

# Borderline-low testosterone levels are associated with lower left ventricular wall thickness in firefighters: An exploratory analysis

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## Abstract

**Background:** Low endogenous testosterone has been associated with increased cardiovascular risk in men.

**Objectives:** To determine the prevalence of low serum testosterone level (TT) in a cohort of male US career firefighters and to examine its relation with left ventricular wall thickness (LVWT).

**Materials and Methods:** We conducted a cross-sectional study among 341 career firefighters, (age:  $37.5 \pm 10.3$  years; BMI:  $28.9 \pm 4.5$  kg/m<sup>2</sup>), who underwent an occupational medical screening examination. TT quartiles were determined, and LVWT distribution among them was plotted. Then, TT values were categorized as low (<264 ng/dL), borderline (264-399 ng/dL), reference range (400-916 ng/dL), and high (>916 ng/dL). To further investigate the association of mildly decreased TT on LVWT, we divided the borderline group into borderline-low (264-319 ng/dL) and borderline-high (320-399 ng/dL) ranges. LVWT values were classified as low LVWT when <0.6 cm. A multivariate model was used to compare LVWT, age, BMI, systolic blood pressure (SBP), and HbA1c among groups by TT values.

**Results:** The prevalence of low TT was 10.6% and of borderline was 26.4%, while 58.7% had levels in the reference range. The low-TT group was older and had higher BMI and SBP as compared to the reference group ( $P < .01$ ). LVWT values were different among groups ( $P = .04$ ) and significantly lower in firefighters with borderline-low TT as compared to the reference group ( $P < .05$ ). This finding also occurred within obese firefighters ( $P = .03$ ). The borderline-low group had a higher adjusted risk for a low LVWT as compared to the reference group [OR: 4.11 (95% CI: 1.79-9.43)].

**Discussion:** Our findings highlight the possible relationship between a mild reduction in testosterone levels (borderline) and lower LVWT.

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**Conclusions:** A high prevalence of subnormal TT levels (low and borderline: 37%) was observed in this relatively homogeneous cohort of career firefighters. Mildly decreased TT levels and lower LVWT might represent a preclinical condition and a window of opportunity for cardiovascular preventive interventions in firefighters.

**KEYWORDS**

cardiac structure, cardiovascular risk, firefighter, heart, left ventricular, preclinical testosterone deficiency, testosterone

## 1 | INTRODUCTION

Testosterone deficiency in men has been increasingly recognized in clinical settings, and its pathologic correlates have generated increased research interest worldwide. Both basic and clinical studies have provided evidence that testosterone acts on the cardiovascular system in both health and disease.<sup>1,2</sup> Specifically, low serum testosterone has been associated with increased cardiovascular risk in men.<sup>3-5</sup> A recent robust meta-analysis of prospective observational studies compared men with baseline serum testosterone levels in either the lower or higher quartiles and supported that low testosterone predicts cardiovascular mortality and morbidity in aging men.<sup>6</sup> Furthermore, interactions between endogenous total testosterone levels (TT) and cardiac structural and functional parameters have been reported recently,<sup>7-10</sup> although causality has not been unequivocally established.<sup>3,8,11</sup> The association between low TT and impairments in cardiovascular health is of particular concern among firefighters who are exposed to high levels of cardiovascular strain and who have a high duty-related death rate due to sudden cardiac events.<sup>12,13</sup>

Firefighting is dangerous and involves multiple hazards; however, the leading cause of on-duty firefighter fatalities is sudden cardiac death (SCD), which account for approximately 50% of US firefighter's on-duty deaths.<sup>14</sup> Although fire suppression activities account for a small portion of duty time (~1%), a large percentage of fatalities occur during this activity (~32%), resulting in greatly increased odds of suffering a sudden cardiac event following fire suppression versus station duties.<sup>15,16</sup> Cardiovascular disease in the fire service is influenced by occupational exposures and individual factors, and the triggering of a serious cardiovascular event in a firefighter involves multiple overlapping and synergistic factors.<sup>12</sup> Firefighters with hypertension, dyslipidemia, obesity, and diabetes have an increased risk of suffering a duty-related cardiac event compared to those without these risk factors.<sup>17</sup> Structural changes to the myocardium, specifically cardiomegaly and left ventricular hypertrophy (LVH), are important modifiers of such risk among US firefighters.<sup>18</sup> However, one important factor that has not received research attention in this important public safety occupational cohort is the role of endogenous TT. This is an important area of study due to the known cardiovascular risks of firefighting and the involvement of testosterone on cardiovascular physiology and pathophysiology.<sup>3,5,7,19</sup>

