·Original Article·

Postprandial triglyceride metabolism in elderly men with subnormal testosterone levels

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Abstract

Aim: To investigate the level of postprandial triglycerides (TG)s in elderly men with subnormal testosterone level ($\leq$ 11.0 nmol/L) compared to men with normal testosterone level (> 11.0 nmol/L). **Methods:** Thirthy-seven men with subnormal and 41 men with normal testosterone aged 60–80 years underwent an oral fat load and TG levels were measured fasting and 2, 4, 6 and 8 h afterwards. **Results:** Men with subnormal testosterone had significantly higher body mass index (BMI) and waist circumference ($P < 0.001$) than men with normal testosterone. They had significantly higher area under curve (AUC, $P = 0.037$), incremental area under curve (AUCi, $P = 0.035$) and TG response (TGR, $P = 0.014$) for serum-TG and significantly higher AUC ($P = 0.023$), AUCi ($P = 0.023$) and TGR ($P = 0.014$) for chylomicron-TG compared to men with normal testosterone level. Adjusting for waist circumference erased the significant differences between the groups in postprandial triglyceridemia. **Conclusion:** Men with subnormal testosterone have increased postprandial TG levels indicating an impaired metabolism of postprandial TG-rich lipoproteins (TRL), which may add to an unfavourable lipid profile and promote development of atherosclerosis. *(Asian J Androl 2008 Jul; 10: 542–549)*

Keywords: testosterone; sex hormone-binding globulin; postprandial triglycerides; abdominal obesity; waist circumference

1 Introduction

Abnormal lipid levels in fasting subjects are associated with atherosclerosis [1, 2]. We do, however, spend most of our lives in a postprandial state, between the consumption of regular meals. In the postprandial state, our vessel walls are exposed to triglyceride (TG)-rich dietary lipoproteins and the magnitude of postprandial triglyceridemia is associated with cardiovascular disease [3]. Remnants of postprandial lipoproteins are shown to rapidly penetrate arterial tissue and accumulate in the subendothelial space, showing that atherosclerosis is in

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part a postprandial phenomenon [4]. Men have a higher incidence of cardiovascular disease (CVD) than women in the same age group, and they have a less favourable lipid profile than women, with higher levels of TGs and lower levels of high density lipoprotein (HDL) cholesterol [5]. Therefore, it has been suggested that testosterone might influence the development of CVD [6]. However, most cross-sectional studies in fasting men show a negative association between endogenous total testosterone and TG [7] and a positive association between endogenous total testosterone and HDL cholesterol [8]. Low endogenous testosterone levels are also associated with atherosclerosis [9–11]. However, so far no relation between endogenous testosterone and cardiovascular events has been reported [6].

Recently, epidemiological data from the Tromsø study showed increased non-fasting TG during the day in men with lower total testosterone compared to men with higher total testosterone [12]. To further investigate the relationship between endogenous testosterone and postprandial TG levels, we performed a case-control study in elderly men with subnormal and normal total testosterone to compare postprandial TG levels after intake of a standard oral fat load.

2   Materials and methods

2.1 Participants

A sub-group of men participating in the study "Older Men and Testosterone", which will be presented in a separate publication, were included in this study. Briefly, based on total testosterone levels from the fifth survey of the Tromsø study in 2001 [12], men aged 60–80 years in 2005 were asked to participate in a study with the objective of evaluating subnormal testosterone levels in a variety of aspects. Men with persistent subnormal testosterone (≤ 11.0 nmol/L) or normal testosterone (> 11.0 nmol/L) in both 2001 and 2005 were included in the study. In this sub-study, 37 men with persistent subnormal testosterone and 41 men with persistent normal testosterone accepted to participate in a fat-tolerance test with the objective of investigating postprandial TG-rich lipoproteins.

The Regional Committee for Research and Ethics approved the study, and all participants gave written, informed consent.

