Testosterone Administration Alters Hepatic Blood Flow Across Age: Systematic Review of Animal Experimental Studies

Ricardo Aparecido Baptista Nucci[1,2] Valéria Simões Tanasov[2] Walter Krause Neto[3] Romeu Rodrigues de Souza[2,3] Eliane Florencio Gama[1,2,3]

[1] Aging Studies Program (MS), Universidade São Judas Tadeu, São Paulo, SP, Brazil
[2] Laboratory of Morphoquantitative Studies and Immunohistochemistry, Department of Aging Sciences, Universidade São Judas Tadeu, São Paulo, SP, Brazil
[3] Laboratory of Morphoquantitative Studies and Immunohistochemistry, Department of Physical Education, Universidade São Judas Tadeu, São Paulo, SP, Brazil

Address for correspondence Ricardo Aparecido Baptista Nucci, PhD, Laboratório de Estudos Morfoquantitativos e Imuno-histoquímica, Departmento de Ciências do Envelhecimento, Universidade São Judas Tadeu, Rua Taquari, 546, CEP 03166-000, Mooca, São Paulo, SP, Brazil (e-mail: r.aparecido.nucci@uol.com.br).

J Morphol Sci 2018;35:96–101.

Abstract

Testosterone levels decline gradually with advancing age. At this point, testosterone administration as a therapy has been largely used to improve different outcomes. However, testosterone induces dose-dependent negative effects on the structure and function of the liver across age. Therefore, the present study aimed to carry out a systematic review of the effects of testosterone administration on the hepatic structure of adult and aged animals. We have searched the PubMed, Google Scholar, Science Direct, Scielo and Lilacs databases for animal experimental studies on the effects of testosterone administration on the hepatic structure across age. After applying the inclusion and exclusion criteria, we included two articles in a systematic review and meta-analysis (regarding adult/aged rats). We have shown through a systematic review with meta-analysis that testosterone may cause chronic hepatic congestion. However, the present review had a small number of studies, which was considered a limitation. At this point, we encourage the development of more studies to elucidate the cellular and molecular mechanisms involved in hepatic injuries, as well as the hepatic metabolism of exogenous testosterone across age.

Keywords
- aging
- liver
- hepatic structure
- testosterone
- androgenic anabolic steroids
- review

Introduction

After the second and third decades of life, testosterone levels decline gradually with advancing age, without a clear inflection point or andropause.[1]

The age-related decline in testosterone levels has been associated with reductions in muscle mass, strength, physical function, and libido.[2–5]

At this point, testosterone administration as a therapy has been largely used to improve muscle mass, physical function, mobility, and frailty.[1,6–10]

However, for several reasons, older men can be at a higher risk of experiencing adverse events during testosterone therapy when compared with young men. The plasma clearance of testosterone is lower in men aged ≥59 years than in young men (aged 19–35 years),[11] resulting in higher testosterone levels in older men at any testosterone dose.

Some adverse events associated with testosterone administration are prostate-related effects, and cardiovascular-related events.[12–14] Furthermore, testosterone induces dose-dependent

received
April 6, 2017
accepted
August 3, 2018
published online
August 31, 2018

DOI https://doi.org/10.1055/s-0038-1669470.
ISSN 2177-0298.

negative effects on the structure and function of the liver across age.[15–17]

The liver has its functions changed with advancing age, resulting in impaired regeneration and in a decrease in drug metabolism.[18,19] Thus, testosterone administration can induce pathological conditions across age.[15,16]

Currently, the clinical literature uses systematic reviews and meta-analyses to identify possible methodological differences in the studies, in the quality of the surveyed studies on a given topic, and in the most suitable intervention for a specific treatment.[8] Therefore, the present study aimed to carry out a systematic review of the effects of testosterone administration on the hepatic structure of adult and aged animals.

Materials and Methods

The present systematic review was developed based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline,[20] which is currently used for clinical studies. Therefore, Krause Neto and Nucci adapted it for this research.

