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Review

Update on cystic fibrosis-related diabetes

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Abstract

Diabetes mellitus has emerged as a common comorbidity in cystic fibrosis and is considered a clinical entity (cystic fibrosis-related diabetes, CFRD) distinct from that of type 1 diabetes (T1DM) and type 2 diabetes (T2DM). The relevance of this diagnosis extends not only from its imposition of additional medical burden but its association with worse health outcomes in individuals with CF. This paper will review the 2010 U.S. and other international guidelines for screening and treating CFRD. It will highlight newer data regarding early glucose and insulin secretion defects, mechanisms linking CFRD to worse outcomes, and recent advances in T2DM that may provide insights for CFRD; insulin secretion will be reviewed as background for these recent developments.

Keywords: Cystic fibrosis; Diabetes; Hyperglycemia; Cystic fibrosis-related diabetes

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1. Introduction

1.1. Insulin physiology

Pancreatic β-cell insulin secretion strictly governs glucose, amino acid, and fat disposition. A highly anabolic agent, insulin targets these fuels for storage [1], stimulating glycogen synthesis and glucose uptake by fat and muscle while suppressing hepatic glycogenolysis and gluconeogenesis, lipolysis, and ketogenesis. In the absence of nutrient ingestion, insulin secretion is down-regulated and a catabolic state is invoked whereby glucose is accessed from glycogen and through conversion from amino acids. With more prolonged fasting, lipolysis and ketogenesis provide alternate fuels.

Insulin secretion is regulated by the availability of nutrients, other hormones, and neural factors. Following oral glucose ingestion, insulin levels normally rise within the first 30 min, peak at about 60 min, and return to baseline levels by 2–3 h. In contrast, following intravenous glucose bolus, insulin secretion occurs in a biphasic manner. An early rapid peak (acute insulin response, first phase insulin secretion) occurs within the first 10 min and then a more slow increase in insulin secretion (second phase insulin secretion) occurs over the next 20 min (reviewed in [2]). Insulin secretion in response to oral glucose is greater than insulin secretion in response to the same amount of glucose delivered intravenously. This augmented response arises from incretin secretion from gastrointestinal tract neuroendocrine cells in response to nutrient ingestion, Fig. 1. This "incretin" effect may account for 50–70% of total insulin response to an oral glucose load, with glucagon-like peptide (GLP-1) and gastric inhibitory peptide (GIP) accounting for ~90% of this response [3]. Fat also stimulates GLP-1 and GIP secretion — an effect that requires hydrolysis of fat [4].

1.2. Diabetes classification/clinical features

The pathophysiology of diabetes development, particularly in the setting of T2DM, is complex, but ultimately all diabetes arises as a result of either an absolute or relative insulin-deficient state. The American Diabetes Association (ADA) classifies diabetes mellitus based upon etiology [5], Table 1. T1DM arises from β-cell destruction, primarily of autoimmune origin. Insulin deficiency is severe, and provision of exogenous insulin is required to minimize hyperglycemia and prevent ketoacidosis. Insulin treatment in T1DM targets basal insulin needs and nutrient ingestion. Individuals with T1DM are at increased risk of other autoimmune diseases including hyper- and hypothyroidism, adrenal insufficiency, and Celiac disease.

Insulin secretory defects are now thought to underlie T2DM development. Frequently, obesity and an insulin resistant state place increased demands on β-cells. A compensatory increase in insulin secretion occurs. As β-cells are "over-worked," the secretory defect(s) is unmasked, β-cells can no longer meet the increased insulin requirements, and hyperglycemia ensues. Treatment approaches vary from diet and exercise to address obesity and insulin resistance, to use of medications that either improve insulin sensitivity or insulin secretion, to insulin replacement. Ketoacidosis is rare. Dyslipidemia, hypertension,

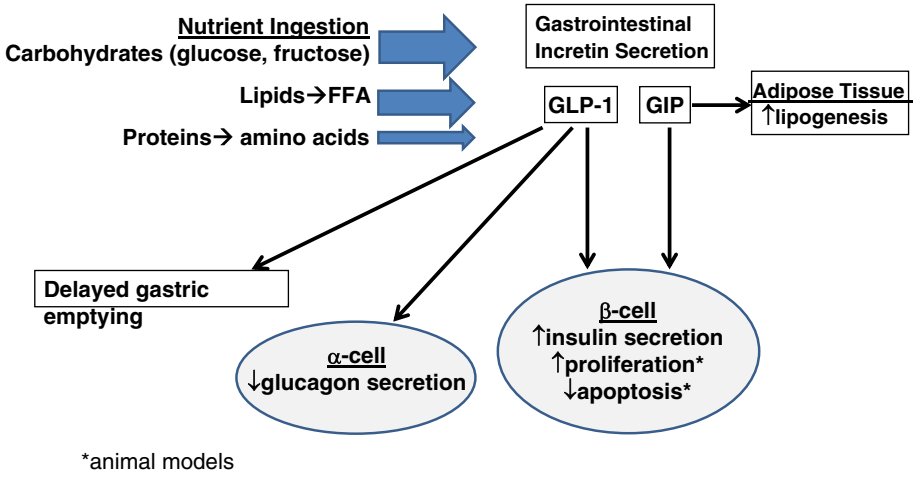

Fig. 1. Incretin secretion and action. Glucose, fructose, free fatty acids, and to a lesser extent amino acids stimulate GLP-1 and GIP secretions. GLP-1 and GIP augment glucose stimulated insulin secretion and in animal models inhibit β-cell apoptosis and promote β-cell proliferation. GIP also promotes lipogenesis. GLP-1 suppresses glucagon secretion and delays gastric emptying.