2.2 Methods

The study was performed at the Clinical Research Unit at the University Hospital of North Norway. A physical examination and a complete medical history, including the use of prescription medication, were conducted. Height, weight and waist circumference were measured with the participants in light clothing without shoes and body mass index (BMI) as weight per height squared (kg/m^2) was calculated. Blood pressure was measured while the subject was in a seated position using an automatic device (Propaq 102 El, Protocol Systems, Beaverton, Oregon, USA), three recordings at 1 min intervals were conducted, and the mean of the last two values was used in this report. Baseline blood samples were drawn in the morning at 07:45 hours from an antecubital vein on the right arm after 12 h overnight fasting, using an 18-gauge needle in a vacutainer system with minimal stasis. Serum was prepared by clotting whole blood in a glass tube at room temperature for 30 min, centrifuged at $2\,000 \times g$ for 15 min at 20ºC, and then analyzed using standard laboratory procedures at the Department of Clinical Chemistry, University Hospital of North Norway, Tromsø, Norway. Total testosterone was measured by electrochemical luminescence immunoassay on Modular Analytics SWA (F. Hoffmann-La Roche, Basel, Switzerland). The intra-assay and inter-assay coefficients of variance (CV) for testosterone were 4.6% and 5.9%, respectively. Sex hormone-binding globulin (SHBG) was analyzed by chemoluminescence immunoassay on Immulite 2000 (Diagnostic Product, Los Angeles, CA, USA). The intra-assay and inter-assay CV for SHBG were 3.4% and 6.8%, respectively. Free testosterone was calculated from total testosterone and sex hormone-binding globulin (SHBG) according to Vermeulen *et al.* [13].

2.2.1 Fat-tolerance test

A fat-tolerance test was conducted using a test meal prepared from standard porridge cream containing 70% calories of fat, of which 66% was saturated fat, 32% was monounsaturated fat and 2% was polyunsaturated fat [14]. A freshly prepared test meal was served with two teaspoons of sugar, cinnamon and two glasses (150 mL) of sugar-free juice. The participants were served a weight-adjusted meal (1 g fat per kg body weight) at 08:00 hours and the meal was consumed within a 15-min period. The participants were allowed a 500-mL calorie-free beverage and one apple during the following 8 h. Blood samples for isolation of chylomicrons and serum were collected before the meal and every second hour over the next 8 h.

2.2.2 Isolation of chylomicrons

Chylomicrons were isolated by overlayering 8 mL EDTA plasma with 5 mL of NaCl gradient (density 1 006 kg/L NaCl solution with 0.01% EDTA) in a nitrate cellulose tube (Beckman Instruments, Palo Alto, CA, USA) and centrifuged in a Beckman SW40 Ti swinging bucket rotator at 20 000 × g for 1 h at 20ºC. The chylomicrons were carefully removed by aspiration, divided into three aliquots in cryovials and frozen at −70ºC until further analysis.

2.2.3 Serum lipid measurements

Serum lipids were analyzed on an ABX Pentra 400 (Horiba ABX Diagnostics, Montpellier, France) with reagents from Horiba ABX Diagnostics (Montpellier, France). Total cholesterol (CHOD-PAP) was measured using an enzymatic photometric method and TG (GPO-PAP) was measured using an enzymatic colorimetric method. Low-density lipoprotein cholesterol and HDL cholesterol were measured directly using selective inhibition colorimetric assays (Horiba ABX Diagnostics, Montpellier, France).

2.2.4 Lipoprotein lipase and hepatic lipase activity

Eight hours after ingestion of the test meal, blood was drawn into lithium heparin vacutainers (BD Vacutainer Systems, Belliver Industrial Estate, Plymouth, UK) containing heparin as anticoagulant and the heparinised blood was immediately placed on ice. Unfractionated heparin was given as a bolus injection (100 IU/kg body weight) on the contra lateral arm to mobilize lipoprotein lipase (LPL) and hepatic lipase (HL) from the endothelial surface into the circulation. A second blood sample was collected exactly 15 min after heparin administration and immediately placed on ice. Heparinised plasma was recovered within 30 min by centrifugation at 2 000 × g for 15 min at 4ºC, divided into aliquots of 0.5 mL in cryovials and frozen until further analysis.

