

Human immunodeficiency virus endocrinopathy

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ABSTRACT

Human immunodeficiency virus (HIV) endocrinopathy encompasses a broad spectrum of disorders. Almost all the endocrine organs are virtually affected by HIV infection. HIV can directly alter glandular function. More commonly secondary endocrine dysfunction occurs due to opportunistic infections and neoplasms in immunocompromised state. The complex interaction between HIV infection and endocrine system may be manifested as subtle biochemical and hormonal perturbation to overt glandular failure. Antiretroviral therapy as well as other essential medications often result in adverse endocrinal consequences. Apart from adrenal insufficiency, hypogonadism, diabetes and bone loss, AIDS wasting syndrome and HIV lipodystrophy need special reference. Endocrinal evaluation should proceed as in other patients with suspected endocrine dysfunction. Available treatment options have been shown to improve quality of life and long-term mortality in AIDS patients.

Key words: Antiretroviral therapy, endocrinopathy, human immunodeficiency virus, lipodystrophy, wasting

INTRODUCTION

Human immunodeficiency virus (HIV) infection is unique among all infectious diseases to cause functional derangement of virtually every endocrine organ system of human body. Additionally, a pandemic of HIV infection and acquired immunodeficiency syndrome (AIDS) worldwide as well as the survival benefit of highly active antiretroviral therapy (HAART) gave rise to the high incidence of endocrinopathies in HIV-infected patients in the last two decades. HIV-endocrinology is thus evolving as a new research corner in the field of modern medicine and endocrinology as well.

The spectrum of HIV endocrinopathy is broad. There may be primary endocrinopathy as a result of direct HIV

effect as well as secondary endocrine dysfunction due to indirect effects of cytokines, opportunistic infections and rarely neoplasms. Adrenal, gonadal, thyroid, bone and metabolic abnormalities are common in both early and late stages of HIV syndrome, resulting in poor quality of life and significant morbidity and mortality.^[1-3] In many situations, HAART and other medications used in HIV care are critically responsible for the detrimental changes in body composition and metabolic parameters known to cause AIDS wasting syndrome and HIV lipodystrophy syndrome.

The interaction between HIV infection and endocrine system is complex, starting from subtle abnormalities in hormone secretion, transport and metabolism to rare instances of hormonal resistance and organ failure. Causes and clinical significance of many of these altered physiology are still unknown. Disseminated infection, varying nutritional status and drug effects often mimic a primary glandular dysfunction. This article reviews the variety of endocrinal abnormalities reported to be associated with HIV infection, along with the possible underlying pathophysiologic mechanisms and optimal treatment strategies for the patients. A timely suspicion, appropriate diagnosis, correct evaluation and early intervention are often required in the long-term management of AIDS patients.

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PATHOPHYSIOLOGIC BASIS OF HIV ENDOCRINOPATHY

In HIV-infected patients, endocrine functions of different organs may be interfered by different means [Table 1]. Excluding acute and chronic illnesses, the relentless progression of immune dysfunction in AIDS alters the internal environment through activation of a couple of cytokines, chemokines and antibody formation and constitutes the direct effect of HIV over endocrine function.

FUNCTIONAL DERANGEMENT OF ENDOCRINE ORGANS: DIRECT EFFECT OF HIV

The mechanism by which HIV might affect glandular function and hormonal secretion mainly centers on immunomodulatory effects of cytokines at every tier of endocrinal axis (hypothalamic–pituitary–effector organ like adrenal, thyroid, gonads). Adrenal gland has always received most attention as a prime target organ in HIV disease, and HIV adrenalitis is a well-known entity.^[4,5] It is postulated that HIV infection triggers macrophages to secrete interleukins (IL-1) and tumor necrosis factor (TNF) and these are likely to act as potent adrenal stimulators.^[6,7] In contrary, HIV also has the potential to cause polyclonal B cell activation and production of antibodies against glandular cells, thereby inhibiting glandular endocrine function.^[8]