On February, 2017, we performed a systematic review search in the PubMed, Google Scholar, Science Direct, Scielo and Lilacs databases, using the following Medical Subject Headings (MeSH) and entry terms: *Liver* OR *Livers* OR *Bile Ducts*; *Intrahepatic* OR *Bile Duct*; *Intrahepatic* OR *Duct*; *Intrahepatic Bile* OR *Ducts*; *Intrahepatic Bile* OR *Intrahepatic Bile Duct* OR *Intrahepatic Bile Ducts* OR *Hepatocytes* OR *Hepatocyte* OR *Hepatic Cells* OR *Cell*; *Hepatic* OR *Cells*; *Hepatic* OR *Hepatic Cell* OR *Hep G2 Cells* OR *Cell*; *Hep G2* OR *Cells*; *Hep G2* OR *Hep G2 Cell* OR *HepG2 Cells* OR *Cell*; *HepG2* OR *Cells*; *HepG2* OR *HepG2 Cell* OR *Hep G2 Cell Line* OR *Hepatoblastoma G2 Cell Line* OR *Cell Line*; *Hep G2* OR *Cell Line*; *Hepatoblastoma G2* OR *Kupffer Cells* OR *Cells*; *Kupffer* OR *Hepatic Stellate Cells* OR *Cell*; *Hepatic Stellate* OR *Cells*; *Hepatic Stellate* OR *Hepatic Stellate Cell* OR *Stellate Cell*; *Hepatic* OR *Stellate Cells*; *Hepatic* OR *Ito Cells* OR *Cells*; *Ito* OR *Drug-Induced Liver Injury*; *Chronic* OR *Drug Induced Liver Injury*; *Chronic* OR *Liver Injury*; *Drug-Induced, Chronic* OR *Chronic Drug-Induced Liver Injury* OR *Chronic Drug Induced Liver Injury*; AND *testosterone* OR *17-beta-Hydroxy-4-Androsten-3-one* OR *17 beta hydroxy 4 androsten 3 one* OR *androtropy* OR *dr. kade brand of testosterone* OR *histone* OR *hauck brand of testosterone* OR *stereotaxy* OR *ulmer brand of testosterone* OR *sustain* OR *endoderm* OR *watson brand of testosterone* OR *faulding brand of testosterone* OR *paladin brand of testosterone* OR *astrazeneca brand of testosterone* OR *cepa brand of testosterone* OR *testoderm* OR *ortho brand of testosterone* OR *ferring brand of testosterone* OR *testolin* OR *pasadena brand of testosterone* OR *testopel* OR *barton brand of testosterone* OR *testosterone sulfate* OR *androgen* OR *solvay brand of testosterone* OR *univmed brand of testosterone* OR *schering brand of testosterone* OR *8-Iso-testosterone* OR *8 isotestosterone* OR *17-beta-Hydroxy-8 alpha-4-Androsten-3-one* OR *17 beta hydroxy 8 alpha 4 androsten 3 one* OR *andropatch* OR *smithkline beecham brand of testosterone* OR *glaxosmithkline brand of testosterone* OR *testis* OR *auxilin pharmaceuticals inc. brand of testosterone* OR *testosterone propionate* OR *testosteronpropionat eifelfango* OR *propionate eifelfango, testosterone* OR *eifelfango brand of testosterone propionate* OR *virormone* OR *ferring brand of testosterone propionate* OR *agovirin* OR *testosterone 17 beta-cypionate* OR *testosterone 17 beta-cyclopentylpropionate* OR *testosterone cypionate* OR *testosterone 17 beta cyclopentane-propionate* OR *depo-testosterone* OR *pfizer brand of testosterone 17 beta-cypionate* OR *depo-testosterone cypionate* OR *leposternon* OR *duarte s* OR *roberts brand of testosterone 17 beta cypionate* OR *testa-c* OR *vojtech brand of testosterone 17 beta-cypionate* OR *tested