

The Anti-Inflammatory Effects of Testosterone

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Low plasma testosterone (T) levels correlated with metabolic syndrome, cardiovascular diseases, and increased mortality risk. T exerts a significant effect on the regulation of adipose tissue accumulation, and in the glucose and lipids metabolism. Adipocytes are the primary source of the most important adipokines responsible for inflammation and chronic diseases. This review aims to analyze the possible effect of T on the regulation of the proinflammatory cytokines secretion.

A systematic literature search on MEDLINE, Google Scholar, and Cochrane using the combination of the following keywords: “testosterone” with “inflammation,” “cytokines,” “adiponectin, CRP, IL-1B, IL-6, TNF α , leptin” was conducted. Sixteen articles related to the effect of low T level and 18 to the effect of T therapy on proinflammatory cytokine were found.

T exerts a significant inhibitory effect on adipose tissue formation and the expression of various adipocytokines, such as leptin, TNF- α , IL-6, IL-1, and is positively correlated with adiponectin level, whereas a low T level is correlated with increased expression of markers of inflammation. Further studies are necessary to investigate the role of T, integrated with weight loss and physical activity, on its action on the mechanisms of production and regulation of proinflammatory cytokines.

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Freeform/Key Words: testosterone, inflammation, cytokines, adipokines, adiponectin, IL-6

The development and progression of chronic diseases are correlated with low T level and inflammatory biomarkers, but their mechanisms remain poorly understood. T deficiency (also known as hypogonadism) in older men has been associated with metabolic syndrome [1], neurodegeneration [2], and increased risk of cardiovascular diseases (CVDs) and all-cause mortality [3] independently of other numerous risk factors [4, 5]. Similar observations were reported in young men [6]. Before any concurrent manifestations of CVD or other systemic diseases, low T level is correlated with elevated C-reactive protein (CRP) level [7], macrophage inflammatory protein 1- α , macrophage inflammatory protein 1- β , and TNF- α in young and older men [8]. CRP is a sensitive marker of inflammation produced by liver [9] and is correlated with coronary heart disease and deaths from other causes [7].

An inflammatory status due to proinflammatory cytokines is particularly evident in the elderly [10], and in patients with low T levels and obesity [11]. Furthermore, adipokines mediate insulin resistance [12] and the principal adipokines involved are adiponectin, leptin, resistin, visfatin, chemerin, TNF- α , IL-1, IL-6, IL-8, IL-10, plasminogen activator inhibitor-1, monocyte chemoattractant protein-1 (MCP-1), and retinol binding protein-4 (RBP-4) [13]. Higher levels of proinflammatory cytokine play a crucial role in the development of CVD [14], and T therapy provides beneficial effects on the pathophysiological markers and clinical symptoms of coronary heart disease [15].

Furthermore, adipokines are involved in the development and progression of cancer [16]. The etiology of elevated inflammatory markers remains incompletely defined [17],

Abbreviations: BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; ER, estrogen receptor; HMW, high molecular weight; MCP-1, monocyte chemoattractant protein; OPG, osteoprotegerin; PCOS, polycystic ovary syndrome; T, testosterone.

Received 16 June 2018

Accepted 17 October 2018

First Published Online 22 October 2018

January 2019 | Vol. 3, Iss. 1

doi: 10.1210/je.2018-00186 | Journal of the Endocrine Society | 91–107

but nutrition and physical inactivity also exert a primary role. Little is known about if and how sex steroid hormone and inflammation pathways may interact to influence the aging process or the development and progression of chronic diseases, including CVD and prostate cancer, in men. This study aims to evaluate the effect of T on proinflammatory cytokines.

1. Methods

A systematic literature search was performed using PubMed, Google Scholar, and Cochrane using the combination of the following keywords: “testosterone” and “inflammation,” “cytokines,” “adiponectin,” “CRP,” “IL-1B, IL-6, TNF α , leptin.” All cross-sectional and longitudinal trials evaluating the incidence of low T in men with moderate to severe inflammation were included. Furthermore, clinical studies that investigated the effect of T administration on inflammatory markers were also considered.

2. Results

Out of 824 retrieved articles, 35 were included in the analysis and had been divided into two groups: one group includes 17 studies evaluating the incidence of inflammatory diseases in men with low T level enrolling 14,658 patients with a mean age of 59.9 ± 12.8 years (Table 1). The other group includes 18 studies that evaluated the effect of T therapy on plasma level of inflammatory markers enrolling 1654 patients with a mean age of 56.4 ± 15.6 years (Table 2). Among the first group, only one study did not find any correlation between T level and CRP, but this study was conducted on healthy middle-aged men, whereas all the other studies found a significant negative correlation between T level and inflammatory markers. Among the studies evaluating the effect of T therapy on proinflammatory markers, six studies found no effect.

