Possible Benefits versus Potential Risks of Testosterone Replacement Therapy in Elderly Men as Evidenced by Laboratory Parameters and Evaluation of Quality of life and Sexual Activity

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Abstract: Aging is a significant health issue because of the association of low testosterone levels with a lot of diseases and a decrease in life quality and expectancy. The aim of this study was to weigh the benefits versus risks of testosterone replacement therapy (TRT) in old men. The current work was a prospective controlled study that included 54 aged men with ages >50 complaining of weak erection. Cases were recruited from Andrology Outpatient Clinic, Kasr El-Aini Hospital, College of Medicine, Cairo University. All cases were treated by testosterone enanthate, 250 mg every 3 weeks as intramuscular (IM) injection for 6 months. Free and total testosterone (T), PSA, LH, E2, lipid profile, liver function tests and CBC were done before and after TRT. Cases were asked to fill a questionnaire for quality of life and Massachusetts Male Aging Study Sexual Activity Questionnaire. The study revealed that TRT had no detectable risks of cancer prostate as evidenced by absence of significant changes of PSA levels after TRT (p>0.05) in addition to the finding of digital rectal examination. Also, no significant changes in lipid profile or hepatic functions as evidenced by the insignificant changes of mean values of parameters of lipid profile and liver function tests after TRT (p>0.05). No risks for polycythemia as evidenced by insignificant changes in hemoglobin, hematocrite and RBCs count (p>0.05). No significant changes in platelets counts (p>0.05), and thus no fears of thromboembolic sequelae related to changes in platelets counts. There was improvement in both physical and cognitive problems in 33% & 22% of cases with significant differences between scoring grades before and after TRT (p<0.05). There was no detectable improvement in affective problems of this age. Highly significant improvement in all sexual satisfaction parameters and in getting and keeping erection (p≤0.001) was recorded with a percentage of improved cases ranged from 23% to 41%. Little improvement was shown in the frequency of sexual activity (4% of cases), getting and keeping erection (7%). No significant difference in free & total T levels between cases & control which means that other etiological factors with T are responsible for occurrence of andropause. **In conclusion**, IM TRT appeared to be associated with some beneficial outcomes on physical and cognitive functions in old men and it improved most sexual satisfaction parameters and some sexual performance like getting and keeping erection. At the same time, it has no detectable risks on lipid profile, liver function tests or hematological parameters. No cases had developed polycythemia or cancer prostate which are the most debated conditions as regards this therapy.

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1. Introduction

The levels of serum testosterone and free testosterone decline as men get older. This is called andropause or late-onset hypogonadism. However, the decrease in testosterone in aging men is gradual and moderate. The possible clinical consequences have not been well-established in contrast to menopause where complete rapid estrogen deficiency occurs. Specific physical and sexual changes that could affect life expectancy and quality of life usually take place at this age in women. The andropause or "Male menopause" is gradual and have no specific symptoms. This makes its detection and prediction of response to testosterone replacement therapy (TRT) challenging [(1)].

Testosterone usually peaks during adolescence and early adulthood. It gradually decreases, typically about 1% a year after the age of 30. It is essential to determine in aged men if the decline is of normal aging or of pathological origin. The possible benefits of TRT are too much encouraging; it improves some sexual activities such as libido, some cognitive functions like memory and attention, also improves physical status by increasing muscle mass and energy

level. It is considered by some people as an anti-aging agent. But the actual health benefits are still not very clear or conclusive. There are 3 main sexual manifestations that characterize andropause; reduced libido, erectile disorders and absence of morning erection. A testosterone level that is less than 8-11 nmol/l in addition to these 3 sexual manifestations is usually encountered in andropause [2].

There is evidence that TRT improves bone density and fat mass. However there is some controversy as regards its effects on mood, quality of life, muscle strength and the sexual function. Up to our knowledge, the prescriptions of commercial testosterone for elderly men increased by more than 170% in the last years. Some promising data for cases with metabolic syndrome and type II diabetes mellitus are recorded by a lot of epidemiological studies that had detected a negative correlation between diabetes mellitus (type II), metabolic syndrome, insulin resistance and obesity in one side and the concentration of serum androgen on the other side. Unfortunately, conflicting data were found as regards TRT effects on glycated haemoglobin concentrations [2-5].

