Endocrine and Metabolic Disorders Associated with Human Immune Deficiency Virus Infection

Endocrinien et métaboliques associés à des troubles d’immunodéficience humaine infection par le virus

C. N. Unachukwu*, D. I. Uchenna , E. E. Young

ABSTRACT
BACKGROUND: Many reports have described endocrine and metabolic disorders in the human immunodeficiency virus (HIV) infection. This article reviewed various reports in the literature in order to increase the awareness and thus the need for early intervention when necessary.

DATA SOURCE: Data were obtained from MEDLINE, Google search and other journals on ‘HIV, Endocrinopathies/Metabolic Disorders’ from 1985 till 2007.

STUDY SELECTION: Studies related to HIV associated endocrinopathies and metabolic disorders in the last two decades were reviewed.

DATA EXTRACTION: Information on epidemiology, pathogenesis, diagnosis and treatment of the target organ endocrinopathies and metabolic disorders in HIV/AIDS were extracted from relevant literature.

RESULTS: 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 euthyroid sick syndrome or sub-clinical hypothyroidism. Hypogonadotrophic dysfunction accounts for 75% of HIV-associated hypogonadism, with prolonged amenorrhoea 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 has been noted to result in insulin resistance and lipodystrophy.

CONCLUSION: 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. WAJM 2009; 28(1): 293–299

Keywords: HIV, endocrinopathies, metabolic disorders, review.
INTRODUCTION

HIV was identified as the causative agent of AIDS in 1983. The spectrum of illnesses associated with HIV infection is broad and is the result of both direct HIV effects and the associated immune dysfunction. While endocrine dysfunction has not been a prominent clinical feature of AIDS, all endocrine glands may be affected by the opportunistic infections and neoplasms or by agents used in their treatment. Direct invasion of the glands by the virus is also implicated. A number of these abnormalities also occur as a result of non-specific endocrine responses to stress, infection and malnutrition. All these result in both pathological changes and disturbances in function.

Various studies have highlighted the different endocrine disorders associated with HIV infection. This report is a review of several studies in literature over the last two decades related to HIV endocrinopathies and metabolic disorders with emphasis on pathology and function. It will also consider whether these changes are functionally significant, HIV specific or due to side effects of anti-retroviral therapy. Each gland will be discussed under epidemiology, pathogenesis and treatment.

A high index of suspicion is required by physicians to be able to identify specific endocrine gland dysfunction and appropriate treatment in patients with HIV infection. This paper seeks to heighten the awareness of clinicians to the existence of endocrinopathies in HIV infection. This may go a long way to improve the quality of care and life of people living with HIV/AIDS.

ENDOCRINE DISORDERS

Pituitary Disorders

Anterior Pituitary/ Epidemiology: The main abnormality in anterior pituitary function which has been reported is hypopituitarism. The growth hormone (GH) axis has received particular attention in children with HIV who can have poor growth velocity. However most of these children demonstrate normal GH levels, with low IGF-I levels. Circadian GH secretion does not appear to be altered in adults with HIV infection. Prolactin levels were found to be normal with a normal response to TRH stimulation, however Hutchinson et al described four patients with galactorrhea as an isolated endocrine abnormality after use of protease inhibitors for HIV treatment and post-exposure prophylaxis.

Pathogenesis: Pituitary infiltration by Toxoplasma gondii causing hypopituitarism in a patient with advanced HIV disease has been described. A possible action of gp120 at the hypothalamus as well as the suppression of growth hormone release has been suggested. This was associated with a significant loss in body weight in HIV-infected individuals and may suggest a specific pathogenesis for the wasting observed in them.

A direct autopsy study of pituitary glands from 49 patients with advanced HIV disease found no increased incidence of adenomas or micronodules in comparison to normal males, although about 10% of adenohypophyses and 4% of posterior pituitaries showed involvement with CMV. The isolated galactorrhea reported after use of PI’s may be due to a direct drug effect or indirect effect on Cytochrome P450; thus potentiating Dopamine antagonist effect of other drugs.

Posterior Pituitary

Posterior pituitary disorders in HIV include unexplained hyponatraemia, syndrome of inappropriate ADH secretion, and Central Diabetes Insipidus.

Epidemiology: Hyponatraemia occurs in 30-50% of inpatients and approximately 20% of outpatients with AIDS. Agarwal et al. reported 36 of 103 HIV patients admitted with opportunistic infections to have serum sodium less than 130 mEq/liter; two-thirds of these patients were clinically euvolemic and had serum arginine vasopressin levels that were inappropriately high for the serum osmolality, consistent with the syndrome of inappropriate antidiuretic hormone secretion.

