Dietary Intake in HIV-Infected Men with Lipodystrophy: Relationships with Body Composition, Visceral Fat, Lipid, Glucose and Adipokine Metabolism

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Abstract: Highly active antiretroviral therapy (HAART) for HIV-infection is associated with lipodystrophy, insulin resistance, increased prevalence of disturbances in glucose tolerance and diabetes, hyperlipidemia and increased cardiovascular risk. Whether dietary intake influences total body fat, visceral fat, insulin resistance, glucose metabolism, lipid metabolism and circulating inflammatory markers in HIV-infected subjects with lipodystrophy is unclear and the focus of this report. We examined the dietary intake of 106 male HIV-infected HAART-recipients with lipodystrophy, enrolled in a study of the effects of rosiglitazone. All subjects had normal glucose tolerance. Dietary intakes were determined at study entry using Food Frequency Questionnaires and examined cross-sectionally against body composition by dual-energy Xray absorptiometry, visceral obesity by computed tomography, fasting glucose, insulin, lipids, adiponectin, leptin, insulin resistance (by HOMA). Energy underreporters were identified and excluded. After exclusion of underreporters (n = 22) we found no relationships between diet composition (% dietary fat, %carbohydrate) and BMI, %body fat and visceral adiposity ($p>0.3$). Only modest relationships were found between BMI and fat subtypes: polyunsaturated fats (g/day) ($r = 0.14$, $p = 0.007$), monounsaturated fat (g/d) ($r = 0.06$, $p = 0.001$), saturated fat (g/d) ($r = 0.02$, $p<0.0001$). Only saturated fat related to % total body fat (g/d: $r = 0.08$, $p<0.0001$, %energy intake: $r = 0.16$, $p<0.0001$). No nutrient related to visceral adiposity by CT. Dietary fat intake (expressed as a % of energy intake) was not related to total cholesterol, HDL cholesterol, triglycerides, fasting insulin, glucose, leptin, adiponectin or HOMA-IR ($p>0.4$). Fat subtype did not relate to fasting insulin, insulin resistance, total cholesterol, HDL, triglycerides, glucose, adiponectin. In conclusion, there are weak relationships between saturated fat intake and adiposity in HIV-infected subjects with lipodystrophy, using gold standard measures of body fat. There were no relationships between nutrient intake and visceral adiposity, any measure of glucose metabolism, insulin resistance or adipokines. Only interventional, prospective studies will determine whether any nutritional strategy can assist in ameliorating the metabolic complications associated with HIV lipodystrophy.

Keywords: HIV, adipokine, obesity, adipose tissue, insulin resistance, diet.

INTRODUCTION

The long-term outcomes for human immunodeficiency virus-1 (HIV) infected individuals treated with highly active anti-retroviral therapy (HAART) have improved significantly, with fewer infective and malignant complications. Metabolic complications of treated HIV-infection include disturbances in body fat distribution (lipodystrophy), insulin resistance, hyperlipidemia and impaired glucose metabolism [1-4].

The metabolic complications of HAART threaten to shorten life expectancy benefits accrued through improved immune function, by increasing the risk of premature and accelerated cardiovascular disease (CVD) in HIV-infected patients [5-11]. Treated-HIV is associated with high rates of lipid disturbances, greater than that found in familial heart disease [6]. Longitudinal studies suggest increased rates of myocardial infarction with exposure to both protease inhibitors and nucleoside reverse transcriptase inhibitors [7, 10]. Increased risk of cerebrovascular events [9] and type 2 diabetes mellitus are also shown [12-15].

Dietary change is recommended first line in those with, or at risk of CVD and type 2 diabetes. The optimal diet specific to the needs of treated-HIV patients with metabolic disturbances is not known. In this paper, we report the dietary intake of HIV-infected HAART-recipients with lipodystrophy and compare with recommended intakes. The relationships between macronutrient intake, cardiometabolic risk factors, insulin resistance, adipokines and total body and visceral fat are examined, to determine contemporaneous associations in this group at high risk CVD and type 2 diabetes.