3. Discussion

Low T levels in men were significantly associated with high level of inflammatory markers in different clinical conditions such as obesity [18], metabolic syndrome [19, 22, 32], heart failure [33], healthy elderly population [20, 22, 27, 28, 30], carotid atherosclerosis [23], hypogonadism [8], urologic symptoms [26], type 2 diabetes [29], primary care center [34] and are summarized in Table 1. In all studies, a negative correlation was found between low T levels and CRP, whereas only a few studies explored IL-6 [18, 30, 33] and TNF- α [8, 33]. Haring *et al.* [24] found a negative correlation between sex steroids plasma level in men with markers of inflammation. Bhatia *et al.* [29] showed that low T was inversely correlated with CRP and may contribute to mild anemia. Maggio *et al.* [30] found that T level was inversely correlated with IL-6r [35]. An extensive epidemiological study revealed that men with low T level had a higher incidence of obesity, metabolic syndrome, cancer, and acute inflammation [34]. Only a few studies had adjusted the data for other sex hormones [21, 35]. In elderly men, the reduced levels of T were correlated with the incidence of metabolic syndrome, insulin resistance, and inflammation evidencing that high CRP levels can be considered independent predictors of metabolic syndrome [19, 22]. Some studies that evaluated the correlation of CPR with low T level did not adjust for other confounders such as smoking and obesity [22, 23, 25, 27, 34]. A few epidemiologic studies did not find any consistent correlation between sex steroid hormones and inflammatory biomarkers in men [30–32]. Others found a negative correlation between the level of androgens with inflammatory markers [21, 25–28].

The majority of the studies found an evident protecting effect of T against inflammation independently of the clinical condition. However, it is difficult to draw a global evaluation because only a few studies have detected more than one cytokine in addition to CRP [8, 18,

Table 1. Correlation Between T Level and Inflammatory Markers in Hypogonadal Men

Authors	Subjects	Age	Clinical Picture	Marker of Inflammation
Tremellen <i>et al.</i> 2017 [18]	50 M	35.1	Adiposity	Negative correlation between T with CRP, IL-6, and endotoxemia.
Wickramatilake <i>et al.</i> 2015 [19]	153 M	30–70	Metabolic syndrome	Low T correlated with high CRP level.
Tsilidis <i>et al.</i> 2013 [20]	1520 M	44.3	NHANES population	High androgen and low estrogen level inversely correlate with inflammation markers (CRP and white blood cells).
Zhang <i>et al.</i> 2013 [21]	1989 M	57	Population-based cohort	High androgens level correlate with reduced CRP.
Chrysohoou <i>et al.</i> 2013 [22]	467 M	75	Metabolic syndrome	T inversely correlated with CRP and insulin level.
Soisson <i>et al.</i> 2012 [23]	350 M	65	Carotid intima-media thickness	Low T level correlated with carotid intima-media thickness and high CRP.
Haring <i>et al.</i> 2012 [24]	1344 M	20–79	Normal population	TT, SHBG, free T, and DHEAS are inversely correlated with CRP, fibrinogen, and oxidative stress.
Brand <i>et al.</i> 2012 [25]	2418 M	40–78	European Prospective Investigation into Cancer	Total T and SHBG are inversely correlated with WBC.
Bobjer <i>et al.</i> 2013 [8]	40 M	37.4	Hypogonadism	Significantly elevated levels of the proinflammatory cytokine TNF- α , MIP-1a, and MIP-1B
Kupelian <i>et al.</i> 2010 [26]	2301 M	30–79	Urologic symptoms	Inverse dose-response correlation between T and SHBG levels with CRP levels.
Kaplan <i>et al.</i> 2010 [27]	467 M	52	Aging men	Inverse relationship between T and CRP.
Tang <i>et al.</i> 2007 [28]	381 M	78.8	Nursing home resident	T level correlated negatively with CRP.
Bhatia <i>et al.</i> 2006 [29]	70 M T2D	56.8	T2D	Low TT and FT level in T2D patients were correlated with CRP and anemia.
Maggio <i>et al.</i> 2006 [30]	467 M	65	Normal older men	IL-6 inversely correlated with total and bioavailable T.
Van Pottelbergh <i>et al.</i> 2003 [31]	715 M	42.7	Healthy middle-aged men	No correlation between total and free T with CRP was found.
Laaksonen <i>et al.</i> 2003 [32]	1896 M	52	Metabolic syndrome	Total and free T correlated inversely with CRP.
Hall <i>et al.</i> 2002 [33]	30 M HF	67	Heart failure	Inverse correlation of T and bio-T with IL-1 β , TNF- α , and IL-6.

