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Increased occurrence of marked elevations of lipoprotein(a) in ageing, hypercholesterolaemic men with low testosterone

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Abstract

Objective. We previously examined the inverse relationship between total serum testosterone (T) and the occurrence of the metabolic syndrome in ageing men using baseline data from two lipid treatment studies. We further examined baseline data from a subset of US men participating in one of these two studies to assess the relationship between T and the cardiovascular risk factor lipid, lipoprotein(a) [Lp(a)].

Methods. Baseline T, lipid, glycaemic and anthropometric data were obtained from 107 men (mean age: 55 years). Inclusion criteria included low-density lipoprotein cholesterol $\geq$3.4–4.9 mmol/l and triglycerides $\leq$4.0 mmol/l. Baseline Lp(a) levels were examined across the following baseline T subgroups: $<$15 nmol/l (low/low-normal T) and $\geq$15 nmol/l (normal T).

Results. There was an overall trend for a higher incidence of clinically significant Lp(a) elevations in men with low T; 17.1% of men in the low/low-normal T subgroup had an Lp(a) level $\geq$3 times the upper limit of normal compared to 8.1% in the normal T subgroup.

Conclusions. The data from this descriptive analysis suggest that ageing men with low serum T levels may have an increase in marked elevations in Lp(a), which would be expected to be associated with a significant increase in their cardiovascular event risk.

Keywords: *Hypogonadism, testosterone, lipoprotein(a), ageing men*

Introduction

Previous studies have demonstrated an inverse relationship between serum testosterone (T) levels and a number of cardiometabolic diseases/disorders in ageing men, including abdominal obesity, the metabolic syndrome, type 2 diabetes and elevated C-reactive protein [1–10]. In addition to these diseases and disorders, lipoprotein(a) [Lp(a)] has also been shown to be related to T levels in ageing men. Lp(a) is an independent cardiovascular risk factor – higher Lp(a) levels are associated with greater cardiovascular risk in men and women [11–15]. Castration has been shown to lead to an increase in Lp(a) levels in ageing men with prostate cancer [16]. Moreover, administration of exogenous T has been shown to lower Lp(a) levels in men [17–19]. In light of these findings, we were interested in examining the relationship between T and Lp(a) in ageing men. We had previously reported on the inverse relationship between T and the metabolic syndrome in ageing men participating in two lipid treatment studies. One of the two studies used in this previous analysis included collection of Lp(a) measurements in a subset of US patients [7]; the present analysis examined baseline T and Lp(a) data from this patient subset.

Methods

Inclusion criteria for this study included men and women aged 21–70 years with coronary heart disease (CHD) and/or atherosclerotic disease (AD) with low-density lipoprotein cholesterol (LDL-C) $\geq$3.4 mmol/l; or $\geq$2 CHD risk factors without CHD and/or AD with a LDL-C $\geq$4.1 mmol/l; or without CHD and/or AD and $<$2 risk factors with a LDL-C $\geq$4.9 mmol/l. Additional inclusion criteria included triglycerides (TG) $\leq$4.0 mmol/l. Exclusion

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criteria included a diagnosis of types I, III, IV, V hyperlipidemia or homozygous familial hypercholesterolaemia; lipid-lowering agents taken within 6 weeks and fibrates taken within 8 weeks prior to screening; uncontrolled hypertension (treated or untreated) with systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg; type 1 diabetes or type 2 diabetes with haemoglobin $A1_c \geq 10\%$; and body weight $>50\%$ above or below ideal body weight according to the 1983 Metropolitan Height and Weight Tables [20]. The study protocol was approved by all relevant ethics review committees. Written informed consent was obtained from all patients prior to their participation in the study.

Blood samples were taken in the morning. Serum T was measured by radioimmunoassay and Lp(a) was measured by a competitive enzyme-linked immunosorbent assay. Baseline total serum T and Lp(a) data were examined from a subset of 107 men (mean age: 55 years) who participated at the US sites in this study. Baseline Lp(a) levels were compared across the following baseline T subgroups: <15 nmol/l (low/low-normal T) and ≥ 15 nmol/l (normal T).

Results

Baseline characteristics

Table I provides a summary of the baseline characteristics of the US men included in the present analysis. The low/low-normal T levels accounted for the majority (70/107, or 65%) of men in our analysis population. Compared to men in the normal baseline T subgroup, men in the low/low-normal baseline T subgroup had higher BMI, higher TG levels, lower high-density lipoprotein cholesterol (HDL-C) levels, higher fasting blood glucose (FBG), higher blood pressure and higher mean Lp(a) levels. Additionally, the low/low-normal baseline T subgroup had a higher percentage of men with the metabolic syndrome compared to the normal baseline T subgroup.

