APPENDIX 1

Investigations of serum testosterone concentrations and cardiovascular disease and mortality.

Table 1. Association Between Levels of Endogenous Testosterone and Mortality.

Study Name	Subfraction of Testosterone Used for Analysis	Sample Size	Sample Age Range/Sample Mean Age (Years)	Mean Follow-up Period (Years)	Major Finding	Remarks
Haring et al[35] (CS, n=1954)	TT	1954	20 to 79/58.7	7.2	Low TT is associated with increased risk of mortality from all causes and CV disease	● HR of low TT for all-cause mortality, 1.92 95% CI, 1.18 to 3.14; P<0.001 ● HR of low TT for CV mortality, 2.56; 95% CI, 1.15 to 6.52; P<0.05
Khaw et al[36] (CCS, n=11 606)	TT	11 606	40 to 79/67.3	7	Low TT is associated with higher risk of all-cause and CV mortality. Same trend was noted for CHD mortality but statistical significance was not achieved	● OR of low TT for all-cause mortality, 0.59; P<0.001 ● OR of low TT for CV mortality, 0.53; P<0.01
Menke et al[39] (CS, n=1114)	TT, FT, BT	1114	≥20/40	16	Decrease in FT and BT from 90th to 10th percentile is associated with increased risk of all-cause and CV mortality during the first 9 years of follow-up	● HR of FT decrease for all-cause mortality, 1.43; 95% CI, 1.09 to 1.87 ● HR of BT decrease for all-cause mortality, 1.52; 95% CI, 1.15 to 2.02 ● HR of FT decrease for CV mortality, 1.53; 95% CI, 1.05 to 2.23 ● HR of BT decrease for CV mortality, 1.63; 95% CI, 1.12 to 2.37
Vikan et al[40] (CS, n=1568)	TT, FT	1568	Not reported/ 59.6	11.2	24% Higher risk of all-cause mortality for men with low FT levels	● HR of low FT for all-cause mortality, 1.24; 95% CI, 1.01 to 1.54
Tivesten et al[42] (CS, n=3014)	TT, FT	2639 with TT; 2618 with FT	69 to 80/75.4	4.5	Increasing levels of TT and FT are associated with decreasing risk of all-cause mortality	● HR of high TT for all-cause mortality, 0.59; P<0.001 ● HR of high FT for all-cause mortality, 0.50; P<0.001
Shores et al[44] (CS, n=858)	TT	858	≥40/61.4	4.3	Low TT is associated with higher risk of all-cause mortality	● HR of low TT for all-cause mortality, 1.88; P<0.001

Laughlin et al[46] (CS, n=794)	TT, BT	794	63 to 78.9/ 71.2	11.8	Low TT and BT are associated with higher risk of all-cause and CV mortality	● HR of low TT for all-cause mortality, 1.44; P<0.002 ● HR of low BT for all-cause mortality, 1.50; P<0.001 ● HR of low TT for CV mortality, 1.38; 95% CI, 1.02 to 1.85 ● HR of low BT for CV mortality, 1.36; 95% CI, 1.04 to 1.79
Malkin et al[47] (FU, n=930)	TT, BT	930	Not reported	6.9	Low BT is inversely associated with time to all-cause and vascular mortality	● HR of low BT for all-cause mortality, 2.2; 95% CI, 1.4 to 3.6; P<0.0001 ● HR of low BT for vascular mortality, 2.2; 95% CI, 1.2 to 3.9; P=0.007
Araujo et al[48] (FU, n=1686)	TT, FT	1686	40-80	15.3	High FT and low DHT levels are associated with ischemic heart disease	● TT and SHBG levels are not associated with all-cause mortality

BT, bioavailable testosterone; CAD, coronary artery disease; CCS, case–control study; CHD, coronary heart disease; CI, confidence interval; CS, cohort study; CV, cardiovascular; FAI, free androgen index; FT, free testosterone; FU, follow-up study; HR, hazard ratio; OR, odds ratio; TT, total testosterone, DHT, dihydrotestosterone, SHBG, sex hormone binding globulin.

35. Haring R, Volzke H, Steveling A, Krebs A, Felix SB, Schofl C, Dorr M, Nauck M, Wallaschofski H. Low serum testosterone levels are associated with increased risk of mortality in a population-based cohort of men aged 20-79. Eur Heart J. 2010;31:1494–1501.

36. Khaw KT, Dowsett M, Folkerd E, Bingham S, Wareham N, Luben R, Welch A, Day N. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation
into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. Circulation. 2007;116:2694–2701.

39. Menke A, Guallar E, Rohrmann S, Nelson WG, Rifai N, Kanarek N, Feinleib M, Michos ED, Dobs A, Platz EA. Sex steroid hormone concentrations and risk of death in US men. Am J Epidemiol. 2010;171:583–592.

40. Vikan T, Schirmer H, Njolstad I, Svartberg J. Endogenous sex hormones and the prospective association with cardiovascular disease and mortality in men: the Tromso Study. Eur J Endocrinol. 2009;161:435–442.

42. Tivesten A, Vandenput L, Labrie F, Karlsson MK, Ljunggren O, Mellstrom D, Ohlsson C. Low serum testosterone and estradiol predict mortality in elderly men. J Clin Endocrinol Metab. 2009;94:2482–2488.

44. Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR. Low serum testosterone and mortality in male veterans. Arch Intern Med. 2006;166:1660–1665.

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

47. Malkin CJ, Pugh PJ, Morris PD, Asif S, Jones TH, Channer KS. Low serum testosterone and increased mortality in men with coronary heart disease. Heart. 2010;96:1821–1825.

