

Research Article

Insulin Clearance, Hepatic Glucose Regulation, and Glycemic Control in Patients With Type 2 Diabetes Mellitus: An Observational Clinical Study

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Abstract

Background:

Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance, progressive pancreatic β -cell dysfunction, and impaired regulation of hepatic glucose production. Insulin clearance influences circulating insulin concentrations and may contribute to differences in glycemic control among patients with T2DM. However, the relationships between insulin clearance, hepatic glucose regulation, and long-term glycemic control remain complex and are influenced by obesity, disease duration, renal function, and antidiabetic treatment.

Objective

To investigate the association between estimated insulin clearance, markers of hepatic glucose regulation, and glycemic control among adults with T2DM.

Methods

This cross-sectional observational study was designed to include 160 adults with established T2DM attending an outpatient internal medicine clinic. Demographic characteristics, diabetes duration, body mass index (BMI), waist circumference, medication history, fasting plasma glucose

(FPG), glycated hemoglobin (HbA1c), fasting insulin, C-peptide, liver enzymes, and renal function were assessed. An exploratory fasting C-peptide-to-insulin molar ratio was calculated as an indirect marker related to insulin clearance. Glycemic control was evaluated using HbA1c, while fasting glucose was used as a marker of fasting glycemia. Because direct hepatic glucose production measurement requires specialized techniques, hepatic glucose regulation was assessed indirectly through fasting glycemia and related metabolic parameters. Associations were examined using correlation and multivariable regression analyses.

Results

In a sample of 160 participants, the mean age was 52.4 ± 10.6 years and the mean diabetes duration was 7.8 ± 5.1 years. Mean HbA1c was $8.1 \pm 1.4\%$, and mean fasting plasma glucose was 164.7 ± 42.6 mg/dL. The exploratory C-peptide-to-insulin ratio showed a inverse correlation with HbA1c ($r = -0.31$, $p < 0.001$) and fasting plasma glucose ($r = -0.28$, $p < 0.001$). Higher HbA1c was also associated with longer diabetes duration and greater waist circumference.

These values are examples for manuscript development and must not be presented as observed clinical findings.

Conclusion

Insulin clearance and hepatic glucose regulation are physiologically relevant to glycemic control in T2DM. Clinical studies may help clarify these relationships, but fasting C-peptide-to-insulin ratios cannot independently quantify hepatic insulin clearance, and fasting glucose cannot directly measure hepatic glucose production. Prospective studies using validated kinetic or tracer-based methods are needed to establish the independent contribution of insulin clearance to glycemic outcomes.

Keywords: Type 2 diabetes mellitus; insulin clearance; hepatic glucose production; C-peptide; insulin resistance; fasting plasma glucose; HbA1c; glycemic control.

1. Introduction

Type 2 diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia arising from a combination of insulin resistance, impaired insulin secretion, and abnormalities in glucose regulation. The liver plays a central role in maintaining glucose homeostasis by regulating glycogen synthesis, glycogen breakdown, and gluconeogenesis. Under normal physiological conditions, insulin suppresses hepatic glucose production, promotes glucose storage, and coordinates metabolic responses to nutritional status. In T2DM, hepatic insulin resistance can impair the suppression of endogenous glucose production, contributing particularly to fasting hyperglycemia [1–3].

Insulin concentrations in peripheral blood reflect both pancreatic insulin secretion and insulin removal from the circulation. Following secretion from pancreatic β -cells, insulin enters the portal circulation and undergoes substantial first-pass extraction by the liver. Additional insulin clearance occurs

in extrahepatic tissues, including the kidneys. Consequently, circulating insulin concentrations cannot be interpreted as a direct measure of pancreatic secretion or insulin sensitivity without considering insulin clearance [4,5].

Insulin clearance is an important component of insulin homeostasis. Changes in clearance can alter circulating insulin exposure even when pancreatic secretion remains unchanged. Reduced clearance may contribute to elevated circulating insulin concentrations, whereas increased clearance may reduce insulin availability. The direction and clinical significance of these changes vary with obesity, insulin resistance, β -cell function, liver fat accumulation, and the metabolic state of the individual [4,6].

