ORIGINAL ARTICLE

Impacts of highly active antiretroviral therapy (HAART) on metabolic status of patients with AIDS: What happens from the initiation of AIDS to the initiation of treatment?

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Background: Our study aimed to determine if alteration of metabolic parameters is associated with the severity of human immunodeficiency virus (HIV) infection, progress to acquired immunodeficiency syndrome (AIDS), or with the type of antiretroviral treatment (ART). **Materials and Methods:** In a cross-sectional study among 114 HIV infected patients, we measured hematological and biochemical parameters to assess metabolic alterations according to the disease process and anti-retroviral treatment. **Results:** Of 114 HIV-positive patients, there were 82 AIDS patients receiving ART and 32 HIV patients without treatment. Alkaline phosphatase and parathyroid hormone (PTH) had lower serum levels in HIV patients with $CD4^+$ cell count ≤250 ($P < 0.01$). $CD4^+$ cell count was higher in patients receiving Protease Inhibitors (PI) and Nucleoside Reverse Transcriptase Inhibitors (NRTI) regimen compared with those treated with Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI) and NRTI or NRTI alone. Calcium (Ca) serum level was lower in patients with only NRTI regimen while Phosphorus (P) serum level was higher in patients on NNRTI and NRTI ($P < 0.05$). **Conclusion:** $CD4^+$ cell count ≤250 cells/μl in HIV-positive patients is associated with decreased level of triglyceride and PTH. Moreover, patients receiving NRTI regimen alone have lower Ca level while this regimen in combination with NNRTI or PI has a positive correlation with P serum level.

Key words: AIDS, Biochemistry, cART, HAART, HIV, Metabolic Status

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INTRODUCTION

Infection with human immunodeficiency virus (HIV) is a pandemic issue.[1,2] With adventure of anti-retroviral treatments (ART), HIV infection is now treated as a chronic disease.[3,4] HIV infection is often associated with a variety of changes in blood biochemical and metabolic parameters including changes in serum glucose and lipid profiles,[5-9] bone metabolism,[10] lactic acidosis,[7] and thrombocytopenia. These changes have been also observed in relation to the antiretroviral regimens.[3,6-8,11,12]

Despite increasing number of studies about metabolic and hematologic alterations in relation to HIV infection and the antiretroviral treatments, there is a paucity of knowledge regarding these alterations in relation to process of HIV infection, its progress to AIDS, and type of antiretroviral regimens which are widely administered.

The present study aimed to investigate metabolic, biochemical, and hematological alterations in relation to HIV infection status, development of AIDS, and type of HAART in and Iranian population of HIV positive patients.

MATERIALS AND METHODS

Between January 2010 and January 2011, a cross-sectional observational study was performed in Imam Hospital Complex affiliated to Tehran University of Medical Sciences (TUMS) in Tehran, Iran. One hundred fourteen HIV-positive patients referring to the high risk behavior clinic of our hospital were included in this study.

Written informed consent was obtained from all the patients and the research and ethic committee of TUMS approved the study protocol (89-02-30-10962). Recommendation of national AIDS control organization (NACO 2007) for diagnosis of HIV infection was followed throughout the study.

HIV-positive patients were divided into two groups based on their disease status with 32 patients in HIV infection status and the remaining 82 patients in AIDS stage receiving a combination of antiretroviral therapy

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(cART).[1] Another classification was also performed according to $CD4^+$ cell counts ($CD4^+ < 250$ cells/ml and $CD4^+ > 250$ cells/ml). A comparison of study parameters was then performed between each of these 2 paired groups of patients. In another set of analysis, patients on antiretroviral treatment were compared with patients who were not under any antiretroviral regimen. We also compared each group of AIDS patients according to their cART regimen (Protease Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, or Nucleosidase Reverse Transcriptase Inhibitors).