elmu* OR *byk brand of testosterone 17 beta-cypionate* OR *andronati* OR *pasadena brand of testosterone 17 beta-cypionate* OR *depostomead* OR *spencer mead brand of testosterone 17 beta-cypionate* OR *testosterone enanthate* OR *testosterone heptylate* OR *testosterone heptanoate* OR *delatestryl* OR *theramex brand of testosterone enanthate* OR *btg brand of testosterone enanthate* OR *duraphat* OR *roberts brand of testosterone enanthate* OR *theramex* OR *testosterone depot rotexmedica* OR *rotexmedica brand of testosterone enanthate* OR *testosterone depot eifelfango* OR *eifelfango brand of testosterone enanthate* OR *testosterone depot jenapharm* OR *jenapharm brand of testosterone enanthate* OR *westrin p.a.* OR *pasadena brand of testosterone enanthate* OR *and repository* OR *rugby brand of testosterone enanthate* OR *primoteston depot* OR *schering brand of testosterone enanthate* OR *testosterone-17-succinate* OR *testosterone hydrogen succinate* OR *testosterone-17hemisuccinate* OR *T-17-HS* OR *testosterone hemisuccinate* OR *testosterone-17-succinate, sodium salt, (17beta) isomer* OR *testosterone-17-sulfate* OR *testosterone 17-sulphate* OR *testosterone-17-sulfate, sodium salt* OR *testosterone-17-sulfate, ammonium salt* OR *testosterone-17-sulfate, (17alpha) isomer* OR *testosterone undecanoate* OR *testosterone undecylate* OR *nebido* OR *understory* OR *andriole* OR *batstone* OR *restandol* OR *organon brand of testosterone undecanoate* OR *methyltestosterone* OR *17 beta-Hydroxy-17-methyl-4-androsten-3-one* OR *17 beta hydroxy 17 methyl 4 androsten 3 one* OR *17beta methyltestosterone* OR *17beta methyltestosterone* OR *17-Epimethyltestosterone* OR *17 epimethyltestosterone* OR *17beta-Hydroxy-17-methyl-4-androsten-3-one* OR *17beta hydroxy 17 methyl 4 androsten 3 one* OR *17 beta methyltestosterone* OR *17 beta-methyltestosterone* OR *android* OR *in band 1 of methyltestosterone* OR *Android-10* OR *android 10* OR *Android-25* OR *android 25* OR *Android-5* OR *android 5* OR *western* OR *mesterolone* OR *math test* OR *global pharmaceutical brand of methyltestosterone* OR *oregon* OR *schering brand of methyltestosterone* OR *testoviron* OR *tested* OR *in band 2 of methyltestosterone* OR *virion* OR *star brand of methyltestosterone* OR *17alpha-Methyltestosterone* OR *17 alpha* OR *methyltestosterone* OR *17alpha-Methyltestosterone* OR *17alpha methyltestosterone* OR *17alpha-MethylTestosterone* OR *17alpha methyl testosterone* OR *perandren* OR *testosterone 17-phenylpropionate* OR *testosterone phenylpropionate* OR *restandol* OR *testosterone decanoate* OR *testosterone replacement* OR *androgenic anabolic steroids* OR *anabolic steroids* AND *Aging* OR *Senescence* OR *Biological Aging* OR *Aging, Biological* OR *aged* OR *elderly* OR *Frail Elderly* OR *Elderly, Frail* OR *Frail Elders* OR *Elder, Frail* OR *Elders, Frail* OR *Frail Elder* OR *Functionally-Impaired Elderly* OR *Elderly, Functionally-Impaired* OR

