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C-PEPTIDE; NEW DIAGNOSTIC TOOL IN THE EVALUATION OF HYPOGLYCAEMIC AND HYPERGLYCAEMIC STATES

Pages with reference to book, From 295 To 296

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INTRODUCTION

Human C-peptide or 'connecting' peptide is a 31 amino acid chain which originates in the pancreatic beta cells as a by-product of enzymatic cleavage of the precursor of insulin^{1,2}. This precursor is proinsulin and was first described by Steiner and Oyer³. Transformation of proinsulin to insulin begins in the golgi apparatus and continues in the secretory granules of the beta cells⁴. Insulin and C-peptide are secreted in equi-molar concentrations into the portal circulation^{5,6} but this relationship is not preserved in the peripheral circulation due to differences in first pass metabolism by the liver and due to insulin binding antibodies. The liver extracts approximately 50% of insulin delivered to it, in the first pass metabolism⁷. This first pass metabolism of insulin is variable and unpredictable in individual patients. Hepatic extraction of C-peptide is negligible⁸. Circulating insulin antibodies, found in some patients on insulin therapy, would interfere with insulin assays, rendering them unreliable as a predictor of residual beta cell activity. Also, the metabolic clearance rate of C-peptide is constant under different physiological circumstances and over the range of plasma concentrations usually encountered⁹. Hence C-peptide assays, which are now available, would serve as a more useful indicator of beta cell activity and insulin secretion than peripheral insulin assays.

URINARY C-PEPTIDE

Urinary excretion of various hormones and their metabolites have been used to calculate their secretion rates. The potential of using this approach to measure insulin secretion is a possibility. Based on glomerular permeability studies it can be predicted that a molecule as small as C-peptide would be freely filtered across the glomerular basement membrane despite its negative charge^{10,11}. Kaneko et al first reported that appreciable quantities of C-peptide were excreted in urine in man and that urinary C-peptide levels increased after an oral glucose load in parallel with the increase in plasma C-peptide levels. Urinary C-peptide and creatinine excretion rates reduce in parallel so that the ratio of their 24 hour excretion rates remained constant in renal disease¹². Horwitz et al¹³ reported that the 24 hour urinary excretion of C-peptide in normal subjects was 36 ± 4 ug while in type I diabetic subject was only 1.1 ± 0.5 ug. Range of urinary C-peptide in type II diabetic subjects overlapped the amounts excreted in normal and juvenile-onset diabetic subjects. Except in uremia, C-peptide levels in 24 hours urine collection provide an accurate reflection of average plasma levels of C-peptide and hence average insulin secretion¹⁴.

METHODOLOGY

Various radioimmunoassay (MA) methods are available for the detection of C-peptide. In our laboratory a competitive radioimmunoassay in which labelled ¹²⁵I C-peptide competes with C-peptide

in the patient's sample for antibody sites is employed. First the patient sample is incubated with C-peptide antiserum and labelled 125I C-peptide for 14-16 hours. The antigen-antibody complexes formed are precipitated by the help of a second antibody. The precipitate is counted for radioactivity and patient sample concentrations are read from a calibration curve prepared from a synthetic human C-peptide analog. Radioimmunoassays are sensitive upto 75 pg/ml. Insulin itself does not cross react with the assay but circulating anti-insulin antibodies may react with proinsulin, the latter in turn may react with C-peptide antibodies and thus may result in misleadingly high C-peptide assay results. C-peptide is mainly cleared by the kidneys and associated renal disease may affect C-peptide values. Interference during assay is produced by lipaemia and icteric samples, however hemolyzed serum samples produced no significant changes.

USES OF C-PEPTIDE ESTIMATION

Measures of C-peptide levels have been most useful in the evaluation of hypoglycaemic states especially in diagnosis of endogenous hyperinsulinemia, e.g., insulinoma. In addition to measurement of levels, the suppression of C-peptide with insulin induced hypoglycaemia can also be checked in insulinoma where there is a loss of C-peptide suppression. Following resection of insulinoma, C-peptide levels can be a marker of recurrence of tumour or metastasis¹⁵. Factitious hypoglycaemia due to exogenous insulin administration in diabetic and non-diabetic patients can also be distinguished from excess endogenous insulin secretion by this assay. Following pancreatectomy for carcinoma of pancreas C-peptide levels will indicate presence of residual pancreatic tissue. In patients with non-insulin dependent diabetes (type II), insulin secretory responses after oral and intravenous glucose challenges are decreased and decline progressively with severity of diabetes¹⁶. Peak C-peptide levels during oral glucose tolerance test have also been shown to be a predictor of insulin requirement in diabetic patients. In their study Turkington et al¹⁷ showed that patients with C-peptide levels less than 4.0 ug/ml could not be treated without supplementation with exogenous insulin. Patients with C-peptide reactivity levels between 4.1-5.4 ug/ml could usually avoid ketosis without insulin therapy but could not normalize blood glucose by weight loss alone. Patients with C-peptide levels greater than 6.0 ug/ml could normalize hyperglycaemia by weight loss alone. Other studies have also shown the value of C-peptide to predict the insulin requirements at diagnosis of diabetes mellitus¹⁸. Also C-peptide levels are useful to assay in type I diabetics, to see residual beta cell function which in these patients is expected to be low in contrast to high levels in beta cell over activity in insulinomas¹⁹. Fasting C-peptide levels have used to determine clinical type of diabetes²⁰. Diabetic complications like proliferative retinopathy appears to be higher in patients with low C-peptide levels²¹. C-peptide assays are being used in various research orientated studies in type I and type II diabetic patients at present.

CONCLUSION

Plasma and urinary C-peptide levels can serve as a valuable index of insulin secretion. The assay is now available and has many diagnostic uses. It marks a significant advancement as a diagnostic tool in the evaluation of diabetic patients as well as determining the causes of hypoglycaemia.

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