

Postprandial C-peptide Index: The Best Marker of Beta Cell Function?

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Type 2 diabetes (T2DM) is characterized by insulin resistance and beta cell dysfunction. Although in contrast to type 1 diabetes (T1DM), insulin resistance is often emphasized as the major characteristic of T2DM, T2DM never develops unless beta cells fail to compensate insulin resistance[1].

Recent studies have shown that beta cell mass is reduced in T2DM [2-4], confirming that beta cell deficit is an essential component of T2DM. In the UK Prospective Diabetes Study (UKPDS) it was shown that beta cell function in patients with T2DM progressively declined after the diagnosis, and treatment failure was associated with beta cell dysfunction[5]. Since these results suggest that beta cell function predicts treatment efficacy, beta cell function should be assessed for the management of T2DM in clinical settings.

We have recently reported that postprandial serum C-peptide to plasma glucose ratio, called postprandial C-peptide index, was associated with the future need for insulin therapy [6,7]. C-peptide is a well-established marker of beta cell function [8,9]. C-peptide is split from insulin and co-secreted with insulin from beta cells at the same molar ratio. While ~50% of insulin is extracted by the liver, C-peptide is not extracted by the liver. Therefore, the measurement of C-peptide more directly reflects beta cell secretory rate compared with insulin, independent of hepatic clearance. Moreover, one of the advantages of C-peptide measurement in clinical settings is that C-peptide can be assessed in patients treated with insulin, which cross-reacts with the insulin measurement.

In our study, interestingly, postprandial C-peptide index was superior for predicting the need for future insulin therapy compared with fasting C-peptide index or urinary C-peptide excretion [6,7]. More recent studies have also confirmed our findings [10,11]. It has also been reported that postprandial serum C-peptide, but neither fasting C-peptide nor urinary C-peptide, independently predicted successful switching from insulin therapy to liraglutide monotherapy [12], suggesting that postprandial C-peptide has the best ability to predict treatment efficacy among other C-peptide indices. The reason for this is unknown; however, several possibilities have been postulated.

Postprandial C-peptide likely reflects maximal insulin secretion induced by a combination of postprandial hyperglycemia and incretin effects, compared with fasting C-peptide. Besser et al. have reported that in patients with T1DM, 90 min postprandial C-peptide value is highly correlated with peak C-peptide value and area under the curve (AUC) of C-peptide during a mixed-meal tolerance test, which is the gold-standard measure of endogenous insulin secretion in T1DM [13]. Intriguingly, it has been reported that postprandial C-peptide index was more closely correlated with beta cell mass in humans compared with fasting C-peptide index [14]. These results suggest that postprandial C-peptide reflects maximal beta cell functional capacity.

Disposition index is a measure of beta cell function adjusted for insulin sensitivity, which reflects "true" beta cell function [15, 16]. Recently, it has been reported that postprandial C-peptide index, but not fasting measures such as fasting C-peptide index and homeostasis model assessment (HOMA)- β is significantly correlated with disposition

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index assessed by hyperglycemic and euglycemic clamp [17]. The authors speculate that postprandial C-peptide index reflects systemic insulin sensitivity, i.e., mainly glucose disposal in peripheral tissues, whereas fasting C-peptide index or HOMA- β reflects hepatic insulin sensitivity.

Recently, the usefulness of postprandial urinary C-peptide creatinine ratio has also been proposed. It has been reported that postprandial urinary C-peptide creatinine ratio was highly correlated with C-peptide and insulin AUC during an oral glucose tolerance test (OGTT) in non-diabetic subjects [18]. Thong et al. have reported that postprandial urinary C-peptide creatinine ratio weakly correlated with HbA1c change after liraglutide treatment [19]. However, since in patients with chronic kidney disease (CKD), urinary C-peptide creatinine ratio did not correlate with serum C-peptide or insulin, this method cannot be applied to patients with CKD [18].

We have also reported that postprandial C-peptide index is inversely associated with future glycemic control [20] and glycemic variability [21,22], independently of anti-diabetic medication, indicating a critical role of beta cell function in the management of T2DM. In addition to the UKPDS, recent large scale prospective trials with newer treatment options have also shown that treatment failure is associated with beta cell dysfunction [23,24]. Therefore, it is important to assess beta cell function in the management of T2DM, and the establishment of better markers of beta cell function in clinical settings is warranted. In this context, postprandial C-peptide index appears to be a simple and useful marker of beta cell function in clinical settings. Remaining issues for the use of postprandial C-peptide index include the timing of sampling, components of the meal, and the impact of renal impairment on the measurement. Future research will be needed to clarify these issues to establish the best marker of beta cell function.

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