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Testosterone and Abnormal Glucose Metabolism in an Inner-City Cohort

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Abstract

Background—Low testosterone (T) has been associated with insulin resistance and diabetes mellitus (DM) among men in population-based studies. These studies included racially diverse men, but did not target for inclusion individuals with opiate use, Hepatitis C Virus (HCV) infection, or Human Immunodeficiency Virus (HIV) infection, which disproportionately affect inner-city populations and may alter the relationship between T and DM.

Methods—We studied the association between free T (FT) and abnormal glucose metabolism among male participants in the Study of HIV, Injection Drug Use, Nutrition, and Endocrinology (SHINE). We used logistic regression to examine the relationship between log FT and both insulin resistance and prediabetes/DM.

Results—Of 175 men, 43 (24.6%) had low FT (FT < 52 pg/mL). There were more men in the low FT group on methadone maintenance (39.5% v. 15.2%, $p=.001$), but there was no difference in FT by HIV or HCV status. Overall, 23 men (13.1%) had prediabetes/DM, which was unrelated to FT (OR of prediabetes/DM for each log increase in FT = 0.56, 95% CI 0.13–2.41). FT was also not related to insulin resistance.

Conclusions—The prevalence of hypogonadism was high in this inner-city cohort and was associated with methadone use. However, low FT was not related to insulin resistance or prediabetes/DM. Continued work to identify diabetes risk factors among inner-city populations will help determine targets for intervention to reduce diabetes incidence. Treatment trials of testosterone to reduce diabetes among hypogonadal men may be of particular relevance to opiate users, many of whom are hypogonadal.

Keywords

Testosterone; Diabetes; Insulin Resistance; Methadone

Introduction

Diabetes disproportionately affects members of racial and ethnic minorities in the U.S. and its prevalence is increasing rapidly. Therefore, it is crucial to identify potential targets for

intervention to decrease the development of diabetes. In large cross-sectional and prospective studies, low testosterone (T) has been associated with insulin resistance and diabetes mellitus (DM) among men [1, 2]. Although prior studies included ethnically diverse men, they did not target for inclusion individuals with opiate use, Hepatitis C Virus (HCV) infection, or Human Immunodeficiency Virus (HIV) infection, which are concentrated in urban areas [3]. These patient-level factors may alter the relationship between T and glucose metabolism, as previous studies have linked opiate use, HCV, and HIV to both hypogonadism [4–6] and DM [7–9].

The objective of our study was to examine the association between free T (FT) and abnormal glucose metabolism in a group of inner-city residents with more comorbid HIV, HCV, and substance use than examined in prior studies.

Subjects, Materials, and Methods

The Study of HIV, Injection Drug Use, Nutrition, and Endocrinology (SHINE) was a cross-sectional study of volunteers aged 18–65 recruited from medical and HIV clinics, community methadone maintenance programs, an existing cohort of injection drug users, and homeless shelters in Baltimore City from 2001–2004. We limited the current analysis to male study participants. Patients with known gonadal dysfunction, untreated endocrine problems, serum creatinine $>3\times$ the upper limit of normal (ULN), transaminases >3 times ULN, or hematocrit >3 times ULN or $<25\%$ were excluded from the parent study. The study was approved by the Johns Hopkins Medicine Institutional Review Board and all volunteers provided informed consent prior to participation.

The independent variable of interest was FT from a morning blood sample, measured by equilibrium dialysis (Esoterix, Inc., Calabasas Hills, CA) and log-transformed to account for non-normal distribution. FT was chosen as a more accurate measure than total T because HIV status can affect sex hormone binding globulin (SHBG), with HIV-infected individuals having increased SHBG [10]. Low FT was defined as FT less than 52 pg/mL. Additional variables of interest included age, race, BMI, HIV status, HCV status, methadone use, and opiate use. HIV status was assessed by self-report of HIV positive status, self-report of antiretroviral medication use, or ELISA/Western blot in those with unknown HIV status. HCV status was assessed by self-report. Individuals enrolled in a methadone program for at least three months prior to their participation in SHINE were considered methadone users. Opiate use was classified into no use, occasional use (<3 times/week), and heavy use (≥ 3 times/week) over the past six months. Substance use data was captured using two validated questionnaires to confirm drug use status: the Structured Clinical Interview for the DSM-IV Axis I Disorders-E module [11] and the Timeline Followback [12]. Visceral adiposity was measured using quantitative computerized tomography (CT) scan at the L4-L5 level.

The two outcomes studied were 1) presence of prediabetes or DM and 2) insulin resistance. Prediabetes was defined as fasting blood glucose (FBG) between 100 and 125 mg/dL or 2-hour OGTT result of 140 to 199 mg/dL. DM was defined as FBG ≥ 126 mg/dL, 2 hour OGTT result ≥ 200 mg/dL, self-reported use of DM medication or DM diagnosis. Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR): $\text{fasting glucose (mmol/L)} \times \text{fasting insulin } (\mu\text{U/mL}) / 22.5$ [13]. Insulin resistance was defined as HOMA-IR >4.65 at any Body Mass Index (BMI) or HOMA-IR >3.60 and BMI >27.5 [14]. We used multiple logistic regression to examine the relationship between log FT and insulin resistance and prediabetes/DM.

