Current or Historic HIV-related Lipodystrophy Largely Associated with Protease Inhibitor Exposure is a Predictor of Future Diabetes Risk

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INTRODUCTION

HIV infection and its management have been implicated in the development of metabolic comorbidities including increased risk for Type 2 Diabetes Mellitus. *In vitro* studies suggests a role for antiretroviral therapy in mediating lipodystrophy through mitochondrial toxicity and pro-inflammatory mechanisms, potentially exacerbating metabolic comorbidity risk (1).

The literature suggests that there may be interplay and overlap between lipodystrophy and other metabolic co-morbidity such as dysglycaemia but few studies have attempted to quantify this relationship [2].

HYPOTHESIS & AIMS

Dysglycaemia is more common in people living with HIV with lipodystrophy.

We aimed to investigate the relationship between lipodystrophy and dysglycaemia in an urban HIV cohort and also investigate any associated clinical parameters.

DESIGN & METHODS

Clinical parameters, demographics and anthropometric data was collected from a cohort of people living with HIV (PLWH) sampled to be statistically representative of patients attending three South London clinics.

Current and historic duration of exposure to individual antiretrovirals, statins and corticosteroids was recorded. Historic or current lipodystrophy was recorded as one of three categories clinically assessed by a specialist metabolic HIV Consultant Physician: lipoatrophy, lipohypertrophy and mixed lipodystrophy.

Glycaemic status was defined as either normal or dysglycaemia using fasting glucose (<6.0 and ≥6.0 mmol/L respectively). Univariate statistical analysis and binary logistic regression were used to estimate risk factors for lipodystrophy, and their relative contributions to dysglycaemia. Statistical significance was taken as $p<0.05$ for all tests.

RESULTS

Of the patients recruited into the cohort (n=338), 22% were diagnosed with lipodystrophy (n=73) (Figure 1). Of the 73 patients diagnosed:

- 52% were classified with mixed lipodystrophy
- 40% were classified with lipoatrophy
- 8% were classified with lipohypertrophy

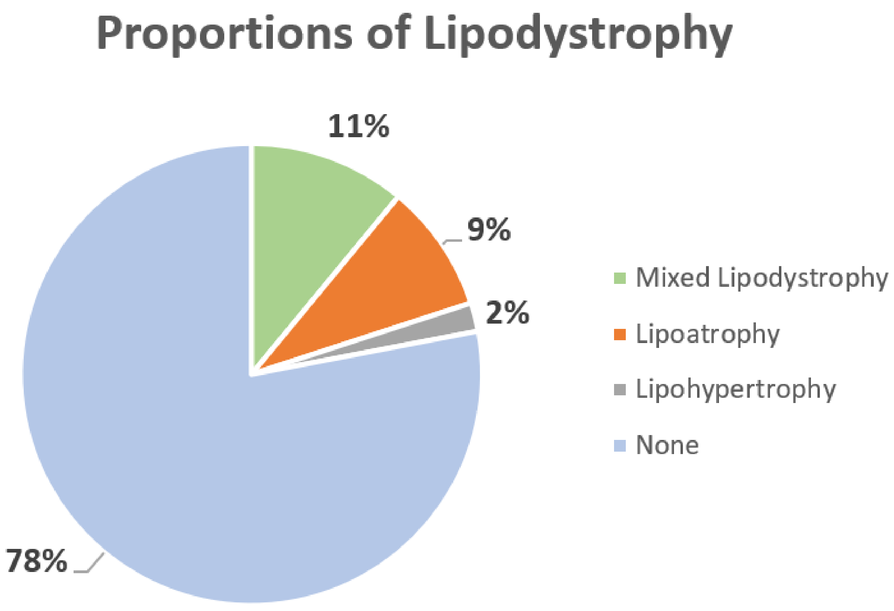

Figure 1. Proportions of lipodystrophy

Variable	Non-Lipodystrophic n = 265	Lipodystrophic n = 73	F	P
Age at Visit (average)	48	55	23.260	**<0.001**
Gender	74% male	75% male	0.091	0.763
Ethnicity	47% Caucasian	60% Caucasian	3.200	0.075
BMI category	59%*	56%*	2.495	0.115
Hepatic Steatosis	19%	27%	2.294	0.131
Statin use	23%	41%	9.425	**0.003**
Corticosteroid use	23%	36%	4.165	**0.042**
PI use ever	47%	80%	18.946	**<0.001**
NRTI use ever	89%	97%	0.806	0.370
NNRTI use ever	65%	78%	1.519	0.219

Figure 2. Univariate analysis of variables (statistically significant variables in bold)

* Percentage of group overweight or obese as per BMI cut-off

For all patients with past or current lipodystrophy the odds ratio (OR) of developing dysglycaemia was 2.05 (95% Confidence Intervals (CI): 1.20, 3.49; p=0.008). ANOVA suggested age, statin use, corticosteroid use and either past or current protease inhibitor use were significantly associated with the development of lipodystrophy (Figure 1).

Binary logistic regression suggests that even when controlling for age, steroid or statin use, current or historic protease inhibitor use remains significantly associated with current or historic lipodystrophy but duration of exposure to any individual protease inhibitor was not (Figure 3).

PI	n	Exp (B)	P	Mean Duration of Exposure (IQR, years) Non-Lipo	Lipo	Exp(B)	P
All PI's	183	4.70 (2.39, 9.25)	**<0.001**				
Darunavir	94	0.417 (0.18, 0.94)	**0.035**	2.5 (3.0)	2.4 (2.75)	0.967	0.799
Indinavir	12	14.21 (2.56, 79.00)	**0.002**	2.5 (-)	2.4 (2.25)	0.974	0.947
Nelfinavir	28	3.13 (1.11, 8.85)	**0.032**	3.2 (4.5)	2.5 (1.00)	0.887	0.453
Saquinavir	44	6.13 (2.64, 14.20)	**<0.001**	3.1 (5.0)	3.4 (2.00)	1.059	0.666

Figure 3. Logistic regression of PI type and duration on lipodystrophy

CONCLUSIONS

1. Lipodystrophy is significantly correlated with future diabetes risk in people living with HIV.
2. Current or historic exposure to protease inhibitors is strongly implicated with lipodystrophy even after adjusting for co-variants.
3. In clinical practice, we suggest that patients with current or historic lipodystrophy should be screened for diabetes.

References

(1) Mallewa JE, Wilkins E, Vilar J, Mallewa M, Doran D, Back D, Pirmohamed M. HIV-associated lipodystrophy: a review of underlying mechanisms and therapeutic options. Journal of Antimicrobial Chemotherapy. 2008 Jun 18;62(4):648-60.
(2) Gutierrez AD, Balasubramanyam A. Dysregulation of glucose metabolism in HIV patients: epidemiology, mechanisms, and management. Endocrine. 2012 Feb 1;41(1):1-0.