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Effects of Hypogonadism on Body Composition and Bone Mineral Density in Type 2 Diabetic Patients

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Short Running title: Hypogonadism, Diabetes and Body Composition

Introduction

It is known that type 2 diabetes is frequently associated with hypogonadism in males (1,2). Free testosterone (FT) concentrations are negatively related with BMI in type 2 diabetic patients (1,3). However, the relationship of FT with adipose tissue mass and lean body mass in diabetic patients is not well described. Studies examining this relationship have been limited by the fact that they have not measured FT by a reliable method such as equilibrium dialysis(ED)(4).

Therefore, we decided to study the body composition of hypogonadal and eugonadal type 2 diabetic patients by using dual energy X-ray absorptiometry (DEXA) to measure subcutaneous adipose tissue, lean body mass, bone mineral content (BMC) and bone mineral density (BMD).

Research Design and Methods

The study was conducted in 2 endocrinology practices in Midland, TX and Buffalo, NY (Diabetes center of the Southwest in Midland, TX and Diabetes-Endocrinology Center of Western New York in Buffalo, NY). It is our practice to screen all diabetic patients for hypogonadism due to the high prevalence of hypogonadism in diabetic patients. We also routinely evaluate body composition of our diabetic patients by DEXA (done at no cost to our patients). Informed consent was therefore not obtained.

Data from 164 consecutive male diabetic patients who presented to endocrinology clinic were collected prospectively for the study. Patients with known history of hypogonadism, panhypopituitarism or chronic debilitating disease such as renal failure, cirrhosis, HIV, back or hip surgery or treatment withsteroids, bisphosphonates or recombinant parathyroid hormone were excluded. 26 patients were disqualified based on the study criteria. Therefore data on 138 patients were included for analysis in this study. Fasting blood samples were then obtained to measure serum TT, FT, SHBG, and hemoglobin A1C (HbA1c) using assays previously described (1). FT was measured by equilibrium dialysis (ED) (Esoterix laboratories normal range:0.174–0.868 nmol/liter).

We measured total body mass, lean mass, subcutaneous fat mass, BMC and BMD by DEXA (Lunar machine, GE Medical Systems). Measurements were made in both arms, both legs and the trunk region. BMD was measured at both arms and legs, ribs, L1-L4 spine and both hips. Hip BMD was defined as mean BMD of both hips.

Data are presented as mean ± S.E.

Results

Data from 138 male type 2 diabetic subjects were analyzed. The mean age of the patients was 59.29±0.97 years [range: 29.8-84.3 years]. The mean BMI was 31.83±0.44 kg/m^2 [range: 18.4 - 44.6 kg/m^2]. The mean TT, FT and SHBG concentrations were 13.29±0.49nmol/L [range: 5.17 -35.97nmol/L], 0.184±0.007nmol/L [range: 0.073-0.465nmol/L] and 56.72±2.45 [range: 8.5-156.0] nmol/L respectively. FT was inversely related to BMI (r= -0.19, p=0.04) and to arm(r=-0.18,p=0.05), leg(r= -0.24,p=0.03), trunk(r= -0.20,p=0.04) and total subcutaneous fat mass(r= -0.23,p=0.02). TT was also inversely related to arm, leg, trunk and total fat mass(r= -0.38,-0.38,-0.40,-0.41 respectively,$p<0.001$). FT and TT were positively related to arm lean mass(r= 0.36,$p<0.001$ for FT; r=0.19,p=0.05 for TT) but not related to leg or total lean mass. FT and TT were positively related to arm BMC(r=0.27 and 0.31

respectively,$p<0.01$) but not to leg or total BMC. FT was positively related with BMD in arms($r= 0.20, p=0.04$) and ribs($r=0.28, p<0.01$). TT was positively related to rib BMD($r=0.18, p=0.05$) but not arm BMD($r=0.11, p=0.25$). FT and TT were not related to leg, hip, spine or total BMD.

Total BMD was positively related to total lean mass($r=0.50, p<0.01$), total fat mass($r=0.34, p<0.01$) and BMI($r=0.37, p<0.01$). In a multiple regression model with total BMD as dependent variable and BMI, total lean mass and total fat mass as independent variables, only total lean mass was a significant predictor of total BMD.

