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KLİNİK ÇALIŞMA / ORIGINAL ARTICLE

HIV pozitif hastalarda dislipidemi ve kardiyovasküler risk değerlendirilmesi

Dyslipidemia and cardiovascular risk assessment in HIV-positive patients

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ÖZET

Amaç: Dislipidemi, antiretroviral tedavinin (ART) sık görülen komplikasyonlarından biridir. Bu çalışmanın amacı, HIV pozitif tanısı konmuş olan hastaların başlangıçtaki lipit düzeylerini ve kardiyovasküler hastalık gelişme risklerini belirlemek ve tedavi başlandıktan sonra bu parametrelerde ortaya çıkan değişimi gözlemlemektir.

Yöntemler: Kliniğimize Nisan 2011 ve Ağustos 2012 tarihleri arasında başvuran HIV pozitif hastalar dâhil edildi. Çalışmaya 19 kadın (%22.1) ve 67 erkek (%77.9) hasta alındı (ortalama yaş: 39.5±10.3). Hastaların ilk başvuru ve son kontroldeki tıbbi kayıtları geriye dönük olarak gözden geçirildi ve kan basıncı, sigara, alkol tüketimi, serum toplam kolesterol (TK), trigliserit (TG), yüksek yoğunluklu lipoprotein (HDL), düşük yoğunluklu lipoprotein (LDL), glikoz düzeyleri kaydedildi. Başlangıca göre TK, TG, HDL, LDL ve Amerikan Kardiyoloji Koleji'nin kardiyovasküler hastalık risk (KVHR) skoru hesaplandı. Takip ve tedavi ile olan ilişkisi irdelendi.

Bulgular: Başlangıçta 73 (%84.9) olgu hiç ART ilaç kullanmamış ya da ilaç kullanmaya başlamış, fakat en ez 3 aydır kullanmamış, 13 olgu da (%15.1) ART kullanmakta idi. Çalışmaya alınmadan önceki son ziyaretlerinde ise 74 (%86) olgunun ART kullandığı, 12 (%14) olgunun hiç ART kullanmadığı saptandı. Başlangıçta ve son ziyarette TK düzeyleri sırasıyla 175.5 (dağılım: 90–346) mg/dL ve 196.5 (dağılım: 104–317) mg/dL (p=0.001), HDL düzeyleri 40 (dağılım: 21–81) mg/dL ve 35 (dağılım: 10–75) mg/dL (p=0.001), LDL düzeyleri 101.5 (dağılım: 32–191) mg/dL ve 120.5 (dağılım: 32–250) mg/dL (p<0.001) ve TG düzeyleri 145.5 (dağılım: 43–2580) mg/dL ve 152.5 (dağılım: 67–884) mg/dL (p=0.102) bulundu. Başlangıçta KVHR skoru %46 (dağılım: 5–69) iken son değerlendirmede %50 (dağılım: 5–69) bulundu (p<0.001). ***Sonuç:*** HIV enfeksiyonunun, lipit profli ve kardiyovasküler risk üzerine olumsuz etkileri vardır. Bu nedenle hastalar yaşam tarzı değişikliği ve lipit düşürücü tedavi için yakından izlenmelidir.

ABSTRACT

Objective: Dyslipidemia is a major complication of antiretroviral treatment. Aim of the present study was to screen baseline lipid levels and cardiovascular disease risk in HIV-positive patients and analyze change in those parameters after initiation of antiretroviral treatment (ART).

Methods: HIV-positive patients who presented at our clinic between April 2011 and August 2012 were included. Study included 19 female (22.1%) and 67 male (77.9%) patients (mean age 39.5±10.3 years). Blood pressure, smoking habit, alcohol consumption, serum total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), glucose level, and antiretroviral treatment status data were reviewed retrospectively. Changes in lipid profle and lifetime risk for atherosclerotic cardiovascular disease (ASCVD) according to the American College of Cardiology guidelines were compared with baseline data and analyzed.

Results: At baseline, 13 (15.1%) patients were already receiving ART and 73 (84.9%) patients were treatment-naive or had stopped therapy ≥3 months prior to enrollment. At last visit, 73 (84.9%) patients were taking ART. Results of baseline and fnal visit TC levels were 175.5 mg/dL (range: 90–346 mg/dL) and 196.5 mg/dL (range: 104–317 mg/dL), respectively (p=0.001). HDL levels were 40 mg/dL (range: 21–81 mg/dL) and 35 mg/dL (range: 10–75 mg/dL; p=0.001), and LDL levels were 101.5 mg/dL (range: 32–191 mg/dL) and 120.5 mg/dL (range: 32–250 mg/dL; p<0.001). TG levels were 145.5 mg/dL (range: 43–2580 mg/dL and 152.5 mg/dL (range: 67–884 mg/dL; p=0.102). Baseline ASCVD risk score was 46% (range: 5–69%) while last visit ASCVD risk score was 50% (range: 5-69%; p<0.001).