METHODS

Subjects were participants in a prospective 48-week study of the effects of rosiglitazone [16]. Participants were

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1570-162X/09 $55.00+.00

recruited at 17 HIV primary care or hospital outpatient sites in Australia and criteria for entry were documented HIV-1 infection, age >17 years and limb fat less than 20% of limb tissue or limb fat percent at least 10% less than truncal fat percent by dual-energy x-ray absorptiometry (DEXA). Exclusion criteria included HIV wasting syndrome, any serious medical condition such as active AIDS, pancreatitis or hepatitis within the prior 6 months. Subjects were excluded if receiving insulin, oral diabetic agents, anabolic steroids (except testosterone replacement), glucocorticosteroids at greater than replacement dose (prednisolone 7·5mg per day or equivalent), growth hormone, agents stimulating appetite or weight gain, immune modulators, hydroxyurea and cimetidine. Laboratory exclusion criteria included fasting glucose >7·0 mmol/l and fasting triglycerides >15·0 mmol/l. All subjects provided written, informed consent after approval by each site's Research Ethics Committee.

All subjects had lipodystrophy, which was defined subjectively by lipoatrophy and/or fat accumulation in the face, dorso-cervical spine, arms, breasts, abdomen, buttocks, or legs using a standardized physical examination [17, 18].

Fasting metabolic parameters included glucose and insulin (including 2 hours after 75g oral glucose loading), C-peptide, estimated insulin resistance (by homeostasis model assessment [HOMA]), total, direct low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, triglycerides, and lactate [17, 18]. Plasma adiponectin and leptin were measured by radio-immune assays (Linco Research, St. Charles, USA). Insulin resistance was calculated using the homeostasis model assessment (HOMA-IR) where HOMA-IR = fasting insulin x fasting glucose/22.5 [19].

Body composition was quantified by DEXA and computed tomography. DEXA measured total and regional body fat and lean tissue (Lunar DPXL, Madison, WI, USA). Computed tomography measured the mean fat areas at the L2, L3 and L4 vertebral levels (intra-abdominal and subcutaneous), as previously described [16]. Quality assurance programs were instituted for DEXA and computed tomography and all scans were analysed centrally.

Energy intake and dietary composition were assessed in all subjects using a semi-quantitative food frequency questionnaire (FFQ), self-administered, after instruction from a single nutritionist. The questionnaire specified standard serving sizes and frequency of consumption from which intake of each food was calculated. Serving sizes in the questionnaire were specified (slices, teaspoons, pints) or defined as portions. The FFQ were analyzed using the Compositional Analyses for food Frequency Estimates (CAFE) program (version 17_1).

Dietary assessment data were further validated in two ways, using methodologies we have previously utilised in other nutritional studies [20, 21]. First we confirmed the necessary relationships between energy and diet composition [22]. Strong, significant relationships were found between energy intake and fat intake ($r = 0.91$, $P<0.0001$) and carbohydrate intake ($r = 0.29$, $p<0.0001$). Second, by identifying and excluding energy underreporters from subsequent analyses, as we have recommended in our prior published studies [20, 21]. Basal energy expenditure (BEE) was estimated by use of a mathematical model (Garby formula: J = 116.76 x fat free mass + 26.88 x body fat mass), using the direct accurate measures of body composition from DEXA scanning. Underreporters were identified as those whose BEE exceeded reported energy intake. Finally macronutrients are also expressed as a ratio of energy intake, a measure less sensitive to nutrient-specific underreporting than intake in grams [23].

After exclusion of energy underreporters, the relationships between dietary intake and metabolic parameters, body composition and visceral adiposity were examined using simple regressions and Spearman correlations for non-parametric measures. Comparisons were made by t-tests. All data presented are means ± standard deviation. Analyses were performed using Stata Statistical Software 8.2 (Statacorp, College Station, TX, USA).