Pathogenesis: Many of the patients reported by Agarwal et al had P. carini pneumonia, which, like any pulmonary infection, can induce the syndrome of inappropriate ADH. Furthermore, most were treated with trimethoprim, which could contribute to hyponatraemia through impaired sodium conservation and/or dilutional hyponatraemia due to the large volumes of hypertonic intravenous fluid required for its administration. Central diabetes insipidus has been reported in an AIDS patient with herpetic meningoencephalitis. This is not peculiar to HIV as any process that destroys the pituitary or damages the hypothalamus can potentially cause diabetes insipidus.

THYROID DISORDERS

Various studies have identified abnormal thyroid function tests in HIV infected patients. Abnormal thyroid function tests have been found to be common in HIV/AIDS even though the prevalence of overt thyroid disease was not found to be more than in the general population. Thyroid disorders identified in patients with HIV/AIDS include: Sick euthyroid state, subclinical hypothyroidism, graves disease and thyroiditis.

The prevalence of the sick euthyroid illness is high in patients with advanced AIDS. Any severe illness can induce changes in thyroid hormone levels, but certain disorders exhibit a distinctive pattern of abnormalities. Subclinical hypothyroidism in which there is isolated elevated TSH has been reported in patients on antiretroviral therapy. Rates of subclinical hypothyroidism between 3.5% to 12.2% have been reported.

Pathogenesis: In patients with the sick euthyroid syndrome, there is reduced T3 level, elevated reverse T3 and relatively normal or decreased TSH level, depending on the severity of the illness. The major cause of these hormonal changes is the release of cytokines especially interleukin-6 and tumor necrosis factor (TNF). In the early stage of HIV infection, T3 and T4 levels rise, T3 levels fall with progression to AIDS, but TSH usually remains normal. Among HIV patients with subclinical hypothyroidism, anti-thyroid peroxidase antibodies are rarely identified.
suggesting another aetiology other than auto-immune.\textsuperscript{18} Stavudine has also been associated with sub-clinical hypothyroidism in a few studies.\textsuperscript{19} Knyisz reported the case of a 27-year-old HIV-1 positive woman who developed Graves disease after commencing potent cART.\textsuperscript{20} Laboratory tests showed evidence that this developed following improvement by 58-fold in her CD4 count. Hence the development of Graves disease in this case was ascribed to the Immune Reconstitution Syndrome\textsuperscript{20}. In patients with advanced HIV disease, systemic opportunistic infections may also affect the thyroid gland. Thyroiditis due to Cryptococcus neoformans, Pneumocystis jiroveci and visceral leishmaniasis have been reported.\textsuperscript{21,22} Lymphoma and Kaposi sarcoma can also infiltrate the gland and impair its function.\textsuperscript{21}

Management

Patients with sub-clinical hypothyroidism show mildly elevated TSH levels with a normal FT4 concentration and either no or mild, non-specific symptoms. The TSH level should be determined again in 1–3 months. Levothyroxine therapy may be considered in patients with persistently elevated levels of TSH is $>10$ mU/L.\textsuperscript{22}

For patients with the sick euthyroid syndrome, treatment of the underlying cause is usually sufficient. However, there is insufficient evidence to recommend routine thyroid screening of asymptomatic HIV-infected individuals.\textsuperscript{15}

ADRENAL DISORDERS

Adrenal insufficiency has been noted to be the most common endocrine disorder in HIV infection.\textsuperscript{2} Cushings syndrome has also been reported.\textsuperscript{21}

The incidence of adrenal gland involvement is high. Bricaire and colleagues\textsuperscript{21} found abnormal adrenal glands in 64 of 83 patients with HIV disease at postmortem examination; 37 showed inflammation and 22 showed necrosis. Cytomegalovirus (CMV) was present in the adrenals in 44 cases, Kaposi’s sarcoma (KS) in 3, and cryptococcosis in one, toxoplasmosis in one, and tuberculosis in one. Klatt and co-worker reported the presence of CMV at autopsy in the adrenal glands of 81 out of 164 patients with HIV\textsuperscript{25}.

Pathogenesis: The adrenal gland shows evidence of both inflammation and necrosis at autopsy. Opportunistic infections are also involved in destruction of the gland.