Abbreviations: bio-T, bioactive testosterone; CRP, C reactive protein; FT, free testosterone; HF, heart failure; M, men; MIP-1 α and -2 β , macrophage inflammatory protein-1 α and 1 β ; NHANES, National Health and Nutrition Evaluation Survey; SHBG, sex hormone globulin; STEMI, ST-Elevation Myocardial Infarction; T2D, type 2 diabetes; TT, total testosterone.

33]. The correlation of T with inflammation should be evaluated on a larger number of biomarkers and adjusted with many confounder factors.

The effect of T therapy on the secretion of inflammatory cytokines levels in men have been investigated by many studies [35–51], which are summarized in Table 2.

Two randomized trials showed that T therapy in hypogonadal men produced a decrease in the concentration of adipokines [42, 47], but other trials did not reach the same results [49]. Singh *et al.* [51] did not observe any correlation between different doses of T enanthate administered with insulin activity and CPR level in young eugonadal patients (of 18 to 35 years old). Nasser *et al.* [52] found that T therapy was effective in Crohn disease, determining a reduction in CRP and Crohn Disease Activity Index. Other studies did not find any variation of CRP level after T administration in elderly men with low plasma T (160 mg per day of T undecanoate orally) [35] and on proinflammatory cytokines (Sustanon 200 mg every 2 weeks over 3 months) [44]. Robust clinical evidence reported that T therapy in hypogonadal men had an attenuating effect on inflammatory markers [36, 42, 43, 46–50]. However, others [35, 38, 40, 44, 45] did not find any significant effect [see Table 2]. In the studies reported in this table, some discrepancies are evident, such as the methodology adopted for the trials, the different dose of T administrated, the time of observation, and different clinical conditions. The transdermal administration of T in older men did not show any inhibitory effect on CRP, TNF- α , and IL-6 [38, 45], whereas T undecanoate 1000 mg every 6 weeks seems capable of reducing the inflammatory markers [42, 43]. Differences observed in these studies can be related to different doses of T administration where transdermal way is lighter compared to the injection.

Furthermore, a higher incidence of inflammation and cancer in patients with low T level was reported [53]. Considering the data from these studies, it appears evident that the