C-peptide provides useful information about endogenous insulin secretion because it is released in approximately equimolar amounts with insulin and undergoes substantially less first-pass hepatic extraction. For this reason, fasting or stimulated C-peptide measurements are frequently used in studies of insulin secretion and metabolism. Nevertheless, the C-peptide-to-insulin ratio is influenced by the different kinetics of the two molecules, renal function, insulin secretion dynamics, and sampling conditions. It should therefore be considered an exploratory surrogate rather than a definitive measurement of hepatic insulin clearance [4,5].

Hepatic glucose regulation is also central to glycemic control. In healthy individuals, insulin suppresses hepatic glucose output, while glucagon and other counter-regulatory hormones stimulate glucose production when required. In T2DM, this balance becomes disrupted, leading to excessive endogenous glucose production in some patients, particularly during fasting. The relative contribution of hepatic glucose overproduction varies between individuals

and may be affected by hepatic steatosis, adiposity, diabetes duration, and medication use [2,3,7].

Glycemic control is commonly assessed using HbA1c and plasma glucose measurements. HbA1c reflects average glycemic exposure over approximately the preceding two to three months, while fasting plasma glucose provides a measure of glucose concentration at a specific time point. These measurements are complementary but do not directly quantify hepatic glucose production or insulin clearance [8].

Understanding the relationships between insulin clearance, hepatic glucose regulation, and glycemic control may improve the physiological interpretation of metabolic measurements in patients with T2DM. However, these relationships cannot be assumed to be causal from cross-sectional observations. A carefully designed observational study can identify associations and generate hypotheses for future mechanistic investigations.

This study was therefore designed to examine the association between an exploratory marker related to insulin clearance, fasting glycemia, and HbA1c among adults with T2DM while accounting for relevant demographic, anthropometric, clinical, and biochemical factors.

2. Rationale of the Study

Insulin resistance and β -cell dysfunction are established features of T2DM, but insulin clearance may also influence the relationship between insulin secretion and peripheral insulin concentrations. Routine clinical measurements can provide useful preliminary information; however, surrogate indices must be interpreted cautiously.

A structured assessment of fasting insulin, C-peptide, glucose, HbA1c, renal function, liver enzymes, and clinical characteristics may help identify metabolic patterns associated with poor glycemic control. The present

study focuses on the clinical associations that can reasonably be examined using routine laboratory measurements, while recognizing that direct quantification of hepatic insulin extraction and hepatic glucose production requires specialized methods.

3. Objectives

Primary objective

To assess the association between an exploratory fasting C-peptide-to-insulin ratio and glycemic control, measured by HbA1c, in adults with T2DM.

Secondary objectives

1. To evaluate the relationship between the C-peptide-to-insulin ratio and fasting plasma glucose.
2. To examine associations between HbA1c, diabetes duration, BMI, and waist circumference.
3. To investigate whether the exploratory ratio remains associated with HbA1c after adjustment for selected clinical and biochemical confounders.
4. To assess the relationship of renal and liver biochemical markers with glycemic parameters.
5. To identify clinical factors that may inform the design of future studies using direct measurements of insulin clearance and hepatic glucose production.

4. Materials and Methods

4.1 Study design

A hospital-based cross-sectional observational study was to investigate associations between insulin-related biochemical markers and glycemic control in adults with T2DM.

4.2 Study setting

The study may be conducted at Suleman Roshan Medical College.

4.3 Study duration

A duration of six months may be used for planning, including participant recruitment,

clinical assessment, laboratory testing, data entry, and statistical analysis.

4.4 Study population

The target population comprises adults aged 30 years or older with established T2DM attending the selected outpatient clinic.

4.5 Sample size

For this manuscript, a sample size of **160 participants** is assumed. The final sample size were justified using an appropriate calculation based on the primary outcome, anticipated effect size or correlation, desired statistical power, significance level, and expected nonresponse or missing data.

The assumed sample size must not be described as a recruitment figure unless 160 eligible participants were genuinely enrolled.

4.6 Inclusion criteria

Participants should meet the following criteria:

1. Adults aged 30 years or older.
2. Established diagnosis of T2DM according to accepted clinical diagnostic criteria.
3. Diabetes duration of at least six months.
4. Ability to provide informed consent.
5. Availability of the clinical and biochemical measurements required for the primary analysis.

4.7 Exclusion criteria

The following exclusions are to reduce major sources of measurement error and confounding:

1. Type 1 diabetes mellitus or other forms of diabetes requiring a different pathophysiological classification.
2. Pregnancy.
3. Acute infection, major surgery, or another acute illness likely to substantially alter glucose metabolism.
4. Recent diabetic ketoacidosis or hyperosmolar hyperglycemic state.

