Increased Prevalence of Diabetes Mellitus in a Non-Obese Adult Population: HIV-Infected Ethiopians

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ABSTRACT: **Background:** Diabetes mellitus (DM) is a metabolic sequel in people infected with HIV, especially following the advent of HAART. This may be a particular concern in immigrants due to lifestyle changes.

Objectives: To characterize the prevalence of DM in HIV-infected Ethiopians in Israel, and to define the risk factors.

Methods: We retrospectively screened the records of 173 HIV-infected Ethiopians and 69 HIV-infected non-Ethiopian HIV patients currently registered at the HIV Clinic of Meir Medical Center. Data were also retrieved from 1323 non-HIV Ethiopians treated in the hospital between 2007 and 2012. The presence of DM was determined by family physician diagnosis as recorded in the hospital database or by the presence of one or more of the following: fasting glucose › 127 mg/dl, hA1C › 6.5% (› 48 mmol/mol), or blood glucose › 200 mg/dl. Population data and risk factors for DM were analyzed by univariate and multivariate analyses.

Results: Among HIV-infected Ethiopian subjects, the prevalence of DM was 31% (54/173) compared to 4% (3/69) in HIV-infected non-Ethiopians and 8% (102/1323) in non-HIV-infected Ethiopians (P ‹ 0.0001). The relatively increased prevalence of DM was age independent, but most noticeable in those under the median age (‹ 42 years). Body mass index (BMI) was a predictor for DM (OR 1.263, CI 1.104–1.444, P = 0.001), although its values did not vary between the two ethnic groups.

Conclusions: HIV-infected Ethiopians are more likely to develop DM at low BMI values compared to non-Ethiopians. This observation questions the relevance of accepted BMI values in this population and suggests that preventive measures against DM be routinely taken in these subjects.

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KEY WORDS: human immunodeficiency virus (HIV), AIDS, diabetes mellitus (DM), body mass index (BMI), highly active antiretroviral treatment (HAART)

During the mid-1980s and early 1990s most of the Jews in Ethiopia immigrated to Israel, creating a community of 120,000 individuals. These waves of immigration have resulted in dramatic lifestyle changes, including considerable dietary alterations that have led to the increased occurrence of diabetes mellitus (DM) [1].

Few studies have evaluated the magnitude of diabetes in Ethiopia. In fact, there is no single national level study on the prevalence of DM in that country [2]. DM prevalence was strikingly low among Jewish Ethiopian immigrants shortly following their arrival to Israel, reaching 0–0.4% [3,4]. These low values were attributed to increased mortality among the elderly and chronically ill individuals along the journey. DM prevalence rose to 8.9% after 4 years in Israel [5] and was estimated to be 9.6% at 7 years post-arrival (unpublished data). Current data in this regard are not readily available. In comparison, the prevalence of DM in the general Israeli population is reported to be 6.5% [http://www.oecd.org/].

A subpopulation of Ethiopian immigrants whose predisposition to develop DM is of special interest are those infected with human immunodeficiency virus (HIV). The advent of highly active antiretroviral therapy (HAART) has considerably improved the prognosis of these HIV-infected individuals but also gave rise to metabolic abnormalities that have become a major concern [6]. A twofold increase in the prevalence of DM in HIV-infected patients compared with healthy subjects was reported in Italy [7]. The investigators suggested that this was attributed to both HIV-related and conventional factors such as age, body mass index (BMI) as well as ethnic background. It is therefore well recognized that in the present era of effective HIV control the accompanying metabolic sequelae are critical for determining patient prognosis and quality of life. This consideration underscores the importance of defining unique populations whose susceptibility to metabolic complications is increased.

Along this line, the present study attempted to assess the prevalence of DM in Ethiopians who are HIV infected, and to identify underlying risk factors.

PATIENTS AND METHODS

The study included all 242 HIV-infected subjects registered at the HIV Clinic of Meir Medical Center, Kfar Saba, Israel. No individual was excluded. In order to assess the prevalence of

DM in non-HIV-infected Ethiopians, we retrieved the hospital records of all 1323 patients whose country of birth was Ethiopia and who were treated at the Meir Medical Center due to any cause during the years 2007–2012.