Table 2. Effect of T Administration on Inflammatory Markers

Authors	Subjects	Age	Type of Study	T Level	T Therapy	Duration	Marker of Inflammation
Dhindsa <i>et al.</i> 2016 [36]			Randomized placebo controlled trial	T = 252 ± 82 ng/dL	T 250 mg/2 wk	6 mo	Insulin sensitivity increased. Significant reduction of CRP, IL-1 β , TNF- α , leptin
Nasser <i>et al.</i> 2015 [52]	44 HH, T2D 92 M Crohn disease	54.6 60	Cumulative, prospective, registry study	FT = 4.4 ± 1.2 ng/dL T ≤ 12.1 nmol/L	T undecanoate 1000/3 mo	7 y	Significant reduction in CRP level and Crohn Disease Activity Index
Sonmez <i>et al.</i> 2015 [37]	60 M, CHH	21.8	Observational	T = 0.26 ± 0.16 ng/mL	T 250 (Sustanon) every 3 wk T transdermal 50 mg/d	6 mo	No changes in CRP level.
Maggio <i>et al.</i> 2014 [38]	109 M	71.9	Cohort study	T < 475 ng/dL	T patch 6 mg/24 h	36 mo	No significant changes in TNF- α , IL-6, PCR.
Traish <i>et al.</i> 2013 [39]	255 M	58.6		T = 9.9 ± 1.38 nmol/L	T undecanoate 1000/3 mo	60 mo	Significant reduction in CRP level.
Basaria <i>et al.</i> 2013 [40]	179 M	73	Double-blind randomized placebo-controlled trial	T = 248 ± 60 FT = 4.9 ± 1.2	T transdermal gel 100 mg/d	6 mo	Significant reduction in PAI-1 and increase in IL-6.
Saad <i>et al.</i> 2011 [41]	110 M	59.6	Observational	T = 9.3 ± 1.7 nmol/L	T undecanoate 1000/3 mo	3–24 mo	Strong decline in BMI and WC; less reduction in CRP.
Kalinchenko <i>et al.</i> 2010 [42]	184 HM MetS	35–70	Double-blind, randomized placebo-controlled trial	T < 12.0 nmol/L	T undecanoate 1000 every 6 wk	18 wk	BMI, leptin, insulin, IL-1 β , TNF- α , CPR decreased. IL-6 and IL-10 unchanged.
Giltay <i>et al.</i> 2008 [43]	100 HM	34–69	Observational nonrandomized study	T = 5.9–12.1 nmol/L	T undecanoate 1000 mg per 12 wk	15 mo	Significant decline in CPR.
Kapoor <i>et al.</i> 2007 [44]	20 HM T2D	63	Double-blind placebo	T = 7.4 nmol/L FT = 2.4 nmol/L	Sustanon 200 mg/2 wk	3 mo	No significant effect on resistin, TNF- α , IL-6, and CPR. Leptin and adiponectin reduced.
Nakhai-Pour <i>et al.</i> 2007 [35]	237 HM	60–80	Double-blind randomized placebo-controlled trial	T < 13.7 nmol/L	T undecanoate 160 mg/d	26 wk	No changes in PCR.
Herbst <i>et al.</i> 2006 [45]	52 W HIV	18–50	Placebo-controlled, randomized clinical trial	T < 33 ng/dL	T patches 300 μ m daily	24 wk	No changes in inflammatory markers.
Page <i>et al.</i> 2005 [46]	25 M	65–85	Observational	Normal range	T enanthate 600 mg/wk	3 wk	Adiponectin and leptin level decreased.
Malkin <i>et al.</i> 2004 [47]	27 M	62	Single-blind randomized placebo-controlled trial	T < 4.4 nmol/L	Sustanon 100 mg/wk	4 wk	Reduction in TNF- α , IL-1 β . Increase in IL-10.
Lanfranco <i>et al.</i> 2004 [48]	31 HM	36.5	Retrospective study	T = 4.4 ± 0.4 nmol/L		6 mo	Significant decrease in adiponectin.
Singh <i>et al.</i> 2002 [51]	61 M eugonadal	18–35	Double-blind, randomized trial	Normal range	T enanthate/wk 25 mg 50 mg 125 mg 300 mg 600 mg	20 wk	No significant effect on blood lipids, insulin activity, and CRP.
Ng <i>et al.</i> 2002 [49]	33 M (DHT) 20 M (hCG) healthy	<60	Double-blind placebo-controlled trial	T < 15 nmol/L	DHT 70 mg transdermal/d hCG 500 μ gr/wk	3 mo	Significant changes in CRP, sVCAM-1, or sICAM-1.
Sigh <i>et al.</i> 1997 [50]	15 HM	68	Observational	FT < 60 ng/dL	T cypionate 200 mg/biweekly	12 mo	Significant decrease in leptin level.

Abbreviations: Bio-T, bioactive testosterone; E2, 17 β -estradiol; FT, free testosterone; HCG, human chorionic gonadotropin; HM, hypogonadal men; M, men; T2D, type 2 diabetes; W, women.

administration of T is more effective in reducing inflammation in hypogonadal than eugonadal men. In eugonadal men, the effect of T seems to be dose-dependent and that low doses are ineffective as observed with oral and transdermal administration [35, 38, 45] also in young men although hypogonadal [37]. Furthermore, the interaction of T with estradiol in the regulation of systemic inflammation [54], adipose and muscular tissue mass, and other hormones should be considered. More studies are necessary to evaluate the potential effect of T in inhibiting the proinflammatory cytokines expressions.

4. Mechanism of Action of T on Inflammation

A. Effects on Adipose Tissue

T and obesity are interactive, and an inverse correlation between T level and body fat mass has been confirmed [55]. T therapy is effective in determining a sustained loss of body fat mass in hypogonadal men [56]. Androgens are very active in the regulation of adipose tissue metabolism and distribution due to the presence of androgen receptor (AR) on adipocytes [57, 58]. AR is present on preadipocytes with greater expression in visceral than in subcutaneous fat depot, and can partially explain the different adipose tissue distribution [57]. Notably, in adipocytes are also expressed estrogen receptor (ER) α and β [59, 60]. The activation of ER α on adipocytes in males and females has a protective effect against body fat accumulation, inflammation, and fibrosis [61] and the deletion of ER α gene reflects obesity in both sexes [62]. In men, visceral fat deposition is significantly greater than in women due to the low activation of ER α [63]. Visceral fat is correlated with metabolic syndrome [64] and CVDs independently from other measures of adiposity [65].