Conclusion: HIV infection has adverse effects on lipid profles and cardiovascular risk of HIV-positive patients. Therefore, patients should be closely monitored for lifestyle interventions and lipid-lowering agents.

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In our community, the number of individuals with unhealthy life styles such as malnutrition, smoking, and alcohol consumption are increasing.[1,2] Many patients living with HIV/AIDS has dyslipidemia at the time of diagnosis. One of the most common adverse effects of antiretroviral treatment (ART) is dyslipidemia, which also increases the already present dyslipidemia levels and subsequently the risk of cardiovascular disease (CVD).[3] Since the number of individuals living with HIV in our country is low and the patients are distributed in a number of HIV centers, data are lacking on the dyslipidemia levels and cardiovascular risk of those patients.

The objective of this study was to determine lipid levels, and risks of developing CVD on admission, to analyze the change in those parameters and to look for a relationship with ART.

METHODS

Approval of the Ethics Committee, and Consent of the Participants

After approval of the Ethics Committee (Document no: 16–4.1/24 Date: 04.26.2016), all HIV patients who presented to the HIV/AIDS Outpatient Clinic of the Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Ege University between April 2011 and August 2012 as an initial visit or for follow-up were informed about the study. All patients who were willing to participate in the study were asked to sign a written informed consent form.

Collection and recording of data

Total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), triglyceride (TG), fasting plasma glucose, systolic, and diastolic blood pressure values were recorded at the initial visit and at the last visit before enrollment. In addition, history of hypercholesterolemia, CVD, smoking, and alcohol consumption habits, family history of CVD, ART use, and antiviral regimens were extracted from the medical files of the patients and were recorded. An electrocardiogram (ECG) was obtained from each patient at the time of enrollment.

Antiretroviral naïve patients and those who have not used ART for the last 3 months were defined as ART non-users, and all other patients as ART users. According to this definition patients were classified as Group 1 (ART-naive patients at admission who initiated ART later), Group 2 (patients who have been using ART and continued to use it up the last visit), and Group 3 (ART-naïve patients who have not initiated ART at the last visit).

Abbreviations
ACC American College of Cardiology
ART Antiretroviral
EKG Electrocardiogram
HDL High-density lipoprotein
CVD Cardiovascular disease
CVDR Cardiovascular disease risk
LDL Low-density lipoprotein
NRTI Nucleoside analogue reverse transcriptase inhibitors
PI Protease inhibitor
TG Triglyceride
TC Total cholesterol

The American College of Cardiology (ACC), and the American Heart Association (AHA) guidelines scoring systems were used to estimate the 10-year and lifelong risk of CVD for each patient.[4,5] ACC-CVDR scores were calculated at admission and at the last visit.[4,5] Changes in risk scores of the participants, serum lipid values, and correlations among ART groups 1,2, and 3 were compared. Criteria used for the evaluation of HDL, LDL, TG and TC levels, and systolic and diastolic blood pressures were presented in Table 1.[6] Any intervention to quit smoking, diet and exercise recommendations and lipid-lowering treatment (LLT) were recorded. Patients who quitted smoking were recorded. The correlation between the newly constructed values by taking the difference between the first, and the last measurements and ART use was evaluated.

Statistical Analysis

Mean and standard deviation were used for qualitative data and numbers and percentages were used for categorical data. Qualitative data were analyzed by the Kolmogorov–Smirnov test, histogram curve, and mean/standard deviation ratio. For each subgroup, the coefficients of skewness and kurtosis were also assessed within a range of -1 and +1 points. Continuous data that did not meet ≥ 2 criteria were considered to have an abnormal distribution.

After the data were analyzed for their fitness to normal distribution, Mann-Whitney U-test was used to detect intergroup differences regarding mean (± standard deviation) values. For the comparison of consecutive measurements Wilcoxon signed- rank test was used. The significance of differences between more than two independent groups for continuous numerical variables was evaluated with Kruskal Wallis test. Herein pairwise comparisons between significant data and ART groups were performed using the Mann-Whitney U test in place of post-hoc test.

