Diabetes Mellitus: Understanding the Physiology and How it Applies to Treatment Approaches

Diabetes mellitus (DM) and cardiovascular disease (CVD) are often found concomitantly. According to data from the University Hospital of the West Indies, ~60% of diabetic patients who are admitted have evidence of CVD. This combination is particularly pervasive among female patients [Ferguson TS et al. *Diab Vasc Dis Res* 2010]. Michael Boyne, MD, FRCPC, Tropical Medicine Research Institute, University of the West Indies, Mona, Kingston, Jamaica, discussed the mechanisms of disease and new evidence that may help clinicians manage these diseases more efficiently.

Islet alpha (α)- and beta (β)-cell hormones play a key role in glucose homeostasis. In healthy subjects, α-cells secrete glucagon and β-cells secrete insulin. However, in diabetic subjects, there is excessive secretion of glucagon from the α-cells and insufficient secretion of insulin as a result of β-cell dysfunction, apoptosis, and β-cell loss. Therefore, early insulin therapy may preserve β-cell function and promote better metabolic control [Alvarsson M et al. *Diabetes Care* 2003; Ryan EA et al. *Diabetes Care* 2004].

Glucagon-like peptide-1 (GLP-1) is also an important incretin hormone that affects glucoregulation. GLP-1 is secreted upon ingestion of food and stimulates insulin secretion only in the presence of elevated plasma glucose levels. In patients with T2DM, GLP-1 infusion improved insulin and glucagon levels as glucose approached normal values (ie, insulin levels decreased and glucagon levels rebounded as a result of GLP-1 infusion when normal glucose values were attained) [Nauck MA et al. *Diabetologia* 1993].

Incretin mimetics (GLP-1 receptor agonists) and incretin enhancers (inhibitors of dipeptidyl peptidase-4, or DPP-4), which increase active GLP-1 function, may provide a treatment solution. The DPP-4 inhibitor sitagliptin has been shown to reduce hemoglobin A1C (HbA1C) levels by 0.5% to 1.0% with few adverse events and no weight gain [Drucker DJ & Nauck MA. *Lancet* 2006; Aschner P et al. *Diabetes Obes Metab* 2010]. In a 54-week study by Williams-Herman and colleagues, initial sitagliptin + metformin combination therapy reduced HbA1C levels significantly and improved markers of β-cell function in patients with T2DM [Williams-Herman D et al. *Curr Med Res Opin* 2009]. These benefits were observed with a low incidence of adverse events, including hypoglycemia.

Additionally, a safety analysis of sitagliptin, performed by Williams-Herman et al, revealed that sitagliptin 100 mg daily was generally well tolerated in clinical trials, lasting up to 2 years. From a CVD standpoint, sitagliptin therapy was not associated with an increase in major adverse cardiovascular event risk [Williams-Herman D et al. *BMC Endocr Disord* 2010].

There is conflicting data concerning the role of DM as a coronary risk equivalent. While some studies have concluded that DM confers equal mortality risk as prior myocardial infarction, other analyses have not found as strong of a relationship [Haffner SM et al. *N Engl J Med* 1998; Bulugahapitiya U et al. *Diabet Med* 2009; Booth GL et al. *Lancet* 2006]. Current guidelines have incorporated the concept of DM as a CVD risk equivalent into their clinical recommendations, but this relationship has yet to be definitively established.

The management of DM and CVD presents a complex clinical challenge. New evidence has brought to light the mechanisms of disease and possible treatment strategies. Further investigation is warranted to assess the long-term safety and efficacy of these novel approaches.

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