The most consistent effect of androgen on body fat is the activation of lipolysis [66] and inhibition of adipose tissue lipoprotein lipase activity [67]. Androgens markedly inhibit adipogenesis blocking the differentiation into adipocytes in subcutaneous and visceral preadipocyte in both sexes [68]. Singh *et al.* [69] showed that T and DHT regulate the pluripotent mesenchymal cells determining their preferential development into the myogenic rather than the adipogenic line. The study demonstrated that pluripotent cells are androgen-dependent and have reciprocal effects on muscle and fat cells. The effect of sex steroids on influencing the preadipocytes differentiation can explain the sexual dimorphism of body fat distribution [70]. Nonaromatizable androgen, such as DHT, has been shown to have a strong inhibitory effect on the differentiation of human mesenchymal stem cells and human preadipocytes, in subcutaneous and visceral (omental and mesenteric) fat deposits in men [71], whereas in women this effect remains unclear. Estrogens favor the development of fat cells in the subcutaneous fat tissue and inhibiting it in the visceral body fat [72]. A high androgen level inhibits the adipose tissue depots and improves insulin resistance and glucose tolerance in women and men [73]. Then, T administration exerts the primary anti-inflammatory effect in reducing fat mass, which is the source of many inflammatory cytokines.

B. Effects on the Expression of Inflammatory Adipokines

The effects of androgen on body fat reflect on many adipocytokines releasing, and the mechanisms are summarized in Fig. 1.

B-1. Leptin

T level interacts profoundly with many proinflammatory cytokines. Leptin, the most specific hormone secreted by adipocytes [74], is associated with adipose tissue expansion and with body mass index (BMI) [75]. Leptin concentration is significantly higher in obese than in lean individuals and for any given BMI more in women than in men [76]. Leptin level reduces T secretion from rodent testes *in vitro* [77], inhibiting leptin receptor isoform present in Leydig cells. From the other side, T level in men inhibits leptin secretion, independently by BMI, suggesting that T exerts an inhibitory effect on adipocyte [78]. In men with metabolic syndrome, the leptin level is higher, whereas T level is lower than in normal subjects [79]. Conversely, in women, androgen levels are positively correlated with high free and total leptin level [80] also in polycystic ovary syndrome (PCOS) [81], evidencing a sexual dimorphism of T on leptin secretion. There is a bidirectional effect between leptin and T secretion. The lack of leptin or leptin receptors in humans and mice develop profound obesity and infertility [82]. Leptin has a modulatory effect on Leydig cells function [83], inhibiting basal T production [84]. Behre *et al.* demonstrated a significant inverse correlation between