5. Advanced chronic kidney disease or dialysis, because renal impairment affects C-peptide handling and insulin metabolism.
6. Decompensated chronic liver disease.
7. Recent use of systemic glucocorticoids or other medicines likely to substantially alter glucose metabolism, where appropriate to the study protocol.
8. Missing essential measurements for the primary analysis.

Patients receiving insulin should not automatically be excluded if the study intends to represent the broader T2DM population. However, exogenous insulin complicates interpretation of measured insulin concentrations. If included, insulin-treated participants were identified and analyzed separately or addressed through a prespecified sensitivity analysis. An assay's cross-reactivity with administered insulin analogues must also be considered.

4.8 Data collection

A standardized case-report form were used to collect demographic, clinical, treatment, and laboratory information.

The following variables were recorded:

- Age and sex.
- Duration of diabetes.
- Current antidiabetic treatment, including insulin and oral or injectable glucose-lowering medicines.
- History of hypertension and dyslipidemia.
- Smoking status, if available.
- Height, weight, BMI, and waist circumference.
- Blood pressure.
- Fasting plasma glucose and HbA1c.
- Fasting insulin and C-peptide.
- Serum creatinine and estimated glomerular filtration rate.

- Alanine aminotransferase and aspartate aminotransferase.
- Lipid profile, if available.

The time since the last meal, fasting duration, recent medication administration, and timing of blood sampling were standardized and documented.

4.9 Anthropometric measurements

Weight were measured using a calibrated scale, and height were measured using a stadiometer.

Waist circumference were measured using a standardized anatomical protocol. The same measurement technique were applied to all participants.

4.10 Laboratory investigations

After an overnight fast of approximately 8–12 hours, venous blood samples were collected according to the laboratory's standard operating procedures.

Fasting plasma glucose: Measured using a validated laboratory method, such as a hexokinase-based assay.

HbA1c: Measured using a standardized assay traceable to recognized reference systems. HbA1c results were reported as a percentage, with mmol/mol included if required by the journal.

Fasting insulin: Measured using a validated immunoassay. The assay platform and units were documented.

C-peptide: Measured using a validated immunoassay. The assay method and units were recorded, and renal function were considered when interpreting concentrations.

Renal function: Serum creatinine and estimated glomerular filtration rate were obtained to assess a major determinant of C-peptide and insulin metabolism.

Liver enzymes: ALT and AST were measured using routine laboratory methods. These enzymes are nonspecific indicators of hepatocellular injury and cannot independently quantify hepatic insulin extraction or hepatic glucose production.

Lipid profile: Total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol may be measured as supplementary metabolic variables.

All laboratory measurements were performed using validated procedures, internal quality control, and appropriate calibration.

4.11 Assessment of insulin clearance

Direct assessment of insulin clearance is technically demanding. Methods may include kinetic modeling, controlled insulin infusion, and appropriately designed tracer or clamp protocols. Routine fasting insulin and C-peptide measurements do not provide a direct measurement of hepatic insulin extraction [4].

For this observational study, the fasting C-peptide-to-insulin molar ratio may be examined as an exploratory surrogate marker related to insulin clearance, provided both analytes are measured in the fasting state and converted to compatible molar units.

The ratio is calculated as:

$\{\text{Fasting C-peptide (pmol/L)}\}$

If the laboratory reports C-peptide in ng/mL and insulin in $\mu\text{IU/mL}$, the results must first be converted to molar units using the appropriate assay-specific conversion factors. A ratio calculated directly from incompatible units is not valid.

A higher ratio may be consistent with a different balance between endogenous secretion and circulating insulin concentration, but it must not automatically be interpreted as a quantitatively higher hepatic extraction rate. The ratio is affected by insulin and C-peptide kinetics, renal function, secretion dynamics, and medication exposure [4,5].

Where a reliable clearance estimate is a central study endpoint, a validated kinetic or modeling-based approach were prespecified instead of relying solely on the fasting ratio.

4.12 Assessment of hepatic glucose regulation

Fasting plasma glucose and HbA1c will be used as clinical markers of glycemia. Fasting glucose is relevant to hepatic glucose regulation because excessive endogenous glucose production contributes to fasting hyperglycemia in T2DM [2,3].

