HIV Endocrinopathies

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Endocrine and metabolic disturbances occur in the course of HIV infection. Pathogenesis includes direct infection of endocrine glands by HIV or opportunistic organisms, infiltration by neoplasms and side effects of drugs. Adrenal insufficiency is the commonest HIV endocrinopathy with cytomegalovirus adrenalitis occurring in 40-88% of cases. Thyroid dysfunction may occur as overt Hypothyroidism, euthyroid sick syndrome or sub-clinical hypothyroidism. Hypogonadotrophic dysfunction accounts for 75% of HIV-associated hypogonadism, with prolonged amenorrhea being three times more likely in the women. Pancreatic dysfunction may result in hypoglycaemia or diabetes mellitus (DM). Highly active antiretroviral therapy (HAART) especially protease inhibitors and NRTIs has been noted to result in insulin resistance and lipodystrophy.

Virtually every endocrine organ is involved in the course of HIV infection. Detailed endocrinological and metabolic evaluation and appropriate treatment is necessary in the optimal management of patients with HIV infection in our environment.

1. FAT REDISTRIBUTION IN PATIENTS WITH HIV DISEASE

HIV-associated lipodystrophy or lipoatrophy, unreported before the introduction of highly active antiretroviral therapy (HAART), was first described in 1998, and has a prevalence ranging from 18% to 83%.

Protein-energetic malnutrition, characterized by both lean mass and fat depletion, was common in the pre-HAART era, and was associated with shortened survival and diminished quality of life. The pathogenesis of protein-energy malnutrition was multifactorial, and nutritional treatments were largely ineffective in the absence of disease stabilization. The introduction of HAART brought markedly improved outcomes, including a decrease in the incidence of malnutrition. However, other nutritional and metabolic alterations were noticed, and included changes in body shape, both lipoatrophy and lipohypertrophy, as well as changes in metabolism, notably hyperlipidemia and insulin resistance. These conditions, though sometimes occurring together, may occur independently, suggesting a complex, multifactorial cause. Several mechanisms have been hypothesized, including impairment to adipocyte differentiation and adipokine regulation, production of proinflammatory cytokines and mitochondrial toxicity. The role of the single drug class is still unclear, because both PI and NRTI have been associated with the syndrome, and the therapeutic protocols include both groups. Most of the medical therapies proposed for lipodystrophy are ineffective, and even if surgery remains an alternative, it is not associated with long lasting outcomes.

Pathogenic mechanisms for fat redistribution in patients with HIV disease

Lipodystrophy syndrome is a common term in the literature traditionally used to describe several morphologic (lipoatrophy; lipohypertrophy; mixed syndrome) and metabolic (Dyslipidemias, insulin resistance) disturbances found in patients with HIV disease, with or without treatment with highly active antiretroviral therapy (HAART). Increasing evidence suggests these disorders, though commonly clustering in a syndrome pattern, have distinct pathologic pathways and can occur independently
of each other. The pathogenesis of these disorders is complex, but recent hypotheses and evidence suggest that impairment to adipocyte differentiation, in particular through alterations in the expression of the transcription factor sterol responsive element binding protein-1c (SREBP1c), impairment of adipokine regulation, unopposed production of proinflammatory cytokines, adipocyte apoptosis mediated by proinflammatory cytokines such as tumour necrosis factor (TNF-alpha) and IL-6, dysregulation of 11-beta-hydroxysteroid dehydrogenase, and mitochondrial toxicity may play a role.

Protease inhibitors are responsible for a decrease in cytoplasmic retinoic-acid protein-1, in low density lipoprotein-receptor-related protein and in peroxisome proliferator activated receptor type-gamma. Nucleoside reverse transcriptase inhibitors, and thymidine analogues, are responsible for mitochondrial dysfunction as demonstrated by a decrease in subcutaneous adipose tissue mitochondrial DNA content. Both phenomena are responsible for a decreased differentiation of adipocytes, increased levels of free fatty acids and lipoatrophy. The increased levels of proinflammatory cytokines, such as tumour necrosis factor (TNF)-alpha and interleukin-6, further contribute to a decrease in subcutaneous adipose tissue mitochondrial DNA content. Both phenomena are responsible for a decreased differentiation of adipocytes, increased levels of free fatty acids and lipoatrophy. The increased levels of proinflammatory cytokines, such as tumour necrosis factor (TNF)-alpha and interleukin-6, may further contribute in development of lipodystrophy. TNF-alpha activates 11-beta-hydroxysteroid dehydrogenase type-1, which converts inactive cortisone to active cortisol, resulting in increased lipid accumulation in adipocytes and insulin resistance. HAART drugs and inflammatory cytokines are associated with a decrease in adiponectin. The levels of adiponectin and adiponectin-to-leptin ratio correlate positively with insulin resistance and negatively with HDL and extremity fat in a sample of HIV-infected patients treated with HAART. The results also indicate that NRTI use may worsen insulin resistance by decreasing adiponectin levels. Thus, adiponectin replacement may be a potential treatment option to ameliorate the metabolic changes observed in this patient population.

2. BONE DISORDERS
Furthermore, whereas HIV/HAART is associated with multiple aspects of endocrine dysfunction, there has been less focus on bone disease, although some studies indicate a higher prevalence of osteoporosis among HIV-positive subjects compared to HIV-negative controls. The relationship between bone and fat metabolism under HIV-positive conditions deserves further attention, and available data suggest the possibility of an intriguing connection. In the future, an increasing population of aging HIV-positive patients with a spectrum of antiretroviral therapies and accumulation of endocrine abnormalities and conventional cardiovascular risk factors will present preventive and therapeutic challenges to our health-care system.

