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The Effect of Testosterone Replacement Therapy on Glycemic Control in Hypogonadal Men with Type 2 Diabetes Mellitus

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Abstract

Objective: The purpose of this study is to examine whether long term testosterone replacement therapy (TRT) improves blood glucose control in aged men with hypogonadism and diabetes mellitus.

Research design and methods: This is a retrospective and observational study using data from patients' Electronic Medical Record (EMR) at Hines Veteran Administration Hospital for 5 years, 2002-2007. The data were obtained from 129 out of 642 individuals with type 2 DM (T2DM) and hypogonadism, either receiving testosterone replacement therapy (TRT group) or not (control group) based on patient's personal decision.

Results: The overall mean HbA1c in the TRT group was lower by 0.25% compared to those of control group, 95% CI=0.016-0.49, p=0.037. After adjusting data by age, BMI, hemoglobin, and antidiabetic medications, HbA1c in TRT group decreased by 0.38%, CI=0.10-0.66, p<0.009. In a subgroup analysis, for the first time, we found that the mean HbA1c in TRT group decreased in those who received lower doses of antidiabetic, compared to those on control group: by 0.61%, CI=0.23-0.99, p=0.002 (oral agents) and by 0.27%, CI=0.011-0.52, p=0.041 (insulin). However, there was no association between TRT and glucose control in those patients who were on larger doses of antidiabetic. All the data were adjusted for age, BMI, and hemoglobin level.

Conclusion: TRT was associated with a modest but significant improvement of HbA1C in aged hypogonadal men with T2DM. Interestingly, the improvement of HbA1C was more significant in individuals whose blood glucose was controlled with less medications and no worsening of HbA1c was noted in TRT group who were treated with large doses of antidiabetic.

Keywords: Type 2 Diabetes mellitus; Glycemic control; Testosterone replacement therapy

Introduction

Presence of a complex interrelationship between testosterone levels and/or testosterone therapy on insulin level and insulin action, as well as incidence of hypogonadism in patients with diabetes mellitus or metabolic syndrome have been subjects of various studies which have generated many controversies.

High prevalence of testosterone deficiency in men with obesity, metabolic syndrome (MS), and/or type 2 diabetes mellitus (T2DM) have been observed for many years [1-6]. The negative association between testosterone level and incidence and/or presence of T2DM was also observed in various longitudinal studies [7-11] However, these observations pose some concerns. First, this bidirectional relationship was not universally consistent in subjects with type 1 diabetes mellitus (T1DM); Second, some reports showed the presence of a reverse association between testosterone level and incidence of T1DM and/or MS [12,13]; Third, others had demonstrated that this association disappears after adjusting for age, duration of DM, and BMI [14,15]. Finally, in cross-sectional study, men with T1DM had significantly higher testosterone which continued to be higher even after adjusting for age and BMI [16]. Interestingly, although DDCT/EDIC did not show increased occurrence of low total testosterone levels in subjects with T1DM, two important observations were noted: First, there was a negative correlation between free testosterone and BMI, and hypertension [17]. In addition, there was a negative correlation between the levels of free testosterone and insulin dosage, potentially indicating that patients with higher free testosterone are more insulin sensitive, and consequently, require less insulin for blood glucose control [17]. This interrelationship becomes more remarkable when validated by reports confirming that testosterone replacement therapy could reduce HbA1c and improve insulin resistance in subjects with T2DM [18,19].

Based on this information and many other observations, utilizing VA electronic database, we have designed a retrospective and observational study with the purpose of assessing the effect of testosterone replacement therapy on blood glucose control in individuals with late onset hypogonadism and T2DM.

Research design and methodology

Data collection: This is an observational and retrospective study collecting data from Hines VA Hospital Patients' Electronic Medical Record (EMR) from 5 years: 2002-2007. The institutional Review Board of Edwards Hines Jr. VA Hospital had approved the study based on Helsinki declaration (1964).

Over the course of the study, we used this database to access all pertinent data such us provider's notes, medication profiles, labs (for various cofounders of this study), age, BMI, and information on subject's cardiac, renal, and other organ status. Moreover, the data was collected from the cohort of community dwellings who were self-sufficient, living in their usual environment, like the general population. Because of this quality, the results of this study may be applicable to the similar community dwelling individuals.

First, we obtained data of 642 individuals with diagnosis of T2 DM, per ADA definition on either diet only, oral antidiabetic agents, and/or insulin and hypogonadism, primary or secondary, (total testosterone less than 9 nmol/L (260 ng/ml) and free testosterone less than 50 pg/ml). They were either receiving testosterone replacement therapy (TRT group) or not receiving testosterone based on their personal decision to reject testosterone therapy (Control Group).

