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Adherence to Mediterranean diet is favorably associated with metabolic parameters in HIV-positive patients with the highly active antiretroviral therapy–induced metabolic syndrome and lipodystrophy

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Abstract

The objective of the study was to investigate whether closer adherence to a Mediterranean dietary pattern is associated with metabolic aspects of the highly active antiretroviral therapy (HAART)–induced metabolic syndrome (fat redistribution [FR], insulin resistance, dyslipidemia) in HIV-positive patients. This was a cross-sectional study. Two hundred twenty-seven HIV-infected patients were evaluated during a single outpatient visit to the General Clinical Research Center of Beth Israel Deaconess Medical Center. Usual dietary intake and physical activity habits were evaluated; the Mediterranean Diet Score (MedDietScore) was calculated. Dual-energy x-ray absorptiometry, computed tomographic findings, anthropometrics, and data from the study interviews and questionnaires were used for the assessment of body composition using specific criteria. A complete metabolic profile was available for all subjects. In the entire study sample, a weak inverse association was found between insulin resistance, estimated using the homeostasis model assessment, and MedDietScore (standardized $\beta = -0.15$, $P = .03$). Interaction models revealed that this was largely driven by an inverse association in patients with FR (standardized $\beta = -0.13$, $P = .02$). Moreover, MedDietScore was positively correlated with high-density lipoprotein cholesterol (standardized $\beta = 0.15$, $P = .01$) and marginally negatively associated with circulating triglyceride levels (standardized $\beta = -0.16$, $P = .13$) in this group of patients. Adherence to a Mediterranean dietary pattern was favorably related to cardiovascular risk factors in HIV-positive patients with FR. Further clinical studies are needed to confirm our data in different populations and to explore the underlying mechanisms.

1. Introduction

Highly active antiretroviral therapy (HAART)–induced lipodystrophy and metabolic syndrome, characterized by fat redistribution (FR), glucose intolerance, insulin resistance (IR), and dyslipidemia, are well recognized among HIV-infected patients on HAART. Both protease inhibitor (PI)–containing and non–PI-containing regimens, that is, nucleoside or nonnucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs), have each been implicated in the pathogenesis of these metabolic disturbances; and the exact underlying mechanisms are still under investigation. Intakes of macronutrients and specific food groups have been studied in relation to their effect on the development of metabolic abnormalities in this syndrome [1]. Specifically, increased consumption of saturated fat has been associated with hypertriglyceridemia among HIV-infected patients with metabolic abnormalities [2]. In a small study of HIV patients with FR, intakes of dietary protein, animal

Authors' contributions: Dr Mantzoros designed this study. Drs Tsiodras, Chimienti, and Wadhwa collected the data. Ms Poulia and Dr Yannakoulia analyzed the dietary information, performed the statistical analysis, and drafted the paper. Drs Mantzoros and Tsiodras contributed to subsequent revisions of the paper and to the responses to the reviewers' comments. Drs Karchmer and Mantzoros secured funding for this study. All authors critically revised the manuscript and approved the final version submitted.

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protein, and *trans*-fatty acids were positively, whereas intake of soluble fiber was negatively, correlated with dyslipidemia [3]. Moreover, dietary vitamin E intake has been found to be negatively associated with diastolic blood pressure, body fat, and possibly IR [4].

Although it is widely recognized that foods and nutrients are not eaten in isolation, but in the context of whole diets, no prior study has to date examined potential associations between aspects of the HAART-induced metabolic syndrome and dietary patterns. Dietary pattern analysis, with the use of diet scores, has been used as an alternative, holistic approach to examine the relationship between diet and disease prevention or treatment [5-7]. Adherence to a Mediterranean dietary pattern—characterized by abundant intake of plant foods, such as whole grain cereals, fruits, vegetables, legumes, and olive oil; moderate intakes of fish and dairy products; and low intakes of red meat, saturated fats, and sweets—in particular has been associated with decreased all-cause mortality, better health status, and improvement of cardiovascular risk factors [8-15]. The aim of the present study was to investigate whether closer adherence to a Mediterranean dietary pattern might be related to metabolic aspects of the HAART-induced metabolic syndrome in HIV-positive patients.