Results

Data were analyzed from 175 male participants, of whom 43 (24.6%) had low FT. The majority of participants were African-American, and median age was 43.8 years. Over half of participants had HIV and about a third had HCV. Sixty percent were normal weight (BMI <25 kg/m²). About half of participants used opiates occasionally or heavily, and a fifth were on methadone maintenance (Table 1). There was no statistically significant difference in age, race, HIV status, Hepatitis C status, BMI, or frequency of opiate use between men with low FT and normal FT. There were more men in the low FT group on methadone maintenance (39.5% v. 15.2%, $p=.001$). There was no difference in mean log FT based on other demographic or clinical characteristics, including age, race, HCV status, BMI, HIV, or opiate use category (Table 2).

Overall, 23 men (13.1%) had prediabetes/DM, which was not associated with FT (OR of prediabetes/DM for each log increase in FT = 0.56, 95% CI 0.13–2.41) (Table 3). Eighteen men (10.9%) had insulin resistance, which was unrelated to FT (OR of insulin resistance for each log increase in FT = 0.37, 95% CI 0.08–1.80) (Table 4). Adjustment for visceral adiposity did not affect the relationships between FT and prediabetes/DM or insulin resistance. In adjusted analysis, there was an association between Hepatitis C status and prediabetes/DM which was not statistically significant (OR=2.13, 95% CI 0.88–5.22). HIV status, opiate use category, and methadone use were not related to either outcome.

Discussion

The prevalence of hypogonadism was high in this inner-city cohort and was associated with methadone use. However, low FT was not related to prediabetes/DM or insulin resistance in our sample. Factors other than hypogonadism may be stronger drivers of abnormal glucose metabolism in this group. Alternatively, our results may be limited by the small number of individuals with insulin resistance or prediabetes/DM in our study sample, which consisted of relatively young men with less overweight/obesity than the general population.

Multiple studies have shown an association between low T and DM in men [1, 2]. An analysis of NHANES III data (1998–94) revealed that men in the lowest T tertile had four times higher odds of DM compared with those in the highest T tertile [2]. Furthermore, a systematic review and meta-analysis by Ding and colleagues revealed associations between low T and both incident and prevalent DM [15]. When specifically examining FT, the association with DM persists in some studies [2, 16, 17] but not all [18, 19]. T may have several mechanisms by which it affects glucose metabolism, including increased visceral adiposity and decreased muscle insulin sensitivity [20]. Prior studies of the T/DM relationship have adjusted for measures of adiposity other than BMI, such as waist circumference or waist-to-hip ratio; we adjusted for BMI only.

Opiate use, and more specifically, methadone maintenance therapy, was not related to prediabetes/DM. In contrast to our results, a prior study by Howard et al. of a large sample of women with and at risk for HIV revealed an association between opiate use and DM in both prospective and cross-sectional analyses [7]. Our results may differ from theirs because the effects of opiates on glucose metabolism are different in women than in men. However, an earlier small study of male heroin users did show higher fasting levels of insulin in the opiate users compared with control subjects and a decrease in plasma insulin response to intravenous glucose [21], indicating that male opiate users also have a propensity to abnormal glucose metabolism. The Howard study included a higher proportion of overweight/obese women than our study and 11% of the women had prevalent diabetes; the authors did not use prediabetes or insulin resistance as outcomes.

This study was limited by the relatively small sample size and the low number of men experiencing the outcomes of interest. We did not have data on family history of diabetes, an important risk factor for development of diabetes. We were unable to adjust for waist circumference or measures of adiposity other than BMI. A strength of our study is the unique population recruited for the study who are often underrepresented in clinical research.

The association between methadone use and hypogonadism is well known [22, 23]. As expected, we found a higher proportion of methadone users among our individuals with hypogonadism. Our study did not reveal a relationship between hypogonadism and prediabetes/DM or insulin resistance. There has been sufficient evidence of a T/DM association in studies done in the general population, however, that studies are underway to determine if treating hypogonadism will decrease diabetes risk. This will be of particular interest in opiate users, who are likely to have low testosterone if they are actively using drugs or are in methadone maintenance therapy. An area of potential future research will be determining whether treating hypogonadal opiate users with T will decrease their diabetes risk.