We used the following exclusion criteria to carefully choose those with very similar status of health without any specific attention on the study arms. The exclusion criteria were: patients with untreated and/or active thyroid disorders, other endocrine disorders such as pituitary and adrenal gland, active malignancies, advance cardiac disease (NY heart association class III and IV), uncontrolled hypertension, renal insufficiency (defined as a e GFR<40 ml/min/1.73 m^2, gastrointestinal problems that may cause malabsorption syndrome, liver disorders such as active or chronic hepatitis and cirrhosis of the liver (ALT, AST more than 2 times normal), polycythemia (Hg>18) and any hemoglobin disorders which may affect HbA1c level, advance chronic obstructive pulmonary disease (COPD), on medication (s) which could decrease mobility, or steroids or any other medications which could affect the hypothalamic-pituitary-testicular axis function. All the study data were available and obtained from the hospital Electronic Medical Record data base. Out of 642 patients a total of 129 patients met the study criteria, age 43-82 in TRT and 45-85 in control group and BMI 22.6-50 in TRT and 22.4-48.6 in control group (Table 1). Out of 129 patients, 63 received TRT (TRT group) and 66 patients in the control group who chose not to receive TRT.

Variables	Control Group	TRT Group	
HbA1C	56+10 (7.3+1.3)	53+7.6 (7+1)	P=0.18
Age	62.1+8.7	64.3+9.1	P=0.17
BMI	32.6+5.3	33.1+5.8	P=0.54
Hemoglobin	217.2+23.3 (14+1.5)	221.8+23.3 (14.3+1.5)	P=0.44

Table 1: Baseline Characteristics.

The baseline point for testosterone treated group was when each subject with diabetes was diagnosed with hypogonadism and testosterone therapy was initiated and in control group when hypogonadism was originally diagnosed. In TRT group the goal for testosterone levels were in mid normal range for young men. The HbA1c and hemoglobin values, BMI, age, and information on antidiabetic medications were collected every 3-4 months from the hospital EMR. Antidiabetic medications consisted of metformin, sulphonylureas (glipizide, Repagnlide, and glyburide), thiazolidines (rosiglitazone and pioglitazone), acarbose, and insulin. To simplify/facilitate the analysis, the anti-diabetic agents were categorized as low (A), medium/high (B), or high dose (C) (Table 2). All the data were collected every 3-4 months except for hemoglobin levels which was collected every six months. Missing data for HbA1c were 11% and 9% for control group *vs.* TRT group, respectively and for hemoglobin were 20% *vs.* 25%, control group *vs.* TRT group, respectively.

	Metformin (mg)	Glipizide (mg)	Repagnlide (mg)	Glyburide (mg)	Rosiglitazone (mg)	Pioglitazone (mg)	Acarbose (mg)	Insulin (Unit)
A	500-1500	2.5-10	2-8	2.5-10	4	15	12.5-100	<50
B	>1500	10-20	>8	10-20	8	30	100-200	50-100
C		>20		>20	16	45	>200	>10

Table 2: To simplify/facilitate the analysis, the anti-diabetic agents were categorized as low (A), medium/high (B), or high dose (C).

All patients (regardless of the study arm) had a comprehensive education on healthy living such as nutrition and physical activities. In addition, all had received similar medical treatment to control blood glucose and its complications and blood pressure and lipid.

Statistical analysis plan

For baseline characteristics, means and standard deviations are displayed for the continuous variables, and the frequency tables, for dichotomous variables. Group differences are tested by t-test for continuous variables with normal distribution and by the Wilcoxon rank-sum for continuous variables with non-normal distributions. Mean, standard deviation (SD) and p-value are provided. For the dichotomous variables, Chi-square test is utilized, but for the small number, Fisher's exact test. Odds ratios (ORs), 95% CI and p-values are reported. A mixed random effect model for longitudinal data is used to assess HbA1c over time during the follow-up periods of the study. Finally, a sensitivity analysis was performed to assess the consistency of the treatment effect after adjusting for baseline A1C, BMI, age, insulin, and medicine usage. The average difference between the treatment group and the control group, 95% confidence Interval (CI), and p-value are provided. All statistical tests used a significance level of 0.05, using SAS, version 9.4, for Windows (SAS Institute, Cary, NC).