To our knowledge, the prevalence of low TT among firefighters has not been investigated, despite several population studies that have demonstrated an association between low testosterone and dysmetabolic conditions,<sup>20</sup> and a high prevalence of obesity, diabetes, and metabolic syndrome

in the fire service, which in turn are associated with increased risk of cardiovascular events.<sup>1,21-23</sup> Thus, we initially sought to determine the prevalence of low testosterone among firefighters, considering their high rates of obesity. Then, in light of the scarcity of data on the relationships between endogenous testosterone levels and the heart in humans, and the uncertainties regarding the strength and direction of the association between low testosterone and increased cardiovascular morbidity, we hypothesized that low testosterone would be related to structural abnormalities of the heart in male firefighters, possibly favoring decreased ventricular mass given the evidence from mouse models showing decreased heart mass and cardiomyocyte size in the absence of testosterone action.<sup>24,25</sup>

Therefore, we performed an exploratory study based on data from a routine medical screening examination of a series of 341 male US career firefighters, with the aims of determining the prevalence of low testosterone in these men and examining its association with a cardiac structure parameter, left ventricular wall thickness (LVWT).

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and subjects

We conducted a cross-sectional study with a convenience sample of US firefighters from a metropolitan fire department in Florida. All career male firefighters who underwent a medical screening examination and had a normal ejection fraction (>55%) and no work restriction were included ( $n = 341$ ). Clinical evaluations were conducted at an occupational health clinic that performs annual medical evaluations on a contract basis. The examination was consistent with guidance in the NFPA 1582: Standard on a Comprehensive Occupational Medical Program, and included a screening cardiac ultrasound and the assessment of serum total testosterone. Data were obtained retrospectively based on the medical records.

Deidentified records were sent to the research team who extracted relevant data. The study protocol was approved by the Skidmore College Institutional Review Board.

### 2.2 | Study population characterization and data collection

Participant's heights and weights were measured using a calibrated stadiometer with a weighing scale, and BMIs were calculated (kg/

m<sup>2</sup>). Resting blood pressure (BP) was measured by a trained health-care provider with the firefighter in a seated position.<sup>26</sup> A trained sonographer obtained left ventricular wall thickness (LVWT) by a resting transthoracic cardiac echocardiogram, done as a simple two-dimensional (2-D) study with limited m-mode recordings.

Blood samples were obtained in the morning when firefighters reported to duty, after 8- to 10-hour overnight fasting as part of the routine visit for medical evaluation. Serum total testosterone (TT) determinations were performed by LabCorp (Laboratory Corporation of America, Burlington, NC, USA), using an electrochemiluminescence assay (ECLIA, Roche Diagnostics, Indianapolis, IN, USA). Reference interval for adult males was determined by the laboratory based on standardization of the assay to the CDC reference method, calculated as 264 - 916 ng/dL<sup>7,27</sup> (labcorp.com/assets/11476).

### 2.3 | Data analysis

Serum TT values were initially presented as a continuous variable, using the assay reference range (264 to 916 ng/dL),<sup>7,27</sup> and TT quartiles were determined to characterize the TT profile of the study population. Thereafter, TT was grouped as low (<264 ng/dL), borderline (264-399 ng/dL), reference range (400-916 ng/dL), and high (>916 ng/dL), as previously reported for standardized CDC reference assays.<sup>7,27</sup>

Subsequently, based on our initial exploratory results, the characteristics of the study population, and the complex nature of our variables (TT and LVWT) which might associate with several modifying factors, we subdivided the borderline-TT group into borderline-low (264-319 ng/dL) and borderline-high (320-399 ng/dL). For this analysis, we used similar cutoff points as those proposed in the current US Endocrine Society guidelines,<sup>7</sup> which considers the correlation of TT levels and the presence or absence of symptoms and more or less severe testosterone deficiency, respectively.

After performing descriptive exploratory and prevalence estimates, we excluded the high TT group (n = 15) as those supraphysiological values could be associated with different situations, including the possibility of testosterone replacement therapy.

Participants' LVWT values were categorized into two groups: low LVWT (<0.6 cm) vs normal-high based on the cutoff point for low LVWT published by the American Society of Echocardiography and the European Association of Cardiovascular Imaging.<sup>28</sup>

We then compared LVWT, age, BMI, systolic blood pressure (SBP), and glycosylated hemoglobin (HbA1c) among groups defined by different TT cutoff values. Comparisons among the groups were also performed according to body mass index using standardized BMI classification for overweight (25.0 ≤ BMI <30.0 kg/m<sup>2</sup>) and obesity (BMI ≥ 30.0 kg/m<sup>2</sup>). For this analysis, we merged the borderline-high with the reference group due to the small number of cases within each BMI category in the borderline-high group and the lack of differences between those two groups (borderline-high

vs. reference) in all analytical steps. A similar analysis among normal-weight firefighters was not applicable because of the small number of participants with low and borderline-low TT levels within this group, which precludes a statistical analysis.

