**Common endocrine disorders and HIV infection**

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**Abstract:**

Functional Abnormalities in almost all endocrine organs have been published in association with HIV infection. The changes in endocrine function may be related to the viral infection of the gland, systemic effects of HIV or an opportunistic infection, infiltration by a neoplasm: such as Kaposi's sarcoma, a complication of treatment, or the generation of cytokines.The adrenal gland is the endocrine organ most commonly involved in patients infected with HIV. Although clinical adrenal dysfunction is rare among patients with AIDS, recent data suggest that subtle impairments in the adrenal reserve are common in this population. Clinical thyroid disease is relatively rare in patients with HIV disease but altered thyroid function test results are common in HIV-infected patients. In addition to the euthyroid sick syndrome, recent large screening studies have demonstrated an increased prevalence of primary hypothyroidism in HIV-infected patients. Gonadal dysfunction is common among men and women with HIV. Low testosterone concentrations are associated with lower CD4 cell count, advanced stage of illness, and weight loss. The endocrinopathies may be contributing significantly to the clinical status of the patients, including sexual function, muscle mass, general well-being, and quality of life of HIV patients.

**Introduction:**

The pathophysiology of endocrine disorders in HIV patients is multifactorial. Potential associated factors include mediators of the systemic inflammatory response, malnutrition, opportunistic infections with pathogens such as Toxoplasma, cytomegalovirus, Pneumocystis jirovecii, and neoplasms such as Kaposi sarcoma and the direct effects of HIV. Metabolic and endocrine abnormalities can also occur as a complication of therapy with antiretroviral drugs and chemotherapeutic agents used for the treatment or prevention of opportunistic infections. For instance, insulin resistance, dyslipidemia, and fat redistribution have been reported in HIV-infected patients, particularly in those treated with effective antiretroviral drugs. Similarly, adrenal and gonadal suppression can occur in patients treated with ketoconazole, whereas pentamidine administration can induce hypoglycemia and pancreatic cell damage, which results in diabetes mellitus. On the other hand, adrenocortical and pituitary abnormalities were not frequently found. The physiopathology of the endocrine abnormalities observed in HIV-l-infected patients remains unclear, but one may suspect that it involved interleukin-1, it has been seen to stimulate corticotrophin-releasing hormone secretion and to act directly on the glycoprotein capsule of the virus whose structure is similar to some neurohormones.[1]

**Adrenal Insufficiency:**

Of all endocrine deficiencies in patients with HIV disease, adrenal insufficiency received the most attention early in the epidemic. Authors of several series reported a high incidence at autopsy of adrenal involvement. In patients with advanced AIDS, primary AI can be caused by adrenal gland infection. Infective agents associated with AI include tuberculosis, CMV, Cryptococcus, Nocardia, HIV itself, Mycobacterium avium-intracellulare, and Histoplasma capsulatum. Infiltration of the adrenal gland by Kaposi's sarcoma or lymphoma can also lead to adrenal insufficiency. Medications causing primary adrenal dysfunction which may be more frequently used in HIV-infected patients include ketoconazole, fluconazole, and rifampin. Primary AI may also result from adrenal hemorrhage or autoimmune adrenalitis similar to the normal population. [Table 1] Consistent with the expectation that observed adrenal pathology is insufficient to cause clinical problems, the incidence of clinical or biochemical adrenal insufficiency in patients with HIV disease is in fact much lower than the incidence of adrenal involvement found at autopsy, despite a number of case reports reporting the association. Certain drugs used in patients with advanced HIV disease such as Ketoconazole inhibits adrenal corticosteroid synthesis and blunts the cortisol response to ACTH, Rifampin alters the metabolism of glucocorticoids, thereby increasing hormone excretion values or necessitating higher exogenous steroid doses to maintain therapeutic effect. Unexplained hyperkalemia persisting despite normal cortisol response to ACTH may represent hyporeninemic hypoaldosteronism, which has been described in hospitalized patients with H1V disease [1, 2] Characteristic findings in these patients include hyperkalemia, usually hyponatremia, mild acidosis, normal basal and ACTH-stimulated cortisol levels, and low basal aldosterone levels (particularly in relation to high serum potassium levels), low basal renin, and impaired aldosterone response to furosemide. Classic adrenal destruction is not the only cause of abnormal adrenal laboratory results in AIDS. An intensive study of adrenal function revealed that the basal serum cortisol level is increased in hospitalized patients with advanced HIV disease, compared with non-HIV-infected patients, presumably due to stress. Biochemical evidence of adrenal insufficiency is relatively more common among hospitalized AIDS patients in comparison to the patients who demonstrate clinical symptoms of AI. Adrenal insufficiency should be suspected in all HIV-infected patients presenting with fatigue, weakness, anorexia, nausea, vomiting, hyponatremia, and hyperkalemia, especially in patients with prolonged HIV infection, severe immunosuppression, and history of the previous opportunistic disease.[Table 2] [4]