Results

After applying the inclusion and exclusion criteria, out of 642 patients a total of 129 patients met the study criteria, aiming 90%

power with the difference of 0.25, standard deviation of 0.4 and alpha level of 0.05, age 43-82 in TRT and 45-85 in control group and BMI 22.6-50 in TRT and 22.4-48.6 in control group (Table 1). Of these 129 patients, 63 patients received testosterone replacement therapy (TRT group) and the remaining 66 patients chose not to receive TRT for the personal reasons (the control group). There were no significant statistical differences in baseline characteristics values for HbA1c, age, hemoglobin, and BMI between the two study groups (Table 1). As we have stated previously all the individuals were controlled with other cofounders that might have had any effect on data.

The Mixed random effect model for the longitudinal data was used to compare the overall HbA1c differences between the two study groups and we found statistically significant difference in HbA1c between the two study groups; the TRT group had lower mean HbA1c of 0.25% compared to those in control group, 95% CI=0.016-0.49, p=0.037, (Table 3). To study these findings further, we performed a sensitivity analysis; after adjusting the model for pertinent and available co-variants such as age, BMI, hemoglobin, and various antidiabetic medications (oral agents and insulin, Table 2), we found that the means HbA1C level was lower in TRT group compared to the control group by 0.38% CI=0.10-0.66, p<0.009 (Table 3).

Decline of HbA1c before adjustment			**Decline of HbA1c after adjustment**		
% Decline	CI	P value	% Decline	C.I.	P value
0.25%	0.016-0.49	0.037	0.38%	0.10-0.66	p<0.009

Table 3: This is a sensitivity analysis; after adjusting the model for pertinent and available co-variants such as age, BMI, hemoglobin, and various antidiabetic medications (oral agents and insulin).

Furthermore, in a subgroup analysis, we examined the interaction between testosterone therapy and the dosage of anti-diabetic medications (oral agents and/or insulin), assuming the higher required dosages of these medications for blood glucose control reflected the severity of diabetes. To simplify the analysis, we divided antidiabetic medications (oral and insulin) to three categories (Table 2). To our surprise, we found that the mean HbA1c in TRT group is lower in those who received lower doses of oral agents and/or insulin compared to those on control group by 0.61%, CI=0.23-0.99, p=0.002 (oral agents) and by 0.27%, CI=0.011-0.52, P=0.041 (insulin), (Table 4). Conversely, there was no association between TRT and glucose control in those patients who were on larger doses of antidiabetic (oral and/or insulin). All the data were adjusted for age, BMI, and hemoglobin level and the adjustment did not change these interactions.

Lower doses of oral Antidiabetic Agents			**Lower doses of Insulin's**		
% Decline	CI	P value	% Decline	C.I.	P value
0.61%	0.23-0.99	0.002	0.27%	0.011-0.52	0.041

Table 4: In a subgroup analysis, the interaction between testosterone therapy and the dosage of anti-diabetic medications (oral agents and/or insulin's) were assessed using the three categories of antidiabetic medications (oral and insulin).

Discussion

Our data demonstrates that TRT improves blood glucose control by a moderate, but significant reduction of HbA1C (0.25%, p=0.037, Table 3), while the association between TRT and glucose control became more significant after adjusting for various covariant, HbA1c decreased by 0.38%, p<0.009 (Table 3). It is noteworthy that for the first time, our data showed that TRT is associated with an improvement of HbA1c in those hypogonadal patients who are on lower antidiabetic medications (oral agent and/or insulin); HbA1c decreased by 0.61% in group of individuals on low doses of oral agents and by 0.27% in groups of subjects on low doses of insulin (Table 4). Moreover, again for the first time, there were no changes in HbA1C between two groups of- individuals on medium or large doses of either oral agents or insulin.

The association between hypogonadism/low testosterone levels and diabetes mellitus have long been accepted by medical community [1,2]. The possible role of testosterone in blood glucose metabolism and various markers of metabolic syndrome (MS) in hypogonadal men have later been supported by presence of negative correlation between serum testosterone levels and fasting serum insulin, C-peptides, and HOMA-IR, all as surrogate markers of insulin resistance [3-6].

