

The relationship between endogenous testosterone and lipid profile in middle-aged and elderly Chinese men

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Abstract

Objective: To evaluate the relationship between serum total testosterone (TT) level and lipid profile after adjusting for some traditional confounding factors, free thyroid hormones and TSH in Chinese men.

Methods: This was a retrospective study based on an epidemiological investigation including 11 000 subjects. Bivariate and partial correlation analysis, multiple linear regression analysis, and a general linear model were used to assess the influence of TT on the lipid profile. Additionally, the odds ratios (ORs) (95% CIs) for hypertriglyceridemia and low HDL-C in relation to TT categories were calculated using logistic regression analysis.

Results: A total of 4114 subjects whose mean age was 56.04 ± 8.75 years were finally analyzed. There was a significant linear trend toward lower total cholesterol (TC), lower triglycerides (TG), and higher HDL-C with increasing serum TT, which remained significant after adjusting for age, BMI, fasting blood glucose, systolic blood pressure, free triiodothyronine, free thyroxine, and TSH. Compared with the bottom quartile of TT, the adjusted OR (95% CI) for hypertriglyceridemia and low HDL-C was 0.082 (0.048–0.138, $P=0.000$) and 0.669 (0.503–0.891, $P=0.006$) respectively in the top quartile of TT.

Conclusions: TT was correlated negatively and linearly with TC, TG, and LDL-C and positively and linearly with HDL-C. Low TT might have adverse effects on the lipid profile and thus represent a risk factor for hypercholesterolemia, hypertriglyceridemia, high LDL-C, and low HDL-C, suggesting the importance of maintaining an appropriate TT level in men.

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Introduction

For a long time, testosterone was deemed to have adverse effects on lipid profile. A low concentration of HDL-C has been associated with an increase in the plasma testosterone concentration in male adolescents (1). Men are also more prone to coronary heart disease (CHD) and

possess higher risks of mortality than women (2, 3). This difference has been partly attributed to sex hormones.

Nonetheless, new evidence has emerged in the last few years that challenges this traditional notion. In men, endogenous testosterone is inversely related to the

severity of carotid atherosclerosis as well as the incidence and severity of CHD (4, 5, 6, 7, 8). Furthermore, low testosterone is related to a number of metabolic diseases or disorders, such as insulin resistance (9), type 2 diabetes mellitus (T2DM) (10), metabolic syndrome (MetS) (11), and all-cause mortality (12). Therefore, testosterone replacement therapy (TRT) is now recommended to ameliorate signs and symptoms of some metabolic and vascular diseases in middle-aged and elderly men with low serum testosterone (13, 14).

Dyslipidemia, one of the main risk factors for hypertension, T2DM, MetS, and CHD, is among the most important threats to public health. Hence, the relationship between testosterone and lipid levels needs intensive study. Epidemiological evidence has shown that low testosterone is related to elevated total cholesterol (TC) (15, 16), triglycerides (TG) (15, 16, 17, 18), LDL-C (16) and decreased HDL-C (15, 16, 17, 18), and an increased incidence of dyslipidemia (19) in men in some but not in all studies (20, 21). Corona *et al.* (22) found that TRT was associated with a significant reduction of TG and an increase of HDL-C and was able to improve central obesity (subjects with MetS) and glycometabolic control (patients with MetS and T2DM) (23). Other studies observed no relationship between TRT and lipid profile, although some even reported unfavorable effects of TRT on serum lipids (24, 25, 26). This suggests that the relationship between testosterone and lipid profile is complex (27).

In addition, in the previous studies, the estimates were not adjusted or were only adjusted for the traditional serum lipid confounding factors, such as age, BMI, and fasting blood glucose (FBG). Recent evidence indicates that thyroid hormones and thyrotropin (TSH) might affect serum lipids. Our previous studies have shown that high TSH is associated with an atherogenic lipid profile independent of thyroid hormone (28, 29), although many other clinical studies have also indicated that free thyroxine (FT₄) as well as TSH are associated with lipid metabolism (30). The associations might be weak but significant. However, the effects of these hormones on the relationship between testosterone and lipids have not been addressed elsewhere, and no study has excluded the potential influences of the thyroid hormones or TSH when assessing the relationship between testosterone and the lipid status.

The inconsistent results of studies concerning the associations between testosterone and lipid profile may also be partly due to relatively small samples. In addition, data about the association between testosterone and lipids are lacking in Chinese men on a large scale. Importantly,

there has been an increase in dyslipidemia prevalence in China. Therefore, in this study, we aimed to explore the association between serum testosterone level and lipid profile after adjusting for classic confounding factors and the thyroid hormones and TSH in middle-aged and elderly Han Chinese men.

Subjects and methods

Subjects

This population-based cross-sectional study was carried out in Ningyang County (Taian, Shandong Province, China) from June to November 2011. During the recruiting phase, the local-registered residents aged 40 years and older who have lived there for at least 5 years were invited to receive a screening examination, and nearly 11 000 persons participated. All participants provided an overnight fasting blood sample and were asked to complete a self-reported questionnaire.

