
Prevalence and Characteristics of Low Serum Testosterone Levels in Men with Type 2 Diabetes Mellitus Naïve to Injectable Therapy

International Society for Sexual Medicine 2014

Presenter: Felipe Borges Dos Reis

Author(s): Paula Polzer, Xiao Ni

Disclosure

- ◆ Medical advisor at Eli Lilly

Background

- ◆ Male hypogonadism is defined by low serum testosterone (T) levels and associated clinical symptoms
- ◆ Prevalence is higher among men with type 2 diabetes mellitus (T2DM)
- ◆ The Endocrine Society, and other relevant international societies, recommend assessment of testosterone levels in men with T2DM.

Objective

- ◆ To assess the prevalence of a low testosterone level and its association with other baseline characteristics in men with T2DM in a phase 3 randomized clinical trial of the once weekly GLP-1 receptor agonist dulaglutide versus metformin.

Methods

- ◆ This was a post hoc analysis of baseline data from participants enrolled in a phase 3, randomized, double-blind, parallel-arm, active comparator, 52-week study designed to assess the safety and efficacy of dulaglutide.

Methods: Inclusion and exclusion criteria

Key Inclusion Criteria:

- ◆ Type 2 diabetes for ≥ 3 months and ≤ 5 years
- ◆ Screening HbA1c $\geq 6.5\%$ to $\leq 9.5\%$
- ◆ Treatment naïve; not optimally controlled with diet + exercise alone; OR receiving 1 oral antihyperglycemic at $\leq 50\%$ of max recommended daily dose for ≥ 3 months
- ◆ Stable weight ($\pm 5\%$) for ≥ 3 months prior to screening
- ◆ BMI 23 to 45kg/m^2 , inclusive
- ◆ Only male participants evaluated in the present analysis, men receiving T replacement (n=3) were excluded from analysis

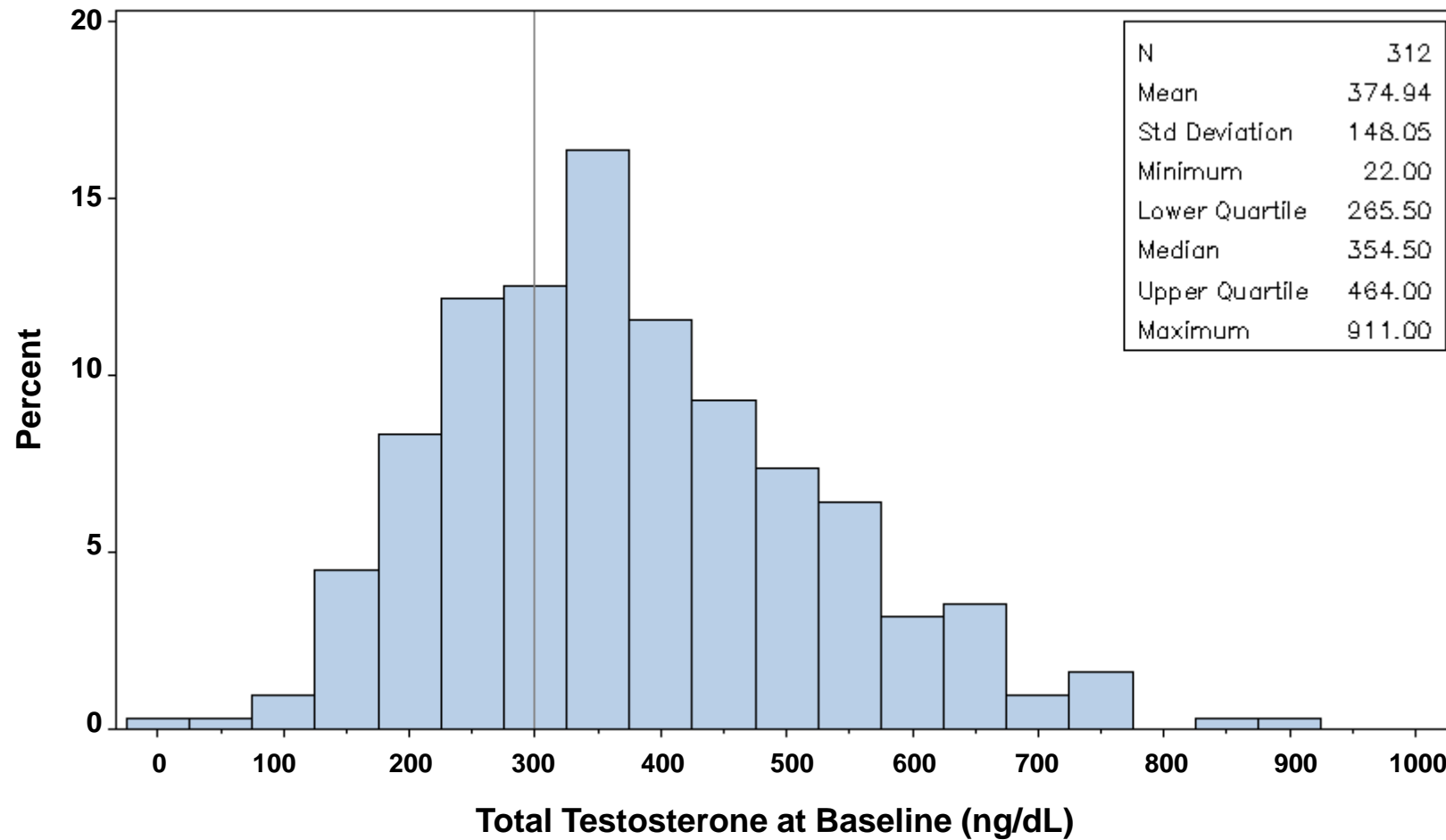
Key Exclusion Criteria:

- ◆ Type 1 diabetes mellitus
 - ◆ Prior chronic use of insulin
 - ◆ Use of glucagon-like peptide-1 receptor agonist within 3 months of study entry
 - ◆ Within 2 months prior to study entry: acute myocardial infarction, New York Heart Association (NYHA) class IV heart failure, or cerebrovascular accident
 - ◆ Received chronic (≥ 14 days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, or inhaled preparations) within 4 weeks prior to screening
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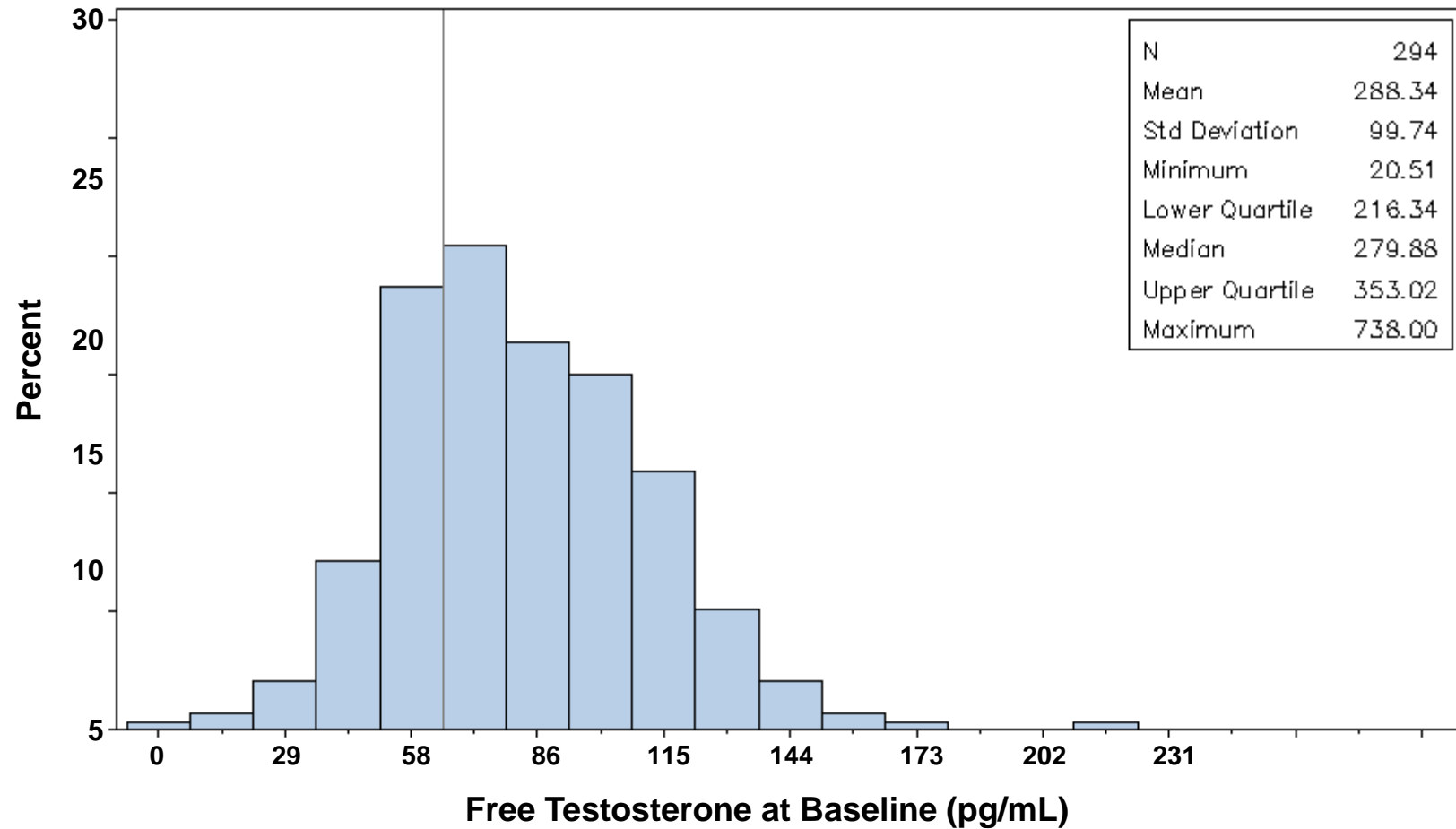
Methods: Measures and statistical analysis