Relationship between baseline total serum testosterone and lipoprotein(a) levels

Figure 1 shows a scatter plot of the relationship between T and Lp(a) levels in the men included in this analysis. There was an overall trend for a higher incidence of clinically significant Lp(a) elevations in the low/low-normal baseline T subgroup compared to the normal baseline T subgroup: 17.1% of men in the low/low-normal T subgroup had Lp(a) levels ≥ 3 times the upper limit of normal (>3.2 μmol/l) compared to 8.1% of men in the normal T subgroup (Figure 2).

Discussion

The findings reported in this descriptive analysis of baseline T and Lp(a) data from hypercholesterolaemic, ageing US men participating in a lipid treatment study are in good agreement with previous findings concerning an association between low T levels and elevated Lp(a) levels in ageing men [16]. In the present analysis, there was an overall trend for an inverse relationship between baseline T levels and the occurrence of marked elevations (≥ 3 times the upper limit of normal) in Lp(a), with a numerically greater percentage of men with low/low-normal T levels (17.1%) having such elevations compared to men with normal T levels (8.1%). Such an increase in the incidence of marked Lp(a) elevations in men with low/low-normal T would be expected to be associated with a poorer cardiovascular risk profile compared to that of the men with normal T levels.

Our analysis population of ageing, hypercholesterolaemic, US men was made up of a relatively high percentage (65%) of patients with low/low-normal T

Table I. Demographics and baseline characteristics.

Baseline characteristics	Baseline testosterone, <15 nmol/l, $N=70$	Baseline testosterone, ≥ 15 nmol/l, $N=37$	All patients, combined, $N=107$
Mean (SD) age (years) at baseline	55.5 (9.0)	54.3 (12.9)	55.1 (10.5)
Median (SD for median) TG (mmol/l)	1.9 (1.1)	1.7 (1.2)	1.9 (1.2)
Mean (SD) HDL-C (mmol/l)	1.2 (0.2)	1.2 (0.3)	1.2 (0.3)
Mean (SD) LDL-C (mmol/l)	5.4 (1.7)	5.2 (1.3)	5.3 (1.6)
Mean (SD) BMI (kg/m^2)	29.3 (3.9)	27.6 (3.2)	28.7 (3.7)
Mean (SD) FBG (mmol/l)	5.7 (1.1)	5.6 (1.0)	5.6 (1.1)
Mean (SD) SBP (mmHg)	128.9 (13.4)	125.5 (13.0)	127.7 (13.3)
Mean (SD) DBP (mmHg)	80.6 (8.1)	79.1 (8.3)	80.1 (8.1)
Mean (SD) testosterone (nmol/l)	11.4 (2.1)	18.5 (2.8)	13.8 (4.2)
Mean (SD) Lp(a) (μmol/l)	1.7 (1.9)	1.4 (1.2)	1.6 (1.7)
No (%) patients with the metabolic syndrome*	27 (38.6)	7 (18.9)	34 (31.8)

TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; Lp(a), lipoprotein(a).

*Patients were defined as having the metabolic syndrome if they met three or more of the following National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria [2]: diagnosis of diabetes or FPG ≥ 6.1 mmol/l or taking anti-diabetic medication; TG ≥ 1.7 mmol/l; HDL-C <1.0 mmol/l; BMI ≥ 30 kg/m^2 (surrogate of waist circumference >102 cm); and diagnosis of hypertension or blood pressure $\geq 130/85$ mmHg or taking anti-hypertension medication.

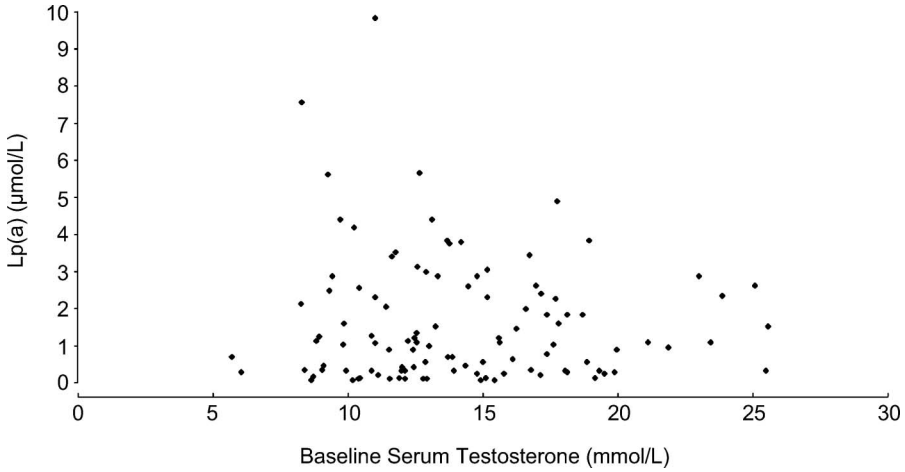

Figure 1. Scatterplot of baseline lipoprotein(a) [Lp(a)] *versus* baseline serum testosterone in 107 US men who participated in a lipid treatment study.