Lipoprotein lipase activity and HL activity were determined as described by Olivecrona *et al.* [15]. In short, sonicated emulsion of ³H-oleic labeled triolein acid in 10% Intralipid (Fresenius Kabi, Halden, Norway) was used as substrate in the LPL cholesterol assay. Samples were preincubated for 2 h on ice with 0.5 volume goat antibodies to HL to suppress HL activity. For determination of HL activity, sonicated emulsion of ³H-oleic labeled triolein acid was used as substrate. Samples were mixed with 5 mol/L NaCl acid and 10% bovine serum albumin to suppress LPL activity and to remove free fatty acids. LPL activity and HL activity are expressed in mU/mL corresponding to nmol of fatty acids released per mL/min. The samples were quantified in duplicate and postheparin plasma from pooled normal control people were used to correct for inter-assay variation. Intra-assay and inter-assay CV for post-heparin LPL activity were 1.9% and 9.3% respectively, and 1.9% and 7.5%, respectively, for HL activity.

2.3 Statistics

Postprandial hypertriglyceridemia was assessed by total area under the curve (AUC), incremental AUC (AUCi) and triglyceride response (TGR), defined as the average of the two highest postprandial TG concentrations minus baseline concentrations, for serum-TG and chylomicron-TG. Normal distribution was evaluated by determination of skewness and histograms. AUC, AUCi and TGR for serum-TG and chylomicron-TG and LPL and HL activity were not normally distributed and, therefore, natural logarithmically transformed. After the logarithmic transformation they were considered normally distributed. Differences between the groups were assessed using independent-samples t-tests. General linear models for univariate analyses of variance were used for adjustments. Multiple linear regression models were used to assess independent predictors of AUC, AUCi and TGR for serum-TG and chylomicron-TG. All analyses were performed using SPSS for windows software (version 13.0, Chicago, IL, USA). All statistical tests were two-tailed, with statistical significance defined as $P < 0.05$.

3 Results

Characteristics of the participants are shown in Table 1. As expected, men with subnormal testosterone levels also had lower free testosterone levels. In addition, SHBG was significantly lower in the men with subnormal testosterone levels. There were no significant differences between men with subnormal testosterone and men with normal testosterone with regard to age, fasting serum lipids, systolic blood pressure, diastolic blood pressure, smoking status or self-reported history of CVD. Men with subnormal testosterone had significantly higher BMI (30.5 *vs.* 26.1 kg/m², $P < 0.001$) and waist circumference (109 *vs.* 95 cm, $P < 0.001$), and reported a higher use of statins ($P < 0.001$).

Table 1. Characteristics of the study population of elderly men with subnormal compared to men with normal testosterone levels. Values are mean ± SD or number and percentage (%) where appropriate. SHBG, sex hormone-binding globulin. [†]Cardiovascular disease includes acute myocardial infarction, cerebral stroke and/or angina pectoris.

| Variables	Subnormal testosterone (n = 37)	Normal testosterone (n = 41)	P-value
Age (years)	69.2 (4.9)	69.2 (4.3)	0.983
Anthropometric characteristics			
BMI (kg/m²)	30.5 (3.9)	26.1 (2.7)	< 0.001
Waist (cm)	109 (10)	95 (9)	< 0.001
Lipids			
Total cholesterol (mmol/L)	5.14 (1.31)	5.66 (1.18)	0.069
High density lipoprotein cholesterol (mmol/L)	1.29 (0.28)	1.38 (0.24)	0.130
Low-density lipoprotein cholesterol (mmol/L)	3.08 (0.85)	3.49 (1.07)	0.075
Triglycerides (mmol/L)	1.34 (0.65)	1.16 (0.71)	0.244
Hormones			
Total testosterone (nmol/L)	8.6 (1.9)	18.1 (4.0)	< 0.001
SHBG (nmol/L)	29.6 (12.7)	50.1 (16.0)	< 0.001
Free testosterone (pmol/L)	184.1 (46.5)	298.2 (58.9)	< 0.001
Systolic blood pressure (mmHg)	131 (20)	130 (19)	0.780
Diastolic blood pressure (mmHg)	77 (14)	75 (10)	0.403
Current smoking, number (%)	11 (28)	9 (22)	0.609
Cardiovascular disease (%)[†]	13 (35)	9 (22)	0.205
Statin use, number (%)	15 (41)	3 (7)	< 0.001
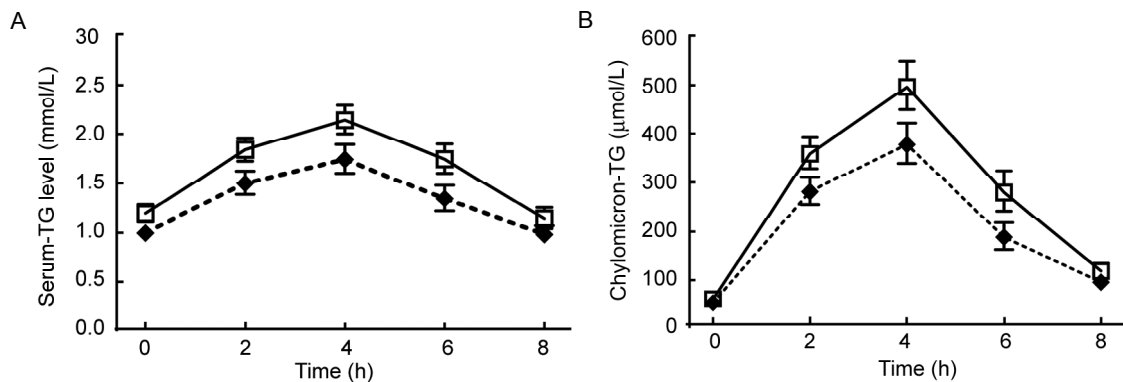
Figure 1. Time-course concentrations of serum-triglyceride (TG) (A) and chylomicron-TG (B) after an oral fat load in men with subnormal total testosterone levels (□) and in men with normal total testosterone levels (♦). Values are mean ± SEM.