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Table 1

Demographic, Clinical, and Drug Use Characteristics of Male Participants in the SHINE cohort

	Entire Cohort n=175
Age – years	
Median (IQR)	43.8 (38.7–48.0)
Race - % (n)	
Black	93.7 (163)
HIV Status - % (n)	
Positive	52.9 (91)
Hep C Status - % (n)	
Positive	35.8 (62)
Weight Status - % (n)	
Normal weight (BMI <25)	60.0 (105)
Overweight (BMI 25–30)	28.6 (50)
Obese (BMI>30)	11.4 (20)
Opiate Use Category - % (n)	
None	50.9 (89)
3×/week	25.1 (44)
> 3×/week	24.0 (42)
Methadone Use Category - % (n)	
On methadone maintenance	21.1 (37)

Table 2

Comparison of Mean log FT by Demographic, Clinical, and Drug Use Characteristics of Male Participants in the SHINE cohort

	Mean log FT	p-value
Age		
< 50 years (n=144)	1.86	0.68
50 years (n=31)	1.83	
Race		
Black (n=163)	1.86	0.19
Non-black (n=11)	1.74	
Hep C Status		
Negative (n=111)	1.86	0.76
Positive (n=62)	1.84	
Weight Status		
Normal weight (BMI <25)	1.83	0.07
Overweight (BMI 25–30)	1.94	
Obese (BMI >30)	1.80	
HIV Status		
Negative (n=81)	1.85	0.97
Positive (n=91)	1.85	
Opiate Use Category		
None	1.84	0.28
3×/week	1.90	
> 3×/week	1.78	
Methadone Use Category		
No methadone maintenance (n=138)	1.90	<0.001
On methadone maintenance (n=37)	1.70	

Table 3

Unadjusted and Adjusted Odds of Prevalent Prediabetes/DM Among Male Participants in the SHINE cohort

	Prediabetes/DM Prevalence, % (n)	Crude OR (95% CI)	Adjusted* OR (95% CI)
Overall Prediabetes/DM	13.1 (23/175)	--	--
Prevalence			
Log FT	--	0.58 (0.14–2.31)	0.56 (0.13–2.41)
Age			
<50 years	13.2 (19/144)	Ref	Ref
50 years	12.9 (4/31)	0.97 (0.31–3.10)	0.94 (0.29–3.06)
Race			
Black	12.9 (21/163)	Ref	Ref
Non-black	18.2 (2/11)	1.50 (0.30–7.44)	1.28 (0.24–6.76)
Hep C Status			
Negative	9.9 (11/111)	Ref	Ref
Positive	19.4 (12/62)	2.18 (0.90–5.29)	2.14 (0.88–5.22)
Weight status			
Normal weight (BMI <25)	12.3 (13/105)	Ref	Ref
Overweight (BMI 25–30)	16.0 (8/50)	1.35 (0.52–3.50)	1.37 (0.51–3.69)
Obese (BMI >30)	10.0 (2/20)	0.79 (0.16–3.78)	0.78 (0.16–3.84)
HIV Status			
Negative	14.8 (12/81)	Ref	**
Positive	12.1 (11/91)	0.79 (0.33–1.90)	
Opiate Use Category			
None	14.6 (13/89)	Ref	**
3×/week	13.6 (6/44)	0.92 (0.33–2.62)	
> 3×/week	9.5 (4/42)	0.62 (0.19–2.02)	
Methadone Use			
No	13.8 (19/138)	Ref	**
Yes	10.8 (4/37)	0.76 (0.24–2.39)	

* Adjusted for Age, Race, Hep C, Weight status

** Omitted from final model

Table 4

Unadjusted and Adjusted Odds of Insulin Resistance Among Male Participants in the SHINE cohort

	Insulin Resistance Prevalence, % (n)	Crude OR (95% CI)	Adjusted* OR (95% CI)
Overall Insulin Resistance	10.9 (18/175)	--	--
Log FT	--	0.33 (0.07–1.45)	0.37 (0.08–1.80)
Age			
<50 years	9.7 (14/144)	Ref	Ref
50 years	12.9 (4/31)	1.38 (0.42–4.50)	1.19 (0.34–4.18)
Race			
Black	10.4 (17/163)	Ref	Ref
Non-black	9.1(1/11)	0.86 (0.10–7.13)	0.73 (0.08–7.01)
Hep C Status			
Negative	10.8 (12/111)	Ref	Ref
Positive	9.7 (6/62)	0.88 (0.31–2.48)	0.94 (0.32–2.75)
Weight status			
Normal weight (BMI <25)	7.6 (8/105)	Ref	Ref
Overweight (BMI 25–30)	8.0 (4/50)	1.05 (0.30–3.68)	1.14 (0.32–4.07)
Obese (BMI>30)	30.0 (6/20)	5.20 (1.57–17.21)	4.80 (1.41–16.31)
HIV Status			
Negative	7.4 (6/81)	Ref	**
Positive	13.2 (12/91)	1.90 (0.68–5.32)	
Opiate Use Category			
None	10.1 (9/89)	Ref	**
3×/week	13.6 (6/44)	1.40 (0.47–4.23)	
> 3×/week	7.14 (3/42)	0.68 (0.18–2.67)	
Methadone Use			
No	10.1 (14/138)	Ref	**
Yes	10.8 (4/37)	1.07 (0.33–3.48)	

* Adjusted for Age, Race, Hep C, Weight status

** Omitted from final model