

Dyslipidemia in patients taking anti-retroviral therapy

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Abstract

Background: People with human immunodeficiency virus (HIV) infection are living longer with the use of anti-retroviral therapy (ART). But as they do, non-HIV medical problems become more relevant. In particular dyslipidemia, an important reversible risk factor for cardiovascular disease, has been linked to HIV infection and its treatment. Its pathogenesis is complex and includes factor related to the virus, the host and ART. Our aim is to study the changes in the lipid profile in the patients of HIV taking ART.

Methods: Data were collected from 50 normotensive, non-diabetic and non-obese, HIV-infected patients who were on ART for at least 6 months at ART Center, Civil hospital, Ahmedabad, Gujarat and 50 healthy normal controls. Fasting lipid profiles were analyzed enzymatically by colorimetric method in fully automated Erba XL-640 Analyser.

Results: The level of serum total cholesterol (TC), serum triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C) were increase while high-density lipoprotein cholesterol (HDL-C) were decrease in patients of HIV who were on ART for at least 6 month as compared to the normal subjects (p value <0.05).

Conclusion: The study has demonstrated dyslipidemia in HIV infected patients receiving ART. There is a need for monitoring lipid profile in patients on ART.

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Introduction

Patients with human immunodeficiency virus (HIV)/ acquired immunodeficiency syndrome (AIDS) frequently present alterations in lipid metabolism due to taking antiretroviral therapy (ART).^[1] The introduction of ART in the mid-1990s led to substantial improvement in the prognosis of HIV/AIDS patients, with a reduction in morbidity and mortality due to opportunistic diseases and consequent improvement of the patient's quality of life.^[2-7]

However, there is evidence that ART is associated with lipodystrophy syndrome, a disturbance of lipid metabolism characterized by insulin resistance, dyslipidemia, and fat mal-distribution, usually presenting as visceral abdominal obesity and cervical fat pad accumulation (buffalo hump), metabolic bone disease (osteopenia and/or osteoporosis), and lactic acidosis.^[2,5,7-12]

ART-associated dyslipidemia is characterized by elevated serum concentrations of total cholesterol, triglycerides, low density lipoprotein (LDL-C), very low-density lipoprotein (VLDL), and apolipoprotein B (apoB), and low levels of high density lipoprotein (HDL-C), constituting an atherogenic lipid profile.^[13,14] This lipid changes occurs within three months of initiating ART, and plateau after six to nine months.^[15]

The prevalence of dyslipidemia and other risk factors for cardiovascular disease are significant in HIV/AIDS patients receiving ART, ranging from 20% to 80% depending on the study design and population investigated.^[8] These lipid alterations were first described in patients who used antiretroviral regimens containing protease inhibitors (PI) like Indinavir, Nelfinavir, Ritonavir, but also were later observed in patients who received regimens consisting of nucleoside reverse-transcriptase inhibitors (NRTI) like Zidovudine, Lamivudine etc and nonnucleoside reverse-transcriptase inhibitors (NNRTI) eg. Nevirapine etc.^[16,17]

Materials and Methods

The cross sectional study was conducted in Civil Hospital, Ahmedabad during June 2013 to December 2013. We have taken institutional ethical approval for conducting this study. Fifty patients of normotensive, non-diabetic and non-obese and confirm diagnosis of HIV who were on ART at

least since 6 month are taken (n=50), their age range between 20-55 years (29 male and 21 female) participated in this study. The mean age of patients was found to be 35.21±12.15. Fifty normal healthy persons as controls (n=50) aged 20-55 years (26 male and 24 female) were used as control. The mean age of control was found to be 34.25±11.20.

Patients with past history of diabetes mellitus, hypertension, ischemic heart disease, renal failure, hepatic failure and acute or chronic pancreatitis were excluded from the study. Patients who were already taking lipid lowering agents were also excluded.

Fasting venous blood samples were collected from patients of HIV who were on ART and same fasting condition was maintain while taking the blood samples of controls. About five milliliters of venous blood from were drawn by utilizing disposable plastic syringes and transferred into sterile test tube. The blood was allowed to clot and centrifuged at 5000 rpm for 5 minute. Sera were separated and stored at -4°C until analysis.

The supernatant blood serum was used for the analysis. Serum total Cholesterol and serum Triglyceride was determined by enzymatic colorimetric-CHOD PAP test. Serum LDL-C, HDL-C were determined by enzymatic colorimetric method using Erba XL 640 fully auto analyzer. Results were analysed with Graphpad Instat software for statistical significance.