48. Araujo, A.B., et al., Sex steroids and all-cause and cause-specific mortality in men. Arch Intern Med, 2007. 167(12): p. 1252-60.

Table 2. Association Between Testosterone Level and Incidence of Coronary Artery Disease

Study Name	Sub-fraction of Testosterone Used for Analysis	Primary End Point Measured (Method)	Main Finding of Study	Potential Confounding Factors
Articles showing an association between low testosterone levels and incident CAD				
Zhao et al[13] (CCS, n=201)	TT	Coronary artery disease (H&P, ECG, cardiac catheterization in 27 patients)	Men with CAD have lower levels of TT	● BT not used for analysis ● Limited number of subjects have undergone catheterization ● Small sample size
English et al[14] (CCS, n=90)	TT, FT, BT, FAI	Coronary artery disease (cardiac catheterization)	Men with catheterization-proven CAD have lower levels of FT, BT, and FAI	● Small sample size
Dobrzycki et al[15] (CCS, n=96)	TT, FT, FAI	Coronary artery disease (cardiac catheterization)	Men with catheterization-proven CAD have lower levels of TT, FT, and FAI	● BT not used for analysis ● Small sample size
Akishita et al[16] (CS, n=171)	TT	Cardiovascular events* (H&P, physician and hospital records)	Men with lower levels of endogenous TT are more likely to suffer cardiovascular events	● BT not used for analysis ● Small sample size ● End points other than CAD were pulled in the analysis ● Subjects did not undergo cardiac catheterization
Rosano et al[17] (CCS, n=129)	TT, FT, BT	Coronary artery disease (cardiac catheterization)	Men with catheterization-proven CAD have lower levels of TT and BT	● Small sample size

Hu et al[18] (CCS, n=87)	TT	Coronary artery disease (cardiac catheterization)	Men with catheterization-proven CAD have lower levels of TT	● BT not used for analysis ● Small sample size
Articles showing no association between testosterone levels and incident CAD				
Cauley et al[19] (CCS, n=163)	TT, FT	Acute, nonfatal myocardial infarction, death from cardiovascular disease (ECG, hospital records)	No difference in TT or FT levels between cases and controls	● BT not used for analysis ● Small sample size ● Subjects did not undergo cardiac catheterization
Barrett-Connor et al[20] (CS, n=1009)	TT	Cardiovascular disease or mortality, ischemic heart disease morbidity or mortality (death certificates, hospital records)	No statistically significant association between levels of TT and primary end points	● BT not used for analysis ● Subjects did not undergo cardiac catheterization
Kabakci et al[21] (CCS, n=337)	TT, FT	Coronary artery disease (cardiac catheterization)	No statistically significant difference in FT or TT levels between cases and controls	● BT not used in analysis ● Small sample size ● Suboptimal method used for measurement of FT
Arnlov et al[22] (PCS, n=2084)	TT	Cardiovascular disease† (physician and hospital records)	No significant association between levels of endogenous TT and incidence of CAD	● BT not used for analysis ● End points other than CAD were pooled in the analysis ● Subjects did not undergo cardiac catheterization
Articles showing an association between high testosterone levels and incident CAD				
None indentified				

BT, bioavailable testosterone; CAD, coronary artery disease; CCS, case–control study; CS, cohort study; ECG, electrocardiogram; FAI, free androgen index; FT, free testosterone; H&P, history and physical exam; PCS, prospective cohort study; TT, total testosterone.

*Cardiovascular events include stroke, coronary artery disease, sudden cardiac death, and peripheral arterial disease.

†Cardiovascular disease includes coronary artery disease, myocardial infarction, angina pectoris, coronary insufficiency, death from coronary artery disease, stroke, transient ischemic attack, congestive heart failure, and peripheral vascular disease.

13. Zhao SP, Li XP. The association of low plasma testosterone level with coronary artery disease in Chinese men. Int J Cardiol. 1998;63:161–164.

14. English KM, Mandour O, Steeds RP, Diver MJ, Jones TH, Channer KS. Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms. Eur Heart J. 2000;21:890–894.

15. Dobrzycki S, Serwatka W, Nadlewski S, Korecki J, Jackowski R, Paruk J,Ladny J, Hirnle T. An assessment of correlations between endogenous sex hormone levels and the extensiveness of coronary heart disease and the ejection fraction of the left ventricle in males. J Med Invest. 2003;50:162–169.

16. Akishita M, Hashimoto M, Ohike Y, Ogawa S, Iijima K, Eto M, Ouchi Y. Low testosterone level as a predictor of cardiovascular events in Japanese men with coronary risk factors. Atherosclerosis. 2010;210:232–236.

17. Rosano G, Sheiban I, Massaro R, Pgnotta P, Marazzi G, Vitale C, Mercuro G, Volterrani M, Aversa A, Fini M. Low testosterone levels are associated with coronary artery disease in male patients with angina. Int J Impot Res. 2007;19:176–182.

18. Hu X, Rui L, Zhu T, Xia H, Yang X, Wang X, Liu H, Lu Z, Jiang H. Low testosterone level in middle-aged male patients with coronary artery disease. Eur J Intern Med. 2011;22:133–136.

19. Cauley JA, Gutai JP, Kuller LH, Dai WS. Usefulness of sex steroid hormones levels in predicting coronary artery disease in men. Am J Cardiol. 1987; 60:771–777.

20. Barrett-Connor E, Khaw KT. Endogenous sex hormones and cardiovascular disease in men. A prospective population-based study. Circulation. 1988; 78:539–545.