However, fasting glucose concentration is not a direct measurement of hepatic glucose production. Direct assessment generally requires specialized methods, such as stable-isotope tracer techniques, often under controlled metabolic conditions. A hyperinsulinemic-euglycemic clamp or related protocol may be required to quantify insulin-mediated suppression of endogenous glucose production.

4.13 Definition of glycemic control

HbA1c will be analyzed as a continuous primary outcome. For a supplementary categorical analysis, HbA1c below 7.0% may be used as a threshold for adequate control in a population where that threshold is clinically appropriate. The glycemic target were individualized according to age, comorbidities, treatment-related hypoglycemia risk, and the applicable clinical guideline [8].

4.14 Statistical analysis

Data were analyzed using an appropriate statistical package, such as SPSS, Stata, R, or an equivalent validated program.

Continuous variables will be summarized as mean $\pm$ standard deviation when

approximately normally distributed and as median with interquartile range when skewed. Categorical variables will be summarized as frequencies and percentages. Pearson correlation will be used for approximately linear relationships between normally distributed continuous variables. Spearman correlation will be considered for skewed variables or monotonic relationships. Multivariable linear regression will be used to examine the association between the exploratory C-peptide-to-insulin ratio and HbA1c. Prespecified potential confounders may include age, sex, diabetes duration, BMI or waist circumference, renal function, liver biochemical markers, and antidiabetic treatment.

BMI and waist circumference should not automatically be entered together without assessing collinearity. Similarly, insulin treatment and assay characteristics must be considered when interpreting fasting insulin measurements.

Model assumptions, influential observations, multicollinearity, and residual distributions were assessed. Results were reported as regression coefficients with 95% confidence intervals and p-values. A two-sided p-value below 0.05 may be considered statistically significant.

Because this is a cross-sectional study, results were interpreted as associations rather than evidence of causation or temporal direction

5. Results

5.1 Demographic and clinical characteristics

Table 1. demographic and clinical characteristics of participants (n = 160)

Variable	result
Age, years	52.4 $\pm$ 10.6
Female sex, n (%)	88 (55.0)

Male sex, n (%)	72 (45.0)
Diabetes duration, years	7.8 ± 5.1
BMI, kg/m ²	29.1 ± 4.8
Waist circumference, cm	99.4 ± 11.2
Systolic blood pressure, mmHg	132.6 ± 15.4
Diastolic blood pressure, mmHg	82.1 ± 9.6
Hypertension, n (%)	91 (56.9)
Dyslipidemia, n (%)	103 (64.4)
Current insulin treatment, n (%)	32 (20.0)

Continuous variables are presented as mean ± SD and categorical variables as n (%).

5.2 Biochemical profile and glycemic control

Table 2. biochemical characteristics

Parameter	result
Fasting plasma glucose, mg/dL	164.7 ± 42.6
HbA1c, %	8.1 ± 1.4
Fasting insulin, µIU/mL	14.8 ± 8.2
Fasting C-peptide, ng/mL	2.9 ± 1.4
Serum creatinine, mg/dL	0.92 ± 0.24
ALT, U/L	31.6 ± 17.2
AST, U/L	27.8 ± 12.9
Triglycerides, mg/dL	183.5 ± 78.6
HDL cholesterol, mg/dL	42.7 ± 10.1

The C-peptide and insulin measurements were interpreted in light of renal function, treatment status, and assay characteristics.

5.3 Relationship between the exploratory ratio and glycemic markers

Table 3. correlations between the fasting C-peptide-to-insulin molar ratio and clinical variables

Variable	correlation coefficient (r)	p-value
HbA1c	−0.31	<0.001
Fasting plasma glucose	−0.28	<0.001
Diabetes duration	−0.19	0.016
BMI	−0.14	0.078
Waist circumference	−0.21	0.008
ALT	−0.16	0.043

5.4 Factors associated with HbA1c

Table 4. multivariable linear regression analysis with HbA1c as the dependent variable

Predictor	adjusted β	95% CI	p-value
C-peptide-to-insulin ratio	−0.24	−0.43 to −0.05	0.014
Diabetes duration, years	0.19	0.08 to 0.30	0.001
Waist circumference, cm	0.02	0.00 to 0.04	0.041
Age, years	−0.01	−0.03 to 0.01	0.280
eGFR, mL/min/1.73 m ²	−0.01	−0.02 to 0.00	0.063

Values are only. The β coefficients shown here are unstandardized examples; the units and interpretation of the ratio coefficient depend on how the predictor is scaled. The final model were prespecified, checked for collinearity, and recalculated using data.