IL-1 produced in median eminence can also affect

Table 1: Common endocrine abnormalities in human immunodeficiency virus disease

Endocrinopathies due to direct effect of HIV
HIV adrenalitis and impaired adrenal reserve
Hypercortisolism
Idiopathic adenohypophyseal necrosis
Hyperprolactinemia
Primary hypogonadism
Growth failure
AIDS wasting syndrome
Endocrinopathies due to structural destruction of glands
Cytomegalovirus (CMV) adrenalitis
Mycobacterial infection, cryptococcosis, toxoplasmosis, hemorrhages and abscesses causing insufficiency of glands (hypopituitarism, hypothyroidism, hypoadrenalism)
Pneumocystis thyroiditis
Secondary hypogonadism
Drug-related endocrinopathies
Insulin resistance and diabetes mellitus
Dyslipidemias
Bone mineral and electrolyte disturbances
Immune reconstitution syndrome – Graves' disease
HIV lipodystrophy syndrome
Pancreatitis

HIV: Human immunodeficiency virus

hypothalamus and pituitary. Increased release of corticotropin releasing hormone (CRH) from the hypothalamus may cause increase in corticotropin or adrenocorticotrophic hormone (ACTH) secretion reported in early HIV disease.^[9-11] However, IL-1 has been found to directly stimulate cultured pituitary cells to secrete ACTH.^[12,13] HIV-infected mononuclear cells stimulate the production of interferons (IFN) whose serum concentration increases with advanced HIV disease.^[14] AIDS patients with advanced disease can rarely develop glucocorticoid resistance with hypercortisolism and increased ACTH level. In such patients, glucocorticoid receptor function has been found abnormal in association with increased IFN α level.^[15] Whether it is the result of immunomodulation by IFN α is not clear. Pituitary involvement also occurs in AIDS. Idiopathic adenohypophyseal necrosis observed in 10% HIV-infected patients at autopsy is thought to be due to direct effect of HIV.^[16] Increased prolactin levels and gynecomastia have been demonstrated among these patients. More than 20% of HIV-infected men with stable disease were reported having hyperprolactinemia and this was significantly associated with opioid use and increased CD4 count but not with gynecomastia.^[17] Current postulation is that HIV infection reduces dopaminergic tone and thereby increases the bioactivity of prolactin, though the mechanism of this effect remains unclear.^[18]

Hypogonadism common to HIV-infected men is mostly secondary. But HIV-induced primary hypogonadism is also seen and may be caused by the effects of cytokine on testes. Virus-induced immunomodulators like TNF can inhibit steroidogenesis by altering the side chain cleavage enzyme and IL-1 prevents Leydig cell steroid production and leutinizing hormone (LH) binding to Leydig cells.^[19-21]

Reduced bone density is common in HIV-infected patients due to multifactorial causes like hypogonadism, relative growth hormone (GH) deficiency with excess visceral adiposity. Debate persists on whether HIV can directly infect osteocytes, but preliminary research works suggest that HIV is very unlikely to affect osteoblasts as reservoir cells for HIV infection.^[22]

STRUCTURAL DESTRUCTION OF ENDOCRINE TISSUE: SECONDARY PHENOMENON

In HIV disease, almost every endocrine organ of the human body can secondarily be affected by means of opportunistic infections, hemorrhage, neoplastic process and other nonspecific inflammation. Regarding structural destruction of adrenal gland, cytomegalovirus (CMV) adrenalitis is the commonest, seen in approximately 40–

90% of patients with CMV infection at autopsy. However, glandular destruction by CMV being less than 50% is thus very unlikely to cause adrenal insufficiency.^[23] Other causes of adrenal destruction in HIV disease include *Mycobacterium tuberculosis*, *Mycobacterium avium*-intracellulare complex (MAC), cryptococcus and hemorrhages. Similarly, pituitary and hypothalamic destruction can also rarely happen by toxoplasmosis, cryptococcosis and CMV infection.