21. Kabakci G, Yildirir A, Can I, Unsal I, Erbas B. Relationship between endogenous sex hormones levels, lipoproteins, and coronary atherosclerosis in men undergoing coronary angiography. Cardiology. 1999;92:221–225.

22. Arnlov J, Pencina MJ, Amin S, Nam BH, Benjamin EJ, Murabito JM, Wang TJ, Knapp PE, D'Agostino RB, Bhasin S, Vasan R. Endogenous sex hormones and cardiovascular disease incidence in men. Ann Intern Med. 2006;145:176–184.

Table 3. Association Between Testosterone Level and Severity of Coronary Artery Disease.

Study Name	Sub-fraction of Testosterone Used for Analysis	Method of Measuring CAD Severity	Main Findings	Remarks
Negative (inverse) correlation				
Dobrzycki et al[15] (CCS, n=96)	TT, FT, FAI	Duke index*	Inverse correlation between FT and CAD severity	r=-0.69, P=0.048
Rosano et al[17] (CCS, n=129)	TT	Coronary artery score†	Inverse correlation between TT and CAD severity	r=-0.52, P<0.01
Li et al[29] (CCS, n=803)	TT	Genisi score‡	Inverse correlation between TT and CAD severity	r=-0.188, P<0.001
Phillips et al[30] (CCS, n=55)	TT, FT	Visual estimation of coronary artery occlusion and calculation of mean percent occlusion§	Inverse correlation between TT and FT levels and CAD severity	TT: r=-0.43, P<0.02; FT: r=-0.62, P<0.001
Positive correlation				
None identified				

CAD, coronary artery disease; CCS, case–control study; FAI, free androgen index; FT, free testosterone; TT, total testosterone.

*Duke prognostic coronary artery index: a prognostic tool involving the extent and severity of atherosclerotic lesions in coronary arteries.

†Coronary artery score: authors multiplied the degree of coronary artery obstruction by the number of stenoses.

‡Genisi score: Calculated based on location and number of stenotic coronary artery segments, and degree of luminal narrowing.

§Authors visually estimated the maximum percent reduction in luminal diameter of the left main, left anterior descending, left circumflex, and right coronary arteries. The mean of these 4 values was used to estimate CAD severity.

15. Dobrzycki S, Serwatka W, Nadlewski S, Korecki J, Jackowski R, Paruk J, Ladny J, Hirnle T. An assessment of correlations between endogenous sex hormone levels and the extensiveness of coronary heart disease and the
ejection fraction of the left ventricle in males. J Med Invest. 2003;50:162–169.

17. Rosano G, Sheiban I, Massaro R, Pgnotta P, Marazzi G, Vitale C, Mercuro G, Volterrani M, Aversa A, Fini M. Low testosterone levels are associated with coronary artery disease in male patients with angina. Int J Impot Res. 2007;19:176–182.

29. Li L, Guo CY, Jia EZ, Zhu TB, Wang LS, Cao KJ, Ma WZ, Yang ZJ. Testosterone is negatively associated with the severity of coronary atherosclerosis in men. Asian J Androl. 2012;14:875–878.

30. Phillips GB, Pinkernell BH, Jing TY. The association of hypotestosteronemia with coronary artery disease in men. Arterioscler Thromb Vasc Biol. 1994; 14:701–706.

Table 4. Association Between Endogenous Testosterone Level and Carotid Intima-Media Thickness.

Study Name	Sample Size	Sample Age Range	Major Findings
Negative (inverse) correlation			
Van den Beld et al[126] (CS)	403 Men	73 to 94 (mean age, 77.8)	● After adjustment for age, serum total testosterone was inversely related to carotid artery IMT.
Fukui et al[127] (CS)	154 Diabetic men	Mean age, 62 (age range not provided)	● FT was inversely associated with carotid artery IMT. ● Free testosterone is inversely associated with carotid artery plaque score, ● Carotid IMT and plaque score were significantly higher in patients with lower levels of FT.
De Pergola et al[128] (CS)	127 Overweight or obese men	18 to 45 (mean age, 34)	● After adjustment for age, total body fat, central obesity, and fasting glucose concentration, carotid artery IMT was inversely associated with FT.
Makinen et al[32] (CCS)	96 Nondiabetic men	40 to 70 (mean age, 57)	● After adjustment for age, BMI, .blood pressure, smoking, and total cholesterol, TT was inversely associated with carotid IMT.
Svartberg et al[129] (CS)	1482 Men	25 to 84 (mean age, 60)	● After adjustment for age, smoking, physical activity, blood pressure, and lipid levels, TT was inversely associated with carotid IMT. ● The association between TT and carotid IMT was not independent of BMI. ● There was no association between FT and carotid IMT.
Fu et al[130] (CCS)	106 Men	50 to 70 (mean age, 64)	● FT was independently inversely associated with carotid IMT.
Vikan et al[131] (CS)	2290 Men	55 to 74 (mean age, 66)	● After adjustment for age, systolic BP, smoking, and use of lipid-lowering medications, total testosterone was inversely associated with total carotid plaque area. ● SHBG was not associated with changes in carotid IMT or plaque area.
Muller et al[132] (CS)	195 Men	73 to 91 (mean age, 77)	● FT was inversely associated with mean progression of carotid IMT independent of age. ● FT was inversely associated with mean progression of carotid IMT after adjustment for cardiovascular risk factors.*
Positive correlation			
None identified			

BMI, body mass index; BP, blood pressure; CCS, case–control study; CS, cross-sectional study; FT, free testosterone; IMT, intima-media thickness; SHBG, sex hormone–binding globulin; TT, total testosterone.

