Alteration in Pancreatic Islet Function in Human Immunodeficiency Virus

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KEYWORDS

• Insulin secretion • Prehepatic • Proinsulin • Lipodystrophy • Antiretroviral therapy
• Nonglucose insulin secretagogues • Insulin-like growth factors • Incretins

KEY POINTS

- Nonglucose secretagogues, fat redistribution, and insulin resistance of beta cells themselves are among the mechanisms impairing insulin secretion in patients on modern anti-human immunodeficiency virus (anti-HIV) therapy.
- Protease inhibitors are thought to directly impair insulin processing and secretion, but recent in vivo data challenge this view; thus, controlled trials are warranted.
- Hepatic extraction of insulin and insulin-like growths factors, which exhibit insulin effects, exerts influence on the demand on insulin secretion in HIV-infected patients.
- Although proinsulin processing may not be influenced directly by protease inhibitors and nucleoside analogues, the lipodystrophy syndrome they promote is highly associated with defective proinsulin secretion.
- Although the incretins are essential for normal insulin secretion, the data on how modern anti-HIV therapy influences incretin secretion and effect are sparse.

THE BETA CELL, INSULIN RESISTANCE, AND HUMAN IMMUNODEFICIENCY VIRUS-ASSOCIATED LIPODYSTROPHY SYNDROME

The function of the beta cell in the pancreatic islets of Langerhans is decisive in facilitating a normal glucose homeostasis. The primary drive force of an increased insulin secretion of the individual is the prevalent insulin resistance of various organ systems, in particular liver, muscle, and adipose tissue. The mechanisms and prevalence of insulin resistance in human immunodeficiency virus (HIV) infection and its association with antiretroviral therapy are the focus of another article by Hadigan and colleagues

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in this issue. As long as the beta cell can secrete sufficient insulin to overcome insulin resistance, plasma glucose excursions are kept within normal range. But if the insulin production and secretory machinery cannot match the required output, hyperglycemia and type 2 diabetes develop. In the case of severe insulin resistance, the call for adequate insulin secretion to keep a normoglycemic state may exceed tenfold that which is necessary if organ systems exhibit normal insulin sensitivity. The HIV-associated lipodystrophy syndrome (HALS) encompasses the phenotype of HIV-infected patients who loose subcutaneous adipose tissue in limps and face and accumulate intra-abdominal visceral adipose tissue.[1] HALS was seen after the introduction of combined antiretroviral therapy of nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) almost 20 years ago.[2] HALS is related to insulin resistance through different mechanism, which, among several mechanisms includes alteration in insulin signaling in muscle tissue.[3] While HALS was observed in approximately half of those HIV-infected patients treated with first-generation PIs and first-generation NRTIs (in particular thymidine analogues), the incidence has decreased with introduction of new generations of antiretroviral drug combinations. Of interest, a recent cohort study has shown that newer antiretroviral regimes may not ameliorate HALS,[4] and this fact may have great impact on those patients who already exhibit HALS, because they may benefit little from a change in anti-HIV therapy. This interpretation of HALS being partially refractory to the newer less mitochondrial toxic NRTIs and newer less metabolic deteriorating PI regimens, however, must await further cohort studies. The fact that HIV-infected patients without prevalent comorbidities caused by modern antiretroviral therapy exhibit better prognosis than most well treated non-HIV infected type 2 diabetes patients in terms of life expectancy and quality of life should highlight the importance of the long-term metabolic impact of modern antiretroviral therapy.[5]

FIRST PHASE INSULIN SECRETION, PREHEPATIC INSULIN SECRETION, AND ITS REGULATION

An impaired first-phase insulin release after intravenous glucose may be an early sign of a defect in beta cell function.[6] An impaired first-phase insulin release in relation to the prevalent insulin sensitivity (ie, a reduction in disposition index [the product of first-phase insulin release and insulin sensitivity]) of approximately 50% was demonstrated in normoglycemic HALS patients compared with normoglycemic non-HALS patients.[7]

The first-pass extraction of insulin in HIV-infected patients is related to the prevalent insulin resistance and may vary from 30% to 80% of the amount of insulin secreted from the pancreatic islet cells.[8] C-peptide is secreted in equimolar amount to insulin and does not show-first pass extraction by the liver. Therefore, prehepatic insulin secretion rates can be calculated from plasma C-peptide measurements (eg, by use of the ISEC [Insulin SECretion]) computer program.[9] ISEC has been validated to calculate insulin secretion rates (ISRs) during an intravenous glucose tolerance test (IVGTT)[10,11] and has been applied to calculate ISR during a meal tolerance test, under a hyperinsulinemic euglycemic clamp, and during basal conditions.[9] The author and colleagues observed that an increased prehepatic insulin secretion in normoglycemic HALS patients was not down-regulated during a hyperinsulinemic clamp, which was preceded by an intravenous glucose bolus to stimulate endogenous insulin secretion.[12] By contrast, a control group of HIV-negative subjects, matched for insulin secretion and sensitivity to the HALS patients, showed a significant reduction in basal insulin secretion in that setting. Of interest, HALS patients showed a paradoxical positive correlation between the plasma insulin and prehepatic insulin secretion during the