5.5 Glycemic characteristics according to the exploratory ratio

For descriptive purposes, participants may be divided into tertiles of the fasting C-peptide-to-insulin ratio. Tertile cutoffs were calculated from the study population and not selected after reviewing the association with HbA1c.

Table 5. glycemic characteristics by ratio tertile

Variable	Lower tertile	Middle tertile	Upper tertile
Participants, n	53	54	53

HbA1c, %	8.6 ± 1.4	8.0 ± 1.3	7.7 ± 1.3
Fasting glucose, mg/dL	178 ± 44	163 ± 40	153 ± 40
Diabetes duration, years	8.4 ± 5.2	7.8 ± 5.0	7.1 ± 5.1

5.6 Summary of findings

In this simulated example, a lower fasting C-peptide-to-insulin ratio was associated with higher HbA1c and fasting plasma glucose. Longer diabetes duration was also associated with poorer glycemic control. These patterns are physiologically plausible but cannot establish the direction or strength of association in a patient population.

6. Discussion

This study framework examines the relationship between insulin clearance, hepatic glucose regulation, and glycemic control in adults with T2DM. The central physiological concept is that circulating insulin levels reflect both insulin secretion and insulin removal, while glucose concentrations are influenced by hepatic glucose production, peripheral glucose uptake, renal glucose handling, and medication effects. These processes interact, but they are not interchangeable measures of a single metabolic abnormality [1–4].

6.1 Insulin clearance and glycemic control

Insulin clearance contributes to the regulation of systemic insulin exposure. Following secretion from pancreatic β -cells, insulin undergoes substantial hepatic extraction, with additional clearance through extrahepatic pathways. Differences in clearance may influence circulating insulin concentrations and complicate the interpretation of fasting insulin as a marker of insulin resistance or secretion [4,6].

The fasting C-peptide-to-insulin ratio can be explored as an indirect marker related to insulin metabolism. However, its limitations are important. C-peptide and insulin have

different half-lives and clearance pathways, and their concentrations respond differently to changes in secretion. Consequently, the ratio does not provide a reliable quantitative estimate of hepatic extraction in all physiological conditions [4,5].

If an inverse association between this ratio and HbA1c is observed in data, several explanations may be considered. It may reflect differences in insulin secretion, clearance, β -cell function, renal function, or the metabolic state of participants. It would not, by itself, prove that reduced hepatic insulin clearance causes poor glycemic control.

6.2 Hepatic glucose regulation in T2DM

The liver maintains glucose availability through glycogenolysis and gluconeogenesis. Insulin normally suppresses endogenous glucose production, particularly after meals and during the fed state. In T2DM, hepatic insulin resistance may impair this suppression and contribute to fasting hyperglycemia [2,3,7].

Nevertheless, fasting glucose is influenced by more than hepatic glucose production. It also depends on insulin secretion, insulin sensitivity, glucagon, fasting duration, medication timing, and other physiological variables. A cross-sectional association between an insulin-related marker and fasting glucose therefore provides indirect clinical evidence rather than a direct measurement of hepatic glucose output.

Tracer-based studies can quantify endogenous glucose production and assess its suppression under controlled conditions. Such methods would strengthen the

mechanistic interpretation of a study specifically focused on hepatic glucose regulation.

6.3 Relationship with HbA1c

HbA1c summarizes glycemic exposure over a longer period than a single fasting glucose measurement. Its value can be influenced by fasting and postprandial glucose, medication adherence, treatment intensity, red-cell turnover, and certain hematological conditions [8].

A patient may have elevated HbA1c despite a relatively acceptable fasting glucose because of postprandial hyperglycemia or glycemic variability. Conversely, an elevated fasting glucose does not necessarily indicate that fasting hepatic glucose production is the sole driver of poor overall control.

For this reason, examining both HbA1c and fasting plasma glucose provides a more informative clinical assessment than relying on either marker alone.

6.4 Role of diabetes duration and adiposity

Longer diabetes duration may be associated with progressive β -cell dysfunction, greater treatment requirements, and worsening glycemic control in some patients. Adiposity may contribute to insulin resistance through altered lipid handling, ectopic fat accumulation, and impaired insulin signaling [1,3].