*Cardiovascular risk factors included body mass index, waist-to-hip-ratio, hypertension, diabetes, smoking, and serum cholesterol levels.

32. Makinen J, Jarvisalo M, Pollanen P, Perheentupa A, Irjala K, Koskenvuo M, Makinen J, Huhtaniemi I, Raitakari O. Increased carotid atherosclerosis in andropausal middle-aged men. J Am Coll Cardiol. 2005;45:1603–1608.

126. van den Beld AW, Bots ML, Janssen JAMLL, Pols HAP, Lamberts SWJ, Grobbee DE. Endogenous hormones and carotid atherosclerosis in elderly men. Am J Epidemiol. 2003;157:25–31.

127. Fukui M, Kitagawa Y, Nakamura N, Kadono M, Mogami S, Hirata C, Ichio N, Wada K, Hasegawa G, Yoshikawa T. Association between serum testosterone concentration and carotid atherosclerosis in men with type 2 diabetes.
Diabetes Care. 2003;26:1869–1873.

128. De Pergola G, Pannacciulli N, Ciccone M, Tartagni M, Rizzon P, Giorgino R.
Free testosterone plasma levels are negatively associated with the intima- glucose-tolerant young adult men. Int J Obes Relat Metab Disord. 2003; 27:803–807.

129. 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;259:576–582.

130. Fu L, Gao QP, Shen JX. Relationship between testosterone and indexes indicating endothelial function in male coronary heart disease patients. Asian J Androl. 2008;10:214–218.

131. Vikan T, Johnsen SH, Schirmer H, Njolstad I, Svartberg J. Endogenous testosterone and the prospective association with carotid atherosclerosis in men: the Tromso study. Eur J Epidemiol. 2009;24:289–295.

132. Muller M, van den Beld AW, Bots ML, Grobbee DE, Lamberts SWJ, van der Schouw YT. Endogenous sex hormones and progression of carotid atherosclerosis in elderly men. Circulation. 2004;109:2074–2079.

APPENDIX 2

Effects of testosterone therapy (TTh) on cardiovascular risk factors in placebo-controlled studies.

Table 5. Changes in Parameters of Obesity with Testosterone (T) Treatment Versus Placebo (Plc).

Table 5. Changes in Parameters of Obesity with Testosterone (T) Treatment Versus Placebo (Plc).

Reference / Parameter	Preparation	Treatment Duration	Change T	Change Plc	Net Change
Total fat mass (kg)					
Marin 1993 [58]	Gel	9 mo	-1.8	0.6	-2.4
Snyder 1999 [59]	Patch	36 mo	-3.3	-1.3	-2.0
Kenny 2001 [62]	Patch	12 mo	-1.7	0.3	-1.4
Ferrando 2002 [63]	TE	6 mo	-3.6	0.3	-3.9
Boyanov 2003 [64]	Oral TU	3 mo	-1.65	-0.25	-1.4
Crawford 2003 [65]	Mixed esters	12 mo	-2.3	0.7	-3.0
Steidle 2003 [66]	Gel	3 mo	-0.8	-0.1	-0.7
Steidle 2003 [66]	Patch	3 mo	-0.4	-0.1	-0.3
Wittert 2003 [61]	Oral TU	12 mo	-0.2	0.85	-1.05
Casaburi 2004 [67] (no tr.)	TE	10 wk	-1.01	-0.08	-0.93
Casaburi 2004 [67] (training)	TE	10 wk	-1.41	-0.13	-1.28
Svartberg 2008 [71]	Inj TU	12 mo	-5.4	-0.6	-4.8
Allan 2008 [57]	Patch	12 mo	-0.5	0.1	-0.6
Emmelot-Vonk 2008 [10]	Oral TU	6 mo	-1.0	-0.1	-0.9
Srinivas-Shankar 2010 [68]	Gel	6 mo	-0.8	-0.3	-0.5
Visceral adipose tissue (kg)					

Marin 1993 [58]	Gel	9 mo	-0.6	0.2	-0.8
Allan 2008 [57]	Patch	12 mo	-0.2	0.5	-0.7
Trunk fat (kg)					
Casaburi 2004 [67] (no tr.)	TE	10 wk	-0.55	0.34	-0.89
Casaburi 2004 [67] (training)	TE	10 wk	-0.67	0.11	-0.78
Page 2005 [69]	TE	36 mo	-1.9	-0.4	-1.5
Allan 2008 [57]	Patch	12 mo	0.1	0.0	0.1
Visceral adipose tissue (cm^3)					
Svartberg 2008 [71]	Inj TU	12 mo	-38	-11	-27
Subcutaneous adipose tissue (kg)					
Marin 1993 [58]	Gel	9 mo	-1.2	0.5	-1.7
Allan 2008 [57]	Patch	12 mo	-0.1	0.0	-0.1
Subcutaneous adipose tissue (cm^3)					
Svartberg 2008 [71]	Inj TU	12 mo	-49	-10	-39
Total adipose tissue (cm^3)					
Svartberg 2008 [71]	Inj TU	12 mo	-86	-27	-59
Right leg fat (kg)					
Page 2005 [69]	TE	36 mo	-0.9	0.1	-1.0
Percentage total body fat (%)					
Sih 1997 [84]	TC	12 mo	-1.9	19.3	-21.2
Boyanov 2003 [64]	Oral TU	3 mo	-3	-0.1	-2.9
Crawford 2003 [65]	Mixed esters	12 mo	-10.9	3.4	-14.3
Steidle 2003 [66]	Gel	3 mo	-1.2	-0.2	-1.0
Steidle 2003 [66]	Patch	3 mo	-0.5	-0.2	-0.3
Casaburi 2004 [67] (no tr.)	TE	10 wk	-6	-0.1	-5.9
Casaburi 2004 [67] (training)	TE	10 wk	-9.4	-2.2	-7.2
Page 2005 [69]	TE	36 mo	-17.0	1.0	-18.0
Kapoor 2007 [51]	Mixed esters	3 mo	-3.7	-1.5	-2.2