Serum-TG and chylomicron-TG before and every second hour after ingestion of a standard fat meal are shown in Figure 1. Table 2 shows that men with subnormal testosterone had significantly higher AUC (P = 0.037), AUCi (P = 0.035) and TGR (P = 0.014) for serum-TG and significantly higher AUC (P = 0.023), AUCi (P = 0.023) and TGR (P = 0.014) for chylomi-cron-TG compared to men with normal testosterone levels. After adjusting for waist circumference the differences between the groups were no longer significant.

There was no difference between the groups in pre-heparin or postheparin levels of LPL and HL activity (Table 2). However, after adjusting for waist circumference, postheparin LPL activity was significantly higher

Table 2. Serum concentrations of postprandial triglyceride-rich lipoproteins (TRL) measured as total area under the curve (AUC), incremental AUC (AUCi) and triglyceride response (TGR) during the 8 h after intake of a standard fat meal in elderly men with subnormal compared to normal levels of total testosterone. Values are median and 25 and 75 percentiles. P^1: crude analyses. P^2: adjusted for waist circumference.

Variables	Subnormal testosterone ($n = 37$)	Normal testosterone ($n = 41$)	P-value P^1	P^2
Serum triglycerides				
AUC (mmol/h/L)	14.28 (10.24, 17.66)	11.17 (8.27, 16.05)	0.037	0.724
AUCi (mmol/h/L)	4.24 (2.75, 6.41)	3.35 (2.05, 5.16)	0.035	0.335
TGR (mmol/h/L)	0.84 (0.58, 1.23)	0.74 (0.46, 0.95)	0.014	0.966
Chylomicron triglycerides				
AUC (µmol/h/L)	2854.75 (1602.13, 4358.00)	1824.25 (1424.25, 2978.10)	0.023	0.765
AUCi (µmol/h/L)	2457.75 (1119.13, 3701.50)	1484.25 (930.75, 2311.94)	0.023	0.471
TGR (µmol/h/L)	445.00 (248.94, 690.38)	303.50 (202.79, 423.04)	0.014	0.976
Lipoprotein lipase activity				
Preheparin (mU/mL)	0.99 (0.67, 1.61)	1.07 (0.70, 1.63)	0.713	0.779
Postheparin (mU/mL)	251.67 (227.74, 293.37)	233.89 (201.50, 297.31)	0.313	0.012
Hepatic lipase activity				
Preheparin (mU/mL)	0.75 (0.55, 1.00)	0.66 (0.45, 1.05)	0.975	0.189
Postheparin (mU/mL)	237.35 (197.35, 329.79)	235.23 (192.15, 314.16)	0.649	0.136

Table 3. Multiple regression analyses with natural logarithmically transformed serum-triglyceride (TG) and chylomicron-TG levels by area under the curve (AUC), incremental area under the curve (AUCi) and triglyceride response (TGR) as dependent variables. β, standardized beta coefficient; R^2, the coefficient of determination; Ln, natural logarithm; LPL, lipoprotein lipase.

