



TIME TO MEASURE C-PEPTIDE IN TYPE 1 DIABETES?

A new study using an ultrasensitive assay shows that C-peptide levels can identify and stratify individuals with Type 1 diabetes at risk of, or protected from, complications and hypoglycaemia. The findings may lead to therapeutic strategies based upon maintaining low C-peptide levels to improve glycaemic control and reduce both hypoglycaemia and the risk of complications

The connection between elevated HbA1c and the risk of diabetic complications is well established. Now the search is on for other biomarkers which may also identify those patients vulnerable to future complications, so they can be offered appropriate interventions, including targeted therapies. One such marker is C-peptide, levels of which fall alongside endogenous insulin production in Type 1 diabetes. A new study, from researchers

at Massachusetts General Hospital (MGH), uses new ultrasensitive C-peptide assays to investigate the clinical significance of low levels of this biomarker in a cohort of patients with Type 1 diabetes.

C-peptide and Type 1

C-peptide is a molecule that is secreted at a 1:1 ratio to insulin and therefore represents a measure of endogenous insulin production. It has long been accepted that, for most people with

Type 1 diabetes, pancreatic beta cells are destroyed after a one- to two-year 'honeymoon' period following diagnosis, resulting in a decline in endogenous insulin. However, this view is now being challenged. It has long been known that intact beta cells still exist, even in long-standing Type 1 diabetes and, also, that onset of Type 1 diabetes in adult life tends to be less acute than when it starts in childhood. Furthermore, if latent autoimmune diabetes of adults is included, then it would appear that the ▶

C-peptide measurement could become a routine part of Type 1 diabetes management

Type 1 phenotype can include those who are not treated with insulin for many years, but do have slow beta cell decline. Could C-peptide measurement be used as a probe to gain new insights into the pathogenesis of Type 1 diabetes? Conventional C-peptide assays have a lower limit of detection of around 50 pmol/l and will therefore show most patients to have undetectable levels. Generally, they are only used when there is diagnostic difficulty.

However, the advent of ultrasensitive assays, which measure levels of C-peptide as low as 1.5–2.5 pmol/l, now allows the exploration of the following research questions:

- Is there clinical value in measuring these lower levels of C-peptide?
- Can measurement of low levels of C-peptide identify heterogeneity in Type 1 patients?
- Is there a link between C-peptide levels and the risk of complications?
- Do low levels of C-peptide protect from hypoglycaemia?
- Do low levels of C-peptide maintain or provide HbA1c regulation?

The new study goes some way towards answering these questions and builds on previous research that used an ultrasensitive assay to show that C-peptide was detectable in 63 per cent of people with Type 1 diabetes with mean duration of 19 years.

C-peptide study details

At the MGH Immunobiology Research Clinics, the researchers surveyed 1,273 patients with Type 1 diabetes, accrued between 2008 and 2013, for fasting C-peptide levels (in a cross-sectional manner). The study was expanded to explore the relationship between C-peptide and HbA1c levels, and between C-peptide and the presence, or absence, of any diabetes-related complications and hypoglycaemia. The lower detection limit of the assay used in this study was 2.5 pmol/l.

Participants were aged between eight and 90 years. The majority of the group were of non-Hispanic white ethnicity. A subgroup of 324 patients took part in the study of complications,



also completing a survey on hypoglycaemia unawareness.

Study findings

The data show, as expected, a clear decline of C-peptide with duration of Type 1 – put simply, C-peptide levels decrease with time from diagnosis. Previous studies have shown a relationship between C-peptide and age of onset, and this new study confirms that the younger the person is diagnosed,

“Could the measurement of low levels of C-peptide identify heterogeneity in Type 1 patients?”

the more rapid their C-peptide decline will be. Those diagnosed in childhood have very rapid C-peptide declines with diabetes duration. In contrast, those who are diagnosed in adult life have a more gradual decline of C-peptide.

When it came to looking at the relationship between C-peptide levels and complications, the study focused on a subgroup of 324 patients, of whom 76 reported at least one diabetes-related complication. Analysis of the C-peptide

data for these patients showed that levels >10 pmol/l were protective against complications, while levels of <10 pmol/l were associated with risk.

Further analysis was used to look at the relationship between C-peptide and HbA1c levels in the group of 1,273 patients. Lower C-peptide levels (2.5–50 pmol/l) were associated with higher HbA1c, while levels greater than 50 pmol/l were linked to lower HbA1c.

Finally, the association between C-peptide levels and hypoglycaemia was investigated. In the subgroup of 324 patients, 64 reported moderate hypoglycaemia and 38 reported severe hypoglycaemia. Grouping patients into mild, moderate or severe showed that those with mild and moderate hypoglycaemia had higher levels of C-peptide compared with those who had severe hypoglycaemia.

Implications

In this study, a sensitive C-peptide assay reveals a gradual decline in pancreatic function in Type 1 diabetes that happens over the decades following diagnosis, confirming previous findings. It also showed that early onset of Type 1 is a risk factor for undetectable C-peptide, while later onset is associated with a slower decline in C-peptide. These observations also confirm earlier work

with less sensitive assays. The authors suggest that low levels of residual C-peptide may have significance in preventing complications, for preservation of levels >10pmol/l were associated with protection. Worsening of HbA1c was noted with the very lowest levels of C-peptide (2.5–50pmol/l) compared with levels in the range 51–200pmol/l. In conclusion, they state that measurement of low levels of C-peptide seems to be helpful in defining the natural history of Type 1 diabetes as ‘a decades-long decline in insulin secretion’.

Residual C-peptide seems to have both biological and clinical significance not previously realised. Not only could C-peptide be used as a biomarker in diagnostics, its preservation could perhaps be the basis of a new therapeutic strategy.

In an accompanying editorial, Bobby Huda of the Royal London Hospital and Graham Hitman, Editor-in-Chief, *Diabetic Medicine*, say: ‘Currently, the measurement of C-peptide with corresponding glucose levels is not a routine part of the clinical care of patients with Type 1 diabetes; we would like to suggest that the time for this is approaching’. They add that the findings of this new study are ‘important and novel’, but perhaps not robust enough to allow physicians to make an accurate prognosis based on C-peptide alone.

In any case, most centres will not have access to the ultrasensitive assays used here. However, C-peptide measurement could perhaps start a useful clinical conversation about severe hypoglycaemia or the risk of complications, therefore influencing

both patient and physician behaviour. C-peptide and autoantibody levels will also continue to have practical utility in helping more precise diagnosis in those cases where clarification is needed.

i This is a digested version of **Kuhreiter WM, Washer SLL, Hsu E et al (2015). Low levels of C-peptide have clinical significance for established Type 1 diabetes. *Diabetic Medicine* 32; 1346–1353 and Huda MSB and Hitman GA (2015). C-peptide: should we be testing this routinely in the Type 1 diabetes clinic? *Diabetic Medicine* 32; 1259–1260. To download the articles, go to <http://onlinelibrary.wiley.com/doi/10.1111/dme.12850/epdf> and <http://onlinelibrary.wiley.com/doi/10.1111/dme.12953/epdf>**

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