Table 1. Evaluation criteria for blood lipids, and blood pressure levels

Parameter	Cut-off values	Criteria	Result
Total cholesterol	≤199 mg/dL	–	Normal group
	200–249 mg/dL	–	Diet and exercise recommended
	>200 mg/dL	In the presence of CAD, MI, DM	Antihyperlipidemic drug required
	≥250 mg/dL	–	Antihyperlipidemic drug required
Triglyceride	≤134 mg/dL	–	Normal group
	135-249 mg/dL		Diet and exercise recommended
	≥250 mg/dL		Antihyperlipidemic drug required
HDL	>55 mg/dL	In men or postmenopausal woman	Normal
	>65 mg/dL	In premenopausal woman	Normal
LDL	<100 mg/dL	In the presence of CAD, MI, DM	Normal
	<130 mg/dL	In the absence of CAD, MI, DM	Normal
Diastolic blood pressure	<80 mmHg		Below normal
	80–84 mmHg		Normal
	85–89 mmHg		Upper limit of normal
	≥90 mm Hg		Hypertension
Systolic blood pressure	<120 mmHg		Below normal
	120–129 mmHg		Normal
	130–139 mmHg		Upper limit of normal
	≥140 mmHg		Hypertension

HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CAD: Coronary artery disease ; MI: Myocardial infarction; DM: Diabetes mellitus.

Differences between categorical and dependent samples were evaluated by the McNemar test. For statistical analysis IBM SPSS 16.0 (Chicago, USA) was used. In all tests $p<0.05$ was accepted as the level of significance.

RESULTS

A total of 86 patients (male, n=19; 22.1%, and female, n=67; 77.9%) were enrolled in the study. Mean age of the patients was 39.5±10.3 years (median: 38.5 range: 19–63 years). Medical histories of the cases revealed the presence of CVD (n=14), hypertension (n=9), atherosclerosis (n=4), myocardial infarction (n=1), and hypercholesterolemia (n=4; 4.7%). Family history of CVD was detected in 27 (31.4%) cases. Median follow-up period was 27.4 months (minimum 2 months, and maximum 80 months).

At first admission, 73 (84.9%) patients were ART-naïve or have not been using ART for the last 3 months, while 13 (15.1%) patients were using ART.

At the last hospital visit before enrollment in the study 74 (86%) patients were using ART, while 12 (86%) patients were still ART-naïve. Accordingly, the number of ART-naïve patients at baseline who had initiated ART at the last visit was 61 (70.9%) The median duration of ART was 22.2 months (minimum 3 months and maximum 129 months)

Among 74 patients who used ART at the last control 42 (56.8%) used a non-nucleoside reverse transcriptase inhibitor (NNRTI) and 25 (33.8%) used a protease inhibitor (PI) in combination with tenofovir/emtricitabine backbone. Other drug regimens were used in 7 (9.5%) patients.

Comparison of measurements obtained at the initial and the last visits revealed significant changes in all lipid profiles except TG and in blood pressure levels ($p<0.001$) (Table 2). ART users had significantly higher TG and LDL levels and significantly lower HDL levels compared to those in ART non-users (Table 3).

Table 2. Comparisons of values detected at the initial and last visits

	Values outside the normal range	Values within normal range	McNemar test *p* value	Median	Min	Max	Wilcoxon Test *p* value
TG (mg/dL)							
Last	38 (44.2%)	48 (55.6%)	0.036*	197	104	317	<0.001*
Initial	26 (30.2%)	60 (69.8%)		176	90	346	
Triglyceride (mg/dL)	55 (64%)	31 (36%)	0.169	153	67	884	0.102
Last							
Initial	47 (54.7%)	39 (45.3%)		146	43	2580	
HDL (mg/dL)							
Last	81 (94.2%)	5 (5.8%)	0.070	35	10	75	<0.001*
Initial	75 (87.2%)	11 (12.8%)		40	21	81	
LDL (mg/dL)							
Last	35 (40.7%)	51 (59.3%)	0.029*	121	32	250	<0.001*
Initial	23 (26.7%)	63 (73.3%)		102	32	191	
Glucose (mg/dL)							
Last	5 (5.8%)	81 (94.2%)		91	67	238	
Initial	11(12.8%)	75 (87.2%)	0.070	90	69	303	0.384
Systolic blood pressure (mmHg							
Last	7 (8.1%)	79 (91.9%)		110	90	170	
Initial	5 (5.8%)	81 (94.2%)		110	90	160	
Diastolic BP (mmHg)							
Last	17 (19.8%)	69 (80.2%)	0.125	80	50	110	0.278
Initial	12 (14%)	74 (86%)		71	55	110	

*Significant values . TC: Total cholesterol ; HDL: High density lipoprotein, BP, B pressure LDL: low density lipoprotein.

