**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:**
In HIV patients adrenal insufficiency is one of the commenest endocrine disorder. A number of studies have shown a high incidence of adrenal involvement at autopsy. In patients with advanced HIV disease, primary Adrenal insufficiency (AI) can be caused by direct adrenal gland infection. Infective agents associated with adrenal insufficiency include tuberculosis, cytomegalovirus, Cryptococcus, Nocardia, HIV itself, Mycobacterium avium-intracellulare, and Histoplasma capsulatum. Infiltration of the adrenal gland by malignancies like Kaposi's sarcoma or lymphoma can also lead to AI. Medicines which may be more frequently used in HIV-infected patients like ketoconazole, fluconazole, and rifampin are also well known to cause primary adrenal dysfunction. Ketoconazole inhibits the synthesis of adrenal corticosteroid and blunts the cortisol response to ACTH, Rifampin changes the metabolism of glucocorticoids. Similar to the normal population primary adrenal insufficiency (AI) may also result from adrenal hemorrhage or autoimmune adrenalitis. [Table 1] The incidence of clinical or biochemical adrenal insufficiency in patients with AIDS is in fact much lower than the incidence of adrenal involvement found at autopsy. Unexplained hyperkalemia persisting despite normal cortisol response to ACTH may represent hyporeninemic hypoaldosteronism.[1, 2] Classical findings in these patients include hyperkalemia, hyponatremia, acidosis, normal level of basal and ACTH-stimulated cortisol and low basal aldosterone levels ( especially in relation to high serum potassium values), low basal renin, and decreased aldosterone response to furosemide. Adrenal destruction is not the only cause of altered adrenal laboratory results in AIDS. A study of adrenal function showed that the basal serum cortisol level is increased in hospitalized patients with advanced AIDS, compared with HIV negative patients, most probably due to stress. In comparison to the patients who demonstrate clinical sign and symptoms of adrenal insufficiency, biochemical evidence of adrenal insufficiency is relatively more common among hospitalized AIDS patients. Adrenal insufficiency (AI) should be suspected in all AIDS patients presenting with fatigue, weakness, anorexia, nausea, vomiting and electrolyte abnormalities, especially in patients with history of the previous opportunistic disease.[Table 2] [3,4]

**Gonadal Dysfunction:**

Hypogonadism is an area of increasing clinical significance in HIV patients. Gonadal disorder is not unusual amongst HIV patients. Initial research indicated biochemical hypogonadism in about 50 % of patients with AIDS in association with advanced disease severity. More recent studies advocate an occurrence of up to twenty percent amongst men in the present time of effective antiretroviral medications. In an article published on HIV disease, the commonest endocrine alteration was a reduced serum testosterone level. A number of symptoms of hypogonadism in both males and females were nonspecific and extend over with those of hopelessness and chronic disorders: e.g., fatigue, lack of energy, loss of libido, bad-self image. The presence of these sign symptoms with low-normal serum testosterone levels in patients with HIV, therefore, does not necessarily mean that the sign symptoms are due to hypogonadism. Extra specific signs of hypogonadism like alteration in the pattern of hair growth (at beard, pubic and axillary areas), testicular atrophy, loss of libido or gynecomastia are commonly not found. Furthermore, the range of normal serum testosterone values in males is pretty extensive in majority of the laboratories, e.g., 250 to 1100 ng/dl. Many patients with with end stage HIV disease do not have frankly low serum testosterone values (below 250 ng/dl) , however have "borderline" low values in the lowest twenty percent (e.g., 250 to 450 ng/dl) but not frankly below "normal.

The diagnosis of hypogonadism need to be taken into consideration in in patients infected with HIV and severe weight loss , unique signs and symptoms of hypogonadism like; testicular atrophy, altered beard growth and sexual dysfunction or nonspecific symptoms like; fatigue, loss of libido, lack of strength, and so on. The most useful test for diagnosis is the meausring of total serum testosterone concentration, with or without gonadotrophin levels (LH and FSH). Measuring the level of total testosterone compare to free testosterone is relatively a less expensive test. Particularly in the setting of significant weight reduction, low lean tissue response to dietary support, or sign symptoms consistent with hypogonadism, laboratory criteria for clinically significant hypogonadism should be more inclusive than the laboratory normal range values. Using a cut-off of less than 500 ng/dl should abolish the need to estimate free testosterone level, which is more costly test, but in some patients may be low when total testosterone is not clearly low.

