**C-peptide Measurement In Type 1 Diabetes**

C-peptide is a measure of endogenous insulin secretion. Broadly speaking, people with Type 2 diabetes will have substantial endogenous insulin (and thus C-peptide) production, while individuals with type 1 diabetes will have severe insulin (and C-peptide) deficiency.

We know that we do not always correctly establish the cause of diabetes in any one individual. The purpose of the C-peptide test is to enhance our diagnostic accuracy.

**Serum vs Urine C-peptide testing**

Both blood or urine C-peptide are suitable screening tests and **can be taken without any prior adjustment or omission of insulin therapy**.

Urine C-peptide testing has the advantage of very robust validation. Urine must be collected in a boric acid container (red top) and is best measured in a sample taken 2 hrs after the largest meal of the day. Samples are analysed in Exeter. The main downside of urine C-peptide is that it will usually require patients to hand back in the sample after the clinic, and as a consequence it is likely that many samples will not be returned.

Serum C-peptide samples can be taken at the time of the clinic visit (brown tube). Serum C-peptide (like urine C-peptide) is very stable and there are no special handling requirements. Validation is less robust as there are many different available C-peptide assays. For example, the assay used in Edinburgh gives slightly lower readings than the Exeter assay. Therefore, when interpreting data, it is very important that **cut-offs are not rigidly applied** and the data must always be interpreted in the clinical context of the patient. Serum C-peptide is most predictive if it is taken when blood glucose is>4 mmol/l **and** the patient is not fasted. Therefore, it is important that a sample for blood glucose measurement is taken at the same time. If blood glucose is <4 mmol/l at the time of testing or the patient was fasted, then this can result in a falsely low C-peptide and arrangements should be made to repeat the measurement (especially if <200 pmol/l).

**Interpretation of C-Peptide Results**

Severe insulin deficiency would clearly be expected in most patients with Type 1 diabetes (though patients with some forms of neonatal diabetes could also fall into this category). Substantial endogenous insulin secretion could be indicative of Type 1 diabetes (particularly of relatively short duration), monogenic diabetes or Type 2 diabetes. Most patients with Type 2 diabetes would be expected to fall into the ‘significant insulin resistance’ category. It is important to stress that these cut-offs and the potential diagnoses must not be interpreted too rigidly. **The C-peptide test is a screening test only, not a diagnostic test.** Further information on interpretation can be found onthe ‘Diabetes Diagnostics’ App from the University of Exeter and on the Exeter MODY website (www.diabetesgenes.org).

Tables to aid interpretation of urine C-peptide results (expressed as a urine C-peptide to creatinine ratio; UCPCR) are also available on the ‘Diabetes Diagnostics’ App from the University of Exeter and on the Exeter MODY website (www.diabetesgenes.org).

**Who should undergo C-peptide testing?**

At the moment, we are recommending C-peptide testing only for individuals with a diagnosis of Type 1 diabetes. The rationale is that this is the patient group in whom a change of diagnosis will have the greatest impact on quality of life. Roll-out to patients with Type 2 diagnosis may be considered at a later date.

C-peptide testing should be considered in anyone with a diagnosis of Type 1 diabetes, but it is unlikely to lead to a change in diagnosis if there were good reasons for making the diagnosis of Type 1 diabetes (e.g. diabetic ketoacidosis AND strongly positive autoantibodies at diagnosis).

 Diabetes antibodies (GAD, IA2 and ZnT8) are found in low titres in the general population and, as with any immunoassay, false positives can occur. It is not possible to give an antibody titre cut-off, but high titre GAD antibodies and/or the presence of multiple positive antibodies at diagnosis increase substantially the likelihood of Type 1 diabetes. Antibody titres can fall with increasing duration of Type 1 diabetes.

Ketoacidosis per se was traditionally considered pathognomonic of Type 1 diabetes, but is increasingly recognised to occur in people with significant endogenous insulin production, especially people of African origin (so-called Flatbush diabetes).

Because individuals with Type 1 diabetes can continue to produce C-peptide for several years after diagnosis, this test should only be performed on those individuals with Type 1 diabetes of **at least 3 years duration**. **If C-peptide is checked in patients with a relatively new diagnosis of diabetes, then it may give a misleading result as to the aetiology of diabetes.**

Exeter offer a Type 1 Diabetes Genetic Risk Score, which looks at variations in 10 genes known to be associated with Type 1 diabetes. Results in this test are expressed in centiles of likelihood of Type 1 diabetes. Therefore, this test gives a probability that the person has Type 1 diabetes. It is a useful test in patients who had one diabetes antibody present in low titre, where there is uncertainty if this is a pathological result or a ‘false positive’.

Therefore, C-peptide testing is recommended in the following:

* Patient has a clinician-diagnosis of Type 1 diabetes
* Duration of diabetes > 3 years



**\*If patient has had GAD and IA-2 measured previously, e.g. at diagnosis, there is no need to repeat this. Simply request ZnT8 antibody testing.**