Moreover, many large populations based and cross-sectional studies had provided valuable information on this subject. For example, Baltimore Male Aging Study [10] and A Longitudinal Study in European Men [11] had noted the association between low testosterone levels and increased markers of MS and indicated that low testosterone level may be a predictor of higher incidence of MS. The Third National Health and Nutrition Examination Survey (NHANESIII) had reported a negative association between free testosterone level and incidence of DM even independent of adiposity [9]. In addition, the survey revealed that individuals with lowest tertile of free or bioavailable testosterone levels had four times higher chance of developing DM, thus suggesting that low testosterone is a risk factor for development of diabetes in men [9]. Similar findings were shared by Massachusetts Male Aging Study [8] and the Kuopio Ischemic Heart Disease Risk Factor Study in Finland [7]. Likewise, Ding et al. in a meta-analysis, out of 80 studies identified 43 prospective and cross-sectional studies, which comprised 6974 women and 6427 men; he discovered that men with T2DM have significantly lower testosterone compared to those without DM. It is worth noting that there was a

reverse relationship in women, where higher testosterone levels were associated with higher incidence of T2DM [20].

Others studied men on androgen deprivation therapy (ADT) for treatment of prostate cancer as a model for patients with hypogonadism. They also found the presence of a strong association between ADT (lower endogenous testosterone levels) and higher incidence of diabetes mellitus, obesity, cardiovascular diseases (CVD) in prostate cancer patients undergoing ADT [21-23].

On the other hand, the association between low testosterone and diabetes became multifaceted when various reports had shown that patients with DM develop defect in hypothalamus and pituitary gland function [24,25]. In addition, a functional defect of Leydig cell in men with DM [26] and Setroli cells development in rat studies [27] were reported. These studies collectively demonstrated that individuals with diabetes develop some defects on various levels of hypothalamic-pituitary-gonadal axis.

In this setting, our finding of a modest yet significant association of TRT with blood glucose control in hypogonadal aged men becomes meaningful and is supported by many previous studies. Despite some controversy on the role of TRT on arteriosclerosis and cardiovascular disorders, many studies demonstrated the possible beneficial effect of TRT on glucose control and markers of MS. For the sake of brevity, we will mention only a few; Janjgava et al treated a group of subjects with diabetes with either TRT or placebo and discovered, that an increase in serum testosterone levels was accompanied by improvement in HbA1C and HOMA-IR index, therefore indicating an improved fasting insulin sensitivity. The improvement in blood sugar control could be observed as early as 6 months into the TRT [19]. Finally, TRT reversed the markers of metabolic disorders in newly discovered T2DM [28,29] and decreased visceral adiposity, which further supports the hypothesis that TRT decreases insulin resistance in hypogonadal men [30]. However, in a meta-analysis, out of 112 placebo-controlled and double-blind trials, seven studies, encompassing 883 hypogonadal men who were treated with either TRT or placebo, showed only a modest improvement on insulin resistance by HOMA1 without any significant effect on glucose control [31].

We draw two major conclusions from our study. First, the most interesting finding of this study is the association of significant improvement of blood glucose control in hypo gonadal individuals in TRT group who are on smaller doses of either insulin or oral agent(s) (Table 4). We believe that this finding demonstrates that TRT may have a positive effect on blood glucose control in individuals with less advanced DM who require lower doses of either insulin or oral agents. Second, more importantly, we did not observe any worsening of blood glucose control in TRT group with more advanced diabetes, requiring larger doses of antidiabetic medications. It's worth pointing out that these two discoveries are unique to this study since to our knowledge, they have not been reported in the past.

The results of our study, coupled with many prior studies, support the previously suggested recommendation [32] that TRT may be considered as an adjunct therapy for blood glucose control in individuals with T2DM and hypogonadism.

We understand that our study has some limitations. For instance, because of its retrospective nature, we relied on the availability and accuracy of the medical record. Since in this type of studies pertinent data is often missing, we realized for example, that there was not enough data to determine whether the glucose control was due to improvement of insulin resistance or possibly enhanced physical activity and "feeling good" due to higher testosterone level. Nevertheless, the VA EMR is a great online source of comprehensive patient's information available on secure servers.

In summary, we draw three major conclusions from this study. First, we found an association between TRT and better blood glucose control to a modest but significant degree in middle age hypogonadal men with T2DM. Second, the association was more significant in individuals with less advanced T2DM who required smaller doses of antidiabetic medications. Finally, there was no worsening of blood glucose control in TRT group who were on larger doses of oral medications or insulin. Ultimately, the results from a large prospective double blind study of these associations would be able to either fully support or refute these findings.

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Authors Contributions

NA designed the study and wrote the manuscript, NA is the guarantor of the study and, as such, had full access to all the data and takes full responsibility for the integrity of the data. NS Collected the data and GB Performed the Statistical analysis and takes full responsibility for the accuracy of data analysis.

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