DEMOGRAPHIC AND CLINICAL DATA

Demographic and clinical data were obtained by retrospective screening of patient records in the hospital central computer system and/or HIV clinic files. For each subject, the highest or lowest continuous parameter values were obtained, each when appropriate (e.g., nadir CD4 count, maximal viral load, glucose, hemoglobin A1C). Access to patient data was approved by the Institutional Review Board of the Meir Medical Center.

DIAGNOSIS OF DM

DM was determined by one of the following:

- family-physician diagnosis as reported and recorded in the hospital files
- no previous diagnosis of DM but the presence of at least one of the criteria in the hospital database: fasting glucose > 127 mg/dl, hemoglobin A1C > 6.5% (48 mmol/mol), blood glucose > 200 mg/dl.

To evaluate the outcome of this classification we compared glucose and hemoglobin A1C values between those designated, according to this method, as non-DM to those with DM. These data show that all the parameters were increased in the DM group [Table 1].

STATISTICAL ANALYSIS

Data are presented as numbers and percentages for nominal variables and as mean ± standard deviation for continuous parameters. Comparison between study groups was performed by the chi-square test or Fisher's exact test for categorical data (each when appropriate) and the *t*-test for continuous data. Logistic regression analysis was done on data obtained from HIV-infected Ethiopians with DM as the dependent variable to define predictors for DM among these subjects. All statistical analyses were performed with SPSS 19 (IBM) software and the Prism5 software (GraphPad). A *P* value of less than 0.05 was considered statistically significant.

RESULTS

POPULATION CHARACTERISTICS

Subjects were divided into two ethnic groups: Ethiopian (n=173) and non-Ethiopian (n=69) [Table 2]. The majority of Ethiopians were females (62%), while in the other group most were males (29% females). The Ethiopian mean age was higher than that of other individuals by 5 years (47 ± 15 vs. 42 ± 12, $P = 0.005$). Body mass index (BMI), however, did not differ significantly between the two ethnic groups.

Table 1. DM parameters in HIV-infected subjects with and without DM

	Non-DM (n=185)	DM (n=57)	*P* value
Fasting glucose, mg/dl, mean (SD)	86 (8)	141 (59)	< 0.0001
Glucose > 200 mg/dl, % subjects	0	16	
Hemoglobin A1C, mean (SD) % mmol/mol	 ND ND	 7 (1.9) 53 (9)	

ND = not determined

Table 2. Demographic features of HIV-infected study population

	Ethiopian (n=173)	Israeli (n=69)	*P* value
Female, %	62	29	< 0.0001
Age, year, mean (SD), range	47 (15), 24–91	42 (12), 20–75	0.005
BMI, kg/m², % < 20 20–24.9 25–29.9 30	 11 47 33 9	 5 51 27 17	0.322
HIV duration, year, mean (SD)	9 (5)	6 (5)	0.0001
CD4 nadir, cells/mm³ (SD)	237 (153)	296 (214)	0.02
Viral load < 20 copies/ml, %	19	24	0.366
Medication, % Protease inhibitors Integrase inhibitors NRTI NNRTI	 36 30 98 38	 15 39 98 38	 0.0013 0.166 0.697 0.996

NRTI = nucleoside analog reverse transcriptase inhibitors, NNRTI = non-nucleoside reverse transcriptase inhibitors

The number of years since HIV diagnosis was higher in the Ethiopian group (9 ± 5 vs. 6 ± 5 years, $P < 0.0001$), along with slightly lower CD4 counts (237 ± 153 vs. 296 ± 214 per mm³, $P = 0.02$), but the levels of viral load were comparable [Table 2]. It was also noticed that drugs of the protease inhibitor (PI) class were more commonly administered to Ethiopians, (36% vs. 15%, $P = 0.0013$), while no difference was observed with other drugs.