Comparison of Groups 1 and 2 revealed higher TG and LDL values in those who had started ART recently compared to those who have been using ART, whereas HDL values were not significantly different (Table 3). HDL values were significantly different between patients who had started ART earlier and ART-naïve patients (Table 3). All hyperlipidemic patients were referred to a dietician and regular exercise was recommended. Fifteen cases were prescribed antihyperlipidemic drugs for the first time during this study.

While 41 (47.7%) patients were active smokers at admission, 33 (38.4%) patients continued to smoke at the last visit (Mc Nemar; p=0.008). Smoking cessation intervention was provided for 35 cases, of which 7 (20%) quitted smoking. Another patient quitted smoking without any intervention.

CVDR scores calculated at admission (median 46%; min. 5%- max.69%), and at the last visit (median 50%; min. 5% - max. 69%) were compared. While the scores remained unchanged in 40 (46.5%) cases, they decreased in 11 (12.8%) and increased in 35 (40.7%) cases (Wilcoxon, p<0.001). Life-long CVDR score related to ART use estimated at the last evaluation visit did not differ among Groups 1,2, and 3 (Kruskal Wallis, p=0.599).

In a total of 4 cases electrocardiographic abnormalities (one related to a previous ischemic event and 2nd degree atrioventricular block in 3 patients) were detected. A significant association was not detected between antiretroviral drug use, and electrocardiographic abnormalities. (p=0.625).

Table 3. Comparison of the differences between the initial and last visits with respect to antiretroviral treatment groups

	Results of measurements in antiretroviral treatment groups Median (min/max)			Kruskal-Wallis Test *p*
	Group 1	Group 2	Group 3	
Total cholesterol (mg/dL)				
Initial	173 (90/287)	203 (126/346)	188 (127/260)	<0.001[#]
Last	200 (110/317)	197 (149/310)	184 (104/259)	
Difference *	27 (-128/170)	-2 (-36/51)	-4 (-61/38)	
HDL (mg/dL)				
Initial	35 (25/75)	34 (26/54)	35 (10/65)	0.007[&]
Last	34 (21/53)	36 (27/60)	40 (23/81)	
Difference *	-3 (-30/6)	0 (-7/13)	6 (-16/50)	
LDL (mg/dL)				
Initial	101 (32/191)	123 (63/168)	94 (54/147)	0.014[$]
Last	127 (32/250)	108 (78/173)	96 (61/147)	
Difference *	20 (-57/218)	9 (-43/32)	-11 (-43/47)	
Triglyceride(mg/dL				
Initial	136 (60/786)	148 (43/910)	174 (106/2580)	0.651
Last	150 (68-469)	135 (67/884)	176 (76/770)	
Difference *	10 (-619/301)	15 (-183/132)	-7 (-850/411)	
Systolic BP (mmHg)				
Initial	110 (90/160)	100 (90/130)	110 (90/140)	0.133
Last	110 (90/170)	100 (90/139)	110 (95/140)	
Difference*	0 (-10/60)	0 (0-30)	0 (-5/10)	
Diastolic BP (mmHg)				
Initial	70 (55/110)	75 (60/100)	77 (60/110)	0.488
Last	80 (50/110)	80 (60/100)	80 (65/110)	
Difference *	0 (-30/40)	0 (-5/20)	0 (-8/10)	
Glucose (mg/dL)				
Initial	94 (71/238)	93 (67/110)	87 (67/102)	0.578
Last	93 (9/195)	91 (81/117)	87 (70/97)	
Difference *	-1 (-152/114)	2 (-32/46)	1 (-15/41)	

HDL: High-density lipoprotein; LDL: Low-density lipoprotein ; BP: Blood pressure Group 1: The group of patients who were ART-naïve at admission, but started ART later. Group 2: The group of patients who were using ART both at admission, and at the last evaluation. Group 3: The group of patients who were ART-naïve at admission and did not start ART later. * For each case parameters were calculated considering the difference between the initial and the last measurements; p<0.05 was considered statistically significant ** P values . For intergroup comparisons Mann-Withney U test was used. Only significant values were indicated below.. [#] Between Groups 1, and 2 p=0.017; Between Groups 1, and 3 p<0.001. [&] Between Groups 1, and 3 p=0.003. [$] Between Groups 1, and 2p=0.022 ; Between groups 1, and 3p=0.029.

DISCUSSION

This study showed that the dyslipidemia and cardiovascular risk increased with time in people living with HIV in our country as is the case throughout the world. The most dramatic changes were detected in TG, HDL, and LDL levels.