2. Methods

2.1. Study cohort

We evaluated 227 consecutively enrolled HIV-infected subjects during a single outpatient visit to the General Clinical Research Center of Beth Israel Deaconess Medical Center (BIDMC). The sample of this study constitutes approximately 10% of the entire population admitted at 2 ambulatory care clinics of an urban major academic medical center (≈2000 patients) and is representative of the clinics' population. Inclusion criteria were age of at least 16 years, documented HIV infection, and at least 6 months of cumulative exposure to any antiretroviral regimen. The Institutional Review Board at BIDMC approved the study, and all subjects gave written informed consent before participation.

2.2. Dietary assessment

A validated self-administered food frequency questionnaire (Block 98 Revision of Block/NCI Health Habits and History Questionnaire; Block Dietary Data System, Berkeley, CA) [16,17] was used for the assessment of the usual dietary intake. Estimates of energy, macro- and micronutrient, as well as food group consumption for the year preceding the study were obtained from the analysis of 217 completed questionnaires. Intake of selected food items has been used for the calculation of the Mediterranean Diet Score (MedDietScore), based on the rationale of the Mediterranean dietary pyramid [14]: the score ranges from 0 to 55; higher scores indicate closer adherence to this dietary pattern.

2.3. Exercise assessment

Current exercise was evaluated using 3 multiple-choice questions regarding the type and intensity of exercise (ie, type of exercise: 1, walking on level ground/swimming; 2, running, aerobic classes, or use of cardiovascular machines, treadmill, or stationary bike; and 3, weight training; intensity: 1, slight; 2, moderate; and 3, heavy), exercise frequency (0-7 sessions per week), and session duration (<15, 15-29, 30-59, 60-89, or >90 minutes) [4,18]. Cumulative indexes for either aerobic or total (aerobic and/or resistance) exercise were calculated as number of sessions per week × duration (in minutes) per session × exercise intensity. All subjects completed the exercise questionnaire.

2.4. Body composition, clinical, and biochemical assessment

Body composition was evaluated in all subjects using dual-energy x-ray absorptiometry whole-body scanner (Hologic QDR-2000 version 5.73A; Hologic Inc., Bedford, MA). Anthropometric measurements were also performed, namely, body weight, height, and waist and hip circumferences. Each subject received a complete physical examination with emphasis given to body FR. Single-slice computed tomographic (CT) scan was used to assess the cross-sectional areas of abdominal subcutaneous and abdominal visceral fat (Sensation 4 and Sensation 16; Siemens, Forchheim, Germany). A single-slice CT section was obtained at the level of the L4 interspace using 120 kV (peak) and 100 mA. Calculation of area was done by semiautomatic measurements of pixels, with density within specific attenuation numbers. Fat was defined as having attenuation number of −150 to −15 Hounsfield units; and soft tissues, −15 to +100 Hounsfield units. All recorded data including anthropometric measurements, body mass index (BMI), the widest diameter of the "buffalo hump" (when present), standardized digital photographs of selected body region (face, arms, legs, chest, abdomen side view, gluteus regions), dual-energy x-ray absorptiometry scan results, and the single-slice CT scan of the lumbar spine were presented to a specific external Fat Redistribution Adjudication Committee that used specific strict criteria [19] to support the classification of study subjects as having FR or not. The adjudication committee composed of 3 clinical investigators who were not involved with subject interviews, data collection, or analysis or in the clinical care of the study subjects performed the evaluation [19]. After the committee members assigned a first preliminary classification of each subject (according to medical chart information and data from study questionnaires and interviews), they subsequently proceeded to a second classification according to documented physical examination findings and digital photographs. This was performed according to published criteria [19]. Final classification of each subject was verified according to the

diagnostic test criteria specified in the same publication [19]. All committee members were provided with identical information on which to base their decisions. The final classification of each subject required the unanimous agreement of the committee. Subjects whose classification was not unanimously agreed on (n = 9) were not included in the analysis. This procedure was followed to obtain an objective assessment of the FR subjects. Duration of illness was estimated from the time of diagnosis by the serologic testing of each patient that was recorded in the medical chart.