### 2.4 | Statistical analyses

The normality of the variables' distributions was confirmed in the groups and subgroups using the Kolmogorov-Smirnov test and the Q-Q plot analysis<sup>29</sup>. Homogeneity of variance was also confirmed using Levene's test in all groups and subgroups.

As the first step of the exploratory analysis, we plotted testosterone in relation to LVWT for all men and for each BMI category. ANOVA was performed to compare differences between groups using Tukey's post hoc analysis and ANCOVA to adjust comparisons of LVWT by confounder variables (age, BMI, SBP, and HbA1c) followed by Bonferroni's post hoc analysis. The differences were considered statistically significant when a two-tailed *P*-value was less than or equal to 5% (≤0.05). Chi-squared test was used to analyze the association between TT and LVWT. To express the strength of association, the crude and the adjusted odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. IBM SPSS Statistics® 21 (IBM Corporation, USA) software package was used for data processing and analysis and Prism 8 for Mac (GraphPad Software, USA) for graphic design.

## 3 | RESULTS

The characterization of our study population is summarized in Table 1. Mean age ± standard deviation (SD) of the firefighters was 37.5 ± 10.3 years old, ranging from 19 to 69 years. Almost 85% of the participants were 50 years old or less, and 99.4% were below 60 years old. The mean ± SD BMI was 28.9 ± 4.5 kg/m<sup>2</sup>, ranging from 17.5 to 45.5 kg/m<sup>2</sup>. Only 18.8% (64 firefighters) of the sample had normal BMI, while 45.7% (n = 156) were overweight, and 35.5% (n = 121) were in the obese range; 36.0% (n = 123) had arterial hypertension, and only 12.9% (n = 44) had HbA1c levels at the diabetic or pre-diabetic range.

The descriptive analysis of TT and LVWT distribution among all men and separated by BMI is presented in Figure 1. The distribution of LVWT by quartiles of TT obtained in the entire study population is shown in Figure 2, which preliminary suggested lower LVWT levels in the lower TT quartile (Figure 2; Q1: TT < 347 ng/dL).

The adjusted comparisons of all variables by TT categories using different cutoff points are presented in Table 2. After comparison according to TT quartiles, we further analyzed all variables according to the standardized reference range of TT. The prevalence of severe low testosterone among this US career firefighter cohort was 10.6% (36 participants) using the most stringent criteria (<264 ng/dL). Ninety participants (26.4%) had borderline values of TT, the majority (n = 200; 58.7%) were in the reference range,

**TABLE 1** Demographic Characteristics of the sample

	Participants (n = 341)
Age	37.5 ± 10.3 y
BMI	28.9 ± 4.5 kg/m <sup>2</sup>
BMI—categories, n (%)	
Normal weight	64 (18.8)
Overweight	156 (45.7)
Obese	121 (35.5)
Systolic BP	121.3 ± 7.7 mmHg
Diastolic BP	77.0 ± 5.4 mmHg
Hypertension—categories, n (%) <sup>†</sup>	
Stage one (SBP: 130-139 or DBP: 80-89 mmHg)	114 (33.4)
Stage two (SBP: ≥140 or DBP: ≥90 mmHg)	9 (2.6)
HbA1c	5.4 ± 0.7%
HbA1c—categories, n (%) <sup>#</sup>	
Pre-diabetes (5.7%-6.4%)	36 (10.6)
Diabetes (>6.4%)	8 (2.3)
Serum total testosterone	491.8 ± 245.5 ng/dL
LVWT	0.79 ± 0.2 cm
LVWT < 0.6, n (%)	62 (18.2)

Note: Continuous variables are expressed as mean ± standard deviation. #: 2020 American Diabetes Association; \*: 2017 American College of Cardiology/American Heart Association.

Abbreviations: BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; LVWT, left ventricular wall thickness; SBP, systolic blood pressure.

while 15 (4.4%) had values above the upper TT reference range. The low-TT group was older ( $43.3 \pm 9.2$  vs.  $36.6 \pm 10.2$  years old) and had higher BMI ( $32.7 \pm 5.3$  vs.  $27.9 \pm 4.2$  kg/m<sup>2</sup>) and SBP ( $124.7 \pm 6.8$  vs.  $120.2 \pm 7.1$  mmHg), as compared to the reference group ( $P < .01$  for all those variables). In contrast, the borderline-TT group was younger and had a significantly lower BMI than the low-TT group ( $37.6 \pm 10.8$  years old and  $29.7 \pm 4.0$  kg/m<sup>2</sup>, respectively;  $P < .01$ ). LVWT tended to vary among TT groups with lower values in firefighters in the borderline-TT group ( $P = .06$ ). There were no differences between ejection fraction (EF) in these groups (63.1%-64.4%;  $P = .31$ ) (data not shown).