Drugs which are used in management of various associated disorders also contribute to adrenal insufficiency (see Table 2). Ketoconazole which is used to treat certain fungal infections, inhibits adrenal corticosteroid synthesis and blunts cortisol response to adrenocorticotropic hormone (ACTH) and may be an under recognised cause of impaired adrenal reserve and even frank adrenal insufficiency.\textsuperscript{21} Rifampicin (an antituberculous agent) also alters the metabolism of glucocorticoids, thereby increasing hormone excretion values or necessitating higher exogenous steroid doses to maintain therapeutic effect.\textsuperscript{21}

However, the incidence of clinical and biochemical adrenal insufficiency in patients with HIV is much lower than the incidence of adrenal involvement at autopsy. It is likely that the observed adrenal pathology may be insufficient to cause clinical problems. Eighty to 90% of the adrenal gland can be necrotic without impairing adrenal function.\textsuperscript{21}

Classic adrenal destruction may not be the only cause of abnormal adrenal laboratory results in AIDS. Two cases of Cushings syndrome with secondary adrenal insufficiency have been reported from concomitant use of ritonavir and inhaled fluticasone in children with HIV infection.\textsuperscript{26} 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.\textsuperscript{26}

Unexplained hyperkalemia persisting despite normal cortisol response to ACTH may represent hyporeninemic hypoaldosteronism, which has been described in hospitalized patients with HIV disease.\textsuperscript{27} Characteristic findings in these patients include hyperkalemia, usually hyponatraemia, mild acidosis, normal basal and ACTH-stimulated cortisol levels, low basal aldosterone levels (particularly in relation to high serum potassium levels), low basal renin, and impaired aldosterone response to furosemide.\textsuperscript{27} Pentamidine used for the treatment of Pneumocystis jiroveci pneumonia in AIDS, has also been reported to cause hyperkalaemia\textsuperscript{28} and this must be excluded.

Management

This essentially involves the use of glucocorticoids during stress episodes. Chronic replacement with supra-physiologic doses is not advocated to prevent worsening an already immunosuppressed condition. HIV disease is however not a contraindication to pharmacologic glucocorticoid therapy (e.g. in central nervous system toxoplasmosis).\textsuperscript{21}

TESTICULAR FUNCTION

Hypogonadism is the major abnormality testicular endocrinopathy reported and has been found to be due to several mechanisms. Low testosterone concentrations are associated with lower CD4 cell count, advanced stage of illness, medication use, and weight loss. Signs and symptoms may be non-specific. The most useful laboratory indicator is the

### Table 1: Abnormalities in Thyroid Function Tests in HIV Infection

<table>
<thead>
<tr>
<th>Variable</th>
<th>Seronegative, severe non-thyroidal illness</th>
<th>HIV infected, stable</th>
<th>HIV infected, ill</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3</td>
<td>↓↓</td>
<td>Normal</td>
<td>↓↓</td>
</tr>
<tr>
<td>rT3</td>
<td>↑</td>
<td>↓</td>
<td>↓ or Normal</td>
</tr>
<tr>
<td>TBG</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>T4</td>
<td>Normal or ↓</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>TSH</td>
<td>Normal, may be increased in recovery</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

↑ or ↓ degree of increase or decrease.
HIV/AIDS

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Table 2: Endocrinological Effects of some Medications in Treatment of HIV/AIDS

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Clinical Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>Induces hepatic microsomal enzymes leading to increased hormonal clearance.</td>
<td>Hypothyroidism in patients with impaired thyroid reserve. Adrenal insufficiency in patients with limited reserve.</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Inhibits adrenal and gonadal steroidogenesis.</td>
<td>Adrenal insufficiency in patients with limited reserve. Decreased testosterone levels.</td>
</tr>
<tr>
<td>Megestrol acetate testing</td>
<td>Intrinsic glucocorticoid-like activity</td>
<td>Lower serum cortisol levels, Impaired response to provocative Hyperglycaemia Lower testosterone levels</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>Impairs potassium secretion by inhibiting sodium channels in distal nephron, impairs sodium conservation</td>
<td>Hyponatremia Hypokalaemia</td>
</tr>
<tr>
<td>Pentamidine</td>
<td>Nephrotoxicity; Pancreatic toxicity</td>
<td>Acute hypoglycaemia Chronic hyperglycaemia Hyperkalaemia</td>
</tr>
</tbody>
</table>

Pathogenesis of Male Hypogonadism in HIV/AIDS

Dobs et al reported that hypogonadism was hypogonadotrophic in 75% of cases they studied. Coodey and associates found that weight loss proceeded the fall in serum total testosterone concentrations in men during the course of progressive HIV disease. Low serum testosterone levels with elevated LH and FSH have also been reported suggesting primary testicular failure. Tuberculous orchitis has also been documented. These various mechanisms may act in concert to result in hypogonadism.