Kapoor 2006 [70]	Mixed esters	3 mo	-3.0	-1.8	-1.2
Svartberg 2008 [71]	Inj TU	12 mo	-18.9	-1.9	-17.0
Allan 2008 [57]	Patch	12 mo	-2.9	0.4	-3.3
Emmelot-Vonk 2008 [10]	Oral TU	6 mo	-4.7	0.0	-4.7
Aversa 2010 [85]	Inj TU	24 mo	-18.5	0.5	-19
Aversa 2010 [87]	Inj TU	12 mo	-18.4	0.6	-19.0
Waist circumference (cm)					
Marin 1993 [58]	Gel	9 mo	-2.5	-0.6	-1.9
Kapoor 2007 [51]	Mixed esters	3 mo	-2.0	0.1	-2.1
Kapoor 2006 [70]	Mixed esters	3 mo	-1.6	N/A	N/A
Svartberg 2008 [71]	Inj TU	12 mo	-3.0	-1.0	-2.0
Heufelder 2009 [12]	Gel	12 mo	-14.6	-6.7	-7.9
Aversa 2010 [85]	Inj TU	24 mo	-8.5	-0.5	-8.0
Kalinchenko 2010 [74]	Inj TU	30 wk	-5.8	-1.5	-4.3
Aversa 2010 [87]	Inj TU	12 mo	-8.7	1.1	-9.7

Gel: testosterone gel Patch: testosterone patch
TE: parenteral testosterone enanthate Oral TU: oral testosterone undecanoate
Mixed esters: mixed parenteral testosterone esters
Inj TU: parenteral testosterone undecanoate TC: parenteral testosterone cypionate

[58] Marin P, Holmang S, Gustafsson C*, et al*. Androgen treatment of abdominally obese men. Obes Res 1993; 1: 245-51.

[59] Snyder PJ, Peachey H, Hannoush P*, 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.

[61] Wittert GA, Chapman IM, Haren MT, Mackintosh S, Coates P, Morley JE. Oral testosterone supplementation increases muscle and decreases fat mass in healthy elderly males with low-normal gonadal status. J Gerontol A Biol Sci Med Sci 2003; 58: 618-25.

[62] Kenny AM, Prestwood KM, Gruman CA, Marcello KM, Raisz LG. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels. J Gerontol A Biol Sci Med Sci 2001; 56: M266-72.

[63] Ferrando AA, Sheffield-Moore M, Yeckel CW*, et al*. Testosterone administration to older men improves muscle function: molecular and physiological

mechanisms. Am J Physiol Endocrinol Metab 2002; 282: E601-7.

[64] Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. Aging Male 2003; 6: 1-7.

[65] Crawford BA, Liu PY, Kean MT, Bleasel JF, Handelsman DJ. Randomized placebo-controlled trial of androgen effects on muscle and bone in men requiring long-term systemic glucocorticoid treatment. J Clin Endocrinol Metab 2003; 88: 3167-76.

[66] Steidle C, Schwartz S, Jacoby K, Sebree T, Smith T, Bachand R. AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. J Clin Endocrinol Metab 2003; 88: 2673-81.

[67] Casaburi R, Bhasin S, Cosentino L*, et al*. Effects of testosterone and resistance training in men with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004; 170: 870-8.

[68] Srinivas-Shankar U, Roberts SA, Connolly MJ*, et al*. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab 2010; 95: 639-50.

[69] Page ST, Amory JK, Bowman FD*, et al*. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. J Clin Endocrinol Metab 2005; 90: 1502-10.

[70] Kapoor D, Goodwin E, Channer KS, Jones TH. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. Eur J Endocrinol 2006; 154: 899-906.

[71] Svartberg J, Agledahl I, Figenschau Y, Sildnes T, Waterloo K, Jorde R. Testosterone treatment in elderly men with subnormal testosterone levels improves body composition and BMD in the hip. Int J Impot Res 2008; 20: 378-87.

[72] Sheffield-Moore M, Dillon EL, Casperson SL*, et al*. A Randomized Pilot Study of Monthly Cycled Testosterone Replacement or Continuous Testosterone Replacement Versus Placebo in Older Men. J Clin Endocrinol Metab 2011; 9(11): 1831-7.

[73] Jones TH, Arver S, Behre HM*, et al*. Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). Diabetes Care 2011; 34: 828-37.

[74] Kalinchenko SY, Tishova YA, Mskhalaya GJ, Gooren LJ, Giltay EJ, Saad F. Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebocontrolled Moscow study. Clin Endocrinol (Oxf) 2010; 73: 602-12.

[75] Saad F, Haider A, Giltay EJ, Gooren L. J. Age, obesity and inflammation at baseline predict the effects of testosterone administration on the metabolic syndrome. Horm Mol Biol Clin Invest 2011; 6: 193–199.

[76] Witham MD, Avenell A. Interventions to achieve long-term weight loss in obese older people: a systematic review and meta-analysis. Age Ageing 2010; 39: 176-84.