RESULTS

108 HIV-positive subjects with lipodystrophy (106 males) were evaluated; their HIV data have been reported elsewhere (16). Age, BMI, waist, hip and blood pressure are reported in Table **1**, for both adequate- and under-reporters. There were 22 energy underreporters (20% of the cohort). Compared to adequate-reporters, underreporters had significantly greater BMI, waist, total fat mass, trunk fat, limb fat and lean tissue mass (Table **1**). Underreporters were similar to adequate energy reporters in blood pressure, lipids, fasting insulin, glucose, leptin and adiponectin (Table **1**). Dietary intakes are presented in Table **2** and, as would be expected, underreporters had lower intakes of energy and all macronutrients expressed as g/day, but not as a percentage of energy intake. Underreporters were excluded from further analyses. Dietary fat intake was approximately 30% of ingested energy, similar to that recommended by nutrition guidelines (eg National Health and Medical Research Council of Australia) (Table **2**). Saturated fat was 11% of energy intake, slightly above the recommended 10%. Fibre intake was 31 g/day (Table **2**).

Nutrient Intake and Body Fat

There were no relationships between % dietary fat intake and BMI, total body fat (%) by DEXA and visceral fat by CT ($p>0.3$, data not shown). Similarly there were no relationships found between % carbohydrate and BMI, total body fat (%) by DEXA and visceral fat by CT ($p>0.2$, data not shown). In the dietary fat subtypes, a significant positive relationship was found between polyunsaturated fats (g/day) and BMI ($r = 0.14$, $p = 0.007$), however no relationships were found between and polyunsaturated fats (g/d) and any direct measure of adiposity, such as %total body fat by DEXA and visceral fat by CT ($p>0.38$, data not shown). No relationship was found between polyunsaturated fat intake and BMI when intake was expressed as % of energy intake ($p = 0.1$). Similarly, a modest positive relationship was found between monounsaturated fat (g/d) and BMI ($r = 0.06$, $p = 0.001$), but not with any direct measure of adiposity ($p>0.7$); the relationship with BMI persisted when monounsaturated fats were expressed as % of energy intake ($r = 0.17$, $p = 0.05$). However, there was no relationship with gold standard

Table 1. Demographic Details of Adequate-Energy Versus Under-Reporters in 108 HIV Positive Subjects with Lipodystrophy

	Under-Reporters N = 22 (20%)	Adequate-Reporters N = 86 (80%)	p-Value
Age (yrs)	45 (6)	45 (8)	0.73
BMI (kg/m2)	24 (3)	23 (2)	0.008
Waist (cm)	90 (8)	86 (7)	0.02
Hip (cm)	91 (9)	89 (4)	0.10
Diastolic BP (mmHg)	77 (9)	77 (10)	0.97
Systolic BP (mmHg)	120 (12)	121 (12)	0.67
Basal energy expenditure (MJ)	7.5 (0.9)	6.9 (0.8)	0.67
Body Composition (DEXA)			
Total fat mass (kg)	14 (6)	10 (4)	0.003
Total fat mass %	18 (5)	15 (5)	0.03
Trunk fat mass %	23 (6)	20 (7)	0.04
Limb fat mass %	12 (5)	9 (4)	0.04
Lean body mass (kg)	61 (7)	57 (6)	0.006
CT- Abdominal Fat			
IAF (cm^2)	147 (68)	120 (67)	0.11
Blood Parameters			
Total cholesterol (mmol/L)	6 (2)	6 (2)	0.66
HDL-cholesterol (mmol/L)	1.1 (0.3)	1.2 (0.4)	0.21
LDL-cholesterol (mmol/L)	3.1 (0.8)	3.4 (0.9)	0.16
Triglycerides (mmol/L)	4.05 (3)	3.56 (3)	0.49
Insulin (mU/L)	11 (9)	11 (10)	0.98
Glucose (mmol/L)	5.2 (0.5)	5.2 (0.5)	0.98
Leptin (mg/L)	3.4 (2)	2.9 (1)	0.15
Adiponectin (ug/mL)	4.2 (4)	4.6 (3)	0.67

Data are expressed as means ± (SD). BMI: body mass index, DEXA: dual-energy Xray absorptiometry, CT: computed tomography, IAF: intra-abdominal fat, HDL: high density lipoprotein, LDL: low density lipoprotein.

measures of total and visceral adiposity ($p>0.22$). Significant relationships were found between saturated fat (g/d) and BMI ($r = 0.02$, $p<0.0001$) and %total body fat ($r = 0.08$, $p<0.0001$), but not visceral fat ($p = 0.6$). When saturated fat was expressed as % energy intake, relationships were found between BMI ($r = 0.07$, $p<0.0001$) and %total body fat ($r = 0.16$, $p<0.0001$) but not visceral fat ($p = 0.2$). Percent saturated fat intake explained 3% of the cohort variance in total body adiposity. Interestingly, there was an inverse relationship between %lean body mass and saturated fat (g/d) ($r = -0.16$, $p<0.0001$), explaining 3% of the cohort variance in lean mass.