It has also been found that men with HIV may also be prone to an early “andropause” marked by dysregulation of the hypothalamic-pituitary axis and the associated signs and symptoms. Wunder in a multicentre cohort of HIV-infected men, found an association between lower CD4 cell counts and hypogonadism and this did not resolve after two years of anti-retroviral therapy.

Crum-Cianflone also reported a prevalence of 61.4% of erectile dysfunction in HIV-positive men which had no correlation with hypogonadism.

Management

The standard therapy for hypogonadism has been intramuscular (IM) testosterone given every 1 to 3 weeks to provide roughly 100 mg per week (e.g., 200 mg q 2 weeks, 300 mg q 3 wk). Intramuscular (IM) testosterone is usually given as the enanthate or cipionate esters. Administration of IM testosterone significantly increases weight and lean body mass, energy, quality of life, and depression scores in HIV-infected men with low testosterone levels.

Alternative therapeutic approaches include transdermal and oral routes of androgen administration. Skin patches are available either as trans-scrotal patches or transdermal patches. Newer transdermal and gel preparations provide more-consistent steady-state dosing but are not as well tested. Oral androgens are also available. Oxandrolone is an oral androgen that is currently approved for use in AIDS-associated weight loss at a daily dose of up to 20 mg.

OVARIAN FUNCTION

Information on gonadal function in women with HIV infection is limited. However regular menstrual cycles were reported in 92% of asymptomatic and 100% of symptomatic women though all the subjects were in the early stages of the infection with CD4 counts over 200. Prolonged amenorrhoea has also been reported in HIV-positive women. HIV-positive women were three times more likely than negative women to have prolonged amenorrhoea without ovarian failure.

Management

Treatment options in women with HIV-associated hypogonadism are less well described. Preliminary studies suggest that use of physiological testosterone administration, to achieve testosterone levels within the normal range, is of benefit in HIV-infected women, but further studies are necessary to define the therapeutic role of androgen therapy in this population. Standard hormone replacement therapy involves the use of oral estrogen (e.g., Premarin 0.625 mg daily) and progesterone (10 mg daily) or of oral contraceptive preparations. Some clinicians have considered adding a low dose of an anabolic androgen preparation (e.g., oxandrolone, 2.5 mg daily) in women with AIDS-associated weight loss, but this approach has not been tested and may result in androgenic side effects.

METABOLIC DISORDERS

Pancreatic Dysfunction and Glucose metabolism

Pancreatic abnormalities are
common in autopsy series of AIDS patients. In a study of 82 autopsied HIV-infected patients, opportunistic infections and malignancies were more frequent in the pancreas of patients with HIV than controls with other forms of immunosuppression. However these autopsy findings did not result in pancreatic dysfunction routinely as up to 90% of the pancreas needs to be destroyed to result in altered physiology. In terms of glucose homeostasis, clinically stable HIV-infected men were in earlier studies found to have higher rates of insulin clearance, increased sensitivity of peripheral tissues to insulin and an increase in non-oxidative glucose disposal. Hepatic glucose production rates also increase, perhaps in response to the increased glucose disposal.

Drugs are implicated in significant pancreatic dysfunction. Pentamidine has been found to cause beta cell toxicity initially causing hypoglycaemia and then diabetes mellitus in the long term. Patients on HAART especially protease inhibitors have been noted to develop insulin resistance. This has come under special interest and studies have demonstrated this using different protease inhibitors. Carr et al demonstrated an 8% prevalence of diabetes mellitus among HIV-infected patients receiving HAART. Bakari and colleagues also reported a case of DM in a 48 year old Nigerian male six months after addition of a PI to anti-retroviral therapy. Hadigan et al demonstrated a 6-fold increase risk of impaired glucose tolerance among HIV-infected patients with clinical and subjective evidence of fat redistribution compared to age and BMI-matched subjects from the Framingham Offspring Cohort (30 vs 5%). Subjects with abnormal fat redistribution also had an increased prevalence of diabetes mellitus (8% vs. 0.5%) compared to the Framingham subjects. The insulin resistance demonstrated in HIV patients is considered by most authors to confer a high risk of coronary artery disease (CAD) in these subjects.

Pathogenesis: In vitro studies suggest that Indinavir, Ritonavir and Amprenavir cause insulin resistance by inhibiting glucose uptake in a dose dependent manner in adipocytes by selectively inhibiting the GLUT-4 transporter function. Evidence from laboratory studies also suggest that indinavir downregulates the peroxisome proliferators-activated receptor-gamma (PPAR g) receptor in adipocytes. Genetic factors and other predisposing factors may also play a role since not all individual on PIs develop DM and other metabolic complications.