Immunological assessment including $CD4^+$ and $CD8^+$ cell count and evaluation of blood biochemistry were performed on obtained peripheral blood samples. $CD4^+$ and $CD8^+$ lymphocyte count was measured by flow cytometry (Partec Company, Japan). Lipid profile including serum levels of total cholesterol, high-density lipoprotein (HDL-c), low-density lipoprotein (LDL-c), and triglyceride, serum calcium, serum phosphorus, and alkaline phosphatase serum level were measured by biochemistry set-ups (BT-3500, Italy-Bio system-Spain, Kits). Parathyroid Hormone (PTH) (Biomerica, Germany) and 25 $(OH)_2$ vitamin D (Immunodiagnostic systems, United Kingdom) were also measured by Enzyme linked immunosurbant assay (ELISA).

Statistical analysis was performed using statistical package for windows (SPSS16, Chicago, Inc). Fisher's exact test was employed to assess the categorical variables and student t-test for continuous variables. Linear correlation between quantitative parameters was assessed with Pearson correlation test. Data are presented as mean ± standard error of mean (SEM) and a *P* value less than 0.05 was considered statistically significant. Normal and pathologic values are also provided for laboratory parameters.

RESULT

A total of 114 HIV-positive patients were enrolled in this study, 80 males and 34 females. HIV-positive patients were classified into two groups according to their disease status, 32 HIV-infected patients and 82 AIDS patients receiving cART.

Hematological and biochemical parameters

Table 1 presents biochemical and hematological parameters in the study patients. A considerable proportion of patients had significantly high TC serum levels and low HDL-c. Low serum level of Vit D (<50 nmol/L), low serum PTH (<10 pg/ml), and high serum level of P (4.5 mg/ml) were prevalent in this population (92.1%, 11.4%, and 8.8%, respectively). Moreover, 83.8% of patients had $CD4^+$ cell count <500 /µl while $CD8^+$ cell count <375 /µl was found in 10.5% of patients. On the other hand, 91.9% of HIV patient had $CD4^+/CD8^+$ ratio less than 0.9 [Table 1].

Transmission routes of HIV infection

Sixty HIV-infected patients (52.6%) reported their infection through intravenous drug use (IDU) followed by heterosexual contact (40 patients, 35.1%), blood born transmission (3 patients, 2.6%), and prenatal transmission (1 patient, 0.9%). Transmission route was not determined in 10 patients (8.8%). When the IDU patients were compared with the heterosexual patients, there was no significant difference ($P > 0.05$) for biochemical parameters except for platelet counts (188.15 ± 10.48 /µl in IDU group *vs* 224.60 ± 12.06 /µl in the heterosexual group).

Correlation between hematological and biochemical parameters

According to Table 2, there is a significant reverse correlation between serum levels of Ca and P (r = −0.63), a significant correlation between LDL-c and TC (r = 0.50), a significant weak correlation (0.2-0.4) between $CD4^+$ and $CD8^+$ cell count (r = 0.22), a weak reverse correlation between $CD4^+$ and ALKP (r = −0.25), a weak correlation between $CD8^+$ cell count and platelet count (r = 0.27), a weak reverse correlation between PTH and Vit D (r = −0.21), a weak correlation between LDL-c and TG (r = 0.27), a significant moderate correlation between LDL-c and HDL-c (r = 0.39), and a weak correlation (0-0.2) between HDL-c and TC (r = 0.19) in HIV positive patients. A linear regression analysis for $CD4^+$ and ALP also showed a

Table 1: Characteristics of different serum biochemical parameters in HIV-positive patients