[77] Dyson PA, Beatty S, Matthews DR. An assessment of low-carbohydrate or low-fat diets for weight loss at 2 year's follow-up. Diabet Med 2010; 27: 363-4.

[78] Menshikova EV, Ritov VB, Toledo FG, Ferrell RE, Goodpaster BH, Kelley DE. Effects of weight loss and physical activity on skeletal muscle mitochondrial function in obesity. Am J Physiol Endocrinol Metab 2005; 288: E818-25.

[79] Simoneau JA, Veerkamp JH, Turcotte LP, Kelley DE. Markers of capacity to utilize fatty acids in human skeletal muscle: relation to insulin resistance and obesity and effects of weight loss. Faseb J 1999; 13: 2051-60.

[80] Chomentowski P, Dube JJ, Amati F*, et al*. Moderate exercise attenuates the loss of skeletal muscle mass that occurs with intentional caloric restriction-induced weight loss in older, overweight to obese adults. J Gerontol A Biol Sci Med Sci 2009; 64: 575-80.

[81] Kirwan JP, Barkoukis H, Brooks LM, Marchetti CM, Stetzer BP, Gonzalez F. Exercise training and dietary glycemic load may have synergistic effects on insulin resistance in older obese adults. Ann Nutr Metab 2009; 55: 326-33.

[82] Weinheimer EM, Sands LP, Campbell WW. A systematic review of the separate and combined effects of energy restriction and exercise on fat-free mass in middle-aged and older adults: implications for sarcopenic obesity. Nutr Rev 2010; 68: 375-88.

[83] Solomon TP, Sistrun SN, Krishnan RK*, et al*. Exercise and diet enhance fat oxidation and reduce insulin resistance in older obese adults. J Appl Physiol 2008; 104: 1313-9.

[84] Sih R, Morley JE, Kaiser FE, Perry HM, 3rd, Patrick P, Ross C. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. J Clin Endocrinol Metab 1997; 82: 1661-7.

[85] Aversa A, Bruzziches R, Francomano D*, et al*. Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study. J Sex Med 2010; 7: 3495-503.

[86] Giannetta E, Isidori A, Pierotti S, *et al*. Testosterone replacement improves metabolic syndrome and inflammation independently of body fat mass changes. J Endocrinol Invest 2010; 33: 3.

[87] Aversa A, Bruzziches R, Francomano D, Spera G, Lenzi A. Efficacy and safety of two different testosterone undecanoate formulations in hypogonadal men with metabolic syndrome. J Endocrinol Invest 2010; 33: 776-83.

Table 6. Effects of Testosterone Replacement Therapy on Cholesterol Levels - Meta-analyses.

Study Name	Major Findings
Haddad et al[31]	• In patients with low levels of baseline testosterone, exogenous testosterone did not affect any of the lipid sub-fractions. • In patients with normal levels of baseline testosterone, exogenous testosterone resulted in a significant decrease in total cholesterol levels. • In patients with normal levels of baseline testosterone, exogenous testosterone did not affect the levels of LDL, HDL, or triglyceride levels. • In patients with chronic disease or in those on glucocorticoid therapy, exogenous testosterone resulted in a small decrease in levels of HDL cholesterol. • In patients with chronic disease or in those on glucocorticoid therapy, exogenous testosterone did not affect the levels of total cholesterol, LDL cholesterol, or triglycerides.
Whitsel et al[88]	• Exogenous testosterone resulted in small but significant reduction in the levels of total, LDL, and HDL cholesterol. • Exogenous testosterone did not affect triglyceride levels.
Isidori et al[89]	• Exogenous testosterone resulted in reduced levels of total cholesterol. • The improvement in total cholesterol was more significant for patients with reduced levels of baseline testosterone. • No significant change in total cholesterol in patients with baseline testosterone of >10 nmol/L. • Exogenous testosterone did not affect levels of LDL or HDL cholesterol. • The effect of testosterone replacement therapy on triglyceride levels was not examined in this meta-analysis.

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

31. Haddad R, Kennedy C, Caples S, Tracz M, Bolona E, Sideras K, Uraga M, Erwin P, Montori V. Testosterone and cardiovascular risk in men: a systemic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc. 2007;81:29–39.

88. Whitsel EA, Boyko EJ, Matsumoto AM, Anawalt BD, Siscovick DS. Intramuscular testosterone esters and plasma lipids in hypogonadal men: a meta-analysis. Am J Med. 2001;111:261–269.

89. 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. Clin Endocrinol.2005;63:280–293.

Table 7. Effects of Testosterone Therapy on Indices of Glycemic Control.

Study Name	Testosterone Formulation Used	Sample Size	End Points Measured	Main Findings
Corona et al[26] (meta-analysis, n=37 studies)	Various formulations (meta-analysis)	1822 Diabetic men and 10 009 nondiabetic men (meta-analysis)	HgA1c, fasting plasma glucose, triglycerides	● HgA1c decreased by 0.76% with TRT ● Fasting plasma glucose decreased by 1.18 mmol/L with TRT ● TG decreased by 0.67 with TRT
Jones et al[68] (DBRCT)	TD*	220 Hypogonadal men with T2DM and/or MetS	HOMA-IR, HgA1c, b ody composition	● HOMA-IR decreased by 15.2% after 6 months with TRT (P=0.018) ● HOMA-IR decreased by 16.4% after 12 months with TRT (P=0.006) ● HgA1c decreased by 0.44% after 9 months with TRT (P=0.035)
Kapoor et al[69] (DBPCC)	IM†	24 Hypogonadal men with T2DM	HOMA-IR, HgA1c, fasting plasma glucose	● HOMA-IR decreased by 1.73 in TRT group (P=0.02) ● HgA1c decreased by 0.37% in TRT group (P=0.03) ● Fasting plasma glucose decreased by 1.58 mmol/L in TRT group (P=0.03)
Heufelder et al[70] (SBRCT)	TD‡	16 Hypogonadal men with T2DM	HOMA-IR, HgA1c, fasting plasma glucose	● HOMA-IR decreased by 4.2 in TRT group (P<0.001) ● HgA1c decreased by approx. 1% after 13 weeks in TRT group (P<0.001) ● HgA1c decreased by approx. 1.5% after 52 weeks in TRT group (P<0.001) ● Fasting plasma glucose decreased by 1.9 mmol/L in TRT group (P=0.062)