Result

Table 1 shows the biochemical results of the cases and the controls. The mean age of patients were found to be 35.21±12.15 and mean age of control were found to be 34.25±11.20. HIV infected patients who were on ART have significantly high TC, TG and LDL-C compared with controls (p <0.05). However, serum HDL-C level of HIV patients were significantly lower than in control group (p <0.05).

Table 1: Serum lipid profiles in HIV patients and controls (values are reported as mean ± SD)

Parameter (mg/dl)	Cases	Controls
Triglycerides	168±48	129±21
Cholesterol	226±10	139±11
HDL-C	25±11	57±12
LDL-C	138±8	98±11

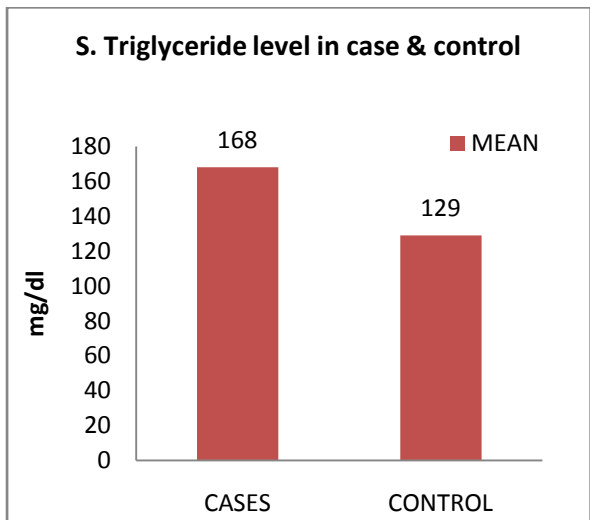


Figure 1: Serum Triglyceride level in cases and controls

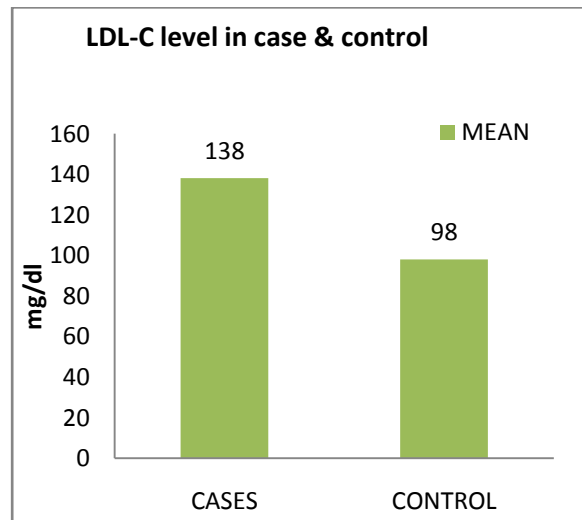


Figure 4: Serum LDL-C level in cases and controls

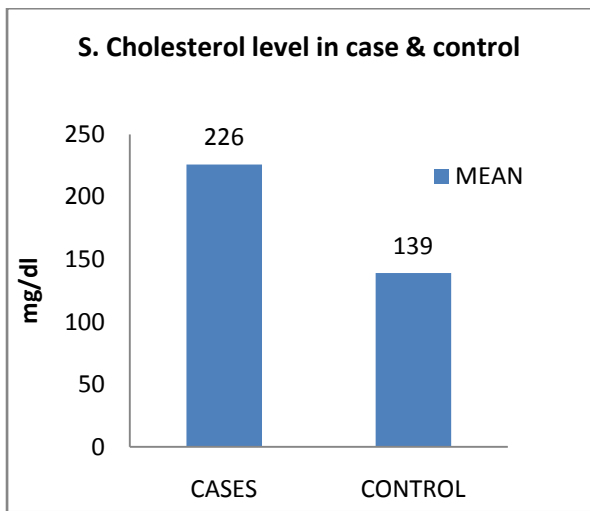


Figure 2: Serum Cholesterol level in cases and controls

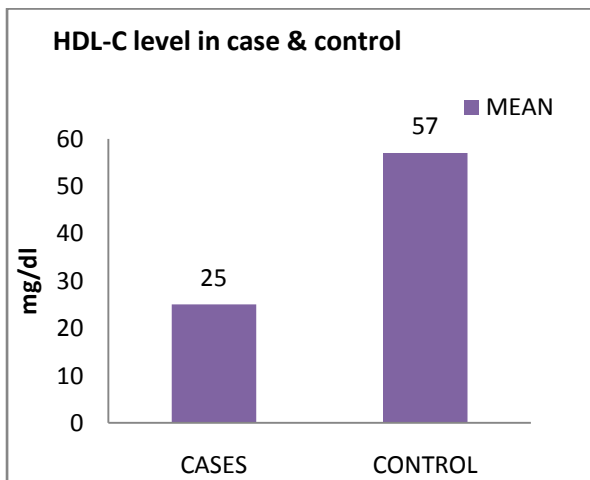


Figure 3: Serum HDL-C level in cases and controls

Discussion

In our study, it was found that the majority HIV patients on ART at least since 6 month having significantly increase the level of serum TC, serum TG and LDL-C while significantly decrease level of HDL-C as compared to the normal subjects (p value <0.05).