Nutrient Intake and Cardiometabolic Variables

Dietary fat intake (expressed as a % of energy intake) was not related to total cholesterol, HDL cholesterol, triglycerides, fasting insulin, glucose, leptin, adiponectin or HOMA-IR ($p>0.4$). Saturated fat, as a percentage of energy intake, was not related to total cholesterol, HDL cholesterol, triglycerides, fasting insulin, glucose, adiponectin, leptin or HOMA-IR ($p>0.2$). Importantly, there was no relationship to total cholesterol ($p = 0.35$) or triglycerides ($p = 0.65$). No relationships were found between % monounsaturated fat intake and total cholesterol, HDL cholesterol, triglycerides, fasting insulin, glucose, HOMA-IR, adiponectin or leptin ($p>0.2$). No relationships were found between % polyunsaturated fat intake and total cholesterol, HDL cholesterol, triglycerides, fasting insulin, glucose, leptin, adiponectin or HOMA-IR ($p>0.4$). Similarly, no relationships were found between % carbohydrate intake and total energy intake and total cholesterol, HDL cholesterol, triglycerides, fasting insulin, glucose, leptin, adiponectin or HOMA-IR ($p>0.1$).

DISCUSSION

This study examined the nutritional intake of HIV-infected subjects with HAART-induced metabolic complications, with specific investigation of the relationships between macronutrients and lipids, insulin resistance, adipokines and total body and visceral fat. Our

Table 2. Dietary Intakes of HIV Positive Subjects with Lipodystrophy

Nutrient Intake Per Day	All	Adequate Reporters (n = 86)	Underreporters (n = 22)
Energy intake (kJ)	9897 (3306)	10,791 (2,959)	6400 (2041) *
Carbohydrate (g)	280 (103)	183 (75)	305 (95) *
Total sugars (g)	140 (69)	154 (66)	88 (51) *
Total fat (g)	80 (32)	88 (30)	51 (18) *
Saturated fat (g)	29 (12)	32 (12)	19 (8) *
Polyunsaturated fat (g)	12 (5)	13 (5)	7 (3)*
Monounsaturated fat (g)	32 (145)	35 (15)	20 (8) *
Protein (g)	115.1 (38.3)	125 (34)	76 (27)*
Alcohol (g)	10.2 (13.9)	11.4 (14.9)	5.1 (6.8) *
Fibre (g)	28.0 (12.6)	31 (12)	17 (8) *
Dietary cholesterol (mg)	342 (173)	376 (173)	211 (83) *
Dietary folate (ug)	348 (140)	379 (132)	227 (95) *
Dietary Composition (% of Energy Intake)			
% Carbohydrate	45.1 (6.5)	45 (6)	45 (6)
% Fat total	30 (6)	30 (5)	30 (6)
% saturated	11 (4)	11 (3)	12 (3)
% polyunsaturated	5 (1)	5 (1)	4 (1)
% monounsaturated	12 (3)	12 (3)	11 (3)
% Protein	20 (3.4)	20 (3)	20 (4)

Data are expressed as means ± (SD). Nutrients are expressed as g/day or as a percentage of total daily energy intake. * $p<0.0001$, adequate- versus under-reporters.

study used precise measures of total body fat (DEXA) and visceral fat (multi-slice CT). Our nutritional data were rigorously interrogated than most nutritional studies, in that we eliminated data that might skew or bias results, by excluding energy underreporters. Inclusion of underreporters biases analyses towards finding positive relationships between BMI and dietary fat [20, 21].

This is one of very few studies to examine the relationships between dietary intake and body composition in HIV-infected subjects with lipodystrophy, a group at high risk of CVD and type 2 diabetes mellitus. It is the first to use two precise measures of body fat: DEXA for total adiposity and CT for visceral adiposity.

