin clearance in its hepatic versus extrahepatic components. In fact, surrogate indices provided by molar ratios or AUC have serious limitations, and in vivo methods are either inaccurate or cannot be performed in human subjects. Among the models historically proposed in the literature, most of them only allow the estimation of hepatic insulin clearance (3,33,35,39), have individual parameter estimation issues (3,27,30), or do not consider hepatic insulin recirculation (33,35,39).

Conclusions

In conclusion, among the models historically developed and summarized above, we propose that the one by Polidori et al. (2) is superior to others to obtain both accurate hepatic and extrahepatic insulin clearance components in individuals. Further studies are needed to distinguish hepatic versus extrahepatic insulin clearance during oral tests (to be performed in a clinical setting) or to modify the oral tests allowing for discrimination of the hepatic from the extrahepatic constituents.

It is important to note that the accurate measurement of insulin clearance may be more important than previously realized. The early debate regarding the relative importance of insulin secretion versus insulin resistance in the pathogenesis of type 2 diabetes was resolved by the understanding that it is apparently the ability of the endocrine pancreas to compensate for environmentally determined insulin resistance, which is important to predict the eventual onset of the disease (4). However, it is becoming increasingly clear that hepatic insulin degradation rates, per se, may play an equal or even greater role in the pathway from normal to impaired glucose tolerance and to diabetes itself. On the basis of the model by Polidori et al. (2), we were able to measure hepatic and extrahepatic insulin clearance in several cohorts. Our application of this model is based upon the FSIGT. The advantage of this protocol is that the early appearance of insulin, following glucose injection, is endogenous, i.e., from the pancreatic islets. However, after insulin injection 20-min later, the appearance is exogeneous. This disparity makes it possible to obtain excellent estimates of first-pass hepatic insulin versus extrahepatic insulin clearance. Fortunately, Gower and colleagues (37) at the University of Alabama had performed FSIGT tests on a sizeable cohort of European American and African American adults. We were able to analyze their data with the Polidori model, revealing two outcomes: there was a wide range of values of hepatic insulin extraction among adults, and this parameter was considerably lower in African Americans, explaining the contribution of lower clearance to hyperinsulinemia in these individuals (37). We hypothesized (4) that the lower clearance and higher ambient insulin levels might be an important risk factor for eventual development of type 2 diabetes.

Even more fortunate, we could access the excellent data obtained by Fernandez and colleagues (16) in children 7–13 years old. These data confirmed lower hepatic insulin clearance in African American children, suggesting that this impairment could be either due to different environment (e.g., diet, exercise) or a possible genetic or epigenetic component (16).

It is becoming clear that it is important to assess insulin clearance in individuals at risk for additional diseases. There is a link between diabetes and Alzheimer disease, so that hyperinsulinemia (due to reduced clearance) may be a common risk factor for both. Additionally, elevated insulin may increase the risk for some forms of cancer (5). Thus, elevated insulin might turn out to be a global risk factor for several common diseases. Therefore, it remains very important to identify an optimal model enabling the estimation of insulin

Downloaded from http://diabetesjournals.org/care/article-pdf/43/9/2296/630461/dc200750.pdf by guest on 20 August 2022

clearance to support the clinical evaluation of glucose metabolism connected to diabetes risk. Thus, the precise role of insulin clearance to the pathogenesis of diabetes and other metabolic diseases remains to be explored.