For our analysis, the exclusion criteria were as follows: i) female; ii) no information on vital statistics (such as age or sex) or missing data on serum total testosterone (TT) or lipid levels; iii) taking medications that might affect TT level or lipid profile in the past 3 months (such as androgens, steroid hormones, Proscar, opiates, anti-convulsants, statins, or fibrates); and iv) neurologic diseases, severe hepatic or renal disorders, lung diseases, acute systemic illness, hypothalamus and/or pituitary gland diseases, or tumors that might affect TT level (such as brain cancer or prostate cancer). Finally, a total of 4114 male subjects from the general population were evaluated.

The Ethics Committee of Shandong Provincial Hospital affiliated to Shandong University approved the retrospective review of the patients' medical records and licensed the records for research purposes only.

Anthropometric measurements and laboratory methods

Weight was measured adjusting by 0.1 kg for subjects not wearing shoes. Height was measured adjusting by 0.1 cm for subjects in light clothes. BMI was calculated by dividing weight (kg) by the square of height (m). Waist circumference (WC) and hip circumference (HC) were assessed with an accuracy of 0.1 cm, and the waist/hip ratio was calculated by dividing WC by HC. Blood pressure was measured at least three times in the sitting position after a 5-min rest and estimated as the average of three readings of systolic and diastolic blood pressure.

Past medical history was assessed with a questionnaire. The diseases (hypertension, diabetes mellitus, and CHD) were based on previous diagnosis by a physician.

Venous blood samples were collected from all the patients between 0800 and 1000 h after a minimum 10-h overnight fast. Serum was separated and stored at -80°C until analysis. Serum concentrations of FBG, TC, TG, LDL-C, and HDL-C were measured directly with an ARCHITECT ci16200 Integrated System (Abbott). Serum free triiodothyronine (FT_3), FT_4 , TSH, and TT were measured using electrochemiluminescent procedures (Cobas E601; Roche) at the clinical laboratory of Shandong Provincial Hospital. We performed quality control before and after the analysis every day. The intra-day and inter-day coefficients of variation were always below 5% for the lipid parameters, FT_3 , FT_4 , TSH, and TT.

The clinical laboratory carried out a small sample verification to the reagent kit, and the manufacturer's reference intervals could be used directly for the detection. The laboratory reference ranges were 9.72–27.76 nmol/l for TT, 3.10–6.80 pmol/l for FT_3 , 12.00–22.00 pmol/l for FT_4 , and 0.27–4.20 mIU/l for TSH. Dyslipidemia was defined as fasting TC ≥ 6.22 mmol/l (240 mg/dl, hypercholesterolemia), fasting TG ≥ 2.26 mmol/l (200 mg/dl, hypertriglyceridemia), fasting LDL-C ≥ 4.14 mmol/l (160 mg/dl, high LDL-C), and fasting HDL-C < 1.04 mmol/l (40 mg/dl, low HDL-C) (31).

Statistical analysis

The values are presented as the means (s.d.) or medians (interquartile ranges). The non-normally distributed data (TG) were log transformed. Due to the close correlation among thyroid hormones and TSH (28, 29, 30), principal component analysis was used to overcome the multicollinearity among FT_3 , FT_4 , and TSH and improve the predictive ability of the model. Therefore, two uncorrelated principal components (factor 1 and factor 2) were extracted to replace the original variables. Factor 1 was more responsible for FT_3 and FT_4 , although factor 2 was more responsible for TSH. The two principal components accounted for a large proportion (81.438%) of the variance, but they were correlated with the dependent variables as well. The equations are as follows:

$$\text{Factor 1} = 0.488 \times \frac{\text{FT}_3 - 5.1685}{1.43428} + 0.535 \times \frac{\text{FT}_4 - 17.3740}{2.85390} - 0.350 \times \frac{\text{TSH} - 2.3367}{2.08629}.$$

$$\text{Factor 2} = 0.511 \times \frac{\text{FT}_3 - 5.1685}{1.43428} + 0.134 \times \frac{\text{FT}_4 - 17.3740}{2.85390} + 0.914 \times \frac{\text{TSH} - 2.3367}{2.08629}.$$

All subjects were divided into four categories by quartile of TT: Q1 (TT < 14.34 nmol/l), Q2 (TT 14.34–18.46 nmol/l), Q3 (TT 18.47–23.36 nmol/l), and Q4 (TT > 23.36 nmol/l).

Bivariate correlation and partial correlation were carried out to analyze the relationship between TT and lipid variables by calculating the Pearson correlation coefficients and partial correlation coefficients. Multivariate linear regression analyses were carried out using TC, TG, LDL-C, and HDL-C as dependent variables and age, BMI, FBG, SBP, TT, and factor 1 and factor 2 (FT_3 , FT_4 , and TSH) as independent variables. To further explore the relationship of TT with TC, TG, LDL-C, and HDL-C, we carried out a general linear model (GLM). The associations were adjusted for the potential confounding effects of age, BMI, FBG, SBP, factor 1, and factor 2. The χ^2 test was used to compare the prevalence of dyslipidemia among subjects with different levels of TT. Furthermore, the odds ratios (ORs) and the 95% CIs for hypertriglyceridemia and low HDL-C in relation to TT were calculated using an adjusted logistic regression model with Q1: TT < 14.34 nmol/l as the reference category.