	Ln-serum-TG AUC β	P	Ln-serum-TG AUCi β	P	Ln-serum-TGR β	P	Ln-chylomicron-TG AUC β	P	Ln-chylomicron-TG AUCi β	P	Ln-chylomicron-TGR β	P
Model 1:												
Total testosterone	−0.25	0.029	−0.35	0.002	−0.32	0.005	−0.28	0.012	−0.27	0.018	−0.31	0.006
R^2	0.061		0.119		0.099		0.080		0.072		0.095	
Model 2:												
Total testosterone	−0.13	0.007	−0.29	0.001	−0.25	0.008	−0.18	0.011	−0.19	0.024	−0.22	0.009
Fasting TG	0.84	< 0.001	0.48	< 0.001	0.43	< 0.001	0.70	< 0.001	0.60	0.001	0.57	< 0.001
Postheparin LPL	−0.27	< 0.001	−0.33	< 0.001	−0.34	< 0.001	−0.28	< 0.001	−0.28	0.001	−0.34	< 0.001
R^2	0.849		0.463		0.418		0.664		0.507		0.539	
Model 3:												
Total testosterone	−0.03	0.555	−0.12	0.259	−0.11	0.306	−0.07	0.434	−0.01	0.993	−0.10	0.302
Fasting TG	0.81	< 0.001	0.40	< 0.001	0.40	< 0.001	0.67	< 0.001	0.54	< 0.001	0.53	< 0.001
Postheparin LPL	−0.25	< 0.001	−0.27	0.002	−0.31	0.001	−0.25	< 0.001	−0.23	0.006	−0.31	< 0.001
Waist circumference	0.17	0.004	0.31	0.006	0.23	0.045	0.19	0.019	0.34	0.001	0.20	0.051
R^2	0.867		0.520		0.450		0.693		0.576		0.566	

in men with subnormal testosterone ($P = 0.012$).

In multiple linear regression analyses (Table 3), fasting TG, postheparin LPL activity and waist circumference were independent predictors of AUC, AUCi and TGR for serum-TG and of AUC and AUCi for chylomicron-TG. Fasting TG and postheparin LPL were independent predictors of TGR for chylomicron-TG. Total testosterone and SHBG (data not shown) were inversely

associated with AUC, AUCi and TGR for serum-TG and for chylomicron-TG. These associations were lost after waist circumference was added to the models. There were no associations between free testosterone and triglyceride-rich lipoproteins (TRL).

4   Discussion

In this case-control study of 78 elderly men, we found that men with subnormal testosterone had significantly higher postprandial concentrations of TRL than men with normal testosterone. In addition, total testosterone was negatively associated with postprandial concentrations of TRL. Our results are unchallenged as we have not found any previously reported fat-tolerance tests performed in men with subnormal testosterone. However, in a study by Hislop *et al.* [16], postprandial TGs were reduced after a standard fatty meal in body builders using high dose androgens compared to controls not using androgens. In addition, cross-sectional data on elderly men from Tromsø, showed that low testosterone levels were associated with higher non-fasting TG levels, suggesting that testosterone may influence the TG metabolism [12]. Finally, other epidemiological studies in both middle-aged and older men have also reported an inverse relationship between total testosterone and fasting TG [7, 17, 18].

In our study, men with subnormal testosterone had increased waist circumference compared to men with normal testosterone. Waist circumference was positively associated with postprandial TGs and identified as an independent predictor of postprandial TG levels. Our results are supported by previous studies showing that both increased BMI and visceral adipose tissue are associated with increased postprandial TRL [19, 20]. Adjusting for abdominal obesity, as measured by waist circumference, erased the significant differences in postprandial TGs between the groups. These findings suggest that there are interrelations between low testosterone, postprandial TG concentrations and body fat distribution, but our study design is not suitable for determining the causal relations between these factors. It has been suggested that age-related decline in testosterone might be responsible for the changes in body fat and body fat distribution seen in elderly men [21]. This is supported by the observation that men with low testosterone have increased abdominal obesity [22] and that low-dose androgen treatment decreases abdominal fat mass in both younger and older men, regardless of cause of the decreased testosterone level [23]. In addition, in a 12-year follow-up study, lower levels of testosterone was predictive of central obesity [24]. In contrast, others have suggested that obesity plays a causal role in the decline of total and free testosterone [25], and that weight loss in younger obese individuals is reported to partially reverse low testosterone levels [26]. A recent publication from the Rancho Bernardo cohort also reports that weight loss in older men during a 10-year-period was associated with higher testosterone levels, whereas weight gain was associated with lower testosterone levels [27] .