Functionally Impaired Elderly OR *Frail Older Adults* OR *Adult, Frail Older* OR *Adults, Frail Older* OR *Frail Older Adult* OR *Older Adult, Frail* OR *Older Adults, Frail*.

Inclusion and Exclusion Criteria

We have searched for animal experimental design studies on the administration of testosterone on the hepatic structure and the effect of aging on it. The inclusion criteria were articles with healthy young, adult or aged rodents, testosterone administration, and detailed data on hepatic morphology. We have excluded all of the papers that investigated testosterone administration on genetically modified animals, interventions such as surgery, or the use of any drug or nutritional supplement combined with testosterone administration. The strain of the rodents was not stated as an inclusion criterion.

Outcomes

The outcomes of interest were the area and the number of nuclei of hepatocytes, which indicate mitosis related to hepatic injury, as well as lobular (capillaries sinusoids, perisinusoidal spaces, and biliary ducts) and non-lobular (portal spaces, veins, and center-lobular branches of blood vessels) parenchyma components, which indicate changes in the hepatic blood flow.

Data Extraction and Analysis of Data Quality

We have extracted data about the strain of the rodents, as well as their age, gender, testosterone administration dosage and duration, and primary outcomes. Usually, clinical systematic review researchers apply a data quality analysis on the methodology of the analyzed papers through specific topic questionnaires. However, questionnaires for these purposes do not exist for animal studies. Therefore, we did not apply any data quality analysis in the present study. Data such as strain and/or age of the rodents were not used in the search strategy so as to not limit the amount of included studies.

Data Synthesis and Analysis

The systematic review data was organized in ►**Tables 1** and **2**.[15,16] For the meta-analysis, RevMan 5.2 software (The Nordic Cochrane Centre, Copenhagen, Denmark) was used to calculate heterogeneity by the i-squared (I^2) and chi-squared (χ^2) values. We have used the I^2 to assess the heterogeneity/homogeneity between the studies, using fixed effect models. We have also used the inverse variance method and 95% total confidence interval (95%CI).

The present study is an analysis of published data; thus, it did not require the approval of an ethics committee.

Results

Selected Studies

After the initial intersection of mesh terms, entry terms, and/or related keywords, the search identified 12,924 article titles. From this point, 4 evaluators (Nucci, Tanasov, de Souza and Gama) read the titles. Then, the abstracts were selected following the PRISMA[20] guideline. Of the total 12,924 articles, 52 were used for the initial abstract analysis. The abstracts should contain sufficient data on the parameters of the hepatic structure, on the animals studied, and on the treatments and/or interventions used in the studies. From these, five articles were included for full text analysis. After the inclusion and exclusion criteria were applied, two papers were included in the systematic review and meta-analysis.[15,16] However, the small number of included papers should be considered a limitation.

Animal Strain, Age and Gender

In the selected articles, the strain of rodents used was Wistar rats (*Rattus norvegicus*). This strain is widely used in aging studies. Both studies presented data about the effects of testosterone administration on the hepatic structure of adult or aged animals. Both studies used male animals.

Testosterone Administration, Duration and Dosage

Tanasov et al[16] used testosterone propionate via intramuscular administration (3 mg/kg) for 3 months. However, Nucci et al[15] used testosterone propionate via intraperitoneal administration (10 mg/kg) for 4 months.

Data Synthesis

Both studies[15,16] used morphometrical and stereological methods to analyze the area and the number of nuclei of hepatocytes, as well as the lobular and non-lobular parenchyma components.

All data are presented by the analysis of 2 studies, and 24 animals were included. Only adult and aged rodent data was considered. Age effect has not been evaluated at this point because the included articles did not present enough internal statistical data.

Meta-analysis

Number of Nuclei of Hepatocytes

The forest plot analysis demonstrated homogeneity ($p = 0.97$; $I^2 = 0\%$) between the studies, and the testosterone

Table 1 Data description regarding the strain of the rodents, as well as their age, gender, testosterone dosage, frequency (times/week) and duration

Reference	Animal strain	Age (months)		Gender	Testosterone		
		Before	After		Dosage	Frequency (times/week)	Duration (months)
Tanasov et al, 2014[16]	Wistar	13	16	Male	3 mg/kg	3	3
Nucci et al, 2017[15]	Wistar	20	24	Male	10 mg/kg	2	4

Table 2 Summary of primary outcomes regarding the area and the number of nuclei of hepatocytes, and of lobular and non-lobular parenchyma components in the groups that received testosterone

Reference	Hepacotyces nuclei		Parenchyma components	
	Number	Area	Lobular	Non-lobular
Tanasov et al, 2014[16]	Increased	Decreased	Increased	Decreased
Nucci et al, 2017[15]	Increased	Decreased	Increased	Decreased

administration had a non-significant ($p = 0.15$) increase of 3.23 hepatocyte nuclei per field (95% CI: -1.15–7.61). ►**Fig. 1** presents the data and the forest plot.

Area of Nuclei of Hepatocytes

The forest plot analysis demonstrated homogeneity ($p = 0.56$; $I^2 = 0\%$) between the studies, and the testosterone administration had a non-significant ($p = 0.52$) decrease of 2.44 μm^2 in the hepatocyte nuclei area (95% CI: -9.90–5.01). ►**Fig. 2** presents the data and the forest plot.

Lobular Parenchyma Components

The forest plot analysis demonstrated heterogeneity ($p = 0.04$; $I^2 = 77\%$) between the studies, and the testosterone administration had a significant ($p = 0.0008$) increase of 5.77% in the lobular parenchyma components (95% CI: 2.40–9.15). ►**Fig. 3** presents the data and the forest plot.