All statistical analyses were carried out using SPSS Statistical Analysis System (version 18.0 for Windows). P value < 0.05 was considered statistically significant.

Results

Table 1 shows the baseline characteristics of the study subjects. The mean serum TT value of the study subjects was 19.12 ± 7.26 nmol/l. The prevalence of TT deficiency was 6.85% according to the laboratory reference range. The mean serum lipid values were 5.00 ± 1.08 mmol/l TC, 1.40 ± 0.82 mmol/l TG, 3.00 ± 0.87 mmol/l LDL-C, and 1.40 ± 0.36 mol/l HDL-C. The prevalence of hypercholesterolemia, hypertriglyceridemia, high LDL-C, and low HDL-C were 12.62, 12.64, 9.41, and 13.81% respectively, among the total study population.

Correlation between TT and serum lipid profile in the study population

In bivariate correlation analysis, TT was significantly correlated with TC ($r = -0.077$, $P = 0.000$), LogTG ($r = -0.374$, $P = 0.000$), LDL-C ($r = -0.069$, $P = 0.000$),

Table 1 Clinical characteristics of 4114 men participating in the study. Data are presented as means (s.d.), medians (interquartile ranges), or number (%). The diseases were based on previous diagnosis by a physician.

Characteristic	n=4114
Age (years)	56.04 (8.75)
BMI (kg/m ²)	25.04 (3.74)
WHR	0.92 (0.06)
SBP (mmHg)	139.39 (24.69)
DBP (mmHg)	82.61 (13.96)
FBG (mmol/l)	6.43 (1.93)
TC (mmol/l)	5.00 (1.08)
TG (mmol/l)	1.17 (0.86)
LDL-C (mmol/l)	3.00 (0.87)
HDL-C (mmol/l)	1.40 (0.36)
TT (nmol/l)	19.12 (7.26)
FT ₃ (pmol/l)	5.17 (1.43)
FT ₄ (pmol/l)	17.37 (2.85)
TSH (mIU/l)	2.34 (2.09)
History of hypertension	607 (14.75%)
History of DM	387 (9.41%)
History of CHD	219 (5.32%)

WHR, waist/hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglycerides; TT, total testosterone; FT₃, free triiodothyronine; FT₄, free thyroxine; TSH, thyrotropin; DM, diabetes mellitus; CHD, coronary heart disease.

and HDL-C ($r=0.195$, $P=0.000$). Interestingly, the correlations, except for that between LDL-C and TT, remained significant after adjusting for age, BMI, FBG, SBP, factor 1, and factor 2 (Table 2).

Multiple regression analysis yielded similar results (Table 3). The independent correlates of serum lipids were assessed by taking into account age, BMI, FBG, SBP, TT, factor 1, and factor 2. TT was significantly associated with the TC level, Log TG level, and HDL-C level.

Comparison of lipid profile among different TT categories

We then analyzed the association between TT and serum lipid levels with the GLM. There was a consistent and significant decrease in the TC and TG and an increase in HDL-C with increasing TT. These estimates were also adjusted for age, BMI, FBG, SBP, factor 1, and factor 2. Table 4 shows the significant linear trend between TT and TC, TG, and HDL-C ($P<0.05$). Thus, subjects with lower serum TT had slightly higher adjusted TC and TG and lower HDL-C compared with those with higher serum TT. These results clearly indicate a significant negative correlation of TT with TC and TG and a significant positive correlation of TT with HDL-C, which were independent of other confounding factors.

The relationship between TT and the prevalence of dyslipidemia

The prevalence of hypercholesterolemia, high LDL-C, and low HDL-C, especially hypertriglyceridemia, decreased significantly in patients who showed increased TT (Fig. 1). The patients with TT higher than 23.36 nmol/l (Q4) showed a significantly lower prevalence of hypercholesterolemia, hypertriglyceridemia, and low HDL-C than those with the lowest TT at the rates of 10.12 vs 14.77% ($P=0.001$), 1.65 vs 26.53% ($P=0.000$), and 9.34 vs 17.69% ($P=0.000$), respectively. The patients with TT < 14.34 nmol/l (Q1) showed a relatively higher prevalence of high LDL-C (9.82%). However, there were no significant differences in the prevalence of high LDL-C among the four TT categories (Fig. 1).

The above data collectively reveal the significant association of TT with TG and HDL-C. Thus the ORs for dyslipidemia adjusted by TT categories were calculated. Compared with the bottom quartile of TT (Q1: TT < 14.34 nmol/l), the adjusted ORs (95% CI) for hypertriglyceridemia and low HDL-C were 0.082 (0.048–0.138, $P=0.000$) and 0.669 (0.503–0.891, $P=0.006$) respectively, in the top quartile of TT.