Despite the mentioned benefits, it is crucial to know that the use of this kind of therapy is still challenging. There is a possibility of increased risk of some pathological changes in the prostate. Actually the possibility of harmful effects on cardiovascular system (CVS) is still very limited and more research work is needed to clarify the possible risks on CVS. However, TRT in old immobile men should be considered as a critical situation especially in those with CVS diseases [2,4,6,7]. Other adverse effects related to TRT include erythrocytosis, gynecomastia and fluid retention. Testicular atrophy can occur also and may resolve after transdermal TRT rather than IM one. Other adverse effects include irritability, acne and deterioration of lower urinary tract symptoms [8, 9]. If there is some suspicion that TRT could be carcinogenic to prostate, TRT is thus contraindicated in prostate cancer. This suggestion developed from the fact that androgen deprivation leads to regression of prostate cancer [10]. However, other findings believe that testosterone reaches a saturation level when binding its prostatic receptors at very low levels. A lot of conflicting reports on the effect of TRT on prostate size and the possibility of malignant changes are recorded. This issue requires additional studies that should clarify this dilemma [11-14].

The aim of this work was to assess the possible clinical benefits and potential risks of testosterone replacement therapy in aged men over 50 that complain of weak erection.

2. Material and Methods

The study was a prospective controlled study that included 54 men with ages more than 50 years complaining of weak erection. Cases were recruited from the Andrology Outpatient Clinic, Kasr El-Aini Hospital, College of Medicine, Cairo University. Another 54 age matched normal healthy males without erectile problems and fulfilling the same inclusion criteria were included as a control group for the hormonal status. The required approval consents were taken from each subject.

Inclusion criteria:

Cases should be normotensive, non diabetic, with no history or clinical manifestations of chronic obstructive pulmonary disease or sleep apnea. No criteria suggestive of psychogenic impotence or psychological disturbances, also, not suffering from coronary artery insufficiency and also with no evidence of cancer prostate (by serum PSA and digital rectal examination). Cases should not be receiving medications known to interfere with hormonal level and with no history of regular exercises.

Complete history taking and general, local genital and digital rectal examinations with conventional assessment of prostate size were done [15-17].

All cases were asked to complete questionnaires that evaluate both quality of life and sexual activity: WHO questionnaire for quality of life and Massachusetts Male Aging Study (MMAS) Sexual Activity Questionnaire [18, 19].

Laboratory Tests

Morning fasting blood samples were obtained between 07.00 & 11.00 h after fasting for 12-14 hrs. Samples for CBC were collected on EDTA tubes and assayed immediately but those for hormonal assays, PSA and chemical assays (liver function tests and lipid profile) were taken in plain tubes and sera were separated after clotting of samples and stored at – 70 °C till assayed. Serum samples for lipid profile were stored at 4°C for < 3days.

PSA and Hormonal assays

The PSA, total testosterone, LH and Estradiol were measured by Electrochemiluminescence-immunoassay method (ECLIA) on automated Cobas e 411 immunoassay analyzer from Roche (HITACHI) [20]. Free testosterone was measured by Radioimmunoassay [21]. The kit was supplied by DPC (Diagnostic Products Corporation, Los Angeles, CA 90045-5597).

Chemical Analysis

Liver functions tests (total and direct bilirubin, AST, ALT and Alkaline Phosphatase) and lipid profile (total cholesterol, triglycerides, HDL and LDL cholesterol) were done on a fully automated analyzer (Dimension RxL/ RxL Clinical Chemistry System

from Dade Behring Inc. Chemistry group P.O. Box 6101 Newark, DE 19714-6101 USA).

Complete Blood Counts

The EDTA anticoagulated blood was used for measuring haemoglobin, haematocrit and red blood cell count. A fully automated multichannel instrument was used for measurements (Sysmex Analyzer: T 1800 I, SYSMEX CORPORATION KOBE, JAPAN, Born–Barch 1, 22848 Norderstedt, Germany) [22].

Testosterone Replacement Therapy

All cases were treated by testosterone enanthate, 250 mg every 3 weeks as intramuscular injection (Primoteston Depot 250, Schering, Berlin, Germany) for 6 months.

Statistical Analysis

The SPSS (Statistical Package for Social Sciences, version 10) was used for data management and analysis. Quantitative data were presented as mean ± SD. For comparison of means, the Student's t-test was used (paired & unpaired tests according to type of comparison). Mann-Whitney test was used when indicated. The p value < 0.05 was considered statistically significant.

3. Results

I-Clinical Evaluation

1-General Examination:

No changes were found before and after TRT as regards blood pressure, peripheral pulses, secondary sexual characters, body fat distribution and the presence of gynecomastia.