	HIV Patients (Mean ± SE)	Range	HIV Patients (N %)
$CD4^+$ ($/_{\mu l}$)	300.30±17.66	<500	83.8 (93)
$CD8^+$ ($/_{\mu l}$)	772.71±35.63	<375	10.5 (12)
$CD4^+/CD8^+$ Ratio	0.43±0.03	<0.9 >1.9	91.9 (102) 0 (0)
TC ($^{mg}/_{dl}$)	188.50±4.51	>=220 <220	22.8 (26) 77.2 (88)
TG ($^{mg}/_{dl}$)	141.71±8.00	>=200 <200	9.6 (11) 90.4 (103)
HDL-c ($^{mg}/_{100}$)	44.97±2.66	<40	41.2 (47)
LDL-c ($^{mg}/_{100}$)	88.12±2.28	>= 130 <130	5.3 (6) 94.7 (108)
LDL-C/HDL-C Ratio	2.21±0.80		
TG/HDL-C Ratio	3.58±0.21		
TC/HDL-C Ratio	4.91±0.29		
ALP ($^{u}/_{L}$)	229.07±15.01	>306	11.4 (13)
Ca ($^{mg}/_{dl}$)	9.05±0.1	<8.4 >10.6	5.3 (6) 93 (106) 1.8 (2)
P ($^{mg}/_{dl}$)	3.63±0.10	>4.5	8.8 (10)
PTH ($^{pg}/_{ml}$)	20.28±1.13	<10	11.4 (13)
25 (OH) VitD ($^{nmol}/_{L}$)	20.80±1.76	<50	92.1 (105)
PLT ($/_{\mu l}$)	200.58±7.43	<150	25.4 (29)

TC = Total cholesterol; TG = Triglyceride; HDL-c = High-density Lipoprotein -c; LDL-c = Low-density lipoprotein cholesterol; ALP = Alkaline phosphatase; Ca = Calcium; P = Phosphorus; Plt = Platelet

Table 2: Correlations between different serum biochemical and hematological parameters in HIV-positive patients

Pearson Correlation	CD4+	CD8+	PLT	TG	TC	HDL	LDL	ALP	P	Ca	PTH	VITD
CD4+		0.22*	0.06	0.15	0.12	0.04	0.05	−0.25*	0.02	−0.01	0.10	0.02
CD8+			0.27*	0.10	−0.02	0.01	−0.02	0.05	0.18	0.05	−0.03	−0.06
PLT				−0.03	0.13	0.07	0.13	0.13	0.05	0.12	0.10	0.09
TG					0.18	0.13	0.27*	0.01	−0.02	−0.01	0.04	−0.07
TC						0.19*	0.50*	−0.07	0.08	−0.03	−0.02	0.16
HDL							0.39**	−0.05	0.06	0.08	0.07	0.03
LDL								−0.09	0.05	−0.13	−0.01	0.08
ALP									0.001	0.01	−0.05	−0.001
P										−0.63**	−0.14	0.06
Ca											−0.03	−0.05
PTH												−0.21*

*: P<0.05; **: P<0.01

regression coefficient of −0.48 in the HIV-infected group and −0.22 in the AIDS group ($P < 0.05$).

Comparison of HIV-positive patients based on CD4+ cell count (<250 cells/µl)

We classified all the patients by CD4+ cell count into two groups based on the AIDS classification (1), one group with CD4+ < 250 cells/µl and another group with CD4+ > 250 cells/µl. Study variables were compared between the two groups. Mean serum levels of triglyceride and PTH were significantly lower in patients with CD4+ < 250 cells/µl compared with the group of CD4+ > 250 cells/µl (123.22 ± 5.67 mg/dl and 17.37 ± 1.36 pg/ml *vs* 154.27 ± 13.86 mg/dl, and 22.90 ± 1.75 pg/ml, $P = 0.03$ and $P = 0.02$, respectively). No significant difference was observed between the two groups in terms of other parameters ($P > 0.05$). Of patients with CD4+ < 250 cells/µl, two patients (3.3%) and 9 patients (15%) had alkaline phosphatase and triglyceride levels above the normal range, respectively, which was significantly different when compared to 10 patients (19.9%) and 1 patient (2%) in another group with CD4+ > 250 cells/µl ($P < 0.05$).