Discussion

The present study reported the relationship between TT and lipid profile after adjusting for traditional confounding factors, thyroid hormones, and TSH in 4114 middle-aged and older Han Chinese subjects. The results show that TT was significantly and inversely correlated with TC, TG, and LDL-C and positively with HDL-C. Moreover, these relationships remained significant, except for LDL-C, after further adjusting for age, BMI, FBG, SBP, FT₃, FT₄, and TSH. We also found that the

Table 2 Pearson coefficients for the associations between total testosterone (TT) and serum lipid parameters. Adjusted for age, BMI, FBG, SBP, FT₃, FT₄, and TSH.

		Coefficient (r)	P
TC	Unadjusted	-0.077	0.000
	Adjusted	-0.034	0.032
LogTG	Unadjusted	-0.374	0.000
	Adjusted	-0.259	0.000
LDL-C	Unadjusted	-0.069	0.000
	Adjusted	-0.007	0.646
HDL-C	Unadjusted	0.195	0.000
	Adjusted	0.108	0.000

Table 3 Multivariate models of the relations between total testosterone (TT) and serum total cholesterol (TC), triglyceride (TG), LDL-C, and HDL-C in the study. Data are *B* (unstandardized coefficients), 95% CI of *B*, Beta (standardized coefficients) and *P* value for linear regression analysis of TT. Values shown were adjusted for age, BMI, FBG, SBP, FT₃, FT₄, and TSH.

	TT (nmol/l)			
	<i>B</i>	95% CI	Beta	<i>P</i>
TC (mmol/l)	−0.006	−0.011, −0.001	−0.041	0.015
LogTG (mmol/l)	−0.008	−0.009, −0.007	−0.265	0.000
LDL-C (mmol/l)	–	–	−0.006	0.738
HDL-C (mmol/l)	0.006	0.004, 0.007	0.111	0.000

prevalence of dyslipidemia, particularly hypertriglyceridemia and low HDL-C, decreased as TT increased.

Our results are in agreement with earlier reports. In a case–control study performed in France (16), TC, TG, and LDL-C were higher and serum HDL-C lower in men with low serum testosterone. Similar relationships were found between testosterone and lipid profile in American (5), Finnish (15), Japanese (18), and German populations (19). Nevertheless, the confounding factors adjusted in these studies were only the traditional ones, such as age, BMI, and FBG. Significant correlations can be found among FT₃, FT₄, TSH, and lipid profile in hypothyroidism and even in euthyroid subjects (32, 33, 34), although not consistently (35, 36). Consistent with these results, we still found significant correlations among FT₃, FT₄, TSH, TC, and TG levels (28). Besides, in the GLMs of TC and HDL-C in our study, R-square increased due to inclusion of factors 1 and 2 (FT₃, FT₄, and TSH), while in that of TG and LDL-C, it remained unchanged (data not shown). Consequently, in addition to age, BMI, FBG, and other classical confounding variables, thyroid hormones and TSH may be considered. If they are not, the association between testosterone and lipid profile becomes more doubtful. In the present study,

even after adjusting for FT₃, FT₄, and TSH in addition to the traditional confounding factors, TT was negatively correlated with TC and TG and positively with HDL-C. These results are more credible for revealing the relationship between serum TT level and serum lipid levels.

In some studies, TRT was negatively correlated with TC, TG, and LDL-C and positively with HDL-C (22, 23), while in several studies, the relationship was found to be the opposite (21, 25, 27). Possible explanations for the different effects involve different preparations, dosages, and durations of testosterone treatment. Additionally, the samples were relatively small. Tan *et al.* (37) revealed that the reduction of HDL induced by TRT was mainly HDL3-C and LpA-I:A-II particles, but not anti-atherogenic HDL2 and LpA-I particles.

We showed that the subjects with relatively low TT were more likely to have hypercholesterolemia, hypertriglyceridemia, high LDL-C, and low HDL-C, which is consistent with previous studies (19, 38). This suggests that the subjects with relatively low TT might be prone to dyslipidemia. Thus, more attention should be paid to the lipid profile of those patients who have relatively low serum TT.

The molecular mechanisms underlying the effects of TT on serum lipids are still unclear. One study (39) showed that testosterone might be associated with changes in scavenger receptor B1 (SR-B1) and hepatic lipase, the enzyme that hydrolyzes phospholipids on the surface of HDL, facilitating the selective uptake of HDL by SR-B1, thereby exerting an anti-atherogenic rather than an atherogenic role. Other possible explanations may involve the effects of TT on insulin resistance (9) or the intermediate roles of visceral obesity (24), adiponectin (40), leptin (40, 41), and hepatic production of apolipoprotein A-I (42). However, the net effect of testosterone's regulation of lipids is poorly characterized. We should also note that all currently revealed associations between TT and lipid profile were weak to modest; so, the detailed

Table 4 Estimated marginal means of serum lipids (95% CI) (mmol/l) according to total testosterone (TT) category in the study subjects. Values shown were adjusted for age, BMI, FBG, SBP, FT₃, FT₄, and TSH.