3. THYROID DISORDERS
Thyroid function abnormalities were observed in substantial number of patients. In one study of 50 patients, nine (18%) patients had FT-3 levels below the normal range, ten (20%) patients had decreased FT-4 levels and twelve (24%) patients had s. TSH levels above the normal range. When the results were statistically analyzed for the 50 patients enrolled in the study using Pearson’s correlation coefficient, there was a direct correlation between CD4 count and FT3 and FT4 values (r = 0.357 with p < 0.05; r = 0.650 with p < 0.05 respectively). There was an inverse correlation of CD4 counts with TSH levels (r = -0.470 with p < 0.050).

Thyroid dysfunction is frequent in HIV infection and with progression of disease there is a primary hypothryoid like stage that occurs in patients with HIV infection. FT3 / FT4 serum TSH can be used as a surrogate marker of the progression of the disease. Thyroid dysfunction may also occur as euthyroid sick syndrome or sub-clinical hypothyroidism.

4. ADRENAL DISORDERS
Abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis have been documented in HIV patients in the early as well as late stages of the infection and range from subtle subclinical disturbances to frank adrenal insufficiency. Potential aetiologies of these disorders include opportunistic infections, neoplasms, drugs administered to
treat infections, cytokine abnormalities associated with the HIV disease process and acquired alterations in tissue sensitivity to glucocorticoids. HPA abnormalities in HIV infection and disease with regard to their aetiology with emphasis on syndromes of hypersensitivity/resistance to glucocorticoids associated with antiviral medications and/or the HIV infection itself.

Adrenal dysfunction can increase morbidity and mortality among patients with HIV infection. Disorders and medications affecting cortisol, aldosterone or adrenal androgens in patients with HIV infection are seen.

Iatrogenic Cushing’s syndrome and hypothalamic-pituitary-adrenal suppression from concomitant use of ritonavir without systemic corticosteroids such as intra-articular triamcinolone in addition to the previously reported interactions with inhaled fluticasone are increasingly recognized in HIV patients. Integrated measure of aldosterone throughout the day is higher in patients with HIV-associated visceral adipose tissue accumulation.

Abnormalities in adrenal function are more common in HIV patients than in the general population. HIV care providers should pursue workup for adrenal dysfunction in HIV patients when symptoms or signs are present, especially in patients with advanced AIDS or receiving medications that can affect adrenal function. The clinical implications of aldosterone elevation in HIV patients with visceral adiposity will need to be examined in future research studies.

5. NEUROENDOCRINE SYSTEM

Different lines of evidence suggest that human immunodeficiency virus type 1 (HIV-1) infection is complicated by a variety of adverse effects on neuroendocrine systems. Soon after the discovery of HIV-1, reports began to appear suggesting that a number of neuronal transmission and neuroendocrine activities were negatively impacted by this infection. In 1987 it was observed that fine-needle aspiration of the lung in patients with acquired immunodeficiency syndrome resulted in syncopal reactions. Subsequently, an abnormality in the autonomic nervous system was reported in these patients. However, investigations in this area have remained limited due to the assumption that HIV-1-mediated activation of various endocrine systems was related to the major life stressor of living with a fatal disease. Evidence accumulated over the years has indicated, instead, that there are various other mechanisms in addition to life stressors that also play an important role in negatively impacting the neuroendocrine systems in this infection.

6. DIABETES MELLITUS

HIV and diabetes are both chronic diseases that significantly affect lifestyle. When they intersect, the treatment regimens required for both diseases can be overwhelming for patients. Understanding the glucose disturbances that are possible with PI therapy, performing appropriate screening for glucose intolerance and diabetes and making prudent changes in HIV therapy when necessary, and treating patients for alterations in glucose metabolism are the key components of care for at-risk patients.

Metabolic disturbances associated with HIV medications, such as lipoprotein and fat distribution abnormalities, place patients with HIV at risk for cardiac disease. Glucose metabolism alterations in HIV patients present much like those of type 2 diabetes. Therefore, the best clinical care regimen will address all of the cardiac risk factors: insulin resistance/diabetes, lipid abnormalities, and body fat abnormalities. For patients with diabetes, the additional diagnosis of HIV increases the challenge of self-care management. However, in patients with HIV who develop hyperglycemia, the added responsibilities can be overwhelming.

For the past 20 years or more, researchers and clinicians have reported changes in glucose homeostasis in patients with HIV/AIDS. First noted in the population of patients who received pentamidine isothionate for the prevention and treatment of Pneumocystis carinii pneumonia, the possible etiologies for the disruption of glucose metabolism in those with HIV/AIDS continues to be a topic of discussion among infectious disease and endocrine physicians.

Effects of HIV on Glucose Homeostasis

Early articles reported that clinically stable, symptomatic HIV-infected men who were subjects in euglycemic clamp studies had higher rates of insulin clearance and increased insulin sensitivity in peripheral tissues compared with the noninfected control group. The increase in non-insulin-mediated glucose uptake seen in those infected with HIV has been accounted for by an increase in nonoxidative glucose disposal. Glucose production from the liver tends to increase, but glucose cycling does not change. Although there are many studies linking the use of protease inhibitors (PIs) to the development of insulin resistance, there is also evidence suggesting that insulin resistance may have an HIV disease-associated component as well.
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