Comparison of AIDS patients under antiretroviral regimen *vs* non-treated HIV-positive patients

Mean CD4+ Count was 411.21 ± 132.87 cells/µl in HIV-positive patients compared to 248.49 ± 175.09 cells/µl in AIDS patients. CD4+/CD8+ Ratio in HIV and AIDS patients were 0.58 ± 0.40 and 0.36 ± 0.27, respectively ($P < 0.001$). Calcium, alkaline phosphatase, and HDL-c were slightly elevated among AIDS patients while PTH, Vit D, and TG serum levels were slightly reduced. However, none of these alterations revealed a statistically significant difference ($P > 0.05$).

Comparison of metabolic parameters between AIDS patients according to the types of antiretroviral therapies [Table 3]

There was no statistically significant difference in terms of serum metabolic and biochemical parameters between AIDS patients under ART including Zidovudine (66 patients; 80.5%), Lamivudine (78 patients; 95.12%), Stavudine (4 patients; 4.9 %), Tenofovire (5 patients; 6.1%), and Didanosine (3 patients; 3.65%) and HIV-positive patients without ART ($P > 0.05$).

Table 3: Changes in the serum levels of biochemical parameters between different cART regimens

	PI + NRTI (Mean ± SE)	NNRTI + NRTI (Mean ± SE)	Only NRTI (Mean ± SE)
Number (%)	13 (15.85%)	65 (79.26%)	4 (4.89%)
Age	45.15±3.88*	37.43±1.11*	30.75±1.79*
CD4+	380±47.81*	234.05±22.65*	340.25±63.79
TC	198.15±17.58	193.40±6.04	168.25±18.62
TG	182.31±32.92	136.63±9.41	113±1.18
HDL-c	64.70±19.27	45.33±2.31	43.25±3.72
LDL-c	92.06±9.05	89.75±2.81	79±12.76
ALP	194.46±2.47	250.95±24.66	206±2.28
Ca	9.13±0.12*	9.20±0.10*	8.75±0.09*
P	3.26± 0.13	3.72 ±0.12*	3.11±0.10
PTH	16±1.26	19.66±1.28	27.6±11.90
VitD	15.8±2.67	21.8±2.77	9.65±1.16
Plt	204.15±17.61	208.68±10.72	183.25±17.93

NRTI: Nucleoside Reverse Transcriptase Inhibitors; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitors; PI: Protease Inhibitors; * ($P < 0.05$)

A significantly lower level of CD4+ cell count (234.05 ± 22.65 cells/µl *vs* 370.12 ± 35.52 cells/µl, $P < 0.05$) as well as a significantly higher level of phosphorus (3.73 ± 0.12 mg/dl *vs* 3.21 ± 0.11 mg/dl, $P < 0.05$) were observed in patients treated with Efavirenz (NNRTI) (63 patients; 76.83%) compared with patients treated with a cART lacking Efavirenz.

Patients treated with PI (Kaletra in this study) (13 patients; 15.85%) were significantly older (45.15 ± 14 years *vs* 37.04 ± 8.86 years) and had higher levels of CD4+ cell count (380.08 ± 43.45 cells/µl *vs* 240.39 ± 21.77 cells/µl, $P < 0.05$) compared to the patients receiving other types of ART.

Our AIDS patients receiving cART were divided in turn into 3 groups, 65 patients (79.26%) were on NNRTI and

NRTI regimen, 13 patients (15.85%) were on PI and NRTI regimens, and 4 patients (4.89%) only received NRTI. Table 3 shows the impact of different cART regimens on serum biochemical parameters. Mean age and serum level of Ca were significantly lower in patients receiving only NRTI compared to the patients on PI and NRTI or NNRTI and NRTI regimen ($P < 0.05$). Moreover, a significantly higher level of phosphorus was found in patients receiving NNRTI and NRTI compared with those patients not receiving this type of regimen ($P < 0.05$). However, mean levels of ALP and Vit D were not significantly different among these patients.