Pneumocystis thyroiditis has been reported to cause a painful thyroiditis resembling the picture of hyperthyroidism followed by hypothyroidism.^[24] Thyroid getting affected by CMV, MAC, cryptococcus, Kaposi's sarcoma, abscesses from aspergillosis, rhodococcus infection, etc. has been demonstrated at autopsy, but neither of these manifests clinically as thyroid dysfunction.

ENDOCRINE EFFECTS OF MEDICATIONS

Medications are a common cause of endocrine dysfunction in HIV-infected patients. More than 20 antiretrovirals from different groups [protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs) and entry inhibitor] have been approved in the treatment of AIDS. They are mostly metabolized in liver, and also in kidney and plasma. They primarily contribute to the alteration in lipid metabolism, insulin sensitivity and bone mineral homeostasis. A short account of these drugs is given here.

Protease inhibitors

Lopinavir/ritonavir, nelfinavir, amprenavir, saquinavir, etc. are the drugs that are metabolized in liver mainly via CYP3A pathway. Relevant endocrine effects are seen in the form of fat redistribution, hyperlipidemia with hypertriglyceridemia, diabetes mellitus and increased production of small, dense, atherogenic LDL2 molecules. PIs may have direct effect on adipogenesis [via decreased nuclear localization of sterol regulatory element binding protein 1 (SREBP1) and reduction in peroxisome proliferator-activated receptor gamma (PPAR γ) expression] and on glucose metabolism (by decreasing GLUT4 activity and insulin sensitivity, resulting in hyperglycemia).^[25,26] Specific PIs can cause direct stimulation of prolactin.^[27] These drugs have also been known to decrease bone density and rarely cause avascular necrosis (AVN) of the bone, but the relationship of AVN and HAART is unclear. PIs can decrease the level of 1 α -hydroxy vitamin D, causing osteomalacia.^[28]

Nucleoside reverse transcriptase inhibitors

These first-line antiretrovirals include lamivudine, zidovudine, emtricitabine, didanosine, abacavir, etc. Just

like PIs, they alter lipid and carbohydrate metabolism, decrease insulin resistance, inhibit mitochondrial polymerase γ activity, and thereby cause fat redistribution, subcutaneous fat loss, gynecomastia, hyperglycemia and loss of appetite.^[29,30] NRTI drugs (especially didanosine and zalcitabine) can also affect renal tubular function, causing hypophosphatemia, hypomagnesemia, hypocalcemia and hypokalemia.

Nucleotide reverse transcriptase inhibitors

Tenofovir, fumarate, and disoproxil comprise this group. All the drugs are metabolized by esterases in plasma. They have been associated with fat redistribution and hypophosphatemia in the long run.

Non-nucleoside reverse transcriptase inhibitors

NNRTI drugs include delavirdine, nevirapine and efavirenz. All are metabolized in the liver by cytochrome pathways (CYP3A, CYP2B6, CYP2C9, etc.) and are associated with hyperlipidemia and fat redistribution in AIDS patients.

Additional medications

Drugs other than antiretrovirals, like antibiotics, antifungals and chemotherapeutic agents, often used in AIDS patients for controlling several opportunistic infections, can also have adverse consequences on endocrine function. These are listed in Table 2.

ENDOCRINE DISORDERS

Adrenal dysfunction

Adrenal dysfunction may be suspected in HIV-infected patients with advanced stage of AIDS. In AIDS patients, subtle impairment of adrenal function is manifested as fatigue, hyponatremia or rarely with clinical symptoms of adrenal insufficiency. Biochemical presentation of adrenal insufficiency is relatively common in hospitalized AIDS patients (17%) in comparison to clinically symptomatic patients (4%).^[31]