Blood was drawn from each subject on the morning of the study visit after an overnight fast. Serum samples were immediately frozen at −70°C. Hormonal analyses were performed simultaneously on a subsequent day. The core laboratory of the Clinical Research Center at the BIDMC performed the insulin measurements. Glucose levels were measured by the BIDMC Clinical Laboratory (Roche/Hitachi, Indianapolis, IN). Insulin levels were measured using a commercially available radioimmunoassay (DSL-1600; Diagnostic Systems Laboratories, Webster, TX) with a sensitivity of 1.3 μIU/mL and inter- and intraassay coefficients of variation between 4.7% and 12.2% and between 4.5% and 8.3%, respectively. Insulin resistance was estimated using the homeostasis model assessment (HOMA) with the following formula: IR = (fasting insulin × fasting glucose)/22.5. Fasting lipoprotein profile was measured in the Clinical Chemistry laboratory at Children's Hospital in Boston as previously described [20]. Both CD4 counts and viral load were measured in the BIDMC Clinical Laboratory (via flow cytometry/3-color CD4 reagent [from Becton Dickinson, Franklin Lakes, NJ] for CD4 and ultrasensitive polymerase chain reaction [Amplicor HIV-1 monitor test, version 1.5; Roche-Cobas, Branchburg, NJ] for HIV RNA measurements).

2.5. Statistical analysis

All data were expressed as mean values ± standard deviation. Kruskal-Wallis tests followed by post hoc (Mann-Whitney) analyses were used for comparisons of continuous

Table 1
Characteristics of the patients according to their FR status

	Non-FR group (n = 85)	FR group			Overall *P*
		FA group (n = 42)	Mixed FR group (n = 56)	FW group (n = 35)	
Demographic and lifestyle characteristics					
Age (y)	42 ± 8	45 ± 7	46 ± 9*	45 ± 7	.03
Sex (% female)	10.6	28.6*,‡	17.9‡	2.9	.01
Race (% white)	71.4	54.8¶	91.1§,‖	88.6*	<.001
Exercise (no. of sessions/wk)	4.7 ± 2.6	4.1 ± 2.8	3.7 ± 2.8†	5.3 ± 2.3	.03
Alcoholic drinks (no. of drinks/wk)	2.2 ± 3.7	1.3 ± 2.3	1.7 ± 4.0	3.3 ± 7.4	.21
Current smoker (%)	44.7	31.0	32.1	40.0	.34
Anthropometric, body composition, and metabolic variables					
BMI (kg/m^2)	23.7 ± 2.5	30.9 ± 7.0§,¶	24.5 ± 2.9‖	22.7 ± 2.6‖	<.001
WHR	0.92 ± 0.06	0.98 ± 0.09§	0.99 ± 0.07§,¶	0.94 ± 0.04	<.001
% Body fat	19.8 ± 6.1	29.5 ± 8.4§	19.2 ± 6.5‖,¶	12.7 ± 4.5§	<.001
Systolic blood pressure (mm Hg)	127 ± 19	132 ± 19	130 ± 18	132 ± 18	.51
Diastolic blood pressure (mm Hg)	73 ± 10	78 ± 13	76 ± 9	75 ± 11	.06
Total cholesterol (mg/dL)	204 ± 52	227 ± 64	219 ± 75	212 ± 55	.21
LDL cholesterol (mg/dL)	120 ± 43	129 ± 44	111 ± 48	117 ± 33	.22
HDL cholesterol (mg/dL)	43 ± 14	41 ± 11‡	32 ± 9§,‖	32 ± 10§	<.001
Triglycerides (mg/dL)	193 ± 158	286 ± 232	436 ± 489§	352 ± 240	<.001
Glucose (mg/dL)	85.6 ± 12.7	113.9 ± 60.4‡,§	93.5 ± 33.0†	87.0 ± 14.1	<.001
Insulin (μIU/mL)	10.4 ± 9.6	22.3 ± 21.0‡,§	23.3 ± 23.3*	22.3 ± 26.9	<.001
HOMA-IR	2.4 ± 3.2	6.9 ± 8.1§	6.1 ± 8.9*	4.8 ± 5.2§	<.001
Variables related to HIV infection and antiretroviral therapy					
Duration of illness (mo)	101 ± 55	116 ± 56	126 ± 48*	127 ± 40	.01
CD4 cell count (cells/mm^3)	484 ± 281	568 ± 350	506 ± 315	502 ± 263	.55
Viral load (copies/mL)	6551 ± 20377	10162 ± 24710	15792 ± 48096	33881 ± 104306	.08
Total PI use (mo)	30 ± 28	40 ± 35	44 ± 29	44 ± 33	.04
Total NRTI use (mo)	96 ± 91	104 ± 59	141 ± 72†,§	143 ± 71*	<.001
Total NNRTI use (mo)	10 ± 11	16 ± 19	14 ± 17	12 ± 14	.23

