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Commentary

Central obesity & dyslipidemia in HIV patients on antiretroviral therapy

The body fat has been classified as subcutaneous or peripheral fat and visceral or central fat. The visceral fat, which is the fat around the viscera, is metabolically active, and releases certain inflammatory cytokines which predisposes to atherogenic end events, such as acute coronary syndrome, stroke and peripheral vascular disease. The central obesity along with hypertension, diabetes mellitus and dyslipidaemia is known as metabolic syndrome and has been clubbed together, because of their heightened atherosclerosis predisposing risks. 'Asian phenotype' is a term used to denote this body habitus of central obesity with thin limbs, which is so commonly seen in Indian, Japanese, Chinese and other Asian populations[1]. This has been attributed to lifestyle changes of decreased physical activity, intake of high calorie but less nutritious food, psychosocial stress, poor sleep and possibly different genetic milieu in Asians[2,3].

Lipoatrophy (LA) is the loss of subcutaneous fat from face, arm, legs, abdomen and buttocks whereas lipohypertrophy is accumulation of subcutaneous fat in the upper back, neck, trunk and around abdominal viscera. Lipodystrophy is a term which encompasses either lipoatrophy, lipohypertrophy or both. In patients with HIV/AIDS, especially those with low CD4 count, a similar lipodystrophy is seen, which is called HIV-associated adipose redistribution syndrome (HARS)[4]. The metabolic and cardiovascular risk of HARS has been studied in many previous studies[5-7]. It was initially found to be related to protease inhibitors, especially indinavir, but later proved to be related to other class of antiretroviral drugs as well, especially the nucleoside reverse transcriptase inhibitors (NRTIs), such as lamivudine, stavudine and didanosine. Lipoatrophy is commonly associated with NRTIs while the lipohypertrophyis commonly seen with protease inhibitors[8]. Inhibition of the mitochondrial DNA (mtDNA) polymerase, by the NRTIs is the reason for the development of lipoatrophy and other toxicities. Changing the drugs within the class of NRTIs with lesser mtDNA toxicity will be able to limit or reverse the lipoatrophy.

In this study, 257 HIV-positive patients, with more than one year of follow up, were studied prospectively by Dutta *et al*[9]. The biochemical tests, body composition parameters and DEXA scan were done in all. Approximately 47 per cent patients had hypertriglyceridaemia, followed by hypercholesterolaemia and low high-density lipoprotein levels. Nearly 79 per cent of the 257 HIV-positive patients had at least one dyslipidaemic abnormality, and they also had higher insulin resistance, body fat, truncal fat and trunk-limb fat ratio. It was also seen that the percentage truncal fat, body mass index and duration of HIV were significant predictor of dyslipidaemia. In this study, lipoatrophy was graded from 0 to 3, using the visual scale as described by Carr *et al*[10] and defined it as score ≥2. Lipoatrophy was found in 8.57 per cent patients and was significantly associated with metabolic syndrome, such as insulin resistance, central obesity and a higher fasting blood glucose level. It was however, not associated with dyslipidaemia[9].

The authors argued that it was the lipodystrophy and not lipoatrophy that was linked to dyslipidaemia[9]. Dyslipidaemia was related to higher central obesity and a higher truncal-limb fat ratio. It was further seen in the study that central obesity and dyslipidaemia were also associated with insulin resistance and increase in fasting glucose to complete the metabolic syndrome[9].

Immune reconstitution inflammatory syndrome (IRIS) is usually seen in HIV patients with low CD4 count (<200 cells/µl) especially when antiretroviral therapy (ART) is re-constituted and CD4 count rises

to above 200 cells/µl. The occurrence of dyslipidaemia has also been correlated with the initiation of ART. This may be due to the inflammatory mediators released once the ART is re-constituted which leads to both metabolic syndrome and IRIS[11]. The lower the CD4 count and hence the immunity, the higher is the abnormal fat distribution, namely central adiposity and loss of peripheral fat. Although ART medication has been linked to the development of lipodystrophy (LD)[12], none of the drugs were found to be associated with LD in this study. This has been debated by the authors that since stavudine and protease inhibitors are the main drugs implicated in the development of LD, none of their patients were on stavudine and the use of PI was only 2.7 per cent.

There are different ways of objectively measuring the visceral and peripheral fat, namely body scans, such as magnetic resonance imaging (MRI), computed tomography (CT), X-ray absorptiometry and bioelectric impedance analysis, which determine the lean body mass. CT scan and MRI are considered gold standard for quantification of visceral adipose tissue (VAT)[13] and a value of ≥130 cm^2 is regarded to be associated with high risk of cardiovascular adverse effects[14]. However, one can also measure the triceps skinfold thickness, body mass index, waist circumference and waist-hip ratio to measure the fat of the body.

Various agents have been tried in the past to stop/revert the changes associated with lipodystrophy, such as rosiglitazone, recombinant growth hormone (GH) analogue tesamorelin, with mixed success. The use of GH or its analogue in patients with LD, especially lipohypertrophy is due to the finding that the patients with HIV lipodystrophy have a lower or lower-normal levels of physiological GH[15]. Giving very low doses of GH to maintain physiological levels has been associated with reversal of truncal and visceral fat with mixed results on lipid and glucose homeostasis[16,17]. The mortality associated with HARS is independently associated with lower acral muscle mass and higher visceral adipose tissue[18]. The treating physician should keep in mind the associated side effects of the drugs responsible for HARS and followup them with physical examination and appropriate tests to detect the same.

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