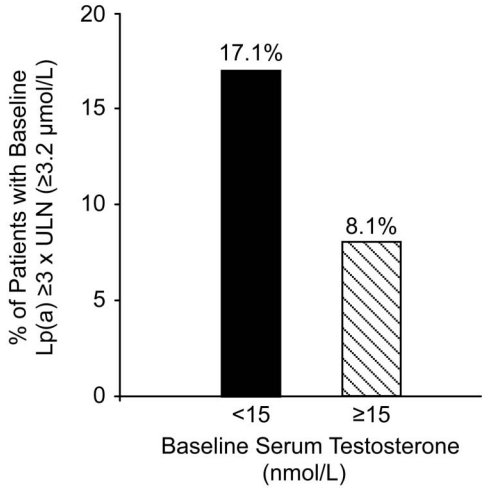

Figure 2. Percentage of men with baseline lipoprotein(a) [Lp(a)] levels $\geq$3 times the upper limit of normal (ULN) ($\geq$3.2 μmol/l), presented by baseline total serum testosterone (T) level.

levels. This was likely reflective of the fact that the inclusion criteria for the study led to the enrolment of patients with a significant cardiovascular risk profile, including marked hypercholesterolaemia (mean baseline LDL-C of 5.3 mmol/l) as well as the allowance for CHD and/or AD or multiple CHD risk factors. In keeping with this significant cardiovascular risk profile, a significant number of patients included in our analysis also had comorbitities including hypertriglyceridemia and metabolic syndrome as well as raised BMI, FBG and Lp(a) levels. These factors are known to be associated with lower T levels in ageing men [1–10,16], which possibly explains the relatively high percentage of patients with low/low-normal T levels that we observed.

The present data expand on the findings from our previous report [7] demonstrating that hypogonadism was significantly associated with three of the five National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) [21] components of the metabolic syndrome in ageing men, namely, hypertriglyceridemia, obesity and the presence of high FBG/diabetes. Elevated Lp(a) levels and type 2 diabetes have been reported in metabolic syndrome patients [22] as well as in patients with coronary artery disease associated with non-insulin-dependent diabetes mellitus [23]. Indeed, in the present analysis, higher Lp(a) levels were associated with a more common occurrence of the metabolic syndrome. It is possible that the increase in Lp(a) levels seen in men with low/low-normal T levels was driven by the increased occurrence of the metabolic and anthropometric components of the metabolic syndrome.

The question arises as to whether T normalisation could lead to a lowering of Lp(a) levels in ageing, hypogonadal men. Studies in healthy men have shown that T supplementation therapy can produce a significant decrease in Lp(a) levels [17–19]. Moreover, T supplementation resulted in larger Lp(a) reductions in men with higher baseline Lp(a) levels compared to that in men with lower Lp(a) levels [19]. These Lp(a)-lowering effects may have been driven by activation of hepatic androgen receptors [24], which may affect hepatic lipid production, including that of Lp(a). Whether such effects can be produced with T supplementation in ageing, hypogonadal men, and whether this would result in a reduction in cardiovascular risk in these patients, awaits determination in prospective cardiovascular outcome trials.

One limitation of the current analysis concerns the relatively small sample sizes in the subgroups of men with low/low-normal and normal baseline T levels. However, the trends seen in Lp(a) levels across the two T subgroups in our analysis are consistent with those reported previously [16].

In conclusion, this analysis of baseline data from ageing, hypercholesterolaemic US men participating in a lipid treatment study suggested an inverse relationship between total serum T and the occurrence of marked elevations in Lp(a) in these patients. Practitioners concerned with managing ageing men

with symptomatic hypogonadism may need to be mindful of the deleterious effects of low T levels not only on muscle mass/strength and sexual function, but also on factors such as Lp(a), which could contribute to increased cardiovascular risk in these patients. Further studies are needed to determine whether T supplementation therapy could lead to an improvement in cardiovascular outcomes in ageing, hypogonadal men.

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