Non-lobular Parenchyma Components

The forest plot analysis demonstrated homogeneity ($p = 0.98$; $I^2 = 0\%$) between the studies, and the testosterone administration had a non-significant ($p = 0.69$) decrease of 1.21% of in the non-lobular parenchyma components (95% CI: -7.12–4.69). ►**Fig. 4** presents the data and the forest plot.

Discussion

Through a systematic review with meta-analysis, the present article analyzed the effects of testosterone administration on the hepatic structure of adult and aged animals. We have shown through a meta-analysis that testosterone may increase the mitotic capacity of the hepatocytes. The merging of both studies showed a decrease in the hepatocyte nuclei area, as well as an increase in the number of hepatocyte nuclei per field. This is consistent with studies that highlighted the role of testosterone

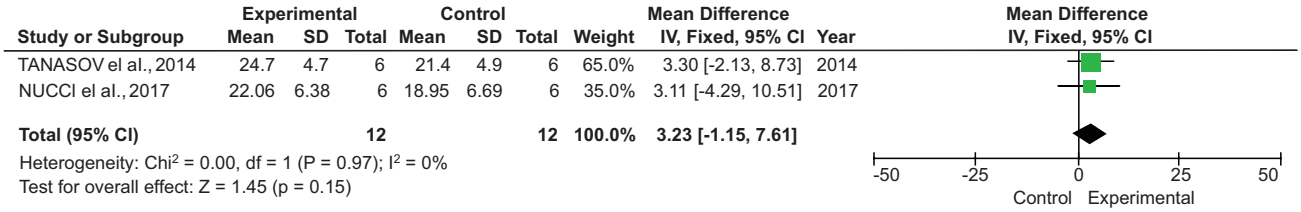

Fig. 1 Forest plot presenting information about the effects of testosterone administration on the number of nuclei of hepatocytes in adult and aged rats (figure created using theRevMan 5.2 2017)

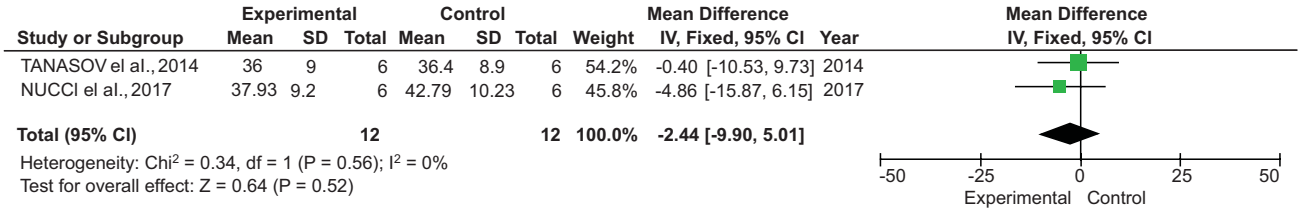

Fig. 2 Forest plot presenting information about the effects of testosterone administration on the area of nuclei of hepatocytes in adult and aged rats (figure created using the RevMan 5.2 2017)

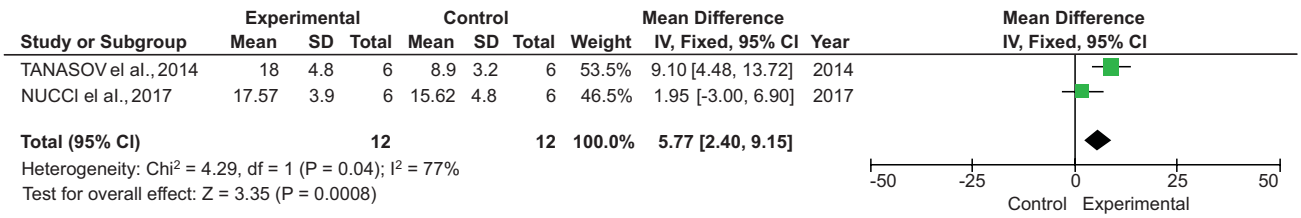

Fig. 3 Forest plot presenting information about the effects of testosterone administration on the lobular parenchyma components in adult and aged rats (figure created using the RevMan 5.2 2017)