Lipoprotein lipase hydrolyses TG in circulating TRL [28], thereby removing TG from the bloodstream and supplying underlying tissues with free fatty acids [29]. In abdominally obese men, supplementation with testosterone decreases LPL activity [30, 31] and inhibits uptake of fatty acids in subcutaneous abdominal adipocytes [30], thereby inhibiting abdominal obesity. Therefore, reduced inhibition of LPL activity in abdominal adipocytes in men with low testosterone might partly explain their abdominal obesity. In our study, endothelial-associated LPL, mobilized into circulation by heparin administration, was not different between groups in crude analysis, but significantly higher in men with subnormal testosterone after adjustment for waist circumference. Therefore, our findings support previous studies showing an inhibitory effect of testosterone on LPL activity [30, 31].

Endothelial-associated LPL in the capillary bed plays a pivotal role in the metabolism of postprandial TRL [32]. Deficiency of LPL or its cofactor apoCII is known to induce accumulation of chylomicrons in plasma, suggesting that triglyceride hydrolysis is important for clearance of these particles [33, 34]. In agreement with previous studies [35], postheparin LPL activity was found to be an inverse and independent predictor of the magnitude of postprandial hyperlipidemia in our study.

Statin treatment is known to reduce postprandial triglyceridemia [36] in a dose dependent manner by 5%–30% [37]. In our study, 41% of the men with subnormal testosterone used statins compared to 7% of the men with normal testosterone. Therefore, it is likely that the actual increase and delayed clearance of postprandial TRL in men with subnormal testosterone is even more pronounced. Because cholesterol is the precursor of steroid hormones, it has been suggested that use of statins might influence steroidogenesis, including gonadal ste-

roids production [38]. Previous studies have reported that statin treatment has a neutral effect on [39] or causes only a modest reduction in [40] testosterone. However, the clinical relevance of statin treatment on testosterone metabolism remains to be settled.

Increased and delayed postprandial hyperlipidemia have been reported to be strong predictors of coronary artery disease (CAD), verified by angiography in middle-aged men with severe disease [41, 42]. Furthermore, patients with CAD have increased levels and delayed elimination of postprandial TRL [42], and the plasma concentrations of postprandial remnants have been related to the progression of coronary lesions [41]. Postprandial TRL are able to penetrate and retain in the arterial wall [4], followed by uptake into macrophages to form foam cells [43]. Therefore, increased postprandial TRL in men with subnormal testosterone might represent an additional unfavorable lipid disturbance that might promote development of atherosclerosis.

In summary, in this case-control study, men with subnormal testosterone had increased postprandial concentrations of TRL compared to men with normal testosterone. Increased postprandial TRL might promote atherosclerosis and constitute a risk factor of cardiovascular disease in these men. Adjustment for waist circumference erased the differences in postprandial TRL between groups. Our study design is, however, not suitable in settling the causal relations between testosterone, abdominal obesity and postprandial TRL and intervention studies with testosterone to men with subnormal testosterone are warranted.

Acknowledgment

References

1 Pekkanen J, Linn S, Heiss G, Suchindran CM, Leon A, Rifkind BM, *et al*. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without pre-existing cardiovascular disease. N Engl J Med 1990; 322: 1700–707.

2 Lippel K, Tyroler H, Eder H, Gotto A, Jr. Vahouny G. Relationship of hypertriglyceridemia to atherosclerosis. Arteriosclerosis 1981; 1: 406–17.

3 Patsch JR, Miesenbock G, Hopferwieser T, Muhlberger V, Knapp E, Dunn JK, *et al*. Relation of triglyceride metabolism and coronary artery disease. Studies in the postprandial state. Arterioscler Thromb 1992; 12: 1336–45.

4 Proctor SD, Mamo JC. Retention of fluorescent-labelled chylomicron remnants within the intima of the arterial wall-evidence that plaque cholesterol may be derived from post-prandial lipoproteins. Eur J Clin Invest 1998; 28: 497–503.