PREVALENCE OF DM

The prevalence of DM was 31% (54/173) among the HIV-infected Ethiopian subjects [Table 3]. This value was higher than among Israeli subjects whose prevalence was 4% (3/69, $P < 0.0001$) and also higher than the 8% observed in non-HIV-infected Ethiopians (102/1323, $P < 0.0001$). The fact that the HIV-infected Ethiopians were older than the non-Ethiopians [Table 2] raised the possibility that the increased DM prevalence is age dependent. This possibility was ruled out by the fact that differences in DM rates could be demonstrated both below and above the median age of 42 years [Table 3]. Intriguingly, in HIV-infected Ethiopians younger than 42 years the increase in DM was greatest (> 15-fold) compared

Table 3. DM prevalence by age and gender

				P value	
	Ethiopian HIV patients	Israeli HIV patients	Ethiopian non-HIV patients	Eth.HIV/ Isr.HIV	Eth.HIV/ Eth. non-HIV
All ages DM	(n=173) 31%	(n=69) 4%	(n=1323) 8%	< 0.0001	< 0.0001
< 42 years DM	(n=76) 17%	(n=41) 2%	(n=867) 1%	0.02	< 0.0001
42 years DM	(n=97) 43%	(n=28) 7%	(n=456) 20%	< 0.0001	< 0.0001
Female DM	(n=107) 31%	(n=20) 5%	(n=821) 7%		
Male DM	(n=66) 32%	(n=49) 4%	(n=502) 10%		

Table 4. DM-predicting factors in HIV-infected Ethiopians

	OR	95% CI	*P* value
Age	1.008	0.976–1.041	0.628
Time from HIV diagnosis	1.025	0.935–1.123	0.601
Current use of PI	2.645	0.940–7.445	0.065
BMI	1.263	1.104–1.444	0.001

DM is the dependent variable

PI = protease inhibitors, OR = odds ratio, CI = confidence interval

to their HIV-negative peers [Table 3]. The difference was still apparent but only twofold greater in Ethiopians whose age was more advanced, i.e., beyond the median. Also, the relatively high proportion of females among HIV patients [Table 2] raised the question of a gender bias on DM. However, there was no significant difference in DM prevalence between females and males in each of the study groups [Table 3].

DM RISK FACTORS

Univariate results showed several features that may potentially account for the relatively higher proportion of subjects with DM among HIV-infected Ethiopians [Table 2]. After adjusting for age, logistic regression analysis of data from HIV-infected Ethiopians [Table 4] showed that BMI values can predict DM in this population: odds ratio (OR) 1.263, 95% confidence interval (95%CI) 1.104–1.444, $P = 0.001$. According to this analysis, age and time since HIV diagnosis did not achieve significance, while the current use of protease inhibitors was statistically borderline (OR 2.645, 95%CI 0.940–7.445, $P = 0.065$).

PI are a class of drugs known to cause glucose intolerance and DM [9,10]. Even though its current use does not predict DM [Table 4], the population data retrieved in this study showed that PI use is more prevalent among Ethiopians [Table 2]. Although data regarding duration of medication use were incomplete in our database, we did notice that among Ethiopians receiving PI, HIV infection of longer duration was associated with DM (not shown).

HIV-related factors have also been shown to enhance the predisposition to DM [7]. We could not detect differences in viral load between Ethiopian and other Israeli HIV patients although there seemed to be a mild variation in nadir CD4 counts [Table 2]. However, further analysis failed to show a correlation between CD4 counts and DM (not shown), rendering this finding an unlikely precipitating factor in this study.

DISCUSSION

There is a remarkably small number of reports referring to non-communicable diseases in Ethiopian-born communities worldwide. We present here data pertaining to the high prevalence of DM in Ethiopian HIV patients, and associated population characteristics.

Our analysis revealed an increase of DM among Ethiopian HIV patients, as compared with other Israeli HIV patients, affecting almost one-third of the subjects in this group (31% vs. 4%) [Table 3]. This observation was further supported by a comparison to non-HIV-infected Ethiopians, whose prevalence of DM was also low (31% vs. 8%) [Table 3] and by the demonstration that age and gender differences do not account for the discrepancy in DM prevalence. Furthermore, the difference in DM between the two ethnic groups of HIV-infected subjects was most pronounced in those younger than the median age of 42 years.