- ◆ Low total T (TT) defined as <300 ng/dL or a previous diagnosis of hypogonadism. Serum T levels testing performed using Liquid Chromatography-Mass Spectrometry
- ◆ Low Free T (FT) defined as <65 pg/mL. FT calculated using the Vermeulen equation (de Ronde et al) based on serum albumin collected at screening, and TT and SHBG collected at baseline
- ◆ A two-sample t-test and Fisher's exact test were used to compare testosterone subgroups for continuous and categorical variables, respectively. Pearson's correlation coefficients were calculated between T levels and continuous variables. Findings were considered statistically significance at $p < 0.05$.

Results: Distribution of baseline total testosterone measurements



Results: Distribution of baseline calculated free testosterone values



Results: Baseline characteristics by low vs. normal total or free testosterone levels

| Variable | Total Testosterone (TT) | | | Free Testosterone (FT) | | |
|--|-------------------------|----------------------|------------------|------------------------|----------------------|------------------|
| | Low TT (N=101) | Normal TT (N=211) | P-value | Low FT (N=85) | Normal FT (N=209) | P-value |
| Age (years), mean (SD) | 56.7 (8.5) | 56.0 (10.4) | 0.82 | 60.0 (8.9) | 55.1 (9.7) | <0.001 |
| Age ≥65 years, n (%) | 19 (18.8) | 39 (18.5) | 1.0 | 15 (29.4) | 31 (14.8) | 0.005 |
| Race (%) | | | 0.54 | | | 0.16 |
| White | 81 (80.2) | 151 (71.6) | | 72 (84.7) | 158 (75.6) | |
| Black/African-American | 6 (5.9) | 13 (6.2) | | 7 (8.2) | 12 (5.7) | |
| Asian | 7 (6.9) | 22 (10.4) | | 2 (2.4) | 11 (5.3) | |
| American Indian/Alaska native | 7 (6.9) | 23 (10.9) | | 4 (4.7) | 26 (12.4) | |
| BMI (kg/m²), mean (SD) | 34.6 (5.3) | 30.8 (4.6) | <0.001 | 34.3 (4.7) | 31.4 (5.0) | <0.001 |
| Weight (kg), mean (SD) | 107.1 (21.0) | 92.7 (16.1) | <0.001 | 106.3 (18.4) | 95.0 (17.1) | <0.001 |
| HbA1c (%) | 7.63 (0.92) | 7.62 (0.89) | 1.0 | 7.57 (0.87) | 7.62 (0.89) | 0.92 |
| ≤7.0%, n (%) | 36 (35.6) | 64 (30.3) | 0.37 | 30 (35.3) | 69 (33.0) | 0.79 |
| HOMA2-%B, mean (SD) | 75.4 (38.4) | 73.6 (39.1) | 0.93 | 77.1 (39.7) | 73.2 (38.9) | 0.75 |
| HOMA2-%S, mean (SD) | 40.8 (20.7) | 52.8 (33.3) | 0.008 | 40.3 (21.3) | 51.1 (32.3) | 0.032 |