The borderline-TT group (264-399 ng/dL) had lower LVWT after adjusting for confounders (LVWT =  $0.74 \pm 0.20$ ;  $P = .04$ ). We then performed a subsequent analysis separating the borderline-TT group into borderline-low and borderline-high subgroups. The results of this subgroup analysis demonstrate that LVWT values were significantly lower in firefighters with borderline-low TT levels (LVWT =  $0.69 \pm 0.20$  cm; TT = 264-320 ng/dL) than in those of the reference group (LVWT =  $0.80 \pm 0.20$  cm; TT = ≥400 ng/dL), in the adjusted model. In addition, LVWT levels in the low-TT group were very similar to those in the reference groups, although not significantly different from the borderline-low group in the *post hoc* analysis. The borderline-low group was significantly younger than

the low-TT group and had significantly lower BMI and SBP when compared to the reference group and the low-TT group (Table 2).

To explore the risk of low LVWT, we analyzed the odds ratios for different TT groups. TT and LVWT categories (LVWT < 0.6 vs LVWT ≥ 0.6 cm) were significantly associated ( $P < .05$ ). Only the borderline-low testosterone group had a significantly higher odds for a low LVWT (<0.6 cm) compared to the reference group, which remained significant after adjustment for confounders, as shown in Table 3.

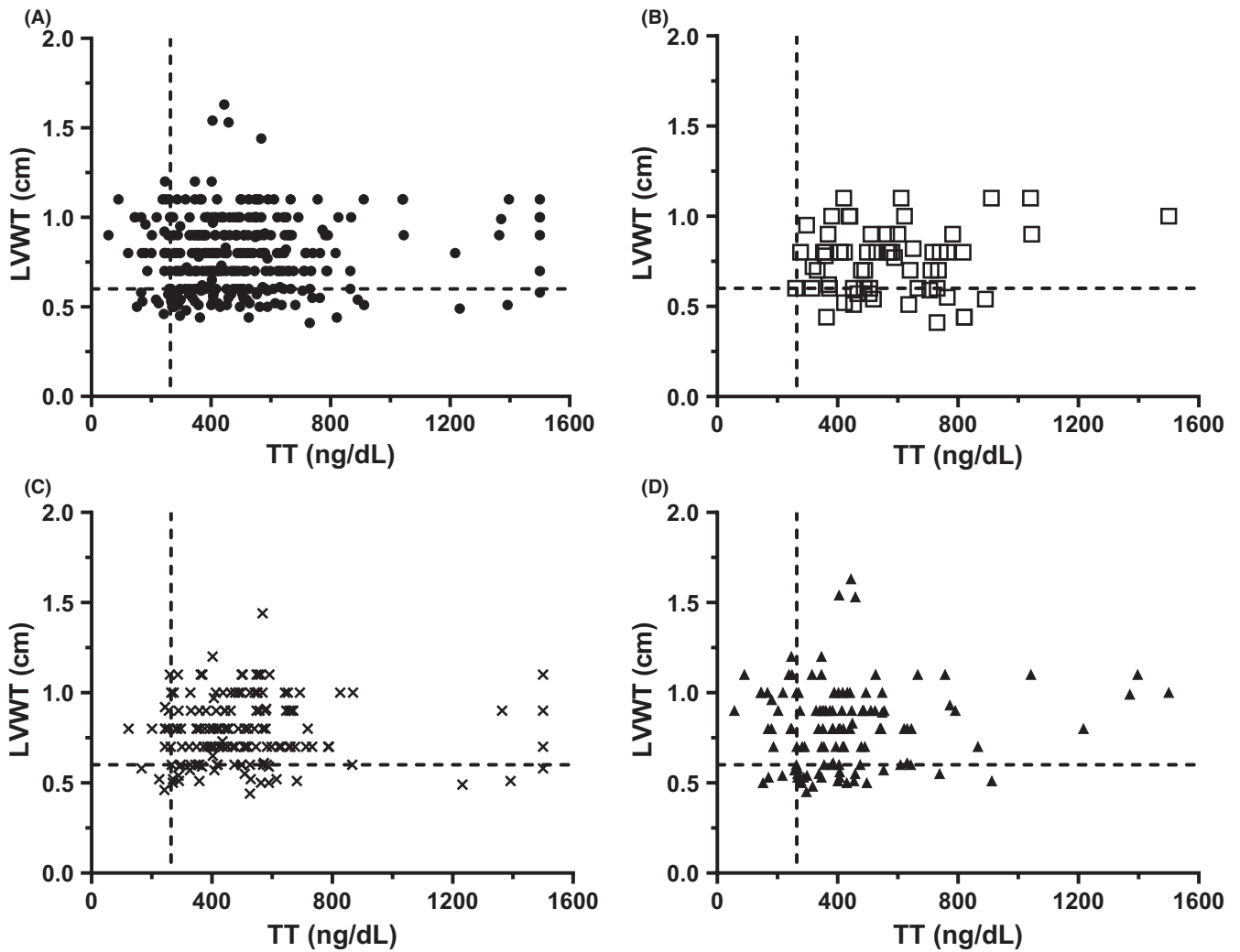
In an additional approach to isolate the effect of BMI on LVWT, we investigated TT and LVWT values within obese or overweight men. As in the entire sample, the obese firefighters with borderline-low TT had a significantly lower LVWT. A similar analysis in the overweight group revealed no differences in LVWT among the TT categories ( $P = .421$ ) nor in HbA1c levels ( $P = .58$ ), whereas age, BMI, and SBP were higher in the low-TT group as compared with the group with reference TT values (data not presented).