Data are presented as mean values ± standard deviations or as frequencies. LDL indicates low-density lipoprotein.

* Statistically different from non-FR group ($P < .05$).
† Statistically different from FA group ($P < .05$).
‡ Statistically different from FW group ($P < .05$).
§ Statistically different from non-FR group ($P \leq .01$).
‖ Statistically different from FA group ($P \leq .001$).
¶ Statistically different from FW group ($P \leq .001$).

variables among the 4 FR subgroups (non-FR, fat accumulation [FA], fat wasting [FW], and mixed FR). Associations between MedDietScore and several aspects of HAART-induced metabolic syndrome (expressed as continuous variables) were investigated using bivariate analysis and multivariate linear regression. Variables that were not normally distributed were logarithmically transformed. SPSS version 10.0 for Windows software (SPSS, Chicago, IL) was used for data analysis. A P value of .05 was used to test for statistical significance, and all statistical tests were 2 tailed.

3. Results

Of the total sample, 133 (61%) patients had FR: 42, FA (19.3%); 56, mixed FR (25.7%); and 35, FW (16.1%). Significant body composition differences were found among groups, with the FA group exhibiting significantly higher BMI, percentage of body fat, and waist-to-hip ratio (WHR) compared with the non-FR group (Table 1). Fasting insulin levels and the HOMA-IR index were significantly higher in the FA and mixed FR patients compared with the non-FR patients, whereas high-density lipoprotein (HDL) cholesterol levels were lower in the mixed FR and the FW groups compared with the non-FR and FA groups. Subjects in the FR group had higher poultry intake and tended to have higher red meat/red meat products intake compared with the non-FR group (P = .03 and P = .10, respectively), but no other differences were detected with respect to food consumption or adherence to the Mediterranean diet among FR groups (Table 2).

In the entire study sample, we found a trend for a weak association between HOMA-IR index and MedDietScore (Spearman r = −0.12, P = .07). This association became statistically significant when we adjusted for potential confounders, namely, age, sex, energy intake, BMI, WHR, smoking and exercise habits, CD4 cell count, total PI (months of use), total NRTI (months of use), total NNRTI (months of use), and duration of illness (standardized β = −0.15, P = .03). As the addition of FR in the above model tended to weaken the significance of the association (standardized β = −0.11, P = .10), we evaluated the effect of a potential interaction between the MedDietScore and the presence of FR in predicting HOMA-IR levels. The interaction term was a statistically significant predictor of HOMA-IR (P = .03); and therefore, all subsequent multivariate analyses were stratified by FR group. No similar statistically significant interaction was found between the MedDietScore and the presence of FW.

Multivariate regression analysis in the FR group, adjusting for age, sex, total energy intake, BMI, and WHR, revealed an inverse relationship between MedDietScore and HOMA-IR index (standardized β = −0.13, P = .02). The association remained significant after further controlling for smoking, physical activity, CD4 cell count, total PI (months of use), total NRTI (months of use), total NNRTI (months of use), and duration of illness (standardized β = −0.23, P = .02). Moreover, the degree of adherence to the Mediterranean diet was found to be positively related with HDL cholesterol (standardized β = 0.15, P = .01) and to be marginally negatively associated with blood triglyceride levels (standardized β = −0.16, P = .13) after adjustment for all the above-mentioned confounders. No similar associations were detected in the non-FR group, apart from a significant negative correlation between MedDietScore and diastolic blood pressure (standardized β = −0.32, P = .01).