Low TT = TT<300ng/dL; normal TT=TT≥300 ng/dL; Low FT=FT<65pg/mL; normal FT=FT≥65pg/mL;
HbA1c=hemoglobin A1c; HOMA2=homeostatic model assessment 2; %B=beta-cell function [c-peptide based];
%S=insulin sensitivity [insulin based]

Results: Baseline Diabetes Symptom Checklist (revised version) scores by low vs. normal total testosterone and free testosterone levels

| Variable | Total Testosterone | | | Free Testosterone | | |
|---|--------------------|-------------------------|--------------|--------------------|----------------------|--------------|
| | Low TT (N=101) | Normal TT (N=211) | P- value | Low FT (N=85) | Normal FT (N=209) | P-value |
| DSC-r Psychology: Fatigue, mean (SD) | 1.28 (1.22) | 1.10 (1.09) | 0.45 | 1.34 (1.23) | 1.12 (1.0) | 0.34 |
| DSC-r: Lack of Energy, N (%) yes | 53 (52.5) | 96 (45.7) | 0.28 | 44 (51.8) | 98 (47.1) | 0.52 |
| Yes, mean (SD) | 2.72 (0.91) | 2.35 (0.79) | 0.044 | 2.75 (0.92) | 2.38 (0.79) | 0.053 |
| DSC-r: Overall Fatigue, N (%) yes | 55 (54.5) | 101 (48.1) | 0.33 | 51 (60.0) | 100 (48.1) | 0.072 |
| Yes, mean (SD) | 2.62 (0.97) | 2.41 (0.89) | 0.39 | 2.61 (0.90) | 2.43 (0.93) | 0.53 |
| DSC-r: Increasing Fatigue, N (%) yes | 46 (45.5) | 103 (49.0) | 0.63 | 41 (48.2) | 103 (49.5) | 0.90 |
| Yes, mean (SD) | 2.65 (1.08) | 2.39 (0.87) | 0.29 | 2.59 (1.00) | 2.43 (0.94) | 0.67 |
| DSC-r: Morning Fatigue N (%) yes | 42 (41.6) | 94 (44.8) | 0.63 | 38 (44.7) | 91 (43.8) | 0.90 |
| Yes, mean (SD) | 2.52 (0.99) | 2.26 (0.95) | 0.33 | 2.47 (0.95) | 2.26 (0.96) | 0.53 |
| DSC-r Psychology: Cognitive, mean (SD)* | 0.79 (0.88) | 0.80 (0.91) | 1.00 | 0.82 (0.91) | 0.79 (0.90) | 0.97 |

For both TT and FT, no significant differences were seen between groups for the DSC-r Cognitive items Sleepy/Drowsy, Difficulty concentrating, Fuzzy-headed feeling, and Difficulty paying attention (all $p \geq 0.287$, data not shown).

Results: Baseline comorbid conditions or medication use by low versus normal total testosterone and free testosterone levels

| Variable, n (% yes) | Total Testosterone | | | Free Testosterone | | |
|--|--------------------|-------------------------|------------------|-------------------|-------------------------|--------------|
| | Low TT (N=101) | Normal TT (N=211) | P-value | Low FT (N=85) | Normal FT (N=209) | P-value |
| LUTS/BPH | 9 (8.9) | 8 (3.8) | 0.106 | 9 (10.6) | 8 (3.8) | 0.049 |
| Cardiovascular | 18 (17.8) | 23 (10.9) | 0.107 | 14 (16.5) | 27 (12.9) | 0.50 |
| Dyslipidemia | 63 (62.4) | 100 (47.4) | 0.015 | 55 (64.7) | 105 (50.2) | 0.028 |
| Depression | 10 (9.9) | 13 (6.2) | 0.25 | 9 (10.6) | 14 (6.7) | 0.34 |
| Erectile dysfunction | 11 (10.9) | 9 (4.3) | 0.045 | 10 (11.8) | 9 (4.3) | 0.033 |
| PDE5i | 3 (3.0) | 2 (0.9) | 0.33 | 3 (3.5) | 2 (1.0) | 0.15 |
| Statin | 53 (52.5) | 59 (28.0) | <0.001 | 41 (48.2) | 68 (32.5) | 0.016 |
| Non-statin lipid lowering medication (LLM) | 9 (8.9) | 24 (11.4) | 0.56 | 10 (11.8) | 23 (11.0) | 0.84 |