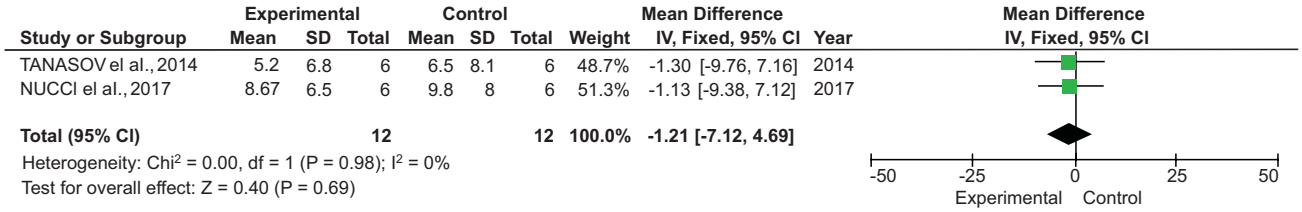

Fig. 4 Forest plot presenting information about the effects of testosterone administration on the non-lobular parenchyma components in adult and aged rats (figure created using the RevMan 5.2 2017)

as a contributing factor in mitosis due to its chemical and toxic aggression to the hepatic tissue.[15–17,22]

However, our major finding was that testosterone changed the hepatic blood flow by increasing the lobular parenchyma components in both studies.[15,16] Testosterone, at physiological concentrations, can selectively suppress the entry of calcium ions (Ca^{2+}) via L-type Ca^{2+} channels, which indicates its vasodilatory actions.[23] Nonetheless, with testosterone administration, its vasodilatory actions could be more negative to the hepatic tissue in a dose-dependent fashion.

As the hepatic sinusoids dilate to accommodate the backflow of blood, the liver becomes tensely swollen.[24] Hence, this process may lead to blood stasis in the non-lobular parenchyma, leading to a hypoxic state. At this moment, a pathological process named hepatic congestion is characterized.[15,24,25]

In addition, Simonetto et al[26] demonstrated through an experimental study in murine that chronic hepatic congestion leads to sinusoidal thrombosis and strain, which in turn promote hepatic fibrosis in the long-term. Additionally, a previous autopsy study of livers from patients with congestive heart failure demonstrated sinusoidal thrombi in the proximity of areas with fibrosis, and suggested a causative role of intrahepatic thrombosis in the incidence of fibrosis.[27] Furthermore, Nucci et al[15] showed that testosterone can injure the liver tissue, resulting in a sharp increase in fibrosis, which indicates chronic hepatic congestion in the short-term.

Conclusion

We have shown through a systematic review with meta-analysis that testosterone may cause chronic hepatic congestion in the short-term. However, the present review analyzed a small number of studies, which was considered a limitation. At this point, we encourage the development of more studies to elucidate the cellular and molecular mechanisms involved in hepatic injuries, as well as the hepatic metabolism of exogenous testosterone across age.

References

1 Spitzer M, Huang G, Basaria S, Travison TG, Bhasin S. Risks and benefits of testosterone therapy in older men. Nat Rev Endocrinol 2013;9(07):414–424 Doi: 10.1038/nrendo.2013.73

2 Orwoll E, Lambert LC, Marshall LM, et al; Osteoporotic Fractures in Men Study Group. Endogenous testosterone levels, physical performance, and fall risk in older men. Arch Intern Med 2006; 166(19):2124–2131 Doi: 10.1001/archinte.166.19.2124

3 Roy TA, Blackman MR, Harman SM, Tobin JD, Schrager M, Metter EJ. Interrelationships of serum testosterone and free testosterone index with FFM and strength in aging men. Am J Physiol Endocrinol Metab 2002;283(02):E284–E294 Doi: 10.1152/ajpendo.00334.2001

4 Travison TG, Morley JE, Araujo AB, O'Donnell AB, McKinlay JB. The relationship between libido and testosterone levels in aging men. J Clin Endocrinol Metab 2006;91(07):2509–2513 Doi: 10.1210/jc.2005-2508

5 van den Beld AW, de Jong FH, Grobbee DE, Pols HA, Lamberts SW. Measures of bioavailable serum testosterone and estradiol and their relationships with muscle strength, bone density, and body composition in elderly men. J Clin Endocrinol Metab 2000;85(09): 3276–3282 Doi: 10.1210/jcem.85.9.6825