However, these relationships vary among individuals. Medication regimens, lifestyle factors, comorbidities, and access to care may confound observed associations. These factors were considered in multivariable analyses rather than assuming that a single biochemical ratio independently explains glycemic control.

6.5 Renal and hepatic function

Renal function is particularly important when interpreting C-peptide concentrations because the kidneys contribute substantially to C-peptide metabolism. Renal impairment can alter circulating C-peptide and insulin

levels, potentially distorting a ratio used as an exploratory clearance marker [4,5].

Liver enzymes may provide information about hepatocellular injury but are not direct measures of hepatic insulin extraction or glucose production. Normal ALT and AST values do not exclude hepatic steatosis or hepatic insulin resistance. Studies that aim to characterize liver-related metabolic dysfunction may benefit from validated liver-fat assessment and direct metabolic testing where feasible.

6.6 Clinical implications

The potential clinical value of studying insulin clearance lies in improving understanding of why patients with similar glucose levels may have different circulating insulin concentrations and different metabolic profiles. However, the fasting C-peptide-to-insulin ratio is not sufficiently specific to be used alone to guide treatment decisions.

Routine diabetes management should continue to be based on established clinical assessment, individualized glycemic targets, comorbidity evaluation, medication safety, and patient preferences [8]. Specialized insulin-clearance measurements should currently be viewed primarily as research tools rather than routine diagnostic tests.

6.7 Strengths of the study

The study has several potential strengths:

1. It examines insulin-related biochemistry alongside clinically relevant glycemic outcomes.
2. It includes renal function and treatment history as important interpretive variables.
3. It considers both short-term fasting glycemia and longer-term HbA1c.
4. It uses a multivariable framework to address selected confounding factors.
5. It explicitly distinguishes indirect clinical markers from direct measurements of insulin clearance and hepatic glucose production.

6.8 Limitations

Several limitations must be acknowledged. First, a cross-sectional design cannot establish temporal relationships or causality. Second, a fasting C-peptide-to-insulin ratio is an indirect surrogate and cannot independently quantify hepatic insulin clearance. Third, fasting glucose and HbA1c do not directly measure hepatic glucose production. Fourth, medication use—particularly exogenous insulin—can influence the interpretation of insulin concentrations. Fifth, renal impairment may alter C-peptide and insulin kinetics. Sixth, liver enzymes are nonspecific and cannot establish hepatic steatosis or hepatic insulin resistance. Finally, a single-center sample may limit generalizability to other populations.

If direct tracer-based measurements, validated kinetic modeling, or clamp studies are not performed, the manuscript should avoid claiming that hepatic glucose production or hepatic insulin clearance was directly measured.

6.9 Future research directions

Future investigations should consider prospective designs, standardized sampling conditions, and validated approaches to quantify insulin clearance. Where feasible, stable-isotope tracer methods and controlled metabolic protocols may allow direct assessment of endogenous glucose production and its suppression by insulin. Longitudinal follow-up could clarify whether insulin-clearance measures are associated with subsequent changes in HbA1c or treatment requirements. Studies should also account for renal function, liver fat, diabetes duration, medication exposure, and β -cell function.

7. Conclusion

Insulin clearance and hepatic glucose regulation are important physiological components of glucose homeostasis in patients with T2DM. Examining insulin-

related biochemical markers alongside fasting plasma glucose and HbA1c may help characterize metabolic differences among patients.

However, a fasting C-peptide-to-insulin ratio were treated as an exploratory surrogate rather than a direct measurement of hepatic insulin clearance. Similarly, fasting plasma glucose cannot independently quantify hepatic glucose production. The clinical significance of any observed associations must therefore be evaluated cautiously, with adjustment for relevant confounders and confirmation through appropriately designed mechanistic studies.

8. Recommendations

1. Use standardized fasting sampling and validated laboratory assays for insulin, C-peptide, glucose, and HbA1c.
2. Document insulin treatment and other glucose-lowering medications carefully.
3. Assess renal function when interpreting C-peptide and insulin concentrations.
4. Treat the C-peptide-to-insulin ratio as an exploratory marker and state its limitations clearly.
5. Avoid describing fasting glucose or liver enzymes as direct measurements of hepatic glucose production or hepatic insulin clearance.
6. Use validated tracer-based or kinetic methods if direct physiological quantification is central to the study.
7. Conduct prospective studies to assess whether insulin-clearance measures provide additional information beyond routine clinical variables.

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