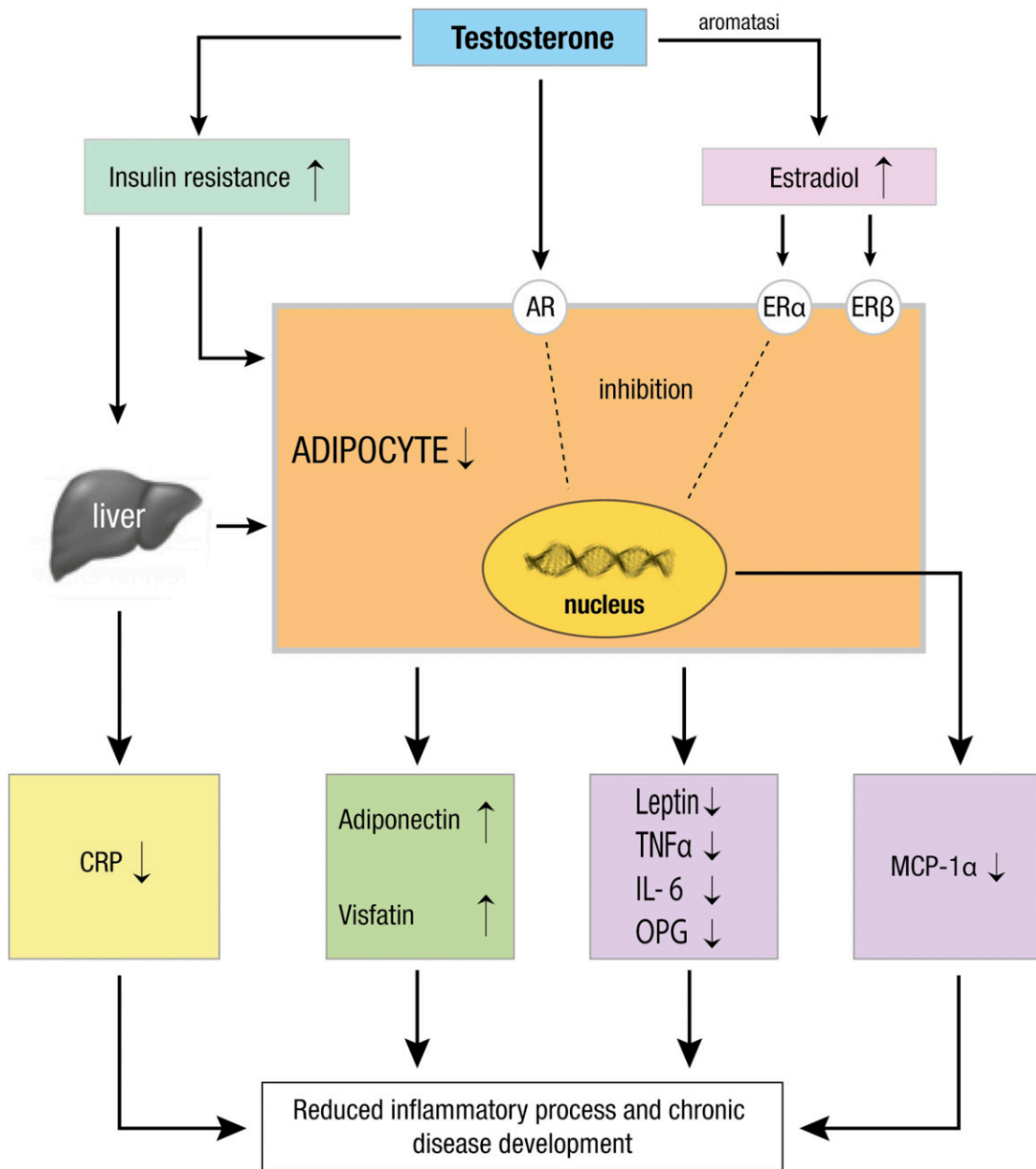


Figure 1. T exerts its anti-inflammatory activity through different mechanisms. Firstly, T inhibits body fat expansion and reduces adipocytes size and metabolism. After its aromatization in estradiol, T can activate AR and ER α and ER β , which contribute to adipocytes regulation decreasing the release of adipokines (leptin, IL-6, TNF- α , OPG, MCP-1 α) and improving adiponectin and visfatin production, which possess an anti-inflammatory effect. Furthermore, T improves insulin activity and reduces the CRP from the liver. Altogether, it results in a reduction of inflammation and development of chronic disease.

serum leptin levels with T and BMI in males, whereas serum estradiol had no influence [85]. The administration of T to young men suppressed serum leptin secretion, which returned to the pretreatment level after cessation of T injections [86]. The short-term T administration, in boys with pubertal delay, decreased leptin and insulin concentrations [87] and therefore obesity [86]. Restoring the physiological level of serum T in men with metabolic syndrome can discontinue the vicious circle of metabolic disorders resulting in a T deficiency and clinical complications [88]. The antiobesity effect of T may be mediated by the leptin suppression.

B-2. Adiponectin

Adiponectin, the highest expressed cytokine in adipocytes [89], is inversely correlated with metabolic disorders and, CVD [90], with waist-to-hip ratio, and visceral fat [91, 92]. A higher level of adiponectin is expressed in lean subjects, both in men and women, and is correlated with better insulin sensitivity and lower TNF- α level [93]. Adiponectin level is lower in obese compared with healthy subjects who have higher adiponectin level and a reduced risk of type 2 diabetes [94]. Type 2 diabetic patients with CVD had a lower level of adiponectin compared to diabetic patients without CVD [95]. Furthermore, the plasma adiponectin level increases relevantly following a reduction in body weight in the diabetic subjects as well as the nondiabetic subjects [95].

Circulating level of adiponectin has a sexual dimorphism because adiponectin levels are normally higher in females than in males [96, 97]. In hyperandrogenic PCOS obese women, adiponectin level was significantly lower compared with normal women, whereas in thin women, no difference has been observed between women with or without PCOS [98]. In PCOS women, the level of adiponectin is reduced and more correlated with insulin resistance and adipose tissue than androgen levels [99]. So it seems that adiponectin in women is more influenced prevalently by the body mass. In young men, acute T treatment determines a reduction of adiponectin high molecular weight (HMW) levels and low T level is associated with increased adiponectin HMW levels [100]. T therapy has been shown to exert a direct suppressive effect on adiponectin secretion in men with type 2 diabetes [44], in elderly men [46] and in transsexual female patients [101]. Frederiksen *et al.* [102] found a decrease in subcutaneous fat and adiponectin level after 6 months of T administration in aging men. Estradiol has an opposite effect on T, determining the stimulation of adiponectin and its receptors expression in skeletal muscle [103].