4. Discussion

Adoption of a dietary pattern close to the Mediterranean dietary pattern has been associated with favorable effects on lipoprotein levels, markers of endothelium function, IR, and the metabolic syndrome in non–HIV-infected populations [21]. Furthermore, available evidence indicates that intensive

Table 2
Consumption of main food groups (as servings per week unless otherwise specified) and MedDietScore of the study participants by FR status

	Non-FR group (n = 81)	FR group			
		Total group (n = 128)	FA group (n = 39)	Mixed FR group (n = 55)	FW group (n = 34)
Nonrefined cereals	7.0 ± 9.9	6.3 ± 7.6	5.8 ± 6.4	5.8 ± 6.9	7.6 ± 9.9
Potatoes	4.1 ± 4.0	4.8 ± 7.8	5.3 ± 5.8	4.5 ± 4.7	4.8 ± 3.8
Fruits	19.1 ± 15.8	17.8 ± 14.6	22.3 ± 16.5	15.2 ± 13.0	17.0 ± 13.8
Vegetables	9.0 ± 8.1	10.6 ± 9.4	10.2 ± 10.1	10.4 ± 9.5	11.3 ± 8.6
Legumes	2.1 ± 2.4	2.0 ± 2.0	1.6 ± 1.4	1.9 ± 1.5	2.6 ± 2.9
Fish	4.4 ± 5.8	5.7 ± 5.5	7.0 ± 11.2	5.4 ± 10.0	4.6 ± 4.6
Red meat/red meat products	5.9 ± 5.5	8.0 ± 10.7*	9.6 ± 12.8	6.0 ± 3.7	9.4 ± 14.7
Poultry	3.9 ± 3.6	5.2 ± 5.3†	6.1 ± 6.2	4.6 ± 4.4	5.2 ± 5.6
Full-fat dairy	7.8 ± 8.2	7.9 ± 81	7.1 ± 7.7	7.1 ± 6.9	10.0 ± 9.9
Alcoholic beverages (mL ethanol/d)	12.1 ± 19.4	11.4 ± 24.1	10.4 ± 19.3	11.0 ± 27.0	13.4 ± 24.5
MedDietScore (0-55) (range)	26.3 ± 5.1 (15-37)	25.8 ± 4.9 (13-39)	25.7 ± 4.3 (18-35)	25.7 ± 5.2 (13-36)	26.0 ± 5.2 (19–39)

Data are presented as mean values ± standard deviation.

* Comparisons vs non-FR group, P = .10.

† Comparisons vs non-FR group, P = .03.

lifestyle interventions are safer and better than or of comparable effectiveness to drugs in reducing the prevalence of the metabolic syndrome and/or preventing diabetes [22]. In HIV-infected patients, the role of lifestyle changes is increasingly recognized for the management of the metabolic abnormalities. Among the potential targets for dietary modification are polyunsaturated fatty acid, dietary fiber, alcohol, and cholesterol intake, that is, dietary factors that could affect IR and blood lipid abnormalities [23]. Current lifestyle recommendations for the treatment of dyslipidemia in HIV-infected adults do not differ from recommendations for the rest of the population at high cardiovascular risk [24]. The potential effect of the adherence to a Mediterranean-type dietary pattern on the parameters of the metabolic syndrome has not been previously examined in HIV-positive patients with HAART-induced metabolic syndrome. According to our study, adherence to this dietary pattern was found to be favorably associated with important cardiovascular risk factors, namely, HOMA-IR and HDL cholesterol, in patients with HAART-induced metabolic changes and FR after controlling for factors considered to be significant in the pathogenesis of the syndrome, such as age and BMI. Thus, dietary interventions enhancing adherence to a Mediterranean dietary pattern may be proven to be an effective strategy for the reduction of dyslipidemia and IR in HIV-infected patients with FR.