**Gonadal Dysfunction:**

Gonadal Dysfunction: Hypogonadism is an area of increasing clinical importance in HIV disease. Gonadal dysfunction is common among HIV-infected men. Initial studies indicated biochemical hypogonadism in approximately 50% of men with AIDS42 in association with increased disease severity. More recent studies suggest a prevalence of up to 20% among men in the current era of potent antiretroviral treatment. In one study of patients with HIV disease, the most common endocrine abnormality was a low serum testosterone level. Many of the symptoms of hypogonadism in both men and women are nonspecific and overlap with those of depression or chronic illness: e.g., fatigue, loss of energy, loss of libido, depressed affect, poor-self image. The occurrence of these symptoms in conjunction with low-normal serum testosterone levels in men with AIDS, therefore, does not necessarily mean that the symptoms are due to hypogonadism. More specific symptoms of hypogonadism, including changes in the pattern of hair growth (loss of pubic or auxiliary hair), reduced beard growth, testicular atrophy, sexual dysfunction, or gynecomastia, are usually not present. Moreover, the range of "normal" serum testosterone levels in men is quite wide in most laboratories, e.g., 250 to 1100 ng/dl. Most patients with advanced HIV disease do not have frankly low serum testosterone levels (below 250 ng/dl) but have "borderline" low levels in the lowest 20% (e.g., 250 to 450 ng/dl) but not frankly below "normal. The diagnosis of hypogonadism should be considered in patients with HIV infection and weight loss (or loss of lean body mass without weight loss), specific symptoms of hypogonadism (altered hair growth, beard growth, testicular atrophy, sexual dysfunction), or nonspecific symptoms (fatigue, loss of libido, loss of energy, etc.). The most useful test is the total serum testosterone concentration, with or without gonadotrophin levels (luteinizing hormone (LH) or follicular stimulating hormone [FSH]). Measuring total testosterone is a considerably less expensive test than that to measure free testosterone and is technically less demanding, thus more reproducible from one laboratory to the next. Particularly in the setting of weight loss, poor lean tissue response to nutritional support, or symptoms consistent with hypogonadism, laboratory criteria for clinically significant hypogonadism should be more inclusive than the laboratory "normal range." Using a cut-off of < 500 ng/dl should eliminate the need to measure free testosterone, which is a more expensive test but in some patients may be low when total testosterone is not frankly low. It might be a useful strategy for clinicians to measure a baseline serum total testosterone level in HIV-seronegative men prior to the development of symptoms. A substantial fall in concentrations that nevertheless remain in the statistically "normal" range will then provide objective evidence to support replacement therapy. Hypogonadism is also probably common in HIV-infected women, especially those with weight loss, although fewer data are available on this subject. Serum testosterone levels in women are difficult to use as diagnostic tests because of the low values and interindividual variability among women.[5]

Etiopathogenesis:

 The mechanisms of hypogonadism in HIV-infected patients might relate to severe illness or effects of undernutrition on gonadotropin secretion, medication effects, or more rarely, tissue destruction from opportunistic infections. Most often, hypogonadism is secondary, with low or inappropriately normal gonadotropin levels. Primary hypogonadism is seen less often and may be caused by cytokine effects on the tests, including effects of TNF to inhibit steroidogenesis via effects on the side chain cleavage enzyme and of IL-1 to inhibit Leydig cell steroidogenesis and LH binding to the Leydig cell. In addition, a number of medications can affect the HPG axis. Ketoconazole inhibits some critical enzymes in testicular steroidogenesis. Megestrol acetate suppresses gonadotropin secretion. Opiate therapy affects GnRH secretion and can result in hypogonadotropic hypogonadism. Clinical Feature: Hypogonadism is often heralded by decreased sex drive, decrease the frequency of sexual intercourse or inability to maintain erection, decrease beard growth, loss of muscle mass, decreased testicular size, and gynecomastia. Less than 10% of patients with erectile dysfunction alone have testosterone deficiency

**Thyroid Dysfunction:**

Thyroid Dysfunction: Altered thyroid function test (TFT) results are common in HIV-infected patients. Similar to other chronic diseases which are associated with malnutrition or inflammation, HIV can cause abnormalities in thyroid function tests. This condition is called "euthyroid sick" syndrome, to indicate that the thyroid gland is normal but that systemic illness has altered thyroid hormone physiology. It would therefore not be surprising if thyroid function abnormalities were common in patients with advanced HIV disease. Some reports, however, note normal thyroid function tests (TFTs) in HIV-infected subjects (e.g., normal TFTs and response to thyrotropin-releasing hormone),whereas others describe abnormalities in TFTs in HIV infection. Patients hospitalized with PCP had the low triiodothyronine (T3) levels expected in severe nonthyroidal illness. A low T level correlated with hypoalbuminemia and hyponatremia [69] and was an accurate predictor of mortality in hospitalized patients with advanced HIV disease.