Impaired adrenal reserve is a common finding in HIV-infected patients. It is evident by reduced aldosterone and dehydroepiandrosterone (DHEA) levels with normal cortisol in response to ACTH challenge. In progressive disease state, ACTH levels increase over time, suggesting impaired adrenal reserve.^[32] Inadequate adrenal stimulation is also demonstrated in the studies involving hospitalized AIDS patients after cosyntropin challenge test. Increased cortisol levels may be seen in HIV-infected patients; mostly, it is a stress response to the disease burden. Few studies have suggested an intra-adrenal shunting toward cortisol synthesis due to 17,20 lyase dysfunction resulting in a reduced DHEA to cortisol ratio on cosyntropin stimulation.^[33]

Table 2: Endocrine effects of additional medications

Drugs	Mechanisms	Endocrine effects
Rifampicin	Enhances catabolism of cortisol	Adrenal insufficiency, hyperglycemia
Ketoconazole	Decreases adrenal and testicular steroidogenesis ↓ Vitamin D formation	Adrenal insufficiency, hypogonadism, gynecomastia Vitamin D deficiency
Phenytoin	↑ Cortisol metabolism	Hyperglycemia, hyperprolactinemia, gynecomastia, vitamin D deficiency
Opiates	↑ Cortisol metabolism, ↓ GnRH secretion	Hypogonadotropic hypogonadism
Sulfamethoxazole-trimethoprim (TMP-SMZ)	Pancreatic inflammation, ion channel impairment in distal nephrons	Hyperkalemia, hyponatremia, hypouricemia
Pentamidine	Inflammation and destruction of pancreatic beta cells, nephrotoxicity	Pancreatitis, hypocalcemia, hypokalemia, hypermagnesemia, abnormal blood glucose level
Foscarnet	↓ Serum ionized calcium	Hypocalcemia, hyperphosphatemia, hypokalemia, nephrogenic diabetes insipidus
Megestrol acetate	Having glucocorticoid property, decreases gonadotropin and ACTH level	Cushingoid features, weight gain, hyperglycemia, adrenal insufficiency on withdrawal, hypogonadism

Adrenocorticotrophic hormone

Adrenal gland shows evidence of both inflammation and necrosis at autopsy. It is likely that the observed pathology may be insufficient to cause clinical problem. Cushing's syndrome has also been demonstrated. Two cases of Cushing's syndrome with secondary adrenal insufficiency have been reported from concomitant use of ritonavir and inhaled fluticasone in children with HIV.^[34] Rarely, glucocorticoid resistance at receptor level has been shown in advanced disease state. Such patients demonstrated increased cortisol and ACTH level with Addisonian symptoms. Monocytes from these patients were found to be dexamethasone resistant, with increase in glucocorticoid receptors and decreased affinity for dexamethasone.

In suspected conditions, all the risk factors (opportunistic infections, drugs) for adrenal insufficiency should be evaluated. Cortisol axis is first evaluated by cosyntropin stimulation test in primary adrenal insufficiency. If secondary adrenal dysfunction (pituitary/hypothalamic lesion) is suspected, morning cortisol level or insulin tolerance test may be necessary. Next step is ACTH testing and appropriate imaging for disease localization. Though chronic steroid replacement at supraphysiologic doses is not advocated in AIDS to prevent further immunosuppression, HIV is not a contraindication to pharmacologic glucocorticoid therapy (as in CNS toxoplasmosis).

Thyroid dysfunction

Thyroid function tests are often abnormal in HIV patients. But prevalence of overt thyroid disorder is not found more than in general population.^[35] CD4 counts correlate inversely with thyroid binding globulin (TBG), with TBG being high in advanced AIDS patients.^[36] Until now, this thyroid dysfunction has been explained by hormonal changes as a stress response to the advanced disease state or comorbidities. However, in HIV-infected patients,

the biochemical picture does not fully fit with sick euthyroid syndrome. Progression of HIV disease exhibits decreased T3 level, increased TBG and reduced reverse triiodothyronine (rT3) level over time.^[37]