A substantial decrease in concentrations that however remain in the statistically "normal" range will then give objective evidence to support hormone replacement therapy. Hypogonadism is also common in females infected with HIV, especially those with lean body mass, even though limited information are available on this group of patients. Due to low value and interindividual variability among women, the estimation of serum testosterone levels are not easy to use as diagnostic tests for them. [5]

Etiopathogenesis:

The pathophysiology of hypogonadism in AIDS patients may relate to severe disease or effects of undernutrition on LH/FSH secretion, treatment effects, or greater hardely ever, tissue destruction by opportunistic infections.

Generally, hypogonadism is secondary, with low or inappropriately normal LH/FSH levels. Primary hypogonadism is seen less frequently and can be as a result of cytokine effects on the testes, including effects of tissue necrosis factor (TNF) to inhibit steroidogenesis through effects on the cleavage enzyme and of interleukin 1 to inhibit Leydig cell steroidogenesis and leutinising hormon binding to the Leydig cell.

Similarly, a number of medicines, can have an effect on the HPG axis. Ketoconazole inhibits few essential enzymes in testicular steroidogenesis. Megestrol acetate put down gonadotropin secretion. Opiate therapy affects GnRH secretion and might bring hypogonadotropic hypogonadism.

**Thyroid Dysfunction:**

Abnormal thyroid function test (TFT) results are common in HIV-infected cases. Similar to other chronic disorders which are associated with malnutrition or inflammation, HIV can cause euthyroid sick" syndrome in which the thyroid is normal but that systemic disease has changed the thyroid hormone physiology.Therefore, thyroid function abnormalities were common in patients with advanced HIV infection.

 A number of studies, however, note normal thyroid function tests (TFTs) in HIV-infected cases (e.g., normal thyroid function tests and response to TRH), whereas some others reports describe abnormalities in TFTs in HIV infected patients. In one study patients hospitalized with pneumocystis pneumonia (PCP) had the low T3 levels expected in severe nonthyroidal illness. A decreased T3 level correlated with low sodium and hypoalbuminemia and was considered an accurate predictor of mortality in hospitalized patients with advanced HIV infection.

Etiopathogenesis:

Thyroid dysfunction has been described with an immune reconstitution syndrome (IRIS) in which autoimmune thyroid disease occurs due to improved immune function because of potent antiretroviral therapy. In one analysis the calculated prevalence of immune reconstitution induced thyroid disorder with the starting of highly active antiretroviral therapy (HAART) was 3% for females and 0.2% for males. Graves' disease has also been described after getting IL-2 therapy in some AIDS patients. In addition to autoimmune causes, thyroid disorder related to infection of the thyroid gland has been reported in these patients. Painful thyroiditis, with hyperthyroidism followed by hypothyroidism, reduced uptake on scanning, and a firm, tender gland has been reported in Pneumocystis thyroiditis. Thyroiditis due to Pneumocystis infection might result from the increased use of inhaled pentamidine, which is associated with extrapulmonary Pneumocystis infections. Cytomegalovirus, Micro bacterium avium complex, cryptococcus and Kaposi sarcoma have been demonstrated in the thyroid at post-mortem in autopsy but have not been correlated to clinical thyroid disease among the HIV patients. Thyroidal abscesses from some infective agents such as Rhodococcus equi and Aspergillus have been reported.

Pituitary or hypothalamic involvement from opportunistic infections, such as toxoplasmosis and Cytomegalovirus , has also been reported to cause secondary hypothyroidism. Some medicines can affect thyroid function. Rifampin alter the hepatic clearance of thyroxine, and interferon is associated with a raised incidence of autoimmune hypothyroidism.[6,7]

**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% |