2-Local Genital Examination:

The testicular size was normal in 46 cases (85%) and moderate in 8 patients (15%). Only 2 cases showed plaques of Peyronies' disease. No changes in local genital examination were observed after treatment.

3-Digital Rectal Examination:

The size of prostate was enlarged in 40 cases before therapy. The enlargement was minimal (1+) in 20 cases (37%) and moderate (2+) in the other 20 cases (37%). After treatment, the size was found to be enlarged in 42 cases. The enlargement was minimal (1+) in 14 cases (26%), moderate (2+) in 24 cases (44%) and severe (3+) in 4 cases (7%).

4-Important data in history:

There was compatibility between cases and control as regards age (60.4±6.9 [50-79] for cases & 63.7 ±7.4 [50-81] for control, p>0.05). The duration of weak erection ranged from 4 months to 10 yrs with mean of 2.5 yrs. The sexual history before and after TRT was shown in table (12).

II-Evaluation of Laboratory Parameters:

Table 1: Comparison between Patients and Control Subjects as regards Androgen Levels

Parameter	Patients, N=54	Control, N=54	p value
Total Testosterone, mean ± SD, (ng/ml)	6.1±1.9	6.2±2.7	>0.05
Free Testosterone, mean ± SD, (pg/ml)	15.6±6	14.3±4.1	>0.05

The following tables (2-5) show the comparison of all laboratory parameters (mean ± SD) before and after treatment.

Table 2: Results for Hormones and Prostatic Specific Antigen (PSA)

Evaluation	Total Testosterone (ng/ml)	Free Testosterone (pg/ml)	LH (mIU/ml)	E2 (pg/ml)	PSA (ng/ml)
Before	6.1±1.9	15.6±6	6.7±9.8	38.4±15.3	1.1±1.1
After	6.8±3.5	16.3±9.3	2.9±2.1	47.7±67.3	1.4±1.3
p value	>0.05	>0.05	<0.05*	>0.05	>0.05

*= significant difference

Table 3: Lipid Profile

Evaluation	Triglycerides (mg/dl)	Total Cholesterol (mg/dl)	HDL-C (mg/dl)	LDL-C (mg/dl)
Before	120.7±53.8	186.2±36.1	40.1±10.6	121.6±31.5
After	108.7±65.5	183.7±35.4	40.6±9.6	122.3±28.3
p value	>0.05	>0.05	>0.05	>0.05

Table 4: Liver Function Tests

Evaluation	Total Bilirubin, (mg/dl)	Direct Bilirubin (mg/dl)	AST (U/L)	ALT (U/L)	ALP (U/L)
Before	0.7±0.3	0.2±0.03	27.1±10.3	28.1±14.6	184.6±72.9
After	0.6±0.3	0.21±0.033	28.5±14.3	32.9±26.5	198.7±59.2
p value	>0.05	>0.05	>0.05	>0.05	>0.05

Table 5: Complete Blood Counts

Evaluation	RBCs (10^{12}/l)	Haemoglobin (g/dl)	Haematocrit (%)	Platelets (10^{9}/l)
Before	4.9±0.59	14.4±1.2	42.5±3.6	231.5±90.5
After	5.1±0.66	14.45±1.8	42.7±5.2	241.9±93.4
p value	>0.05	>0.05	>0.05	>0.05

III-Evaluation of Questionnaires:

A. Quality of Life Questionnaire

Table 6: Number and Percentage of Cases with Improvement in Life Problems

Affection after Therapy	Physical Problems	Cognitive Problems	Affective Problems
Improvement	18 (33%)	12 (22%)	0 (0%)
No Improvement	36 (67%)	42 (78%)	54 (100%)

Table 7: Comparison of Means of Scores Given for Parameters Representing Quality of Life before and after Treatment

Aspects	Before	After	*p* Value
Physical Aspects	73.2±9.5	76.2±4.9	<0.05*
Cognitive Aspects	77.2±8.7	79.7±1.8	<0.05*
Affective Aspects	76.7±7.2	76.7±7.2	--

B. Massachusetts Male Aging Study Sexual Activity Questionnaire:

Table 8: Number and Percentage of Cases with Improved Sexual Parameters

Affection after Therapy	Sexual-Activity Frequency	Full Hard Erection	Awaken-with Erection	Getting Erection	Keeping Erection
Improvement	2 (4%)	4 (7%)	4 (7%)	16 (30%)	18 (33%)
No Improvement	52 (96)	50 (93%)	50 (93%)	38 (70%)	36 (67%)