5 Godsland IF, Wynn V, Crook D, Miller NE. Sex, plasma lipoproteins, and atherosclerosis: prevailing assumptions and outstanding questions. Am Heart J 1987; 114: 1467–503.

6 Liu PY, Death AK, Handelsman DJ. Androgens and cardiovascular disease. Endocr Rev 2003; 24: 313–40.

7 Lichtenstein MJ, Yarnell JW, Elwood PC, Beswick AD, Sweetnam PM, Marks V, *et al*. Sex hormones, insulin, lipids, and prevalent ischemic heart disease. Am J Epidemiol 1987; 126: 647–57.

8 Khaw KT, Barrett-Connor E. Endogenous sex hormones, high density lipoprotein cholesterol, and other lipoprotein fractions in men. Arterioscler Thromb 1991; 11: 489–94.

9 Svartberg J, von Muhlen D, Mathiesen E, Joakimsen O, Bonaa KH, Stensland-Bugge E. Low testosterone levels are associated with carotid atherosclerosis in men. J Intern Med 2006; 259: 576–82.

10 Hak AE, Witteman JC, de Jong FH, Geerlings MI, Hofman A, Pols HA. Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam study. J Clin Endocrinol Metab 2002; 87: 3632–9.

11 van den Beld AW, Bots ML, Janssen JA, Pols HA, Lamberts SW, Grobbee DE. Endogenous hormones and carotid atherosclerosis in elderly men. Am J Epidemiol 2003; 157: 25–31.

12 Agledahl I, Skjaerpe PA, Hansen JB, Svartberg J. Low serum testosterone in men is inversely associated with non-fasting serum triglycerides: The Tromsø study. Nutr Metab Cardiovasc Dis 2007 Jun 7 [Epub ahead of print].

13 Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab 1999; 84: 3666–72.

14 Nordoy A, Bonaa KH, Sandset PM, Hansen JB, Nilsen H. Relationship between apolipoprotein E polymorphism, postprandial hyperlipemia and hemostatic variables in patients with combined hyperlipemia. Nutr Metab Cardiovasc Dis 2000; 10: 15–23.

15 Olivecrona T, Olivecrona G. Lipoprotein lipase and hepatic lipase in lipoprotein metabolism. In: Betteridge DJ, Illingworth DR, Shepard J, editors. Lipoprotein In Health and Disease. London: Arnold. 1999; p223–46.

16 Hislop MS, St Clair Gibson A, Lambert MI, Noakes TD, Marais AD. Effects of androgen manipulation on postprandial triglyceridaemia, low-density lipoprotein particle size and lipoprotein(a) in men. Atherosclerosis 2001; 159: 425–32.

17 Barrett-Connor E, Khaw KT. Endogenous sex hormones and cardiovascular disease in men. A prospective population-based

study. Circulation 1988; 78: 539–45.

18 Chen RY, Wittert GA, Andrews GR. Relative androgen deficiency in relation to obesity and metabolic status in older men. Diabetes Obes Metab 2006; 8: 429–35.

19 Couillard C, Bergeron N, Prud'homme D, Bergeron J, Tremblay A, Bouchard C, *et al.* Postprandial triglyceride response in visceral obesity in men. Diabetes 1998; 47: 953–60.

20 Lewis GF, O'Meara NM, Soltys PA, Blackman JD, Iverius PH, Druetzler AF, *et al.* Postprandial lipoprotein metabolism in normal and obese subjects: comparison after the vitamin A fat-loading test. J Clin Endocrinol Metab 1990; 71: 1041–50.

21 Blouin K, Despres JP, Couillard C, Tremblay A, Prud'homme D, Bouchard C, *et al.* Contribution of age and declining androgen levels to features of the metabolic syndrome in men. Metabolism 2005; 54: 1034–40.

22 Svartberg J, von Muhlen D, Sundsfjord J, Jorde R. Waist circumference and testosterone levels in community dwelling men. The Tromsø study. Eur J Epidemiol 2004; 19: 657–63.

23 Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Lenrow DA, *et al.* Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. J Clin Endocrinol Metab 1999; 84: 2647–53.

24 Khaw KT, Barrett-Connor E. Lower endogenous androgens predict central adiposity in men. Ann Epidemiol 1992; 2: 675–82.