Mean level of $CD4^+$ cell count were significantly higher in patients on PI and NRTI compared with those on NNRTI and NRTI regimen ($P < 0.05$). However, despite a higher serum level of TG, HDL-c, and LDL-c in these patients, the difference was not statistically significant ($P > 0.05$).

DISCUSSION

The aim of our study was to evaluate the effects of HIV infection, advancement of the disease from early infection to development of AIDS, and antiretroviral therapies on metabolic and biochemical parameters. Our findings revealed that except for calcium, other biomarkers of bone metabolism including P, ALKP, 1,25 Vit D, and PTH were significantly different between AIDS and non-AIDS HIV patients. PTH and 1,25 Vit D were significantly lower among HIV-positive patients while P and ALKP revealed a higher serum levels. Other studies have shown a lower mean level for serum Ca among HIV-positive individuals.[2,3] Lower PTH and Vit D has been suggested to be an underlying cause.[21] Piso *et al*. have shown a higher serum level of ALKP in patients receiving antiretroviral treatment[22] and concluded an increased bone turn-over. Osteoporosis and osteopenia have also been associated with HIV infection and more frequently with PIs and ART.[2,4] In our study, Ca and Vit D were lower among HIV-positive patients while ALKP and PTH showed a higher value. The lower level of Vit D and Ca and PTH are consistent with the literature. Increased ALKP as a marker for bone turn-over may also occur due to increased bone resorption and formation.[21] This has been shown to be correlated with ART rather than HIV infection alone which have been responsible for decreased bone metabolism before introduction of ART.

Lipid metabolism has shown extensive alterations due to HIV infection before ART. This includes decreased serum levels of LDL[5-8] and HDL[5-9] along with increased level of TG as a result of increased VLDL.[7,8,10,11] However, the decreased level of LDL was not as frequent as low level of HDL.[8] The most prevalently reported pattern of lipid profile alterations includes decreased level of HDL as well as increased LDL, TG, and VLDL.[5-8,11-13] Despite existing evidence, our HIV-infected population had a different pattern of lipid profile alterations by which all the parameters were decreased. It is strongly hypothesized that a decreased lipid profile may stem from a lower socioeconomic status of people in developing countries. IDU as the most common rout of transmission would point to a low social position as well.

Hematologic parameters have been also shown to alter in HIV infection. This may refer to anemia, thrombocytopenia, and leucopenia due to ART[14,15] or the infection itself.[16,17] Among our variables, Plt change was consistent with other studies in which thrombocytopenia have been widely reported.[14,16,17] Transmission rout only affected the Plt count in our study showing lower values among IDU patients. There is a limited number of studies regarding the possible effect of IDU in Plt count.[18,19] Although it may occur due to autoimmunity, intravenous drug injection has been independently contributed to thrombocytopenia.

Hypercholesterolemia, hypertriglyceridemia, and osteoporosis[4,20,21] have all been reported to be associated with ART.[22] However, no metabolic changes were significantly related with antiretroviral drugs in our study. As our results suggest, only Ca and P were significantly different between different types of ART. However, no lipid alteration was found in relation to the type of cART. NNRTI and NRTI were also shown to increase P serum level. The adventure of HAART has raised concern regarding metabolic complications in the susceptible HIV patients. Although our study could not prove the effect of cART on metabolic and biochemical status, future studies are required to investigate such relationship in larger cohort of patients.

CONCLUSION

$CD4^+$ cell count ≤250 cells/μl in HIV-positive patients is associated with decreased level of triglyceride and PTH. Moreover, patients receiving NRTI regimen alone have lower Ca level while this regimen in combination with NNRTI or PI has a positive correlation with P serum level. There was no other difference in metabolic and biochemical parameters between AIDS patients receiving cART and HIV-positive patients without cART.

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Ethical approval: Written informed consent was obtained from all patients and the research and ethic committee of TUMS approved the study (89-02-30-10962). Recommendation of national AIDS control organization (NACO 2007) for diagnosis of HIV infection was followed.

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