## 4 | DISCUSSION

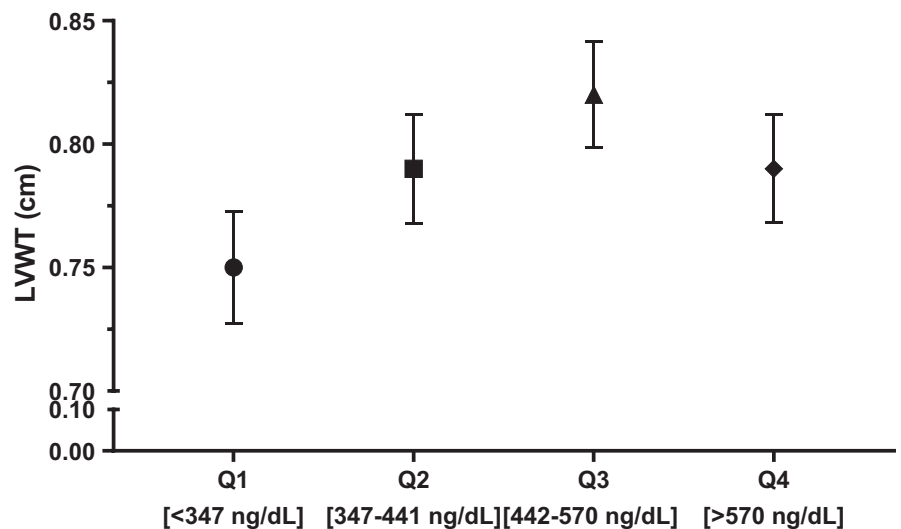
We retrospectively analyzed cross-sectional data from an annual medical evaluation of 341 male US career firefighters and found a 10.6% prevalence of low testosterone values (TT < 264 ng/dL) and 26.4% of borderline values (264-399 ng/dL).<sup>7</sup> LVWT was significantly lower among firefighters in the borderline category of serum TT, mostly in the borderline-low category, and a similar pattern of lower LVWT was also seen when only obese firefighters were analyzed. Importantly, the odds ratio of having a reduced LVWT was fourfold higher among firefighters with borderline-low TT compared to the reference TT group.

To our knowledge, this is the first study to report prevalence data of low testosterone levels in the US fire service. Previous epidemiological studies have estimated the prevalence of clinically diagnosed male hypogonadism as 2% to 6%, whether only in elderly or middle-aged and aging men.<sup>30-32</sup> When prevalence determination was based only on testosterone levels and not on the presence of typical clinical manifestations of hypogonadism, prevalence estimates were as high as 29% and 38.7%.<sup>21,31</sup> Our findings suggest that a significant portion of the fire service may present with low TT and that national estimates of prevalence are needed for the fire service.