	TT (nmol/l)				<i>P</i>	Linear coefficient	<i>P</i> for linear trend
	<14.34	14.34–18.46	18.47–23.36	>23.36			
TC (95% CI)	5.058 (4.988, 5.127)	5.039 (4.973, 5.105)	4.962 (4.896, 5.029)	4.943 (4.874, 5.013)	0.076	−0.094	0.012
LogTG (95% CI)	0.175 (0.162, 0.188)	0.115 (0.102, 0.127)	0.049 (0.037, 0.061)	0.005 (−0.008, 0.018)	0.000	−0.129	0.000
LDL-C (95% CI)	2.975 (2.919, 3.031)	3.048 (2.995, 3.100)	2.997 (2.994, 3.051)	2.967 (2.911, 3.023)	0.147	−0.017	0.580
HDL-C (95% CI)	1.351 (1.329, 1.374)	1.362 (1.341, 1.383)	1.406 (1.385, 1.428)	1.464 (1.441, 1.486)	0.000	0.085	0.000

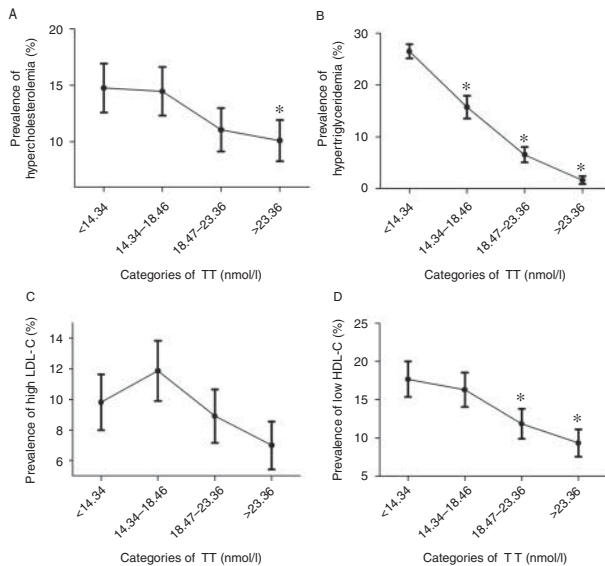


Figure 1

The prevalence of hypercholesterolemia (A), hypertriglyceridemia (B), high LDL-C (C) and low HDL-C (D) stratified according to the serum total testosterone (TT) concentration. The data were presented as the percentage of individuals in each category. χ^2 test, * $P < 0.001$ vs Q1 (<14.34 nmol/l).

mechanisms and clinical implications of the effects of TT on the lipid profile remain to be elucidated.

Low testosterone is associated with T2DM, CHD, and other diseases (4, 5, 6, 7, 8, 9, 10, 11, 12). Several studies have searched for an association between TT and MetS. Some have found that low testosterone was related to MetS and its components (11, 18, 43), such as higher TG and FBG and lower HDL-C, especially in patients with erectile dysfunction (44). In the Tromsø study performed in Norway (17), the cross-sectional analysis of 1274 men without known cardiovascular diseases showed TT was inversely and independently associated with TG and positively and independently associated with HDL-C. In our study, TT was negatively associated with WC, SBP, DBP, and FBG and had a more significant relationship with TG and HDL-C compared with TC and LDL-C. The incidence of MetS might be related to insulin resistance, and testosterone level seems to be negatively associated with insulin resistance (9, 45). It is possible that indirect effects, such as on insulin resistance, or some unknown direct effects may contribute to the relationship between TT and serum lipids.

The strengths of our study include the relatively large sample size for the detection of the relationships between TT and serum lipids, which could partly reflect the

situation of middle-aged and elderly men in our country. Moreover, we brought FT₃, FT₄, and TSH into our analysis, which has never been addressed in previous studies. In addition, the blood samples were obtained between 0800 and 1000 h, which could avoid the possible effects of daily variation of sex hormones and increase the reliability of our measurements.

However, this study had some important limitations. First, as we all know, free testosterone (FT) or bioavailable testosterone is a better index to reflect the genuine level of testosterone in the body as active forms of testosterone. Hence, one limitation of our study is that we did not measure or calculate FT level via sex hormone-binding globulin as a result of the limitation of our detection means and technology. Secondly, although we revealed the relationships between TT level and serum lipid levels, this cross-sectional study could not detect any causal relationship between testosterone and lipid profile. The large prospective studies are needed to clarify the above relationship. Thirdly, even though we made efforts to adjust FT₃, FT₄, and TSH level, there are so many variables that might affect the serum lipid levels that a few variables were not available, such as diet, smoking, drinking, and other lifestyle factors.

In summary, we found that serum TT was negatively correlated with the levels of TC, TG, and LDL-C and positively correlated with the level of HDL-C in middle-aged and older Han Chinese subjects. Furthermore, the prevalence of hypercholesterolemia, high LDL-C, and low HDL-C, especially hypertriglyceridemia, decreased with increased serum TT. From a clinical perspective, we should ponder whether low TT might be related to cardiovascular disease via effects on serum lipid levels. In addition, evidence has shown that high luteinizing hormone (LH) level is related to the CHD risk or is involved in arterial dilatation as well as occlusive vascular disease in older men (46, 47, 48, 49). LH might have an independent effect on the cardiovascular system via the LH receptor or rather be an epiphenomenon of another disease process. Hence, more attention should be paid to men with elevated LH along with low TT levels. Moreover, our study may provide some justification for TRT in spite of its controversy. Thus, further large prospective studies are needed to clarify the relationships between TT and serum lipids and confirm the clinical implications.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

This work was carried out in collaboration between all authors. J Zhao and Q Guan defined the research theme. N Zhang analyzed the data, interpreted the results and wrote the paper. H Zhang and X Zhang designed methods, collected data and contributed equally to this study. B Zhang participated in data detection. F Wang and C Wang performed the statistical analysis. M Zhao co-worked on associated data collection. C Yu and L Gao participated in the design of the study. All authors contributed to reading and approval of the final manuscript.