Changes in lipid metabolism associated with ART use have been commonly reported in all age groups of HIV-infected patients.^[5,6,7]

Cross-sectional studies with HIV-infected children and adolescents receiving ART have shown high frequency of dyslipidemia, lipodystrophy, retinol, and b-carotene deficiencies and, therefore, high risk for cardiovascular diseases.^[19,20,21] In a multicenter study, HIV-infected children with symptoms of fat redistribution presented adiponectin decrease, associated with insulin resistance, increase of TG and reduction of HDL-C.^[22]

Protease inhibitors (PI) are known to inhibit lipogenesis and adipocyte differentiation and to stimulate lipolysis of subcutaneous fat. NRTIs, in turn, can also reduce lipogenesis and adipocyte differentiation in subcutaneous tissue and might be one of the possible causes of mitochondrial toxicity, inhibiting mitochondrial DNA polymerase γ , which leads to the depletion of mitochondrial DNA. In addition, antiretroviral drugs have been shown to increase central visceral fat and the levels of fatty acids in blood, with a further increase of fatty acids oxidation.^[18,23]

Apparently, HIV/AIDS patients receiving ART who develop lipodystrophy have higher serum concentrations of inflammatory cytokines (IL-6 and TNF- α). In addition, evidence indicates a relationship between an increase of IFN- α and elevations of serum concentrations of TC, TG, VLDL, apoB, and apoB/apoA1.^[23] In this respect, protease inhibitors appear to bind to LDL receptor-related protein (LRP), reducing the cleavage of fatty acids from circulating triglycerides by the LRP-lipoprotein lipase complex on vascular endothelium, and impairing the uptake of remnant hepatic chylomicrons and VLDL.^[24,26] Moreover, protease inhibitors may directly stimulate hepatic triglyceride synthesis through up-regulation of mRNA production in hepatic cells for key enzymes involved in the triglyceride biosynthetic pathway, leading to the hepatic accumulation of triglyceride-rich lipoparticles.^[25]

These drugs may also modify lipoprotein metabolism by interfering with the expression of inflammatory cytokine genes and oxidative stress-related genes.^[26] The expression of genes in adipocytes and hepatocytes is modulated by protease inhibitors through sterol regulatory element-binding proteins (SREBPs), cytoplasmic retinoic-acid binding protein type 1 (CRABP-1), peroxisome proliferator activated receptors (PPARs), and apoCIII, events that contribute to the development of atherogenic dyslipidemia.^[3]

Conclusion

From our study we concluded that HIV-infected patients who were on ART at least since 6 month have increase in serum TC, serum TG, serum LDL-C level and decrease in serum HDL-C level. Explanation for this is that protease inhibitors were commonly associated with hypercholesterolemia, hypertriglyceridemia, elevated LDL-C, reduced HDL-C and NRTIs induced lipid alterations, particularly lipoatrophy and hypertriglyceridemia. While patients using NNRTIs, developed hypertriglyceridemia and hypercholesterolemia. Therefore the different classes of drugs of ART appear to exert distinct alterations in lipid metabolism and develop dyslipidemia. So there is need for monitoring lipid profile in patients taking ART, so as to assess risk factor for cardiovascular disease.

