children who will in response to oral challenges is crucial, specifically showing that a reduced early response can differentiate at-risk children who will progress to develop type 1 diabetes from those who will not progress.[22] Similarly, the Type 1 Diabetes Trial Net Study Group showed that autoantibody-positive youths progressing towards overt type 1 diabetes in 5 years or longer have a lower fasting C-peptide and a lower early C-peptide response to an OGTT than their autoantibody-negative peers.[23]

Monitoring of blood glucose has traditionally been by HbA1c, which has been used in most studies that demonstrate the effects of lowering glucose on the development and progression of diabetes complications.[24] There is a strong correlation between HbA1c and mean blood glucose levels during the preceding 3 months . In several conditions, however, HbA1c does not reflect mean glucose; these are mainly situations where erythrocyte turnover is altered or in the presence of hemoglobinopathies.[25] Although HbA1c is an indicator of mean glucose, it does not inform glycemic variability and hypoglycemia and, therefore, is inappropriate as the only method of glucose evaluation in type 1 diabetes.[26]

After clinical onset, measurement of C-peptide may be helpful to confirm insulin deficiency in patients with signs of diabetes-related autoimmunity, without having a clear phenotype for type 1 diabetes, or who have a strong family history of diabetes suggesting monogenic diabetes.[27] C-peptide levels were also able to individuate subgroups of people with type 1 diabetes responding better to liraglutide treatment in a post hoc analysis of the ADJUNCT ONE trial.

C- PEPTIDE IN TYPE 2 DIABETES

The origin of hyperglycaemia in type 2 diabetes is a variable combination of pancreatic â-cell dysfunction along with hepatic and peripheral insulin resistance. [28]

In the prediabetic stage, higher C- peptide levels are associated with an increased risk of progression towards overt type 2 diabetes, with a stronger relationship than insulin levels.[29]

The use of C-peptide instead of insulin as denominator for the calculation of proinsulin ratios may be a better indicator of distressed â-cells and better predict the progression towards type 2 diabetes because it is not affected by the impaired hepatic clearance of insulin.[30,31]

A few studies also suggest C-peptide may help in understanding the heterogeneity of type 2 diabetes, and potentially provide useful guidance for the safe initiation and titration of basal insulin. In particular, C-peptide has been used instead of insulin for the calculation of the homeostasis model assessment to distinguish people who have severe insulin-deficient type 2 diabetes. [32]

C-peptide has recently been shown to have a putative role in predicting the response to treatment with basal insulin and risk of hypoglycaemia.[33] The measurement of random C-peptide can therefore either identify patients with insulin-treated type 2 diabetes who are at increased risk of experiencing hypoglycaemia or alert the clinician to cases who might have other forms of diabetes, including type 1 diabetes, ketosis-prone diabetes or latent autoimmune diabetes.[34]

A population-based cohort study reveals that, elevated C-peptide levels are associated with an increased risk of type 2 diabetes independent of glucose, insulin levels, and clinical risk factors. Elevated C-peptide level was not independently associated with an increased risk of type 2 diabetes in individuals with hypertension or albuminuria.35

C-PEPTIDE TO DIFFERENTIATE TYPE 2 DIABETES FROM AUTOIMMUNE DIABETES

A joint ADA/EASD consensus report on the management of type 1 diabetes in adults[36] recommended the evaluation of C-peptide beyond 3 years after diabetes diagnosis in autoantibody-negative adults receiving insulin treatment, with C-peptide values of less than 0.20 nmol/L suggesting a diagnosis of type 1 diabetes and values of more than 0.60 nmol/L indicating type 2 diabetes. The consensus also highlighted that C-peptide concentrations of 0.20-0.60 nmol/L should be interpreted with caution, as no absolute value in this range is clearly discriminatory between autoimmune or monogenic diabetes, but can