25 Zumoff B, Strain GW, Miller LK, Rosner W, Senie R, Seres DS, *et al.* Plasma free and non-sex-hormone-binding-globulin-bound testosterone are decreased in obese men in proportion to their degree of obesity. J Clin Endocrinol Metab 1990; 71: 929–31.

26 Pasquali R, Vicennati V, Scopinaro N, Marinari G, Simonelli A, Flamia R, *et al.* Achievement of near-normal body weight as the prerequisite to normalize sex hormone-binding globulin concentrations in massively obese men. Int J Obes Relat Metab Disord 1997; 21: 1–5.

27 Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. J Clin Endocrinol Metab 2008; 93: 68–75.

28 Mead JR, Irvine SA, Ramji DP. Lipoprotein lipase: structure, function, regulation, and role in disease. J Mol Med 2002; 80: 753–69.

29 Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med 1999; 340: 115–26.

30 Marin P, Oden B, Bjorntorp P. Assimilation and mobilization of triglycerides in subcutaneous abdominal and femoral adipose tissue *in vivo* in men: effects of androgens. J Clin Endocrinol Metab 1995; 80: 239–43.

31 Rebuffe-Scrive M, Marin P, Bjorntorp P. Effect of testosterone on abdominal adipose tissue in men. Int J Obes 1991; 15: 791–5.

32 Heeren J, Niemeier A, Merkel M, Beisiegel U. Endothelial-derived lipoprotein lipase is bound to postprandial triglyceride-rich lipoproteins and mediates their hepatic clearance *in vivo*. J Mol Med 2002; 80: 576–84.

33 Breckenridge WC, Little JA, Steiner G, Chow A, Poapst M. Hypertriglyceridemia associated with deficiency of apolipoprotein C-II. N Engl J Med 1978; 298: 1265–73.

34 Brunzell JD, Miller NE, Alaupovic P, St Hilaire RJ, Wang CS, Sarson DL, *et al.* Familial chylomicronemia due to a circulating inhibitor of lipoprotein lipase activity. J Lipid Res 1983; 24: 12–9.

35 Patsch JR, Prasad S, Gotto AM Jr, Patsch W. High density lipoprotein 2. Relationship of the plasma levels of this lipoprotein species to its composition, to the magnitude of postprandial lipemia, and to the activities of lipoprotein lipase and hepatic lipase. J Clin Invest 1987; 80: 341–7.

36 Schaefer EJ, McNamara JR, Tayler T, Daly JA, Gleason JA, Seman LJ, *et al.* Effects of atorvastatin on fasting and postprandial lipoprotein subclasses in coronary heart disease patients versus control subjects. Am J Cardiol 2002; 90: 689–96.

37 Karpe F. Postprandial lipemia—effect of lipid-lowering drugs. Atheroscler Suppl 2002; 3: 41–6.

38 Gwynne JT, Strauss JF 3rd. The role of lipoproteins in steroidogenesis and cholesterol metabolism in steroidogenic glands. Endocr Rev 1982; 3: 299–329.

39 Dobs AS, Miller S, Neri G, Weiss S, Tate AC, Shapiro DR, *et al.* Effects of simvastatin and pravastatin on gonadal function in male hypercholesterolemic patients. Metabolism 2000; 49: 115–21.

40 Stein EA, Davidson MH, Dobs AS, Schrott H, Dujovne CA, Bays H, *et al.* Efficacy and safety of simvastatin 80 mg/day in hypercholesterolemic patients. The Expanded Dose Simvastatin U.S. Study Group. Am J Cardiol 1998; 82: 311–6.

41 Karpe F, Steiner G, Uffelman K, Olivecrona T, Hamsten A. Postprandial lipoproteins and progression of coronary atherosclerosis. Atherosclerosis 1994; 106: 83–97.

42 Simons LA, Dwyer T, Simons J, Bernstein L, Mock P, Poonia NS, *et al.* Chylomicrons and chylomicron remnants in coronary artery disease: a case-control study. Atherosclerosis 1987; 65: 181–9.

43 Bradley WA, Gianturco SH. Triglyceride-rich lipoproteins and atherosclerosis: pathophysiological considerations. J Intern Med Suppl 1994; 736: 33–9.