Low TT = total testosterone <300 ng/dL; normal TT = TT≥300ng/dL; Low FT = low free testosterone <65 pg/mL; normal FT = free testosterone ≥65 pg/mL; LUTS/BPH= lower urinary tract symptoms suggestive of benign prostatic hyperplasia; PDE5i= phosphodiesterase type 5 inhibitor

Results: Correlations with total or free testosterone levels

| Variable, | Total Testosterone (N=312) | | | Free Testosterone (N=294) | | |
|--------------------|----------------------------|----------------|------------------|---------------------------|----------------|------------------|
| | N | Corr Coeff. | P | N | Corr Coeff. | P |
| Age | 312 | 0.0382 | 0.50 | 294 | -0.1993 | <0.001 |
| BMI | 312 | -0.3587 | <0.001 | 294 | -0.3086 | <0.001 |
| Weight | 312 | -0.3627 | <0.001 | 294 | -0.3377 | <0.001 |
| HbA1c | 312 | -0.0776 | 0.17 | 294 | -0.0192 | 0.74 |
| HOMA2-%B (insulin) | 296 | -0.0198 | 0.74 | 280 | -0.0461 | 0.44 |
| HOMA2-%S | 280 | 0.2021 | <0.001 | 142 | 0.1826 | 0.030 |
| Free Testosterone | 294 | 0.8501 | <0.001 | | | |

| Variable | Total T (N=312) | | | Free T (N=294) | | |
|-----------------------------------|-----------------|----------------|--------------|----------------|----------------|--------------|
| | N | Corr Coeff. | P | N | Corr Coeff. | P |
| DSC-r Psychology, Fatigue | 311 | -0.0943 | 0.097 | 293 | -0.0689 | 0.24 |
| Lack of Energy (yes) | 149 | -0.2632 | 0.001 | 142 | -0.1826 | 0.030 |
| Overall Fatigue (yes) | 156 | -0.0969 | 0.23 | 151 | -0.0738 | 0.37 |
| Increasing Fatigue (yes) | 149 | -0.0855 | 0.30 | 144 | -0.1247 | 0.14 |
| Morning Fatigue (yes) | 136 | -0.1963 | 0.022 | 129 | 0.1100 | 0.21 |
| DSC-r Psychology, Cognitive | 311 | -0.0288 | 0.61 | 293 | -0.0067 | 0.91 |
| Sleepy/Drowsy (yes) | 165 | -0.1500 | 0.054 | 161 | -0.985 | 0.21 |
| Difficulty Concentrating (yes) | 105 | -0.1127 | 0.25 | 99 | -0.643 | 0.53 |
| Fuzzy-headed feeling (yes) | 81 | -0.541 | 0.63 | 75 | 0.0072 | 0.95 |
| Difficulty paying attention (yes) | 97 | 0.0052 | 0.96 | 92 | 0.0584 | 0.58 |

HbA1c = hemoglobin A1c; HOMA2= homeostatic model assessment 2; %B= beta-cell function [c-peptide based]; %S= 13
insulin sensitivity [insulin based]; Diabetes Symptom Checklist (revised version)

Conclusions

- ◆ In a population of men with T2DM naïve to injectable therapy, approximately one-third (n=101) had untreated low TT, and there were only 3 additional men receiving T replacement therapy.
- ◆ Men with low TT were of similar age and had comparable HbA1c to men with normal TT, but had higher weight and BMI, and reduced insulin sensitivity. Low T levels correlated with patient-reported lack of energy.
- ◆ These data support Endocrine Society Guidelines for measuring testosterone levels in men with T2DM. Further study is needed to evaluate the role of T replacement in T2DM.

References

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