It has been demonstrated that protease inhibitors decrease glucose uptake in adipocytes in vitro and may act similarly in vivo. Decreased insulin sensitivity has been associated with fat loss in the extremities, as well as increased waist circumference and WHR. Accumulation of lipid within the intramyocellular (IMCL) compartment may also contribute to glucose intolerance. In this regard, increased lipolysis and deposition of fatty acids within the myocytes may interfere with insulin signaling through effects on PI3-kinase.

Other studies showed decreased adiponectin in association with reduced extremity fat and increased visceral adiposity in HIV infected patients. Adiponectin increases the oxidation of fat within the muscle. Reduced levels of adiponectin are associated with decreased insulin sensitivity and this mechanism may also contribute to altered glucose regulation in HIV-infected patients.

Management

General measures found to be effective include exercise, weight loss and use of insulin sensitizers. Hadigan et al. demonstrated improved insulin, blood pressure, waist circumference and CAD risk markers of impaired thrombolysis (TPA and PAI-I) in patients treated with metformin for 12 weeks. Metformin is better reserved for patients with central adiposity and not those with lipodystrophy. It is also contraindicated in renal failure and liver dysfunction. An increased benefit with a combination of metformin and exercise as compared with each agent alone has also been demonstrated.

The thiazolidinediones act on the PPARg receptor and increase glucose uptake into muscle. They also increase adiponectin. They are useful in the management of insulin resistance in these patients.

**LIPID DISORDERS AND HIV-ASSOCIATED DYSMETABOLIC SYNDROME**

Triglyceride levels rise progressively with advancing stages of HIV infection and average twice the normal values in patients with symptomatic AIDS. There is a decrease in lipoprotein lipase activity, increased hepatic synthesis of free fatty acids, and increased lipolysis. There is a strong correlation of Interleukin-1 levels with elevated triglyceride levels. Triglyceride levels are also higher in patients with CD4 count less than 200cells/μl.

The advent of HAART has resulted in the emergence of a new dysmetabolic syndrome with associated increased risk of cardiovascular events. The components of the syndrome include insulin resistance, visceral adiposity, peripheral lipodystrophy, dyslipidaemia and glucose intolerance. These components could occur independently or in combination and all are currently classified as the lipodystrophy syndrome. Treatment with protease inhibitors results in increase in triglycerides, total cholesterol, and LDL cholesterol levels. Ritonavir predominantly increases triglyceride and very low-density lipoprotein cholesterol levels. Lipodystrophy characterized by the loss of subcutaneous fat from the face, arms, and legs have been reported to develop in patients especially those on protease inhibitors. Some HIV-infected patients with lipodystrophy may have concomitant deposition of excess fat in the neck and upper back, causing a double chin and a buffalo hump, respectively, and in the trunk. Adipose tissue from patients with lipodystrophy who are receiving protease inhibitors has reduced messenger RNA (mRNA) expression of several key transcription factors involved in adipogenesis, including sterol regulatory element-binding protein 1c (SREBP1c) and peroxisome-proliferator-activated receptor-gamma (PPAR-gamma) receptors.

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receptor γ (PPARγ). These changes in lipid metabolism raise the question of whether there will be accelerated atherogenesis in these patients. Many authors advocate treatment of both insulin resistance and hyperlipidemia to reduce cardiovascular risk.\textsuperscript{41,50}

**Management**

The treatment of hyperlipidaemia involves the use of statins or fibrates just as in treatment in other settings.

Cosmetic surgery such as liposuction have been of some benefit in some patients with lipodystrophy, as also is the injection of silicone or other implants for facial reconstruction in patients with lipoatrophy.\textsuperscript{45,50} Thiazolidinediones have not shown any benefit in the treatment of HIV associated lipodystrophy.\textsuperscript{50}

**CONCLUSION**

Many of the endocrine and metabolic changes in HIV infection are also seen in patients with other chronic illnesses. More importantly are the changes associated with drug treatment. More studies are advocated as more patients are placed on these drugs and more people live longer with this disease. The role of opportunistic infections in the advent of endocrine dysfunction has been clearly elucidated and underscores the need for proper treatment and prophylaxis when indicated. Understanding risk, aetiology and hopefully soon, developing an effective intervention for these endocrinopathies is an urgent priority in AIDS care. There is need for prospective studies to evaluate the common endocrinopathies in people living with HIV/AIDS in our environment.

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