Overall, our findings are consistent with the known decrease in testosterone levels as a function of age and BMI.<sup>1,6,21</sup> The associations between testosterone levels and age are still controversial, in part because TT also decreases as a consequence of common comorbidities found in older men, such as obesity and diabetes.<sup>22,23,33-35</sup> Nevertheless, our study population was composed mainly of young and middle-aged firefighters; thus, aging was an improbable independent factor impacting serum testosterone levels. On the other hand, the majority of firefighters in this cohort were overweight or obese and obesity is the chronic condition associated with the most significant decline in testosterone levels in men.<sup>21,36,37</sup> In our study, as in the general population, a significantly higher BMI was found in



**FIGURE 1** Scatter plot showing the relationship between total testosterone (TT) and left ventricular wall thickness (LVWT) in male career firefighters (n = 341). As body mass index (BMI) is an important confounder, subjects are shown as a whole group (A) or separated by their BMI: normal (B), overweight (C), and obese (D). Dashed lines indicate the threshold for low TT (264 ng/dL) and low LVWT (0.6 cm) adopted in this study



**FIGURE 2** Mean  $\pm$  SE of LVWT adjusted by age, body mass index, systolic blood pressure, and HbA1c in groups divided by the sample quartiles of serum TT concentration ( $P = .19$ )

**TABLE 2** Comparison of LVWT, Age, BMI, SBP, and HbA1c (mean  $\pm$  SD) by total testosterone groups among male career firefighters using different cutoff points for categorization (n = 341)

	Quartile 1 (n = 85) [<347 ng/dL]	Quartile 2 (n = 84) [347-441 ng/dL]	Quartile 3 (n = 87) [442-570 ng/dL]	Quartile 4 (n = 85) [>570 ng/dL]	P
LVWT (cm)	0.76 $\pm$ 0.21	0.79 $\pm$ 0.18	0.82 $\pm$ 0.22	0.78 $\pm$ 0.19	.35
LVWT <sup>#</sup> (cm)	0.75 $\pm$ 0.21	0.79 $\pm$ 0.20	0.82 $\pm$ 0.20	0.79 $\pm$ 0.20	.19
Age (y)	41.2 $\pm$ 10.3 <sup>a,b,c</sup>	37.1 $\pm$ 9.7	36.5 $\pm$ 10.2	35.4 $\pm$ 10.3	<.01
BMI (kg/m <sup>2</sup> )	31.4 $\pm$ 4.6 <sup>a,b,c</sup>	29.0 $\pm$ 4.3 <sup>c</sup>	28.2 $\pm$ 3.5	27.2 $\pm$ 4.7	<.01
SBP (mmHg)	124.7 $\pm$ 7.6 <sup>a,b,c</sup>	120.5 $\pm$ 7.1	119.6 $\pm$ 7.2	120.6 $\pm$ 8.0	<.01
HbA1c (%)	5.61 $\pm$ 0.80 <sup>b,c</sup>	5.45 $\pm$ 0.94	5.25 $\pm$ 0.30	5.27 $\pm$ 0.42	<.01
	Low-TT (n = 36) [<264 ng/dL]	Borderline-Low TT (n = 35) [264-319 ng/dL]	Borderline-high TT (n = 55) [320-399 ng/dL]	Reference range TT (n = 200) [400-916 ng/dL]	P
LVWT (cm)	0.82 $\pm$ 0.20 <sup>d</sup>	0.70 $\pm$ 0.19 <sup>e</sup>	0.78 $\pm$ 0.17	0.79 $\pm$ 0.20	.04
LVWT <sup>#</sup> (cm)	0.80 $\pm$ 0.21	0.69 $\pm$ 0.20 <sup>e</sup>	0.78 $\pm$ 0.20	0.80 $\pm$ 0.20	.04
Age (y)	43.3 $\pm$ 9.2 <sup>e,f</sup>	40.0 $\pm$ 10.5	36.1 $\pm$ 10.8	36.6 $\pm$ 10.2	<.01
BMI (kg/m <sup>2</sup> )	32.7 $\pm$ 5.3 <sup>e,f</sup>	30.4 $\pm$ 3.8 <sup>e</sup>	29.2 $\pm$ 4.0	27.9 $\pm$ 4.2	<.01
SBP (mmHg)	124.7 $\pm$ 6.8 <sup>e</sup>	124.9 $\pm$ 8.2 <sup>e</sup>	121.2 $\pm$ 8.0	120.1 $\pm$ 7.1	<.01
HbA1c (%)	5.64 $\pm$ 0.79	5.55 $\pm$ 0.45	5.40 $\pm$ 0.75	5.33 $\pm$ 0.69	.05

Note: #: Adjusted for age, BMI, SBP, and HbA1c.

Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin; LVWT, left ventricular wall thickness; P, ANOVA P-value; SBP, systolic blood pressure.

<sup>a</sup>Significantly different from the Quartile 2 group.

<sup>b</sup>Significantly different from the Quartile 3 group.

<sup>c</sup>Significantly different from the Quartile 4 group.

<sup>d</sup>Significantly different from the borderline-low group.

<sup>e</sup>Significantly different from the reference group.