In rats, T controlled directly the sex differences in adiponectin by the activation of androgen-mediated effects that regulates the secretion and metabolism of adiponectin [104]. The changes in circulating adiponectin level are highly correlated with the androgen levels, but not with estradiol level. A nonestrogenic and nonaromatizable androgen such as trenbolone determines a reduction in adiponectin level and visceral fat similar to that caused by T. Both T and trenbolone increased the HMW adiponectin in males and females and reduced the lower molecular weight adiponectin [104] showing that aromatizable and non-aromatizable androgen have similar effects on the isoforms of adiponectin.

B-3. Osteoprotegerin

Osteoprotegerin (OPG) is a cytokine of the TNF superfamily [105], which regulates bone resorption [106], and calcium metabolism in both bone and vascular tissues [107]. Body fat is a potential source of OPG [108]. OPG has been proposed as a mediator of vascular calcification [109]. High serum OPG levels were correlated with greater incidence of CVD mortality [110], vascular calcification at coronary and aortic level [109, 111], and arterial disease in type 2 diabetes [112]. OPG level is inhibited by androgens, whereas estradiol shows an opposite effect [113]. The different action T vs estradiol on OPG secretion may explain why T is less efficient than estradiol on inhibiting bone resorption in humans [114]. In hypogonadal men, an increased RANKL activity and an increased bone turnover-related OPG has been observed [115], whereas T administration in men significantly decreased OPG level [116]. The decreased OPG level following T therapy reduced the incidence of cardiovascular risk [116]. In women, OPG levels are positively correlated with T level [117]. In premenopausal women, obesity favorites an increase of serum OPG levels, whereas weight loss favorites a decrease of serum OPG levels [118]. In PCOS women, serum OPG level is lower compared with nonhyperandrogenic control women [119], whereas Glinborg *et al.* [117] showed that OPG levels were more correlated with bone mineral density in PCOS than with T level. In conclusion, OPG production is inhibited by T in men, less evident in women, where body fat mass seems to have a prevalent effect.

B-4. Tumor necrosis factor- α

TNF- α is a potent cytokine prevalently secreted by macrophages after they have infiltrated into adipose tissue in obese humans [120]. TNF- α mediates apoptosis, insulin resistance, and lipolysis [121], inducing serine phosphorylation of insulin receptor substrates [122]. Furthermore, TNF- α determines the alteration of endothelial permeability to immune cells and small particles like low-density lipoprotein [123], promoting the first stage of atherosclerosis increasing the transport of low-density lipoprotein across endothelial cells [124]. TNF- α downregulates the mRNA level of adiponectin, a cytokine which contributes to maintaining glucose and lipids homeostasis [125]. The effect of T on TNF- α secretion is poorly investigated. Recently, Chen *et al.* [126] showed that T significantly attenuated the release of TNF- α in a dose-dependent manner and might reduce the inflammatory responses and modulate the immune system. Withdrawal of T administration in hypogonadal men determined significant increases in IL-6 and TNF- α [44]. Corrales *et al.* [127] evidenced that T therapy in type 2 diabetic men caused a reduction or complete abrogation of natural *ex vivo* production of IL-1 β , IL-6, and TNF- α . In young overweight and obese women with PCOS, higher TNF- α has a positive correlation with androgen level and insulin resistance [128].

B-5. Monocyte chemoattractant protein-1

MCP-1 is a cytokine secreted by adipocytes in obese subjects with the effect to promote the infiltration of monocytes/macrophages into adipose tissue [129]. The MCP-1 level is significantly raised in obese subjects suggesting the concept that chronic inflammation is due to excess adiposity [130]. Low T and high estradiol levels have a direct adverse effect on MCP-1 *in vivo* [131], showing that the action of T is regulated by estrogen level. Morooka *et al.* [132] demonstrated in adipocytes cocultured with monocytes that the activation of AR determined the suppression of MCP-1 release, particularly suppressed by DHT and chronic inflammation in adipose tissue. High androgen level in women, as observed in PCOS, is correlated with a significant increase in MCP-1 level and with abdominal obesity [133].