Table 9: Number and Percentage of Cases with Improved Satisfaction Parameters

Affection after Therapy	Satisfaction-with Frequency of Activity	Satisfaction with Sex Life	Satisfaction with Partner	Partner Satisfaction
Improvement	12 (23%)	22 (41%)	22 (41%)	22 (41%)
No Improvement	42 (77%)	32 (59%)	32 (59%)	32 (59%)

Table 10: Comparison of Means of Scores for Sexual Activities

Evaluation	Sexual Activity Frequency	Full Hard Erection	Awaken with Erection	Getting Erection	Keeping Erection
Before	2.81±1.17	1.3±0.9	1.6±0.9	2.1±0.4	2.2±0.5
After	2.85±1.19	1.5±1.1	1.7±1	2.4±0.6	2.5±0.6
p value	>0.05	>0.05	>0.05	0.003**	0.001**

Table 11: Comparison of Means of Scores for Satisfaction Parameters

Evaluation	Satisfaction with Frequency of Activity	Satisfaction with Sex Life	Satisfaction with Partner	Partner Satisfaction
Before	2.4±0.6	2.1±1.2	2.3±1.2	2.4±1.4
After	2.7±0.7	2.8±1.4	2.8±1.3	3.0±1.5
p value	0.006**	0.001**	0.002**	0.002**

** Testosterone was found to improve getting and keeping erection. Also it resulted in a highly significant increase in the level of sexual satisfaction.

Table 12: Pre and Post Treatment Evaluation of Sexual Activity of Cases

Evaluated Activity	Presence or Absence of Activity	Number (%)	
		Before	After
Nocturnal Erection	Negative	30 (56%)	24 (44%)
	Positive	24 (44%)	30 (56%)
Sexual Desire	Negative	2 (4%)	2 (4%)
	Positive	52 (96%)	52 (96%)
Orgasm	Negative	2 (4%)	2 (4%)
	Positive	52 (96%)	52 (96%)
Successful Vaginal Penetration	Negative	24 (44%)	24 (44%)
	Positive	30 (56%)	30 (56%)

4. Discussion

Since 1993, a lot of benefits of TRT had increased the prescription of testosterone (T) by more than 500% in the United States. However, there is some risk for malignancy especially prostate cancer and for liver toxicity. If an old man is infertile or having previous heart failure, dermatological problem or gynecomastia, the TRT could deteriorate these conditions. Also, T may not be suitable for those seeking for fertility as TRT would inactivate hypothalamic- pituitary -testicular axis [23].

The current study was a trial to weight benefits against potential risks of TRT. The results for total and free testosterone (T) before therapy showed insignificant differences when compared with values for control group. This raises the hypothesis that many of the clinical manifestations of andropause may be ascribed to a decrease in the production of other hormones such as growth hormone, insulin growth factor-1, dehydroepiandrosterone (DEHA) and DEHA sulfate [24, 25]. Some authors suggested a possible role for melatonin deficiency in addition to the previous hormones in the symptomatology of aging [26, 27]. However, other authors suggested that aging is accompanied by a decline, although gradual and shows wide inter individual variability in testicular endocrine function and is characterized by low circulating testosterone levels [23]. This condition was first called partial androgen deficiency in aging male (PADAM) that impairs libido, sexual activity, erection, bone density and muscle mass. The so called andropause (late onset hypogonadism) or androgen deficiency of aging men occurs when elderly men become hypogonadal ones [28]. Also, the current values for testosterone and estradiol showed insignificant differences when compared before and after therapy. This could be attributed to the amount of the suggested dose, duration of treatment, type of preparation of testosterone and timing of the second post therapy sampling. Testosterone is transformed into estrogen by an aromatization process in various tissues [29]. The significant decrease in LH in the second sample is considered as a normal finding related to the normal negative feedback mechanism of the pituitary axis. As men age, serum gonadotropin concentrations increase, FSH more than LH. It is suggested that both primary and secondary hypo-gonadism could be reasons for age related decline in T. In agreement with the current work, was the study of New Mexico Aging Process in which the mean LH concentration increased also but their work was done over 15 years. They recorded a mean of 9.4 to 13.7mIU/mL for LH, and the FSH increased from 14.1 to 27.4mIU/mL [30]. In the Massachusetts Male Aging Study, the LH increased by 0.9% per year and the FSH by 3.1% per year [31]. The fall in testosterone with age was associated with an increase in LH, suggesting a degree of primary hypogonadism in the European Male Aging Study. In young cases with obesity, the decline in testosterone was not suggesting that the effect of obesity was mediated by secondary hypogonadism [32].