6 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(03):E601–E607 Doi: 10.1152/ajpendo.00362.2001

7 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(05):M266–M272 Doi: 10.1093/gerona/56.5.M266

8 Krause Neto W, Ciena AP, Anaruma CA, de Souza RR, Gama EF. Effects of exercise on neuromuscular junction components across age: systematic review of animal experimental studies. BMC Res Notes 2015;8:713 Doi: 10.1186/s13104-015-1644-4

9 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(03):1502–1510 Doi: 10.1210/jc.2004-1933

10 Sih R, Morley JE, Kaiser FE, Perry HM III, Patrick P, Ross C. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. J Clin Endocrinol Metab 1997;82(06):1661–1667 Doi: 10.1210/jcem.82.6.3988

11 Coviello AD, Lakshman K, Mazer NA, Bhasin S. Differences in the apparent metabolic clearance rate of testosterone in young and older men with gonadotropin suppression receiving graded doses of testosterone. J Clin Endocrinol Metab 2006;91(11):4669–4675 Doi: 10.1210/jc.2006-0822

12 Bhasin S, Cunningham GR, Hayes FJ, et al; Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95(06):2536–2559 Doi: 10.1210/jc.2009-2354

13 Calof OM, Singh AB, Lee ML, et al. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. J Gerontol A Biol Sci Med Sci 2005;60(11):1451–1457 Doi: 10.1093/gerona/60.11.1451

14 Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. BMC Med 2013;11(01):108 Doi: 10.1186/1741-7015-11-108

15 Nucci RAB, Teodoro ACS, Krause Neto W, et al. Effects of testosterone administration on liver structure and function in aging rats. Aging Male 2017;20(02):134–137 Doi: 10.1080/13685538.2017.1284779

16 Tanasov VS, Krause Neto W, Gonçalves L, Maifrino LBM, De Sousa RR, Gama EF. Use of Anabolic Steroid Altered the Liver Morphology of Rats. Int J Morphol 2014;32(03):756–760 Doi: 10.4067/S0717-95022014000300002
17 Vieira RP, França RF, Damaceno-Rodrigues NR, et al. Dose-dependent hepatic response to subchronic administration of nandrolone decanoate. Med Sci Sports Exerc 2008;40(05):842–847
18 Nucci RAB, Teodoro ACS. GAMA EF. Liver regeneration and aging: a review. J Morphol 2016;33(04):179–182 Doi: 10.4322/jms.100616
19 Schmucker DL. Age-related changes in liver structure and function: Implications for disease? Exp Gerontol 2005;40(8-9):650–659 Doi: 10.1016/j.exger.2005.06.009
20 Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6(07):e1000100 Doi: 10.1371/journal.pmed.1000100
21 Krause Neto W, Gama EF, Rocha LY, et al. Effects of testosterone on lean mass gain in elderly men: systematic review with meta-analysis of controlled and randomized studies. Age (Dordr) 2015;37(01):9742
22 Michalopoulos GK, DeFrances MC. Liver regeneration. Science 1997;276(5309):60–66
23 Hall J, Jones RD, Jones TH, Channer KS, Peers C. Selective inhibition of L-type Ca2+ channels in A7r5 cells by physiological levels of testosterone. Endocrinology 2006;147(06):2675–2680 Doi: 10.1210/en.2005-1243
24 Gore RM, Mathieu DG, White EM, Ghahremani GG, Panella JS, Rochester D. Passive hepatic congestion: cross-sectional imaging features. AJR Am J Roentgenol 1994;162(01):71–75 Doi: 10.2214/ajr.162.1.8273693
25 Ou QJ, Hermann RE. The role of hepatic veins in liver operations. Surgery 1984;95(04):381–391
26 Simonetto DA, Yang HY, Yin M, et al. Chronic passive venous congestion drives hepatic fibrogenesis via sinusoidal thrombosis and mechanical forces. Hepatology 2015;61(02):648–659
27 Wanless IR, Liu JJ, Butany J. Role of thrombosis in the pathogenesis of congestive hepatic fibrosis (cardiac cirrhosis). Hepatology 1995;21(05):1232–1237