Interestingly, associations between diet and metabolic factors were observed mainly in the FR group. Results from the Fat Redistribution and Metabolic Change in HIV Infection study have suggested that less leg subcutaneous adipose tissue and more visceral adipose tissue are important risk factors for adverse metabolic profile in HIV men and women [25,26]. In our study, we pooled FA, mixed FR, and FW under the comprehensive "FR" variable; but we also evaluated "FW" separately. No interaction between IR and the degree of adherence to the Mediterranean diet was detected when lipoatrophy or fat wasting was considered separately. Because of the relatively small number of subjects in each group, further studies in this direction should be performed with larger numbers of patients. The fact that no major effect of diet was found in HIV patients without FR could be potentially explained by several mechanisms. These patients have a metabolic profile closer to the normal population; thus, the effects would not be expected to be strong. They may also differ from the rest of the patients regarding other factors affecting the metabolic syndrome (eg, they were younger, had shorter duration of illness, had used less NRTIs). It might also be possible that patients who have a predisposition to develop the metabolic syndrome may also be predisposed to have FR changes.

The inclusion of the MedDietScore in the prediction model of HOMA-IR levels changed the percentage variability only by 1% compared with the inclusion of FR only (data not shown). This is similar to the variance reported in recent population-based diet studies [13]. On the other hand, prudent dietary patterns may affect circulating levels of adipocyte secreted hormones that are of major importance in mediating some of the changes observed [27,28]. In addition, dietary patterns may also affect the development of lipohypertrophy and/or regional body composition changes; and adipose tissue changes may be equally or more important predictors of adipocytokines and/or metabolic abnormalities in these patients, as they precede or coincide with the metabolic changes observed. Limitations of this work include its cross-sectional, observational design, which does not allow us to establish firm cause-effect relationships and/or to elucidate underlying mechanisms. Our study may only raise hypotheses that could be further investigated by future prospective cohort studies and randomized clinical trials. Therefore, one cannot rule out the possibility that the effects presented herein could be observed in the metabolic syndrome in general and that they are not uniquely related to HIV infection or its treatment. Furthermore, interventions based on diet should be considered in the context of other therapeutic approaches for the metabolic syndrome, such as lipid-lowering agents, exercise, and drug switching.

Another limitation of the study is that the components of the index (MedDietScore) are equally weighted and similarly scored from 1 to 5. This may affect its accuracy, as not all foods or food groups might influence the investigated health outcomes in the same way [14]. Although a misclassification would be possible, it would have been expected to suppress effect estimates. In addition, misreporting of food items consumed could have influenced the calculation of the diet score and could thus have biased the results toward the null; but neither of the above factors could have strengthened and/or made significant the associations reported herein. Moreover, patients with FR may have been more accurate in reporting their dietary habits because of higher motivation given the metabolic problems they were already facing. It is possible that this could have potentially resulted in a bias toward demonstrating stronger associations among this group. Although we examined separately the effects of the 3 major classes of antiretroviral medications, some of the individual medications may differ regarding their metabolic effects. Much larger studies will be necessary to further elucidate the role of individual medications and their interaction with dietary intake.

Finally, in the present study, IR was assessed using HOMA and not the euglycemic-hyperinsulinemic clamp, that is, the criterion standard method. The HOMA, however, is considered appropriate for cross-sectional epidemiologic studies because it is strongly related to clamp-measured IR in both nondiabetic and diabetic subjects [29].

In conclusion, this is the first study revealing that adherence to the Mediterranean diet is favorably related to cardiovascular risk factors in a sample of HIV-positive patients with the HAART-induced metabolic syndrome studied cross-sectionally. The patients who benefited the most by higher adherence to this dietary pattern were found to be those with FR. As the Mediterranean diet has proven to be a metabolically favorable dietary pattern in the long term,

its adoption may play a role in the prevention and treatment of the HAART-induced metabolic syndrome. Further clinical trials to confirm these findings and to investigate the mechanisms underlying its protective effects are needed.

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