Recent observations have demonstrated an increased prevalence of primary hypothyroidism. Among 350 HIV-infected patients studied in France, 2.6% had clinically evident hypothyroidism, about 6.6% had subclinical hypothyroidism with increased thyroid stimulating hormone (TSH) but normal level of free T4 and 6.8% had a low free T4 level. Male sex, stavudine use and low CD4 count were predictive of hypothyroidism.^[38] However, this hypothyroidism is not often seen in association with antithyroid antibodies, and therefore the underlying cause of hypothyroidism remains unclear.^[39,40]

Recently, thyroid dysfunction has been described as a component of immune reconstitution syndrome. Autoimmune thyroid disorder has occurred in association with initiation of potent antiretroviral therapy and improved immune function. Graves' disease is the commonest among immune reconstitution syndromes, showing higher prevalence in women (3% for women and 0.2% for men).^[41]

In subclinical hypothyroidism with mildly elevated TSH, the TSH level should be rechecked in 1–3 months. Levothyroxine may be considered in patients with persistently elevated levels of TSH >10 mU/L. However, there is insufficient evidence to recommend routine screening of thyroid function in asymptomatic AIDS patients.

Gonadal dysfunction in male

Male gonadal dysfunction is common among AIDS patients. Clinically, around 67% male patients with advanced HIV disease complained of loss of libido and 33% of them complained of impotence.^[42] Increased disease

severity increases the chances of developing biochemical hypogonadism (50% of male AIDS patients).^[43] With the advent of HAART, this prevalence has become around 20% among treated male patients.^[44] Cause of gonadal dysfunction is mostly secondary with low gonadotropin levels due to the effect of undernutrition, infection-inflammation and several drugs on gonadotropin production.

Increased prolactin levels and gynecomastia have been reported among HIV-infected patients. Gynecomastia has been seen in a small percentage of male patients with hypogonadism, hepatitis C and lipodystrophy.^[45] It has been found that men with HIV may also be prone to an early “andropause” marked by dysregulation of hypothalamic–pituitary axis and associated signs and symptoms.^[46] Crum-Ciamflone has reported the prevalence of 61.4% of erectile dysfunction in HIV-positive men, which had no correlation with hypogonadism.^[47]

As sex hormone binding capacity increases in 30–55% patients, use of free testosterone assay is always recommended to diagnose hypogonadism. Hypogonadism is also associated with sarcopenia, weight loss and reduced strength in HIV-infected men.^[48] Physiologic testosterone replacement that does not suppress endogenous gonadal function results in increased lean body mass, improved quality of life and reduction in depression. Studies showed sustained gain of lean body mass of around 8% after 1 year treatment with testosterone.^[49] Standard therapy for hypogonadism has been intramuscular testosterone (enanthate or cypionate esters) every 1–3 weeks to provide 100 mg per week. Alternate transdermal or oral routes for androgen administration are also available. Roles of anabolic steroids like nandrolone, oxandrolone (hepatotoxic), pharmacologic dose of testosterone [suppresses high density lipoprotein (HDL) and hypothalamic–pituitary–gonadal axis] with or without progressive resistance training (increases lean mass and HDL) are variable.^[50] Regular monitoring of prostate-specific antigen level in blood should be done in elderly patients receiving testosterone. There is no clear benefit of combining testosterone and anabolic steroids in male hypogonadism.

Gonadal dysfunction in female

Information on gonadal function in women with HIV infection is limited. Ovarian dysfunction among female AIDS patients is less common. Amenorrhoea is seen in around 25% women during stress of illness and anovulation is seen among half of the female patients with low CD4 counts.^[51] Early menopause has been seen in up to 8% of HIV-infected female patients.^[52] Androgen deficiency has been reported more so in women with significant weight

loss.^[51] It may be due to intra-adrenal shunting toward cortisol production from androgen synthesis in wasted female AIDS patients as human chorionic gonadotropine testing showed intact ovarian androgen production.^[53] Studies with the use of transdermal patch to deliver a low physiologic dose of testosterone demonstrated improved functional capacity without hirsutism or virilization. But this dose appeared too low to increase lean body mass. A doubling of the dose of testosterone in normal weight HIV-infected female patients, though was well tolerated, did not increase lean body mass.^[54]