Funding. R.N.B. is supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases (DK-27619, DK-29867).
Duality of Interest. R.N.B. is an advisory board member of Ingredion and is supported by grants from AstraZeneca and Janssen Research & Development.
Author Contributions. F.P. wrote the manuscript. R.N.B. contributed to data interpretation and edited the manuscript. R.N.B. is the guarantor of this work, and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Bergman RN, Piccinini F, Kabir M, Ader M. Novel aspects of the role of the liver in carbohydrate metabolism. Metabolism 2019;99:119–125
2. Polidori DC, Bergman RN, Chung ST, Sumner AE. Hepatic and extrahepatic insulin clearance are differentially regulated: results from a novel model-based analysis of intravenous glucose tolerance data. Diabetes 2016;65:1556–1564
3. Cobelli C, Pacini G. Insulin secretion and hepatic extraction in humans by minimal modeling of C-peptide and insulin kinetics. Diabetes 1988;37:223–231
4. Bergman RN, Piccinini F, Kabir M, Kolka CM, Ader M. Hypothesis: role of reduced hepatic insulin clearance in the pathogenesis of type 2 diabetes. Diabetes 2019;68:1709–1716
5. Lorenzo C, Wagenknecht LE, Rewers MJ, et al. Disposition index, glucose effectiveness, and conversion to type 2 diabetes: the Insulin Resistance Atherosclerosis Study (IRAS). Diabetes Care 2010;33:2098–2103
6. Rubenstein AH, Clark JL, Melani F, Steiner D. Secretion of pro-insulin, C-peptide by pancreatic beta cells and its circulation in blood. Nature 1969;224:697–699
7. Polonsky KS, Rubenstein AH. C-peptide as a measure of the secretion and hepatic extraction of insulin. Pitfalls and limitations. Diabetes 1984;33:486–494
8. Johnson DG, Alberti KG, Faber OK, Binder C. Hyperinsulinism of hepatic cirrhosis: diminished degradation or hypersecretion? Lancet 1977;1:10–13
9. Faber OK, Christensen K, Kehlet H, Madsbad S, Binder C. Decreased insulin removal contributes to hyperinsulinemia in obesity. J Clin Endocrinol Metab 1981;53:618–621
10. Madsbad S, Kehlet H, Hilsted J, Tronier B. Discrepancy between plasma C-peptide and insulin response to oral and intravenous glucose. Diabetes 1983;32:436–438
11. Meier JJ, Holst JJ, Schmidt WE, Nauck MA. Reduction of hepatic insulin clearance after oral glucose ingestion is not mediated by glucagon-like peptide 1 or gastric inhibitory polypeptide in humans. Am J Physiol Endocrinol Metab 2007;293:E849–E856
12. Heinrich G, Muturi HT, Rezaei K, et al. Reduced hepatic carcinoembryonic antigen-related cell adhesion molecule 1 level in obesity. Front Endocrinol (Lausanne) 2017;8:54
13. Eaton RP, Allen RC, Schade DS, Erickson KM, Standefer J. Prehepatic insulin production in man: kinetic analysis using peripheral connecting peptide behavior. J Clin Endocrinol Metab 1980;51:520–528
14. Toffolo G, Bergman RN, Finegood DT, Bowden CR, Cobelli C. Quantitative estimation of beta cell sensitivity to glucose in the intact organism: a minimal model of insulin kinetics in the dog. Diabetes 1980;29:979–990
15. Sherwin RS, Kramer KJ, Tobin JD, et al. A model of the kinetics of insulin in man. J Clin Invest 1974;53:1481–1492
16. Piccinini F, Polidori DC, Gower BA, Fernandez JR, Bergman RN. Dissection of hepatic versus extra-hepatic insulin clearance: ethnic differences in childhood. Diabetes Obes Metab 2018;20:2869–2875
17. Asare-Bediako I, Paszkiewicz RL, Kim SP, et al. Assessment of hepatic insulin extraction from in vivo surrogate methods of insulin clearance measurement. Am J Physiol Endocrinol Metab 2018;315:E605–E612
18. Ferrannini E, Wahren J, Faber OK, Felig P, Binder C, DeFronzo RA. Splanchnic and renal metabolism of insulin in human subjects: a dose-response study. Am J Physiol 1983;244:E517–E527
19. Arslanian SA, Saad R, Lewy V, Danadian K, Janosky J. Hyperinsulinemia in african-american children: decreased insulin clearance and increased insulin secretion and its relationship to insulin sensitivity. Diabetes 2002;51:3014–3019
20. Goodarzi MO, Langefeld CD, Xiang AH, et al. Insulin sensitivity and insulin clearance are heritable and have strong genetic correlation in Mexican Americans. Obesity (Silver Spring) 2014;22:1157–1164
21. Castillo MJ, Scheen AJ, Letiexhe MR, Lefèbvre PJ. How to measure insulin clearance. Diabetes Metab Rev 1994;10:119–150