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References

- Morrison JA, Barton BA, Biro FM & Sprecher DL. Sex hormones and the changes in adolescent male lipids: longitudinal studies in a biracial cohort. *Journal of Pediatrics* 2003 **142** 637–642. (doi:10.1067/mpd.2003.246)
- Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM & Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 1994 **90** 583–612. (doi:10.1161/01.CIR.90.1.583)
- Morales A, Madrazo Y, Ramírez JI, Castañeda L, Machín W, Álvarez L, Angulo R, Dueñas R & Bermúdez R. Acute myocardial infarction incidence, mortality and case fatality in Santa Clara, Cuba, 2007–2008. *MEDICC Review* 2011 **13** 23–29. (doi:10.1590/S1555-7960201100300006)
- Mäkinen J, Jarvisalo MJ, Pollanen P, Perheentupa A, Irjala K, Koskenvuo M, Mäkinen J, Huhtaniemi I & Raitakari OT. Increased carotid atherosclerosis in andropausal middle-aged men. *Journal of the American College of Cardiology* 2005 **45** 1603–1608. (doi:10.1016/j.jacc.2005.01.052)
- Zmuda JM, Cauley JA, Kriska A, Glynn NW, Gutai JP & Kuller LH. Longitudinal relation between endogenous testosterone and cardiovascular disease risk factors in middle-aged men. A 13-year follow-up of former Multiple Risk Factor Intervention Trial participants. *American Journal of Epidemiology* 1997 **148** 609–617. (doi:10.1093/oxfordjournals.aje.a009326)
- Rosano GM, Sheiban I, Massaro R, Pagnotta P, Marazzi G, Vitale C, Mercurio G, Volterrani M, Avera A & Fini M. Low testosterone levels are associated with coronary artery disease in male patients with angina. *International Journal of Impotence Research* 2007 **19** 176–182. (doi:10.1038/sj.ijir.3901504)
- Araujo AB, Dixon JM, Suarez EA, Murad MH, Guey LT & Wittert GA. Clinical review: endogenous testosterone and mortality in men: a systematic review and meta-analysis. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 3007–3019. (doi:10.1210/jc.2011-1137)
- Corona G, Rastrelli G, Monami M, Guay A, Buvat J, Sforza A, Forti G, Mannucci E & Maggi M. Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. *European Journal of Endocrinology* 2011 **165** 687–701. (doi:10.1530/EJE-11-0447)
- Tsai EC, Matsumoto AM, Fujimoto WY & Boyko EJ. Association of bioavailable, free, and total testosterone with insulin resistance: influence of sex hormone-binding globulin and body fat. *Diabetes Care* 2004 **27** 861–868. (doi:10.2337/diacare.27.4.861)
- Ding EL, Song Y, Malik VS & Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *Journal of the American Medical Association* 2006 **295** 1288–1299. (doi:10.1001/jama.295.11.1288)
- Kalyani RR & Dobs AS. Androgen deficiency, diabetes, and the metabolic syndrome in men. *Current Opinion in Endocrinology, Diabetes, and Obesity* 2007 **14** 226–234. (doi:10.1097/MED.0b013e32814db856)
- Laughlin GA, Barrett-Connor E & Bergstrom J. Low serum testosterone and mortality in older men. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 68–75. (doi:10.1210/jc.2007-1792)
- Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM, Task Force & Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 2536–2559. (doi:10.1210/jc.2009-2354)
- Kang HY. Beyond the male sex hormone: deciphering the metabolic and vascular actions of testosterone. *Journal of Endocrinology* 2013 **217** C1–C3. (doi:10.1530/JOE-13-0052)
- Mäkinen JI, Perheentupa A, Irjala K, Pöllänen P, Mäkinen J, Huhtaniemi I & Raitakari OT. Endogenous testosterone and serum lipids in middle-aged men. *Atherosclerosis* 2008 **197** 688–693. (doi:10.1016/j.atherosclerosis.2007.05.009)
- Simon D, Charles MA, Nahoul K, Orssaud G, Kremiski J, Hully V, Joubert E, Papoz L & Eschwege E. Association between plasma total testosterone and cardiovascular risk factors in healthy adult men: the Telecom Study. *Journal of Clinical Endocrinology and Metabolism* 1997 **82** 682–685. (doi:10.1210/jcem.82.2.3766)
- Agedahl I, Skjaerpe PA, Hansen JB & Svartberg J. Low serum testosterone in men is inversely associated with non-fasting serum triglycerides: the Tromsø study. *Nutrition, Metabolism, and Cardiovascular Diseases* 2008 **18** 256–262. (doi:10.1016/j.numecd.2007.01.014)
- Akishita M, Fukai S, Hashimoto M, Kameyama Y, Nomura K, Nakamura T, Ogawa S, Iijima K, Eto M & Ouchi Y. Association of low testosterone with metabolic syndrome and its components in middle-aged Japanese men. *Hypertension Research* 2010 **33** 587–591. (doi:10.1038/hr.2010.43)
- Haring R, Baumeister SE, Völzke H, Dörr M, Felix SB, Kroemer HK, Nauck M & Wallaschofski H. Prospective association of low total testosterone concentrations with an adverse lipid profile and increased incident dyslipidemia. *European Journal of Cardiovascular Prevention and Rehabilitation* 2011 **18** 86–96. (doi:10.1097/HJR.0b013e32833c1a8d)
- Kabakci G, Yildirim A, Can I, Unsal I & Erbas B. Relationship between endogenous sex hormone levels, lipoproteins and coronary atherosclerosis in men undergoing coronary angiography. *Cardiology* 1999 **92** 221–225. (doi:10.1159/000006977)
- Isidori AM, Giannetta E, Greco EA, Gianfrilli D, Bonifacio V, Isidori A, Lenzi A & Fabbri A. Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. *Clinical Endocrinology* 2005 **63** 280–293. (doi:10.1111/j.1365-2265.2005.02339.x)
- Corona G, Monami M, Rastrelli G, Aversa A, Tishova Y, Saad F, Lenzi A, Forti G, Mannucci E & Maggi M. Testosterone and metabolic syndrome: a meta-analysis study. *Journal of Sexual Medicine* 2011 **8** 272–283. (doi:10.1111/j.1743-6109.2010.01991.x)
- Corona G, Rastrelli G & Maggi M. Diagnosis and treatment of late-onset hypogonadism: systematic review and meta-analysis of TRT outcomes. *Best Practice & Research. Clinical Endocrinology & Metabolism* 2013 **27** 557–579. (doi:10.1016/j.beem.2013.05.002)
- Allan CA, Strauss BJ, Burger HG, Forbes EA & McLachlan RL. Testosterone therapy prevents gain in visceral adipose tissue and loss of

