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Review Article

Insights on C-peptide in diabetes

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ABSTRACT

C-peptide, a key biomarker for beta-cell function in diabetes, has potential in understanding and managing the disease, though its application in type 2 diabetes is limited by insufficient evidence. It provides insights into endogenous insulin secretion and faces challenges in measurement standardization. In type 1 diabetes, C-peptide levels reflect beta cell loss, while in type 2 diabetes, higher levels indicate a higher risk of progression. Preserved C-peptide levels differentiate maturity onset diabetes of the young (MODY) from type 1 diabetes. C-peptide is also associated with gestational diabetes risk. It shows correlations with improved outcomes in type 1 diabetes but controversial associations with macrovascular complications. Despite its promise, standardization, interpretation, and utilization issues require further research and trials for personalized treatments in diabetes.

1. Introduction

Impaired beta-cell function plays a crucial role in the development of diabetes. Assessing insulin secretory capacity is valuable in clinical practice as it helps classify diabetes types, evaluate the risk of complications, and guide treatment decisions. C-peptide secretion, which reflects beta-cell function, has become a significant clinical biomarker, particularly in autoimmune and adult-onset diabetes.[1] However, its clinical utility in type 2 diabetes, where insulin resistance complicates the picture, is limited due to a lack of robust evidence. Additionally, the standardization of C-peptide measurement poses challenges, leading to concerns about the comparability of results across different laboratories. To address the diverse and complex nature of diabetes, there is a need for reliable, simple, and affordable clinical markers that can provide insights into the underlying pathophysiology and disease progression. Such markers would enable personalized management and therapy.[1–3]

2. The Importance of C-Peptide

2.1. How is it important?

C-peptide measurement has been utilized for many years as a biomarker to assess pancreatic beta-cell function. Unlike insulin, C-peptide is not metabolized by the liver and is secreted in equal amounts with insulin. It is unaffected by concurrent insulin therapy. By measuring C-peptide, the endogenous capacity of insulin secretion can be evaluated, reflecting the remaining beta-cell function in various types of diabetes. C-peptide is measured to tell the difference between insulin the body produces and insulin that is injected into the body. Insulin and C-peptide are secreted into portal vein in equimolar amounts, but serum ratio = 1:5 to 1:15 due to removal of approximately 50% of insulin from blood during initial passage through the liver. C-peptide half-life = approximately 30 minutes. However, despite its potential, C-peptide has not been widely utilized in clinical practice until recently.[2]

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2.2. Interpretation of the test

The reference ranges for C-peptide are as follows: Fasting: 0.78-1.89 ng/mL or 0.26-0.62 nmol/L (SI units). A normal result is between 0.5 to 2.0 nanograms per milliliter (ng/mL), or 0.17 to 0.83 nanomoles per liter (nmol/L). The 2 major indications for measuring C-peptide levels include fasting hypoglycemia and assessment of insulin secretory reserve in patients with diabetes.[4]

2.3. Standardization of C-peptide measurement

C-peptide measurement lacks standardization among different assay methods, hindering result comparability.[5] Standardizing C-peptide results is crucial for patient care and research, allowing for data comparison across systems, locations, and time. Efforts have been made to harmonize C-peptide results, establishing reference methods and materials. Recalibration using secondary reference materials has improved result comparability. Manufacturers need clinical recommendations from organizations like the ADA and EASD to promote standardization.[2,6–8]

3. C-Peptide in the Diagnosis and Management of Diabetes Types

1. *Type 1 Diabetes:* In type 1 diabetes, C-peptide levels are consistently low due to insulin deficiency caused by beta cell loss. However, in late-onset diabetes, C-peptide reduction is gradual and very low levels don't always indicate severe insulin deficiency within three years of diagnosis. Evaluating C-peptide response to challenges is important for studying type 1 diabetes. The Index 60 can differentiate those at risk from non-progressors based on their C-peptide response. Autoantibody-positive individuals progressing to type 1 diabetes have lower fasting and early C-peptide levels. After onset, some retain residual insulin secretion, indicated by low but measurable C-peptide levels that help control glucose levels.[9–11]
2. *Type 2 Diabetes:* The development of type 2 diabetes involves pancreatic beta-cell dysfunction and insulin resistance. Beta-cell deterioration drives hyperglycemia progression, with an initial hyper insulinemic phase followed by declining beta-cell function.[12] Higher C-peptide levels in prediabetes predict a greater risk of developing type 2 diabetes compared to insulin levels. Using C-peptide for proinsulin ratios indicates beta-cell distress. After diabetes onset, C-peptide gradually decreases but remains detectable for over 20 years. C-peptide may be a better predictor of cardiovascular risk than CRP in early type 2 diabetes.[13–15]
3. *Maturity Onset Diabetes of the Young (MODY):* Unlike those with type 1 diabetes, patients with MODY have preserved pancreatic beta-cell function three to five years after diagnosis, as evidenced by detectable serum C-peptide levels with a serum glucose level greater than 144 mg per dL and no laboratory evidence of pancreatic beta-cell autoimmunity.[16]
4. *Gestational Diabetes:* Studies have shown that there is a positive association between serum C-peptide levels and the risks of diabetes and pre-diabetes among Chinese women with a history of gestational diabetes.[17,18] After considering various factors such as maternal age, gestational age, education level, smoking status, alcohol consumption, physical activity, pre-pregnancy BMI, history of parental diabetes, history of GDM, and parity, pregnant women with higher C-peptide levels in early pregnancy were found to have a higher risk of developing gestational diabetes mellitus (GDM).[18] Based on the analysis of C-peptide levels, it was determined that if the levels were above 2.00 ng/ml, women should consider using a sufficient diet or a combination of diet and Inofolic. However, if the levels were below 2.00 ng/ml, insulin treatment should be considered for these women.[19]

4. In Relation to Diabetic Complications

C-peptide has been studied as a potential biomarker for diabetes complications. In type 1 diabetes, preserved C-peptide levels are associated with better outcomes, including a reduced risk of retinopathy and nephropathy. However, the association between C-peptide and macrovascular complications is controversial in both type 1 and type 2 diabetes. In type 2 diabetes, higher C-peptide levels are linked to cardiovascular events and increased mortality. The interpretation of C-peptide levels is challenging in type 2 diabetes due to the presence of insulin resistance. Some evidence suggests that C-peptide may have direct effects on inflammatory and vascular cells involved in complications, but more research is needed to confirm this.[20]

5. Conclusion

Measurement of C-peptide has potential value in diabetes management due to its cost-effectiveness and accuracy. However, its utility in predicting type 1 diabetes and managing type 2 diabetes is limited. Uncertainties remain, such as standardization, interpretation of values, and the use of solid mixed meals. Randomized trials are needed to determine how C-peptide can be used to identify clusters and personalize treatment responses.

6. Source of Funding

None.

7. Conflict of Interest

None.

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