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Competing Interests

None declared

References

- 1) Grunfeld C, Kotler DP, Hamadeh R, Tierney A, Wang J, Pierson RN. Hypertriglyceridemia in the acquired immunodeficiency syndrome. *Am J Med.* 1989;86:27–31.
- 2) Boccara F. Cardiovascular complications and atherosclerotic manifestations in the HIV-infected population: type, incidence and associated risk factors. *AIDS.* 2008;3:S19–26.
- 3) Mehta N, Reilly M. Atherosclerotic cardiovascular disease risk in the HAART-treated HIV-1 population. *Clin Trials.* 2005;6:5–24.
- 4) Hoffmann C, Jaeger H. Cardiology and AIDS: HAART and the consequences. *Ann N Y Acad Sci.* 2001;946:130–44.
- 5) Leonard EG, McComsey GA. Metabolic complications of antiretroviral therapy in children. *Pediatr Infect Dis J.* 2003;22:77–84.
- 6) Floridia M, Tamburrini E, Ravizza M, Tibaldi C, Ravagni Probizer MF, Anzidei G, et al. Lipid profile during pregnancy in HIV-infected women. *HIV Clin Trials.* 2006;7:184–93.
- 7) Kramer AS, Lazzarotto AR, Sprinz E, Manfredi WC. Metabolic abnormalities, antiretroviral therapy and cardiovascular disease in elderly patients with HIV. *Arq Bras Cardiol.* 2009;93:561–8.
- 8) Troll JG. Approach to dyslipidemia, lipodystrophy, and cardiovascular risk in patients with HIV infection. *Curr Atheroscler Rep.* 2011;13:51–6.
- 9) Balasubramanyam A, Sekhar RV, Jahoor F, Jones PH, Pownall HJ. Pathophysiology of dyslipidemia and increased cardiovascular risk in HIV lipodystrophy: a model of ‘systemic steatosis’. *Curr Opin Lipidol.* 2004;15:59–67.
- 10) Monier PL, Wilcox R. Metabolic complications associated with the use of highly active antiretroviral therapy in HIV-1-infected adults. *Am J Med Sci.* 2004;328:48–56.

- 11) Powderly WG. Long-term exposure to life-long therapies. *J Acquir Immune Defic Syndr*. 2002;29 Suppl 1:S28–40.
- 12) Herman JS, Easterbrook PJ. The metabolic toxicities of antiretroviral therapy. *Int J STD AIDS*. 2001;12:555–62, quiz 563-4.
- 13) Dronda F. Cardiovascular risk in patients with chronic HIV-1 infection: a controversy with therapeutic, clinical and prognostic implications. *Enferm Infecc Microbiol Clin*. 2004;22:40–5.
- 14) Ducobu J, Payen MC. Lipids and AIDS. *Rev Med Brux*. 2000;21:11–7.
- 15) Sherer R. HIV, HAART, and hyperlipidemia: balancing the effects. *J Acquir Immune Defic Syndr*. 2003;34:S123–9.
- 16) Elías-Calles LC, Calero TMG. Dislipidemia y virus de inmunodeficiencia adquirida/SIDA. *Rev Cuba Endocrinol*. 2010;21:202–22.
- 17) Fantoni M, Autore C, Del Borgo C. Drugs and cardiotoxicity in HIV and AIDS. *Ann N Y Acad Sci*. 2001;946:179-99
- 18) Grinspoon S, Carr A. Cardiovascular risk and body fat abnormalities in HIV infected adults. *N Engl J Med*. 2005;352:48–62.
- 19) Sarni ROS, Souza FIS, Battistini TRB, Pitta TS, Fernandes AP, Tardini PC, et al. Lipodystrophy in children and adolescents with acquired immunodeficiency syndrome and its relationship with the antiretroviral therapy employed. *J Pediatr*. 2009;85:329–34.
- 20) Battistini TR, Sarni RO, Souza FIS, Pitta TS, Fernandes AP, Hix S, et al. Lipodystrophy, lipid profile changes, and low serum retinol and carotenoid levels in children and adolescents with acquired immunodeficiency syndrome. *Nutrition*. 2010;26:612–6.
- 21) Werner MLF, Pone MVS, Fonseca VM, Chaves CRMM. Lipodystrophy syndrome and cardiovascular risk factors in children and adolescents infected with HIV/AIDS receiving highly active antiretroviral therapy. *J Pediatr*. 2010;86:27–32.
- 22) Verkauskiene R, Dollfus C, Levine M, Faye A, Deghmoun S, Houang M, et al. Serum adiponectin and leptin concentrations in HIV-infected children with fat redistribution syndrome. *Pediatr Res*. 2006;60:225–30.
- 23) Christeff N, Melchior JC, Truchis P, Peronne C, Gougeon ML. Increased serum interferon alpha in HIV-1 associated lipodystrophy syndrome. *Eur J Clin Invest*. 2002;32:43–50.
- 24) Carr A, Samaras K, Chisholm DJ, Cooper DA. Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. *Lancet*. 1998;351:1881–3.
- 25) Calza L, Manfredi R, Chiodo F. Hyperlipidaemia in patients with HIV-1 infection receiving highly active antiretroviral therapy: epidemiology, pathogenesis, clinical course and management. *Int J Antimicrob Agents*. 2003;22:89–99.
- 26) Vergès B, Petit JM. Blood lipid abnormalities during treatment with protease inhibitors. *Presse Med*. 2001;30:911–4.