Bad dietary habits, sedentary lifestyles, and smoking have become a common problem in the Turkish population increasingly causing lipid metabolism disorders and CVD.[7] HIV infection was shown to be a significant factor in the development of CVD due to the inflammatory response induced by persisting antigenic stimulation.[8–10]

Already high baseline TC and LDL, TG, and HDL levels in one third, more than half, and the great majority of the study group, respectively in ART-naïve patients in the study supports this finding.

On the other hand, adverse effects of antiretroviral drugs on lipid metabolism are well established. [8–10] Most frequent and severe dyslipidemia occurs with ART regimens including PI with or without ritonavir [11] Though at a lower incidence, NNRTI, especially efavirenz containing regimens reportedly led to dyslipidemia,[12,13] and even in cases where the PI was switched to efavirenz, dyslipidemia still persisted.[14] Dyslipidemia can also occur with some nucleoside analogue reverse transcriptase inhibitors (NRTI) including stavudine, didanosine and zidovudine, which are currently used as alternative treatment options.[15,16] As expected, the results of this study revealed abnormal levels in all lipid parametres of patients who started to receive ART after enrollment in the study. It was not possible to look for a correlation between the change in lipid parametres and ART regimens used because of the low number of patients.

Although dyslipidemia emerging with the use of antiretroviral drugs is not specific to any one of the blood lipid parameters, especially HDL and TG seem to be more severely affected than others [17] and these adverse effects manifest as a decline in HDL and/or increase in TG levels.[17,18] This study revealed that ART induced a significant increase in TG and LDL levels and decreased HDL levels. However it was surprising to find no change in TG and blood glucose levels, which may be attributed to already higher baseline TG levels in more than half of the patients.

Although potentially favorable results provided with dietary, and life style changes against dyslipidemic side effects of ARTs have been demonstrated,[8] other studies showed no favorable effect of a Mediterranean diet used for one year on blood lipid levels.[19] As a holistic approach in the HIV/AIDS center of our clinic, all patients are provided with information on the importance of life style changes such as healthy diet, regular exercise, decreasing or better quitting alcohol use, and smoking and are asked to follow those recommendations. Besides, patients with cardiovascular risk parameters are referred to the department of internal diseases. However, adoption and measurement of lifestyle changes are difficult, require dedication and do not yield favorable results in the short term. Indeed dyslipidemia rates and CVDR scores increased significantly in our patients despite significant decreases in risky behaviors such as smoking

Globally, cardiovascular risk factors are higher in people living with HIV compared with those who are not HIV positive. [20–23] Risk factors are more common in HIV-infected individuals living in the developed regions of the world, especially in North America, Europe, and Australia, compared with those living in other parts of the world.[20] Besides there is solid evidence that some antiretroviral drugs increase the risk of developing cardiovascular events..[24] The D:A:D study reported that the risk of developing cardiovascular events in patients who received especially PIs, and NNRTIs increased markedly together with a deterioration in the lipid profile.[12] Similarly, the Swiss cohort 2006 study analyzed ART-naïve and ART using HIV positive cases and reported a higher cardiovascular risk and dyslipidemia in ART users.[25] Another study in 2013 with the same cohort re-confirmed a higher risk of cardiovascular events, and hypertension in patients under PI or triple-NRTI therapy.[26] Although the mechanisms of the increase in cardiovascular risk have not been completely understood, metabolic, and dyslipidemic effects of antiretroviral drugs, inflammation caused by HIV, and sustained immune activation have been suggested to trigger this condition.[21,27]

In our study cardiovascular risk scores did not significantly change independent from the use and duration of antiretroviral drugs. This may be related to the small number of cases enrolled and the short follow-up period. It is well established that the Framingham score has a lower predictive value in young individuals.[28] Therefore, the ACC scoring system was used in our cases.

hastalarda yaşam tarzı değişikliği, diyet gibi ölçüm sonuçlarına etki eden girişimlerin standardize edilememesi, hasta sayısının az ve izlem süresinin kısa olması çalışmanın kısıtlayıcı yönleridir. The retrospective design of the study, lack of standardization of interventions such as lyfe-style changes, which influence the outcomes of measurements, the small number of patients, and the short follow-up period are the major limitations of the study.

Although the effect of antiretrovirals on cardiovascular risk is still controversial, the adverse effects of some antiretroviral drugs on the lipid metabolism is very well known. Patients who present for HIV management should be screened in detail for cardiovascular risk factors and in patients with risk factors, the selection of the ART regimen should be made accordingly. In addition, patients should be advised to adopt a healthy lifestyle to reduce their risk and should be followed-up closely to prevent the development of cardiovascular complications

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