 Etiopathogenesis:

Recently, thyroid dysfunction has been described with an immune reconstitution syndrome in which autoimmune thyroid disease occurs in association with potent antiretroviral therapy and improved immune function. The estimated prevalence of immune reconstitution thyroid disease with the initiation of highly active antiretroviral therapy (HAART) was 3% for women and 0.2% for men. Graves' disease has also been described after IL-2 therapy in HIV-infected patients. In addition to autoimmune causes, thyroid dysfunction related to infection of the thyroid gland has been reported in HIV-infected patients. Pneumocystis thyroiditis has been reported to cause painful thyroiditis like the picture, with hyperthyroidism followed by hypothyroidism, decreased uptake on scanning, and a firm, tender gland. Pneumocystis thyroiditis might result from the increased use of inhaled pentamidine, which is associated with extrapulmonary Pneumocystis infections. CMV, MAI, Cryptococcus, and Kaposi's sarcoma have been demonstrated in the thyroid at autopsy but have not been related to clinical thyroid disease among patients with AIDS. Clinically apparent thyroidal abscesses from some infective agents such as Aspergillus and Rhodococcus equi have been seen. Hypothalamic or pituitary replacement from opportunistic infections, such as toxoplasmosis and CMV, has also been reported to cause secondary hypothyroidism. Medications can affect thyroid function. Rifampin influences hepatic clearance of thyroxine, and interferon is associated with an increased incidence of autoimmune hypothyroidism.[6]

**Diabetes and other Metabolic disorders:**

Similar to the other endocrine changes the association of HIV with diabetes is well described in the literature.[5] It can be present prior to HIV infection or may develop after the onset of HIV. Insulin resistance has the main role in the pathogenesis of diabetes rather than insulin deficiency in HIV-infected patients. Evidence of beta cell destruction or autoimmunity has not been seen in earlier studies, the predominant factor associated with hyperglycemia in HIV patients is iatrogenic. This may be due to highly active antiretroviral therapy (HAART) or due to other medications. Besides diabetes, some other components of metabolic syndrome have been reported in HIV/AIDS. Highly active antiretroviral therapy (HAART) has led to an increase in the incidence of insulin resistance, lipodystrophy, and dyslipidemia. These disorders can occur singly or in combination. Lipodystrophy may occur with Highly active antiretroviral therapy and needs to be managed aggressively in order to limit cardiovascular morbidity.[6,7]

**Conclusion:**

The endocrine changes in HIV-infected patients have a significant effect on growth and development, sexual function, muscle mass, fat distribution, and quality of life. The scarcity of data related to these changes worldwide makes it difficult to bring a general recommendation about hormone replacement therapy in all HIV-infected patients with reduced circulating levels of a specific hormone to reduce morbidity and mortality

**References**

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**Table 1. Causes of adrenal insufficiency in HIV infected patients**

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| --- | --- |
| **Primary AI** | **Secondary AI** |
| Infection• Cytomegalovirus• Tuberculosis• HIV• Histoplasmosis• Cryptococcus• Toxomplasmosis Tumor• Kaposi's sarcoma• Lymphoma Autoimmune Hemorrhage Medications• Ketoconazole• Fluconazole• Rifampin• Etomidate | Infection/Infiltration• Tuberculosis• Sarcoid• HemochromatosisIsolated ACTH deficiencyTumorTraumaMedications• Exogenous steroids• Megesterol |

**Table 2. Clinical feature of primary Adrenal insufficiency**

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| --- | --- |
| **Symptoms** | **Frequency** |
| Weakness, tiredness, fatigue | 100% |
| Anorexia | 100% |
| GI symptoms• Nausea• Vomiting• Constipation• Abdominal pain• Diarrhoea  | 92%86%75%33%31%16% |
| Salt craving | 16% |
| Postural dizziness | 12% |
| Muscle cramp / joint pain | 6-13% |
|  |  |
| **Signs** |  |
| Weight loss | 100% |
| Hyperpigmentation | 94% |
| Hypotension | 88.94% |
| Vitiligo (in autoimmune) | 10-20% |