Kalinchenko et al[71] (DBRCT)	IM[§]	113 Hypogonadal men with MetS	HOMA-IR, fasting plasma glucose, BMI, WC, waist-to-hip ratio	● HOMA-IR decreased by 1.49 in TRT group (overall P=0.04) ● No significant change in fasting plasma glucose in TRT group ● Significant reduction in BMI, weight, waist–to-hip ratio, hip circumference, and waist circumference in TRT group (P<0.001 for all except for waist-to-hip ratio; P=0.04 for waist-to-hip ratio)
Malkin et al[72] (SBPCC)	IM[k]	13 Men with CHF and no T2DM	HOMA-IR, fasting plasma glucose, glucose tolerance, body composition	● HOMA-IR decreased by 1.9 in TRT (P=0.03) ● Fasting plasma glucose decreased by 0.61 mmol/L in TRT (P=0.03) ● Total body mass increased by 1.5 kg in TRT (P=0.008) ● Percent body fat decreased by 0.8% in TRT (P=0.02)
Studies showing a detrimental effect of testosterone therapy on indices of glycemic control				
None identified				

BMI, body mass index; CHF, congestive heart failure; DBPCC, double-blind placebo-controlled cross over study; DBRCT, double-blind randomized controlled trial; HgA1c, hemoglobin A1c; HOMA-IR, homeostatic model of insulin resistance; IM, intramuscular; MetS, metabolic syndrome; SBPCC, single-blind placebo-controlled crossover study; SBRCT, single-blind randomized controlled trial; T2DM, type 2 diabetes mellitus; TD, transdermal; TG, triglycerides; TRT, testosterone replacement therapy; WC, waist circumference.

*Jones et al administered testosterone 2% gel 3-g metered dose (60 mg testosterone) for 12 months.

†Kapoor et al administered testosterone 200 mg IM once every 2 weeks for 3 months.

‡Heufelder et al administered testosterone gel 50 mg TD for 52 weeks.

§Kalinchenko et al administered testosterone undecanoate 1000 mg IM given at baseline and after 6 and 18 weeks.

kMalkin et al administered Sustanon 250 (testosterone propionate 30 mg, testosterone phenylpropionate 60 mg, testosterone isocaproate 60 mg, and testosterone decanoate 100 mg/mL) IM injection. Two IM injections were given 2 weeks apart.

26. Corona G, Monami M, Rastrelli G, Aversa A, Sforza A, Lenzi A, Forti G, Mannucci E, Maggi M. Type 2 diabetes mellitus and testosterone: a meta-analysis study. Int J Androl. 2010;34:528–540.

68. Jones TH, Arver S, Behre HM, Buvat J, Meuleman E, Moncada I, Morales AM, Volterrani M, Yellowlees A, Howell JD, Channer KS; TIMES2 Investigators. Testosterone replacement in hypogonadal men with type 2
diabetes and/or metabolic syndrome (the TIMES2 Study). Diabetes Care.2011;34:828–837.

69. Kapoor D, Goodwin E, Channer KS, Jones TH. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. Eur J
Endocrinol. 2006;154:899–906.

70. Heufelder AE, Saad F, Bunck MC, Gooren L. Fifty-two-week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. J Androl.2009;30:726–733.

71. Kalinchenko SY, Tishova YA, Mskhalaya GJ, Gooren LJG, Giltay EJ, Saad F. Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study. Clin Endocrinol. 2010;73:602–612.

72. Malkin CJ, Jones TH, Channer KS. The effect of testosterone on insulin sensitivity in men with heart failure. Eur J Heart Fail. 2007;9:44–50.

Table 8. Effects of Testosterone Therapy on Markers of Inflammation.

Study Name	Sample Size	Testosterone Formulation Used	Duration of TRT	Main Outcomes Measured	Major Findings
Kalinchenko et al[71] (DBRCT)	171 Men (105 received TRT and 65 received placebo)	Testosterone undecanoate 1000 mg IM	Given at baseline and after 6 and 18 weeks	CRP, IL-1b, IL-6, IL-10, TNF-a	● Significant reduction in CRP with TRT ● Significant reduction in TNF-a with TRT ● Significant reduction in IL-1b with TRT
Kapoor et al[93] (DBPCC)	20 Men	Sustanon 200 IM once every 2 weeks*	3 Months	CRP, IL-6, TNF-a, leptin, adiponectin, resistin	● No significant change in levels of CRP with TRT ● No significant change in levels of TNF-a with TRT ● No significant change in levels of IL-6 with TRT
Guler et al[100] (CCS)	41 Men (25 received TRT and 16 received placebo)	Sustanon 250 IM once weekly†	3 Weeks	hsCRP, IL-6, TNF-a	● Significant reduction in hsCRP with TRT ● Significant reduction in IL-6 with TRT ● Significant increase in TNF-a in both groups