Pancreatic dysfunction

In HIV disease, pancreas is a frequent target organ of opportunistic infections and malignancies (lymphoma, Kaposi's sarcoma), though clinically relevant endocrine dysfunction rarely happens. Major clinical manifestations are pancreatitis and hypoglycemia. Pancreatitis is commonly seen as a drug effect, especially from the use of pentamidine, trimethoprim, didanosine and zalcitabine. Elevated amylase levels in HIV-infected patients may also be due to microamylasemia and salivary amylase. Hypoglycemia can result from islet cell inflammation and insulin release by pentamidine with subsequent chronic hyperglycemia. Megestrol acetate is also associated with new-onset diabetes mellitus.

Disorders of glucose homeostasis are relatively common in HIV-infected patients with dyslipidemia and HIV lipodystrophy syndrome. Diabetes mellitus is found to be three times more prevalent among patients receiving HAART.^[55] Impaired glucose tolerance and diabetes in these patients occurred due to the primary mechanism of insulin resistance and hyperinsulinemia.^[56] Mechanisms of insulin resistance include abnormal fat distribution such as central adiposity, peripheral subcutaneous fat loss, altered cytokines like elevated TNF and low adiponectin or other factors like increased lipolysis, increased accumulation of fat in liver and muscles, mitochondrial toxicity and use of specific antiretrovirals like PIs.^[57-61] However, insulin resistance among HIV-infected women has not been seen to be associated with common features like polycystic ovarian syndrome.^[56]

Growth failure (GH–IGF1 axis disturbance)

Growth failure, especially failure to thrive, is an important issue in treating HIV-infected children. GH deficiency as well as GH insensitivity has been found to be a potential cause of growth failure in such patients. Reduced level of insulin-like growth factor 1 (IGF1) and reduced IGF binding protein 3 (IGFBP3) due to its enhanced proteolysis have been demonstrated. IGF1 and IGFBP3 responses to GH are also impaired in HIV-infected children.^[62-64] Such

a degree of GH insensitivity might improve with weight gain and improved immunity by HAART. Normal thymic development cannot happen in GH deficiency state.^[65] Among HIV-infected children with lipoatrophy, decreased GH secretion is associated with excess visceral fat.^[66]

Adult AIDS patients also exhibit two distinct patterns of abnormalities of GH-IGF1 axis. In patients with AIDS wasting, GH levels are increased with GH resistance state (IGF1 decreased), a typical pattern seen in malnutrition.^[67] GH resistance is likely to be a secondary phenomenon in AIDS wasting, but the HIV envelope protein gp120 has been shown to decrease GH *in vitro* and also in animal studies.^[68] In contrast, viscerally obese HIV-infected patients with lipodystrophy show GH deficient state with decreased amplitude of mean overnight GH level and GH pulse. This state of suppression of GH release in lipodystrophy syndrome may be explained by increased somatostatin tone, decreased ghrelin and increased circulatory free fatty acid due to enhanced lipolysis.^[69]

Though GH and GH secretagogues (GH releasing hormone 1-29) have already been used in AIDS wasting syndrome and HIV lipodystrophy syndrome, they remain investigational with their large phase III trials to establish long-term clinical benefits in lipodystrophy.^[70] However, GH has got approval from US Food and Drug Administration (FDA) in treatment of severe sarcopenia in AIDS wasting syndrome.

