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Determination of insulin for the diagnosis of hyperinsulinemic hypoglycemia

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Hyperinsulinemic hypoglycemia is the most common cause of persistent hypoglycemia in children and adults. The diagnosis of hyperinsulinemic hypoglycemia relies on the evaluation of the biochemical profile at the time of hypoglycemia, however, contrary to common perception, plasma insulin is not always elevated. Thus, the diagnosis must often be based on the examination of other physiologic manifestations of excessive insulin secretion, such as suppression of glycogenolysis, lipolysis and ketogenesis, which can be inferred by the finding of a glycemic response to glucagon, and the suppression of plasma free fatty acids and beta-hydroxybutyrate concentrations during hypoglycemia.

Introduction

Hyperinsulinemic hypoglycemia is the most frequent cause of persistent hypoglycemia in children and adults. In adults, hyperinsulinemic hypoglycemia is most commonly an acquired problem due to an insulin-secreting tumor; while in children, with only rare exceptions, it represents a congenital disorder [1]. The development of a radioimmunoassay for insulin by Yalow and Berson in 1960 [2] made it possible to demonstrate the role of endogenous insulin in hypoglycemic disorders.

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However, as discussed below, simply measuring plasma insulin concentrations is often not enough to establish the diagnosis of hyperinsulinemic hypoglycemia.

Methods

A literature search of PubMed (http://www.ncbi.nlm.nih.gov/pubmed) was performed for studies published up to April 2013. Keywords used included insulin, C-peptide, proinsulin, insulin assay, insulinoma, hyperinsulinemic hypoglycemia, congenital hyperinsulinism. Additional articles known to the authors or cited by others were also included.

Establishing the diagnosis of hyperinsulinemic hypoglycemia

Insulin secretion by pancreatic β-cells is tightly regulated by an array of stimulatory and inhibitory factors, of which glucose plays the leading role. The plasma glucose threshold concentration for insulin release is determined by the activity of β-cell glucokinase and is precisely maintained at approximately 5 mmol/L in humans [3]. This tight control of insulin secretion in relationship to glucose concentration results in plasma glucose concentrations in normal individuals that remain remarkably stable in the range of 3.9–7.1 mmol/L (70–128 mg/dL) during normal daily cycles of feeding and overnight fasting.

In hyperinsulinemic hypoglycemia this tight control of insulin secretion by glucose is lost. To define whether hypoglycemia is insulin-mediated, it is necessary to establish that β-cell insulin secretion is not appropriately turned off as glucose levels decrease; however, because it is not possible to measure insulin secretion in vivo directly, reliance is ordinarily placed on measurements of plasma insulin concentrations in samples of venous blood at the time of hypoglycemia. However, it is important to note that peripheral plasma insulin concentrations can be affected by the kinetics of insulin distribution and degradation. Following secretion, insulin is distributed into both intra and extravascular spaces and thus, the volume of distribution is several times larger than plasma volume. A large fraction (~50%) of insulin secreted by the pancreas is cleared by the liver at first passage. The rate of insulin degradation is approximately 2 percent per minute [4]. Therefore, the insulin concentration measured in peripheral plasma may be up to 90% lower than the initial peak plasma concentration within less than 30 min [5]. C-peptide, secreted in a 1:1 M ratio with insulin, is cleared primarily by the kidney and has a lower metabolic clearance rate (4.4 mL/min) than insulin and therefore a longer half-life in circulation (20–30 min *vs.* 3–5 min) [6,7]. Thus, peripheral C-peptide concentration reflects portal insulin secretion more accurately than the peripheral plasma insulin concentration. Normally, the molar ratio of insulin to C-peptide should be less than 1 in peripheral circulation; a higher ratio of insulin to C-peptide indicates the likelihood of exogenous insulin administration [8].

Measurement of plasma insulin concentration: pitfalls

When first developed, more than 50 years ago [2], the insulin assay was mainly used in studies aimed at understanding the physiology and pathophysiology of insulin regulation. These studies involved small numbers of subjects and, therefore, reproducibility and standardization were not priorities. Later, in an attempt to limit the large variation in reported values from different laboratories, the World Health Organization provided purified preparations of porcine insulin that could be used as external standards [9]. The development of recombinant DNA technology in the 1980s [10] made available large quantities of purified human insulin and led to further improvements in the performance of the assay. Subsequent improvements have included the development of monoclonal antibodies for use in immunoassays [11] and of guidelines standards for assay performance [12], which have allowed for better reproducibility, sensitivity and specificity. Nevertheless, a complete reference system in conformance with International Organization for Standardization requirements is yet to be established for insulin [13].

The main clinical application of plasma insulin assay is for the diagnosis of hyperinsulinemic hypoglycemia. However, despite the improved performance of the assay, interference by the presence of anti-insulin antibodies [14] and of hemolysis decreases the utility of the assay for this purpose. Hemolysis of the sample, a particular problem in children in whom blood drawing is difficult, can result in