- skeletal muscle in nonobese aging men. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 139–146. (doi:10.1210/jc.2007-1291)
- 25 Berg G, Schreier L, Geloso G, Otero P, Nagelberg A & Levalle O. Impact on lipoprotein profile after long-term testosterone replacement in hypogonadal men. *Hormone and Metabolic Research* 2002 **34** 87–92. (doi:10.1055/s-2002-20521)
- 26 Fernández-Balsells MM, Murad MH, Lane M, Lampropoulos JF, Albuquerque F, Mullan RJ, Agrwal N, Elamin MB, Gallegos-Orozco JF, Wang AT *et al.* Clinical review 1: adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 2560–2575. (doi:10.1210/jc.2009-2575)
- 27 Schleich F & Legros JJ. Effects of androgen substitution on lipid profile in the adult and aging hypogonadal male. *European Journal of Endocrinology* 2004 **151** 415–424. (doi:10.1530/eje.0.1510415)
- 28 Wang F, Tan Y, Wang C, Zhang X, Zhao Y, Song X, Zhang B, Guan Q, Xu J, Zhang J *et al.* Thyroid-stimulating hormone levels within the reference range are associated with serum lipid profiles independent of thyroid hormones. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 2724–2731. (doi:10.1210/jc.2012-1133)
- 29 Tian L, Song Y, Xing M, Zhang W, Ning G, Li X, Yu C, Qin C, Liu J, Tian X *et al.* A novel role for thyroid-stimulating hormone: up-regulation of hepatic 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase expression through the cyclic adenosine monophosphate/protein kinase A/cyclic adenosine monophosphate-responsive element binding protein pathway. *Hepatology* 2010 **52** 1401–1409. (doi:10.1002/hep.23800)
- 30 Garduño-García Jde J, Alvirde-García U, López-Carrasco G, Padilla Mendoza ME, Mehta R, Arellano-Campos O, Choza R, Sauque L, Garay-Sevilla ME, Malacara JM *et al.* TSH and free thyroxine concentrations are associated with differing metabolic markers in euthyroid subjects. *European Journal of Endocrinology* 2010 **163** 273–278. (doi:10.1530/EJE-10-0312)
- 31 Jellinger PS, Smith DA, Mehta AE, Ganda O, Handelsman Y, Rodbard HW, Shepherd MD, Seibel JA & AACE Task Force for Management of Dyslipidemia and Prevention of Atherosclerosis. American Association of Clinical Endocrinologists' Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis. *Endocrine Practice* 2012 **18** (Suppl 1) 1–78.
- 32 Sharma R, Sharma TK, Kaushik GG, Sharma S, Vardey SK & Sinha M. Subclinical hypothyroidism and its association with cardiovascular risk factors. *Clinical Laboratory* 2011 **57** 719–724.
- 33 Asvold BO, Vatten LJ, Nilsen TI & Bjoro T. The association between TSH within the reference range and serum lipid concentrations in a population-based study. The HUNT Study. *European Journal of Endocrinology* 2007 **156** 181–186. (doi:10.1530/eje.1.02333)
- 34 Fernández-Real JM, López-Bermejo A, Castro A, Casamitjana R & Ricart W. Thyroid function is intrinsically linked to insulin sensitivity and endothelium-dependent vasodilation in healthy euthyroid subjects. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 3337–3343. (doi:10.1210/jc.2006-0841)
- 35 Neves C, Alves M, Medina JL & Delgado JL. Thyroid diseases, dyslipidemia and cardiovascular pathology. *Revista Portuguesa de Cardiologia* 2008 **27** 1211–1236.
- 36 Pearce EN. Update in lipid alterations in subclinical hypothyroidism. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 326–333. (doi:10.1210/jc.2011-2532)
- 37 Tan KC, Shiu SW, Pang RW & Kung AW. Effects of testosterone replacement on HDL subfractions and apolipoprotein A-I containing lipoproteins. *Clinical Endocrinology* 1998 **48** 187–194. (doi:10.1046/j.1365-2265.1998.3721211.x)