Fluid-electrolyte imbalance

Hyponatremia and hyperkalemia are the commonest among all fluid-electrolyte disturbances in AIDS patients. Hyponatremia (Na < 130 mmol/L) is more common among hospitalized (40–60%) AIDS patients than outpatients (20%). It is most often related to the secretion of inappropriate antidiuretic hormone (SIADH) contributing around half of all hyponatremic HIV-infected patients. These patients are euvolemic with low serum sodium but increased urinary sodium excretion and inappropriately elevated urine osmolarity. Various infections and tumors are the commonest underlying cause. Symptomatic treatment with fluid restriction and in severe cases infusion of hypertonic saline should be offered. Among hypovolemic hyponatremic HIV-infected patients, majority (30%) suffer from adrenal insufficiency.^[71] Volume-depleted hyponatremia may also be due to diarrhea, vomiting and impaired water clearance (HIV nephropathy). Volume repletion is the required treatment here. Hyporeninemic hypoaldosteronism can rarely be caused by drugs like miconazole and pentamidine.^[72] Hyponatremia may be seen in foscarnet-induced nephrogenic diabetes insipidus.

Trimethoprim use has been reported as the commonest

cause of hyperkalemia, occurring in nearly 20–50% AIDS patients.^[73] Trimethoprim is similar to amiloride in structure and inhibits tubular potassium excretion. Among the other causes, pentamidine tubulopathy, HIV-induced glomerulosclerosis, primary adrenal insufficiency and hyporeninemic hypoaldosteronism are significant.

Bone mineral dysfunction

Both osteoporosis and osteopenia are common among AIDS patients. Reduced bone mineral density is seen in 73% HIV-infected patients versus 30% HIV-negative patients of similar age.^[74] Dual energy X-ray absorptiometry (DEXA) is helpful to detect reduced bone density of hip and lumbar spine among HIV-infected men with weight loss and receiving HAART. Though a couple of previous studies suggested an association of PI therapy with reduced bone density, recent research showed that age-adjusted bone density was reduced in association with HIV infection itself and with traditional risk factors like low body weight, smoking and steroid use but was not affected by HAART.^[75] Similarly, in HIV-infected women, osteopenia was detected in more than 50% outpatients, about 2.4 times more prevalent in comparison to age-matched control population.^[76] No association with specific PI use was found but markers of bone resorption were increased. Reduced vertebral bone density was also associated with increased visceral adiposity among HIV-infected patients.^[77]

Reduced bone density has also been reported in HIV-infected children receiving HAART and maximum reduction was found among children with lipodystrophy.^[78] Reduced bone formation with increased resorption has been suggested in this group by the presence of increased markers of bone resorption and reduced osteocalcin. A potential effect of low GH and IGF1 on bone density may also be responsible for reduction in total bone density.^[79] Other endocrine factors like hypogonadism and excess visceral adiposity have been found to correlate significantly with vertebral bone density. PI-induced relative vitamin D deficiency may also act as an additive factor. Recent studies have shown that alendronate is effective in increasing bone density (5.2% increases in spinal bone density over 48 weeks) among patients with idiopathic bone loss.^[80] Male patients with AIDS wasting syndrome are usually benefited by testosterone at high dose (200 mg/week). Relationship between AVN and HAART is unclear.^[81] Potential association factors include prior use of systemic cortisol, anticardiolipin antibody and mechanical stress.

Calcium and vitamin D balance

HIV-infected patients often suffer from hypocalcemia, with the prevalence being nearly 6.5% of a large cohort of patients of AIDS. Serum calcium concentration decreases

progressively with stage of AIDS. Around half of the patients with hypocalcemia have vitamin D deficiency, but without compensatory increase in parathormone (PTH).^[82] Exact cause of reduced PTH is not known though decreased PTH secretion in immunodeficiency and presence of hypomagnesemia may partially explain the situation. Vitamin D deficiency is multifactorial. Causes include malabsorption (AIDS enteropathy), decreased hydroxylation (PI induced) and Fanconi syndrome with hypophosphatemia (tenofovir, cefodofir). A number of drugs, especially foscarnet, pentamidine, and ketoconazole, can affect calcium homeostasis. On rare occasions, hypercalcemia has been reported among AIDS patients. Granuloma (tuberculosis, lymphoma) induced excess production of active vitamin D₃, enhanced local osteoclastic resorption of bone (disseminated CMV) or activation of PTH-related protein (HTLV1) explain some of the conditions associated with hypercalcemia in AIDS.