<sup>f</sup>Significantly different from the borderline-high group.

both the low-TT and borderline-low TT groups. This has been extensively recognized worldwide, although reverse causality is still a matter in cross-sectional studies. In addition, the intergroup comparisons of age, SBP, and HbA1c suggest a significant covariation of these factors within TT groups. In other words, a multifactorial interaction of age, BMI, SBP, and HbA1c might have influenced TT levels in this cohort of firefighters.

Our main findings of an independently lower LVWT in the standard borderline-TT group and in the borderline-low subgroup are remarkable. However, LVWT differences were not detected when we compared among TT quartiles, possibly due to the relatively high TT

threshold for the lowest quartile (<347 ng/dL) and the low number of men in the lowest TT category (<264 ng/dL; n = 36; 10.6%), which may have obscured the analysis of borderline levels in this approach. Presenting the quartiles, analysis improves external validity of the data, by better reflecting the overall distribution of TT levels among all men of the study population.<sup>6</sup> In contrast, the categorization analysis has the advantage of increasing intragroup specificity by clustering men based on a similar hormonal and/or clinical profile, providing a further description of a multifactorial, complex biological phenomenon.<sup>27</sup>

Indeed, the reference levels of TT measured by routine standardized immunoassays are still debated worldwide. Crucial

**TABLE 3** Contingency table showing odds ratio of having a low LVWT (<0.6 cm) in male career firefighters with borderline-low TT, borderline-high TT, and low-TT groups compared to those in the TT reference range

Testosterone range	n	% LVWT < 0.6 cm	Crude analysis		Adjusted analysis <sup>#</sup>	
			OR (95% CI)	P	OR (95% CI)	P
Reference range TT (400-916 ng/dL)	200	15.5	1.00	-	1.00	-
Borderline-high TT (320-399 ng/dL)	55	10.9	0.67 (0.26-1.69)	.39	0.73 (CI 0.28 - 1.90)	.52
Borderline-low TT (264-319 ng/dL)	35	42.9	4.09 (1.89-8.84)	<.01	4.11 (1.79 - 9.43)	<.01
Low-TT (<264 ng/dL)	36	19.4	1.32 (0.53-3.27)	.55	1.28 (0.47 - 3.49)	.64

Note: #: Adjusted for body mass index, age, systolic blood pressure.

Abbreviations: LVWT, left ventricular wall thickness; P, Pearson's chi-squared P-value, HbA1c; TT, total testosterone.

evidence-based attempts to determine reference levels were first provided with the publication of the EMAS study in 2010, in which TT concentrations below 317 ng/dL measured by GC-MS (gas chromatography-mass spectrometry) were associated with variable symptoms of TT deficiency, after adjusting for age, in a cohort of community-dwelling middle-aged and older men.<sup>30,33,38</sup> Since that publication, new recommendations have been proposed based on several studies and compiled in meta-analyses and clinical specialties' expert societies, which also provided validation of immunoassays for routine determination of TT in men in clinical practice.<sup>7,39</sup> Given the ongoing debate about reference values, we initially used the reference range by the laboratory that performed the blood work for standard categorization of TT groups. Subsequently, we used 320 ng/dL as the cutoff point for borderline-low or borderline-high subgroups, with the aim of further detailing subtle biological differences associated with borderline TT levels in this particular cohort of men with mild testosterone insufficiency, similar to what was done by Westley et al.<sup>7,39,40</sup>

Testosterone production is well-accepted as an indication of men's general health, and there is accumulating evidence that low testosterone is detrimental to cardiovascular health. However, there is a lack of clinical data on the associations between serum TT and cardiac structure, and reverse causality between testosterone levels and cardiovascular health cannot be ruled out. While little work has been done to characterize the relationship between serum TT and LVWT, animal studies have suggested that low TT is associated with decreased cardiac mass, as reported in the androgen receptor knockout (ARKO) mice. These mice displayed a reduced ratio of heart mass to body weight and impaired cardiac contraction. When treated with angiotensin II, they showed impaired adaptive LV concentric hypertrophy and function, and a reduced cardiomyocyte size.<sup>24,25</sup> Additionally, in a rat model, a 16-week testosterone withdrawal due to orchietomy resulted in substantially impaired cardiac contractility, which was restored by testosterone treatment.<sup>41</sup> Similarly, orchietomy caused a reduced left ventricular mass and impaired tolerance to ischemia-reperfusion injury in rats.<sup>42,43</sup> Recently, a clinical study showed that men with heart failure treated with finasteride, a 5- $\alpha$ -reductase inhibitor which impairs testosterone conversion to its most potent active metabolite, had reduced cardiac hypertrophy compared to untreated men, thus suggesting that androgen action may play a role in controlling pathologic LV hypertrophy in humans.<sup>44</sup> Our findings of a lower LVWT in men with borderline-low-TT are consistent with that data.