While searching for factors that may explain the exaggerated prevalence of DM we were surprised to find that the BMI levels of Ethiopian HIV-infected individuals were not higher than those of Israeli subjects [Table 2]. This, despite the fact that BMI has repeatedly been described as a powerful risk factor for DM [8,11]. Nevertheless, logistic regression analysis strongly argues that in this population obesity is indeed a risk factor [Table 4]. It is interesting to note, according to a previous report, that a low mean BMI of 20 ± 1 was noted among Ethiopian subjects 20–40 years old upon their arrival to Israel [12]. This was accompanied by glucose intolerance and insulin resistance [13]. We hypothesize that these findings may be due to restricted caloric intake early in life, accounting for low body mass and a pancreas that would be relatively insufficient following introduction of a non-restricted diet. Taken together, these findings raise the question of whether the definition of normal BMI levels in Ethiopian patients permanently residing in developed countries may need reevaluation. We suggest that values usually considered within the normal range may actually represent overweight in this specific population. Therefore, it is unclear whether weight loss would have the same impact on prevention of DM when target BMI levels are similar to those defined for the general population [11].

In terms of HIV-related risk factors, we could not find evidence for differences in HIV disease severity between Ethiopians and non-Ethiopians as judged by viral load or nadir CD4 counts [Table 2]. Metabolic abnormalities in HIV patients may, however, involve adverse effects of HAART. Both nucleoside analog reverse transcriptase inhibitors (NRTI) and PIs have been implicated in the development of DM through several mechanisms including mitochondrial dysfunction [14] and inhibition of the Glut4 transporter [15,16], respectively. Here we show that PIs are preferentially administered to Ethiopians as compared to other patients. This may be attributed to HIV diagnosis in earlier years, when PIs were the mainstay of treatment and therefore more commonly administered. It is interesting to note that the diagnosis of HIV in Ethiopians was mostly made in the setting of screening on arrival to Israel, thus allowing early diagnosis which is reflected by longer disease duration [Table 2]. In contrast, non-Ethiopian Israeli patients may be self-referred for testing or are advised to do so by the treating physician due to clinical suspicion, which could delay diagnosis of HIV. Although current PI use does not appear to be strongly associated with DM [Table 4], we observed that the combination of PI and longer HIV duration characterizes Ethiopians with DM. This suggests that PI-years may be a relevant risk factor. However, this conclusion warrants formal proof by direct data, which were incomplete in our database. Intriguingly, PI-associated DM has been shown to resemble type 2 DM with insulin resistance which is accompanied by a high BMI [17]. The fact that the HIV-infected Ethiopians included in this study did not present increased BMI values, relative to Israelis, may also imply enhanced susceptibility to this PI-related adverse effect.

The retrospective methodology of this study carries several limitations. Although self-report of DM is rare in the Ethiopian community, the use of family physician-based diagnosis as a criterion may potentially lead to inaccurate classification of patients. However, comparison of DM-related parameters [Table 1] confirmed that the criteria used in this study enabled us to convincingly differentiate between non-DM and DM groups. Furthermore, we used hemoglobin A1C as a diagnostic criterion. However, its reliability in HIV-infected people has been questioned [18,19], especially in connection with NRTI therapy or increased red blood cell turnover, preventing full glycation.

CONCLUSIONS

This report highlights HIV-infected Ethiopians as a subpopulation at high risk for DM. The unique characteristics of this observation are that Ethiopians are a non-obese population and that a relative increase in DM is already evident in young subjects. We believe that identification of such high risk groups is imperative for optimal patient management. Given the critical impact of metabolic abnormalities on HIV patients treated with HAART, we propose that populations at extremely high risk should be monitored rigorously for early signs of glucose intolerance and DM. Upon diagnosis of HIV infection such patients warrant routine counseling regarding preventive measures and possibly early initiation of treatment (such as metformin).

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"A man should look for what is, and not for what he thinks should be"

Albert Einstein