- 38 Stanworth RD, Kapoor D, Channer KS & Jones TH. Dyslipidaemia is associated with testosterone, oestradiol and androgen receptor CAG repeat polymorphism in men with type 2 diabetes. *Clinical Endocrinology* 2011 **74** 624–630. (doi:10.1111/j.1365-2265.2011.03969.x)
- 39 Langer C, Gansz B, Goepfert C, Engel T, Uehara Y, von Dehn G, Jansen H, Assmann G & von Eckardstein A. Testosterone up-regulates scavenger receptor B1 and stimulates cholesterol efflux from macrophages. *Biochemical and Biophysical Research Communications* 2002 **296** 1051–1057. (doi:10.1016/S0006-291X(02)02038-7)
- 40 Gannagé-Yared MH, Khalife S, Semaan M, Fares F, Jambart S & Halaby G. Serum adiponectin and leptin levels in relation to the metabolic syndrome, androgenic profile and somatotrophic axis in healthy non-diabetic elderly men. *European Journal of Endocrinology* 2006 **155** 167–176. (doi:10.1530/eje.1.02175)
- 41 Isidori AM, Caprio M, Strollo F, Moretti C, Frajese G, Isidori A & Fabbri A. Leptin and androgens in male obesity: evidence for leptin contribution to reduced androgen levels. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 3673–3680. (doi:10.1210/jcem.84.10.6082)
- 42 Tang JJ, Srivastava RA, Krul ES, Baumann D, Pflieger BA, Kitchens RT & Schonfeld G. *In vivo* regulation of apolipoprotein A-I gene expression by estradiol and testosterone occurs by different mechanisms in inbred strains of mice. *Journal of Lipid Research* 1991 **32** 1571–1585.
- 43 Laaksonen DE, Niskanen L, Punnonen K, Nyyssönen K, Tuomainen TP, Valkonen VP, Salonen R & Salonen JT. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. *Diabetes Care* 2004 **27** 1036–1041. (doi:10.2337/diacare.27.5.1036)
- 44 Somani B, Khan S & Donat R. Screening for metabolic syndrome and testosterone deficiency in patients with erectile dysfunction: results from the first UK prospective study. *BJU International* 2010 **106** 688–690. (doi:10.1111/j.1464-410X.2009.09145.x)
- 45 Yeap BB, Chubb SA, Hyde Z, Jamrozik K, Hankey GJ, Flicker L & Norman PE. Lower serum testosterone is independently associated with insulin resistance in non-diabetic older men: the Health In Men Study. *European Journal of Endocrinology* 2009 **161** 591–598. (doi:10.1530/EJE-09-0348)
- 46 Rastrelli G, Corona G, Lotti F, Boddi V, Mannucci E & Maggi M. Relationship of testis size and LH levels with incidence of major adverse cardiovascular events in older men with sexual dysfunction. *Journal of Sexual Medicine* 2013 **10** 2761–2773. (doi:10.1111/jsm.12270)
- 47 Hyde Z, Norman PE, Flicker L, Hankey GJ, McCaul KA, Almeida OP, Chubb SA & Yeap BB. Elevated LH predicts ischaemic heart disease events in older men: the Health in Men Study. *European Journal of Endocrinology* 2011 **164** 569–577. (doi:10.1530/EJE-10-1063)
- 48 Hyde Z, Norman PE, Flicker L, Hankey GJ, Almeida OP, McCaul KA, Chubb SA & Yeap BB. Low free testosterone predicts mortality from cardiovascular disease but not other causes: the Health in Men Study. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 179–189. (doi:10.1210/jc.2011-1617)
- 49 Yeap BB, Hyde Z, Norman PE, Chubb SA & Golledge J. Associations of total testosterone, sex hormone-binding globulin, calculated free testosterone, and luteinizing hormone with prevalence of abdominal aortic aneurysm in older men. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 1123–1130. (doi:10.1210/jc.2009-1696)

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