Body composition of hypogonadal (n=66) patients with eugonadal (n=72) patients is presented in *table 1*.

Conclusions Our study demonstrates a strong inverse relation between TT, FT and subcutaneous fat mass in type 2 diabetic patients. Since hypogonadal type 2 diabetic subjects have higher subcutaneous fat mass, they may be more insulin resistant that eugonadal type 2 diabetics. It is, therefore, relevant that type 2 diabetic patients with hypogonadism have markedly elevated CRP concentrations and thus may pose a marked increase in cardiovascular risk (5). The relationship of obesity with testosterone is probably bidirectional (6,7), with hypogonadism possibly being both the cause and the consequence of increased adiposity. From our study, it is not possible to determine if increased subcutaneous fat mass is the cause or the consequence of hypogonadism.

FT was related positively to arm lean mass but not to leg or total lean mass. It is known that diabetics have higher muscle mass (due to higher BMI) but poorer muscle strength (8). We did not measure muscle strength in our study. Since testosterone has a positive effect on muscle strength, it is possible that hypogonadal diabetic patients have poorer muscle strength than eugonadal diabetic patients inspite of having a similar lean body mass.

FT was positively related to BMD at arms and ribs but not at other sites. It is possible that hypogonadism may have affected BMD at various sites differently, causing a more pronounced or rapid bone loss (or slower bone replacement) at arms and ribs as compared to legs, hips or spine. Hypogonadism has previously been known to be associated with low BMD at hip and spine (10). These studies have not specifically been done in obese subjects. From our study, it appears that hypogonadism in obese type 2 diabetic subjects is not a major risk factor for developing osteopenia in hips or spine. We do not know if this would be true if a more elderly diabetic population or a larger number of patients were studied. It would be important to determine whether replacement therapy with testosterone in hypogonadal diabetic males will reverse adiposity, improve BMD in the arm and ribs and also improve cardiovascular outcomes.

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Table 1: Comparison of body composition of hypogonadal and eugonadal patients (significant relations are highlighted)

Table 1

	hypogonadal	eugonadal	p
n	66	72	
Age (years)	63.1±1.3	56.0±1.3	<0.001
BMI (kg/m^2)	32.8±0.7	30.9±0.6	0.024
TT (nmol/L)	10.31±0.45	16.0±0.71	<0.001
FT(nmol/L)	0.131±0.003	0.236±0.009	<0.001
SHBG(nmol/L)	61.2±3.5	60.0±3.5	0.83
HbA1c%	7.99±0.27	7.67±0.25	0.62
Arm fat mass	3.33±0.15	3.07±0.13	0.19
Leg fat mass	9.89±0.58	8.41±0.47	<0.05
Trunk fat mass	21.92±0.90	19.65±0.78	<0.05
Total fat mass	36.27±1.55	32.17±1.32	<0.05
arm lean mass (kg)	6.38±0.14	7.02±0.11	<0.001
leg lean mass (kg)	19.13±0.44	19.27±0.39	0.8
trunk lean mass (kg)	29.31±0.72	29.51±0.55	0.82
total lean mass (kg)	59.64±1.09	60.55±0.93	0.53
arm BMC (kg)	0.39±0.02	0.43±0.01	0.035
Leg BMC	1.27±0.03	1.27±0.03	0.99
Total BMC	3.19±0.06	3.31±0.06	0.19
arm BMD (g/cm^2)	0.99±0.02	1.02±0.01	0.22
rib BMD (g/cm^2)	0.78±0.01	0.80±0.01	0.17
leg BMD (g/cm^2)	1.40±0.02	1.43±0.02	0.25
total BMD (g/cm^2)	1.26±0.01	1.29±0.02	0.42
spine BMD (g/cm^2)	1.24±0.02	1.23±0.04	0.19
hip BMD (g/cm^2)	1.06±0.02	1.05±0.02	0.99
% of osteopenia in hip	27.7%	30.0%	NS
% of osteoporosis in hip	2.13%	0%	NS
% of osteopenia in spine	23.4%	26.7%	NS
% of osteoporosis in spine	0%	0%	NS