We found weak positive relationships between dietary fat subtypes and BMI. There were no relationships with precise measures of adiposity, except for saturated fat intake. Saturated fats (g/d) were weakly related to %body fat and inversely related to %lean tissue. Overall, current saturated fat intake explained less than 1% of the variance in total body adiposity, therefore may be of negligible clinical significance. No relationships were found between current nutrient intake and fasting lipids, glucose, insulin, insulin resistance, leptin or adiponectin.

The apparently conflicting results between gross estimates of body composition (such as BMI) and precise measures of body fat (by DEXA) and visceral fat (by CT) require discussion: the discordance indicate the methodological importance of including direct measures of body composition in nutritional studies, as we have emphasised elsewhere [20]. Our BMI results would suggest apparent relationships with dietary fats that are not confirmed when examined against precise measures of body adiposity. Without use of accurate adiposity measures, incorrect conclusions could be made about dietary fats and erroneously influence dietary practice in this group at high CVD risk. Therefore, we suggest nutritional studies in HIV-infected patients utilise precise adiposity measures, where costs permit.

Few studies have reported nutritional intake in treated-HIV subjects with lipodystrophy. In the only prior study to use DEXA, higher energy intake was found in those with lipodystrophic subjects compared to those without [24]. A higher fibre intake was associated with a lower insulin AUC following a 75 g oral glucose load [24]. Insulin AUC was positively associated with the polyunsaturated:saturated (P:S) ratio [24]. DEXA data in this study were used to discriminate lipodystrophy and non-lipodystrophic subjects, however were not examine against nutritional variables [24].

Shah *et al.* recently reported data in a smaller group of 51 subjects, showing a higher intake of saturated fat (12% of total energy) and lower fibre intake, than recommended by the National Cholesterol Education Program guidelines [25]. Interestingly, % protein intake predicted fasting total cholesterol and triglycerides [25]. Whilst we found a similar intake of saturated fat, we found no relationship between it and total cholesterol. Shah's group concluded that the greater intake of animal protein contributed to the dyslipidemia of

their subjects [25]. It is important to recognise the difference between animal proteins in Australia versus the United States, where marbled meats are the standard (and therefore higher in saturated fats). In contrast, Australian animal protein is bred to low levels of marbling (and therefore less saturated fat).

A further study of HIV-infected subjects examined fat dietary intakes and development of fat deposition 6-24 months subsequently [26]. In this case-control study, Hendricks *et al.* reported that subjects without fat deposition had higher intakes of dietary fibre and protein than those with [26]. Another Australian study showed no relationships between dietary factors and metabolic and anthropometric variables in patients self-reporting fat redistribution [27]. Therefore dietary studies published thus far have been inconsistent in their findings.

Treated HIV-infection is associated with systemic inflammation, with increased pro-inflammatory and decreased anti-inflammatory adipokines [28-36]. We examined nutrient relationships with circulating adipokines and found no relationships between fasting leptin nor the anti-inflammatory adiponectin and any nutrient variable.

Prospective studies are essential to determine the influence of dietary intake in HIV-infected patients with lipodystrophy, given the associated metabolic complications and increased cardiovascular and diabetes risk. It has been widely recommended that guidelines promulgated for the treatment and prevention of cardiovascular disease be adopted in HIV-infected patients with lipodystrophy, however there is no evidence that these guidelines are effective in improving the associated dyslipidemia and insulin resistance or in reducing disease burden. Clearly more studies are necessary in this area, given the severity of dyslipidemia in treated HIV-infection and the limited success of drug therapy in achieving lipid targets [37]. Further, the dietary intake to reduce diabetes risk in this group is also not known. Again it would be incorrect to assume that standard diabetic diets are appropriate or effective in this insulin resistant group at increased risk of type 2 diabetes.

In summary, there are only very weak relationships between saturated fat intake and adiposity and in HIV-infected subjects and no relationships between nutrient intake and visceral adiposity, glucose metabolism, insulin resistance or adipokines. Only interventional, prospective studies will determine whether any nutritional strategy can assist in reducing the cardiometabolic complications associated with HIV lipodystrophy.

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Received: ?????? ??, ???? **Revised: ???????? ??, ????** **Accepted: ??????? ??, ????**