AIDS WASTING SYNDROME

Wasting is an age-old terminal event of AIDS originally termed as “slim disease”. Still in the era of HAART, wasting remains common with high prevalence (34%).^[83] Weight loss is a significant predictor of mortality in HIV infection. Body mass index (BMI) of less than 18.4 kg/m² shows 2.2-fold increased mortality and BMI less than 16 kg/m² shows associated 4.4-fold increased mortality in HIV-infected patients.^[84] Currently, AIDS wasting syndrome is defined as body weight less than 90% of ideal weight or weight loss of more than 10% of body weight over 3 months. A disproportionate loss of lean body mass with a relative sparing of body fat with disease progression in both sexes characterizes the condition. Other important features include muscle wasting, weakness, increased resting energy expenditure and hypertriglyceridemia. Cytokine related increased energy expenditure and decreased appetite, malabsorption and hypogonadism remain central to the potential mechanisms behind such wasting.^[85]

Multidisciplinary approach to AIDS wasting syndrome starts with optimal antiretroviral therapy and adequate nutrition. Testosterone (intramuscular/transdermal) has been successfully used to increase lean body mass in men with this syndrome, whereas it has also been shown to be safe and well tolerated in women. A number of agents like anabolic steroids (oxandrolone, nandrolone), megestrol acetate, thalidomide, human chorionic gonadotropin, pentoxifyline, amino acid mixtures and omega 3 fatty acids have been tried in this setting with variable efficacy but potential side effects.^[86-90] Only testosterone administration has proved useful to increase lean body mass, especially in conjunction with progressive resistance training.

Supraphysiologic dose GH administration is currently reserved for severe wasting refractory to other treatments.

HIV LIPODYSTROPHY SYNDROME

HIV lipodystrophy syndrome is associated with metabolic derangements, changes in body composition and abnormal fat distribution. It has been most widely recognized since the era of HAART but can also be seen in antiretroviral-naïve patients. It is characterized by phenotypic changes like truncal obesity, buffalo hump, peripheral fat loss, atrophy of facial fat and breast enlargement in women. Considering some physical similarities to Cushing’s syndrome, it has been termed as “a pseudo-Cushing’s syndrome” though neither any other specific stigmata of Cushing’s syndrome (proximal muscle weakness, bruising and facial plethora) nor biochemical parameters are associated with this syndrome.^[91] Normal cortisol level with its normal diurnal variation and adequate suppressibility to dexamethasone are seen in HIV lipodystrophy syndrome. However, it is very often associated with insulin resistance, hyperglycemia, and hypertriglyceridemia. In particular, dyslipidemia and diabetes mellitus are increasingly common among patients receiving HAART.^[92] Cardiovascular risk increases many folds, especially the rate of developing myocardial infarction and the prevalence of metabolic syndrome (40% of the HIV-infected patients with fat redistribution having metabolic syndrome as evidenced by Framingham equation) are most increased among HIV-infected patients treated with HAART.^[93] But HIV status and viral load have not been shown predictive of cardiovascular disease.^[94] Treatment options available consist of exercise and lifestyle modification, switching to less-toxic NRTIs or PIs, fenofibrates to decrease serum triglyceride level, and use of insulin sensitizers like metformin to reduce visceral fat and thiazolidinediones to improve subcutaneous fat loss. Testosterone and anabolic steroids have no effect in reducing visceral fat in lipodystrophy syndrome.^[95]

CONCLUSION

HIV endocrinopathy is not so uncommon, though overt glandular failure is a rare entity. Mechanisms by which the virus directly alters the endocrine function are still ill-understood. Adrenal insufficiency is the commonest dysfunction, followed by other hormonal abnormalities complicating the longstanding disease process. Drug-induced endocrine toxicity is another important aspect of patient care. Prospective studies are needed to evaluate the burden of HIV endocrinopathy among Indian population, which will enable us to adopt optimal management strategy for these patients to avert a further compromise in disease and health.

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