22. Ferrannini E, Cobelli C. The kinetics of insulin in man. I. General aspects. Diabetes Metab Rev 1987;3:335–363
23. Mittelman SD, Van Citters GW, Kim SP, et al. Longitudinal compensation for fat-induced insulin resistance includes reduced insulin clearance and enhanced beta-cell response. Diabetes 2000;49:2116–2125
24. Chiu S, Williams PT, Dawson T, et al. Diets high in protein or saturated fat do not affect insulin sensitivity or plasma concentrations of lipids and lipoproteins in overweight and obese adults. J Nutr 2014;144:1753–1759
25. Kim SP, Ellmerer M, Kirkman EL, Bergman RN. β-cell "rest" accompanies reduced first-pass hepatic insulin extraction in the insulin-resistant, fat-fed canine model. Am J Physiol Endocrinol Metab 2007;292:E1581–E1589
26. Ferrannini E, Cobelli C. The kinetics of insulin in man. II. Role of the liver. Diabetes Metab Rev 1987;3:365–397
27. Eaton RP, Allen RC, Schade DS. Hepatic removal of insulin in normal man: dose response to endogenous insulin secretion. J Clin Endocrinol Metab 1983;56:1294–1300
28. Arnould Y, Ooms HA, Franckson JR. Analysis of urinary excretion of insulin in the normal dog. Arch Int Pharmacodyn 1967;167:480–482
29. Franckson JRM, Ooms HA. The catabolism of insulin in the dog: evidence for the existence of two catabolic pathways. Postgrad Med J 1973;49(Suppl. 7): 931–939
30. Tura A, Ludvik B, Nolan JJ, Pacini G, Thomaseth K. Insulin and C-peptide secretion and kinetics in humans: direct and model-based measurements during OGTT. Am J Physiol Endocrinol Metab 2001;281:E966–E974
31. Thomaseth K, Pacini G, Clodi M, et al. Amylin release during oral glucose tolerance test. Diabet Med 1997;14(Suppl. 2):S29–S34
32. Morishima T, Bradshaw C, Radziuk J. Measurement using tracers of steady-state turnover and metabolic clearance of insulin in dogs. Am J Physiol 1985;248:E203–E208
33. Toffolo G, Campioni M, Basu R, Rizza RA, Cobelli C. A minimal model of insulin secretion and kinetics to assess hepatic insulin extraction. Am J Physiol Endocrinol Metab 2006;290:E169–E176
34. Van Cauter E, Mestrez F, Sturis J, Polonsky KS. Estimation of insulin secretion rates from C-peptide levels. Comparison of individual and standard kinetic parameters for C-peptide clearance. Diabetes 1992;41:368–377
35. Campioni M, Toffolo G, Basu R, Rizza RA, Cobelli C. Minimal model assessment of hepatic insulin extraction during an oral test from standard insulin kinetic parameters. Am J Physiol Endocrinol Metab 2009;297:E941–E948
36. Breda E, Cavaghan MK, Toffolo G, Polonsky KS, Cobelli C. Oral glucose tolerance test minimal model indexes of beta-cell function and insulin sensitivity. Diabetes 2001;50:150–158
37. Piccinini F, Polidori DC, Gower BA, Bergman RN. Hepatic but not extrahepatic insulin clearance is lower in African American than in European American women. Diabetes 2017;66:2564–2570
38. Asare-Bediako I, Paszkiewicz RL, Kim SP, et al. Variability of directly measured first-pass hepatic insulin extraction and its association with insulin sensitivity and plasma insulin. Diabetes 2018;67:1495–1503
39. Piccinini F, Dalla Man C, Vella A, Cobelli C. A model for the estimation of hepatic insulin extraction after a meal. IEEE Trans Biomed Eng 2016;63:1925–1932
40. Hennes MM, Dua A, Kissebah AH. Effects of free fatty acids and glucose on splanchnic insulin dynamics. Diabetes 1997;46:57–62
41. Pagano C, Rizzato M, Lombardi AM, et al. Effect of lactate on hepatic insulin clearance in perfused rat liver. Am J Physiol 1996;270:R682–R687
42. Pivovarova O, Gögebakan O, Pfeiffer AF, Rudovich N. Glucose inhibits the insulin-induced activation of the insulin-degrading enzyme in HepG2 cells. Diabetologia 2009;52:1656–1664
43. Utzschneider KM, Kahn SE, Polidori DC. Hepatic insulin extraction in NAFLD is related to insulin resistance rather than liver fat content. J Clin Endocrinol Metab 2019;104:1855–1865
44. Galderisi A, Polidori D, Weiss R, et al. Lower insulin clearance parallels a reduced insulin sensitivity in obese youths and is associated with a decline in β-cell function over time. Diabetes 2019;68:2074–2084

Downloaded from http://diabetesjournals.org/care/article-pdf/43/9/2296/630461/dc200750.pdf by guest on 20 August 2022