Aversa et al[101] (DBRCT)	50 Men (40 received TRT and 10 received placebo)	Nebid 1000 mg IM once every 12 weeks‡	24 Months	hsCRP, HOMA-IR, CIMT	● Significant reduction in hsCRP with TRT ● Significant reduction in HOMA-IR with TRT ● Significant reduction in CIMT with TRT
Singh et al[102] (DBRCT)	61 Men	Subjects randomized to 1 of 5 treatment groups, each group receiving varying doses of testosterone enanthate§	20 Weeks	Total cholesterol, LDL, HDL, VLDL, TG, CRP, apolipoprotein B, apolipoprotein C-III	● No significant correlation between endogenous testosterone levels and levels of CRP ● No change in CRP levels with TRT, regardless of the testosterone dose
Ng et al[103] (CCS)	33 Men (16 received TRT and 17 were control)	Dihydrotestosterone 70 mg TD daily	3 Months	hsCRP, sIL-6, sICAM-1, sVCAM-1	● No significant change in levels of hsCRP with TRT ● No significant change in sICAM-1 with TRT ● No significant change in sVCAM-1 with TRT
Nakhai Pour et al[104] (DBRCT)	237 Men	Testosterone undecanoate 160 mg PO daily	26 Weeks	hsCRP	● No significant change in levels of hsCRP with TRT
Malkin et al[105] (SBRCT)	27 Men	Sustanon 100 IM once every 2 weeks‖	1 Month	TNF-a, IL-1b, IL-10	● Significant reduction in TNF-a with TRT ● Significant reduction in IL-1b with TRT ● Significant increase in IL-10 with TRT
Studies showing negative effect of Testosterone Therapy on Markers of Inflammation					

None identified

CCS, case–control study; CIMT, carotid artery intima-media thickness; DBPCC, double-blind placebo-controlled crossover study; DBRCT, double-blind randomized controlled trial; HOMA-IR, homeostatic model of insulin resistance; hsCRP, high-sensitivity C-reactive protein; IL-10, interleukin-10; IL-1b, interleukin–1b; IL-6, interleukin-6; IM, intramuscular; PO, by mouth; SBRCT, single-blind randomized controlled study; sICAM-1, soluble intracellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1; TD, transdermal; TG, triglycerides; TNF-a, tumor necrosis factor–a; TRT, testosterone replacement therapy.

*Sustanon 200 contains testosterone propionate 30 mg, testosterone phenylpropionate 60 mg, testosterone isocaproate 60 mg, and testosterone decanoate 100 mg.

†Sustanon 250 contains 30 mg testosterone propionate, 60 mg testosterone phenylpropionate, 60 mg testosterone isocaproate, and 100 mg testosterone decanoate.

‡Nebid contains testosterone undecanoate.

§Singh et al study: group 1 (n=12) received testosterone enanthate 25 mg IM weekly, group 2 (n=12) received testosterone enanthate 50 mg IM weekly, group 3 (n=12) received testosterone enanthate 125 mg IM weekly, group 4 (n=11) received testosterone enanthate 300 mg IM weekly, and group 5 (n=14) received testosterone enanthate 600 mg IM weekly.

kSustanon 100 contains 20 mg testosterone propionate, 40 mg testosterone phenylpropionate, and 40 mg testosterone isocaproate.

71. Kalinchenko SY, Tishova YA, Mskhalaya GJ, Gooren LJG, Giltay EJ, Saad F. Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study. Clin Endocrinol. 2010;73:602–612.

93. Kapoor D, Clarke S, Stanworth R, Channer KS, Jones TH. The effect of testosterone replacement therapy on adipocytokines and C-reactive protein in hypogonadal men with type 2 diabetes. Eur J Endocrinol. 2007;156:595–
602.

100. Guler N, Batyraliev T, Dulger H, Ozkara C, Tuncer M, Aslan S, Okut H, Agirbasli M. The effects of short term (3 weeks) testosterone treatment on serum inflammatory markers in men undergoing coronary artery stenting.
Int J Cardiol. 2006;109:339–343.

101. Aversa A, Bruzziches R, Francomano D, Rosano G, Isidori AM, Lenzi A, Spera G. Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study. J Sex Med. 2010;7:3495–3503.

102. Singh AB, Hsia S, Alaupovic P, Sinha-Hakim I, Woodhouse L, Buchanan TA, Shen R, Bross R, Berman N, Bhasin S. The effects of varying doses of T on insulin sensitivity, plasma lipids, apolipoproteins, and C-reactive protein in healthy young men. J Clin Endocrinol Metab. 2002;87:136–143.

103. Ng MKC, Liu PY, Williams AJ, Nakhla S, Ly LP, Handelsman DJ, Celermajer DS. Prospective study of effect of androgens on serum inflammatory markers in men. Arterioscler Thromb Vasc Biol. 2002;22:1136–1141.

104. Nakhai Pour HR, Grobbee DE, Emmelot-Vonk MH, Bots ML, Verhaar HJJ, van der Schouw YT. Oral testosterone supplementation and chronic low-grade inflammation in elderly men: a 26-week randomized, placebo-controlled trial. Am Heart J. 2007;154:1228.e1–1228.e7.

105. Malkin CJ, Pugh PJ, Jones RD, Kapoor D, Channer KS, Jones TH. The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profile in hypogonadal men. J Clin Endocrinol Metab. 2004;89:3313–3318.