B-6. Interleukin-6

IL-6 is a cytokine that plays a fundamental role in inflammation, immune response, and hematopoiesis [134]. IL-6 is secreted prevalently by white adipose tissue (for one-third), and by skeletal muscles and liver [135]. The IL-6 expression is correlated, similarly to TNF- α , with BMI, abdominal obesity, and free fatty acids level [136]. In adipose tissue and liver, IL-6 exerts proinflammatory activity responsible for insulin resistance [137]. IL-6 is also produced by skeletal muscle during exercise mediating muscle hypertrophy and myogenesis [138]. There is consistent evidence that IL-6 plasma level increases in response to exercise [139] and the production of IL-6 is stimulated by ROS from skeletal myotubes [140]. The IL-6 produced by skeletal muscles affects white adipose tissue mass regulating glucose uptake capacity and the lipogenic and lipolytic factors [141]. After weight loss, plasma level of IL-6 is reduced and improves insulin sensitivity [142]. Adrenal androgens, particularly DHEA, had an inhibitory effect on different cell types such as leukocytes and decreased IL-6 secretion [143], and the suppressive effect was greater than that of DHT and estrogen [144]. In aged orchidectomized male rats, at the supra-physiological level of T the inflammatory ILs, specifically IL-2, IL-6, IL-10, IL-12, and IL-13, were elevated, whereas T supplementation decreased plasma IL level [145]. In PCOS women, high androgen levels, in both lean and obese women, were correlated with IL-6 and with insulin resistance [146]. However, IL-6 levels were found to be higher as compared with controls, although IL-6 levels might be more dependent on nutritional status [147]. These effects are inhibited by the neutralization of IL-6 with the anti-IL-6 antibody [148]. After intense physical exercise, the IL-6 production is inversely correlated with T level [149]. T treatment (150 mg every two weeks) of aging type 2 diabetic men after 12 months reduced or abrogate the production of proinflammatory cytokines (IL-1b, IL-6, TNF- α)

entirely by monocytes and dendritic cells observed after stimulation with lipopolysaccharide plus recombinant human interferon- γ . [150].

B-7. Resistin

Resistin is a proinflammatory cytokine that has the greatest effect on promoting atherosclerosis and CVD diseases [151, 152] and is a marker of heart failure [153]. Plasma resistin level is positively correlated with coronary artery disease and mortality risk [154] and predictors of all-cause mortality independent of other risk factors [155, 156]. Resistin showed significant correlation with BMI, insulin resistance, obesity, and inflammation in patients with type 2 diabetes [157, 158]. Resistin may be a link between insulin resistance and androgens [159]. Although T therapy in hypogonadal men with type 2 diabetes decreases leptin and adiponectin levels, no significant effect on resistin level has been observed [44]. Further research is necessary to clarify the effects of androgens on the regulation of resistin plasma level and function.

B-8. Visfatin

Plasma visfatin concentration is increased in subjects with overweight/obesity, type 2 diabetes mellitus, metabolic syndrome, and CVDs [160]. In patients with metabolic syndrome, visfatin is correlated with adiponectin [161], whereas in patients without metabolic syndrome, circulating visfatin levels were significantly correlated with glucose, insulin, and triglyceride levels. A meta-analysis indicates that high-circulating visfatin level is an intrinsic characteristic of PCOS, suggesting visfatin as a potential biomarker for PCOS [162].

C. Future Directions

With advancing age, the decline of sex hormones patronizes the development of the inflammatory processes that represent the basic mechanism for the development of chronic diseases. Adipokines production increases in the condition of low T level. However, more specific and well-controlled clinical trials analyzing the interaction of sex hormones on a wider number of adipokines that interact with other risk factors. A low T level in men represents an important risk factor for health, but its effect is modulated by estrogen level that should always be detected.

5. Conclusions

T level is determinant in the regulation of the inflammatory processes by inhibiting adipocytes expansion, differentiation, function, and suppressing cytokines formation (leptin, IL-6, TNF- α , MCP-1, resistin) while stimulating the adiponectin secretion. Low T level has implications for metabolic health in both males and females and should be considered a risk factor because of its correlation with metabolic syndrome and all-cause mortality [1]. The inhibitory effect of androgens on adipokines secretion can also interfere in cancerogenesis reducing the progression and diffusion of the diseases. Low T level is correlated with a high level of adipokines and inflammation, and T therapy is necessary to restore the physiological, hormonal level. However, T administration in hypogonadal men on the inflammatory markers has shown conflicting results, probably related to the different dose and duration time of T administration and the limited evaluation to a small number of markers. Furthermore, not all studies were corrected for the many confounder factors, such as fat mass distribution, nutritional intake, and muscle mass. Diet restriction and physical exercise are important in the regulation of metabolic disorders. Finally, androgen therapy in older men with T deficiency improves physical efficiency and reduces the risk of rehospitalization [163]. Chronic diseases in aging have a great impact on the lifestyle of patients and public health cost due to the frequency of hospitalization. The reduction of the

inflammatory state is relevant, and further investigations are required to evaluate the mechanisms of proinflammatory cytokines regulation.

Acknowledgments

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Disclosure Summary: The author has nothing to disclose.

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