However, the finding that LVWT was greater in men in the low TT compared to the borderline-low group was, in part, unexpected. An increased left ventricular wall thickness is recognized as a negative prognostic factor in men with heart failure<sup>4</sup> and a predictor of mortality.<sup>45</sup> LVWT increases with aging and is affected by multiple factors, notably hypertension and obesity. While it is clear that increased LVWT is associated with increased risk of sudden cardiac death,<sup>46</sup> the effects of decreased LVWT on cardiac health and performance are less clear. The greater LVWT that we observed in the low testosterone group may be related to other factors, such as

greater age, BMI, and SBP in this group, as all of these factors are associated with ventricular hypertrophy. An increased BMI is associated with increased LVWT and an increased risk for on-duty SCD in firefighters.<sup>16,47</sup> Additional research is necessary to better understand the multifactorial interactions in the biological system.

There are some limitations in this study. Our data were based on the records of regular medical screening examination of a convenience sample and thus preclude the establishment of cause-and-effect relationships and impose an inherent external validity limitation. The participants had age and BMI very similar to other firefighters' samples from the United States;<sup>48,49</sup> however, the extrapolation of the findings to a non-firefighter population is not direct, due to the specificity of professional duties and potential hazards suffered by firefighters. Also, a single testosterone measurement, inherent to the study design, precludes the determination of an unequivocal diagnosis of testosterone deficiency,<sup>7</sup> which was beyond the scope of the study. Moreover, other potential residual confounding from unmeasured factors might be considered, such as information on smoking that was not available to our study. On the other hand, the association between lower levels of TT and higher age, BMI, and SBP, which are widely evidenced in literature, partially mitigates those limitations. Similarly, the lack of SHBG data in our study represents another potential limitation, given that serum SHBG levels are reduced in obese men and inversely correlate with glucose and insulin levels, as in metabolic syndrome. SHBG is the primary binding protein for TT and thus is considered one of the mediators of low TT in obese men, which represent a large percentage of firefighters in our cohort.<sup>20</sup>

Despite limitations, our multivariate analysis results are consistent, and it is therefore reasonable to propose that the higher odds for a lower LVWT in men with borderline-low testosterone represents a pathological adjustment to a multifactorial condition that accompanies decreased testosterone production. In the low testosterone group, other factors stimulating hypertrophy may override this adjustment—such factors may include aging, obesity, hypertension, and diabetes which are known to promote myocardial hypertrophy. Borderline testosterone levels may occur in the absence of clinically significant symptoms of testosterone deficiency,<sup>7,37</sup> and it is possibly related to deleterious effects on the heart. This suggests a potential condition of preclinical or subclinical testosterone insufficiency that may prove to be an important window for detecting, and possibly managing, mild homeostatic derangements, similar to what happens in pre-diabetes. In other words, detecting a borderline testosterone status offers an opportunity to identify a condition that is otherwise clinically inconspicuous, but that brings accompanying physiological disruption and represents a clear path toward a more serious clinical condition. Similarly, our findings of a higher risk of having a low LVWT in the firefighters with borderline-low testosterone also give rise to the hypothesis of a preclinical cardiac structural modification in a subnormal hormonal environment, which also represent a potential window of opportunity for preventive cardiovascular interventions.

## 5 | CONCLUSIONS

We found a high prevalence of low and borderline-low testosterone measurements in male career firefighters. Those men in the borderline-low range of TT had a higher risk of having a decreased LVWT, compared to other TT range categories. Our findings are novel and highlight the possible occurrence of a preclinical condition characterized by a mild, borderline reduction in testosterone production and concurrent decrease in LVWT. Although exploratory, our data provide new urgency to investigating the interactions between testosterone insufficiency and cardiovascular health in adult men and, specifically, in firefighters. Future studies with random assignment of participants, larger samples, additional cardiac structural and functional evaluations, and repeated serum testosterone measures are needed to clarify the effects of endogenous low testosterone levels on the heart.

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### CONFLICT OF INTEREST

DLS served as a consultant in cases involving firefighters' cardiac issues. The remaining authors have no disclosures to report.

### AUTHORS' CONTRIBUTIONS

ALP, ES, LGGP, and DS were involved in the conception and design of the study, data analysis and interpretation, drafting and writing the article, and approval of the manuscript. AM was involved in data entry, initial data analysis, and reviewing the manuscript. ALP and DS were also involved in critical final revision and approval of the manuscript.

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