No significant change in serum prostatic specific antigen (PSA) was shown after TRT in the current work. Only minimal increase of prostate size was detected in 14 cases (26%) at the end of therapy. No change in prostate consistency was detected on digital rectal examination. The small increase in size of prostate could be explained by an increase in the production of dihydro-testosterone (DHT). It is well known that PSA is a glycoprotein specific for prostate epithelium and its serum increase could be caused by prostatic carcinoma as well as non malignant conditions like granulomatous prostatitis or prostatic infarction. Also, it is superior to examination and transrectal ultrasound (TRUS) and a value > 4 ng/ml usually prompts a TRUS guided biopsy for confirmation. Some authors stated that there is no clear evidence that TRT is an etiological factor for developing benign or malignant conditions in male prostate [33-35]. This was in contrast to other authors who reported that removal of the testicles decreased prostate size and also they found that some pathological prostatic conditions were associated with those who received TRT more than those who received placebo [36]. The cancer of prostate is well

known to be an androgen sensitive one, so TRT is absolutely contraindicated in cancer prostate patients if they have low testosterone levels [37]. There are conflicting reports about the effect of TRT on changing subclinical prostate cancer to clinically detectable cancer. In a retrospective study there was no increase in the risk of cancer in men who underwent prostate biopsy prior to TRT as compared to those without prostatic intra-epithelial neoplasm [33, 38-40].

In another study, there was no difference in prevalence of cancer prostate in those receiving TRT and those in the general population. Thus, authors denied any carcinogenic effect of TRT on the prostate [9, 41-45]. We should keep in mind an important fact that prostate cancer becomes more prevalent at an old age which is the period of man's life when testosterone levels decrease. Some authors believe that TRT could be cautiously considered in selected hypogonadal men treated with curative intent for prostate and without evidence of active disease [46].

The current work did not show any significant change in the whole studied lipid profile (total cholesterol, triglycerides, HDL- and LDL-cholesterol). Other reports were markedly conflicting as regards lipid profile. Some authors recorded a correlation between HDL cholesterol and insulin sensitivity in one side and androgen levels on the other side (at physiological level). Others denied any changes in blood lipids related to normalization of testosterone. On the other hand, others reported a decline in the protective HDL-C fraction [47-51]. In a six month study made on close number of men and compared transdermal and IM routes of administration, authors had found insignificant changes in both HDL and the total cholesterol/HDL ratio in the two groups [8]. Also, TRT had reduced the well recognized atherogenic factor, the lipoprotein (a) [52]. The TRT induced reduction of visceral abdominal fat mass reduces the activity of lipoprotein lipase enzyme. Thus, together with the enhanced lipolysis that on its turn improves insulin sensitivity and leads to mobilization of triglycerides from abdominal fat, could be considered as an accepted mechanism for androgen induced lipid lowering effect [53-56]. Some other researchers recorded that the level of T above the physiological levels could reduce the protective HDL-C and at the same time elevate the atherogenic LDL-C. This dual mechanism might elevate risks for development of cardiovascular disease [57-59].

As regards liver function tests and the possibility of hepatic problems, there were no significant changes in the currently studied laboratory parameters. Some author's results were consistent with the current data [60]. This was in contrast to other investigators who detected some cholestatic, hepatotoxicity, neoplastic changes and up to liver cell failure [61, 62]. They reported that these harmful changes are not associated with injectable forms of TRT. The use of IM TRT in the current work may be a cause of absence of abnormal liver function tests in this work in addition to the long period of follow up made in other researches that could allow appearance of more hepatic problems that could be related to non IM testosterone or other factors other than TRT. This is why some oral forms of T are not recommended for TRT.

One of the risks for TRT is the development of polycythemia or erythrocytosis. Although older men tend to have lower haemoglobin levels than younger ones, polycythemia should be considered as an undesirable and not uncommon effect of TRT. Haemoglobin is positively correlated with testosterone (in high concentrations). As it is well known, T stimulates the process of erythropoiesis and when given by injections as TRT, it will enhance erythrocytosis [33]. This is why haemoglobin is higher in men than women in general and increases by 15-20% at male puberty in particular [60, 63]. In elderly men, increasing haemoglobin above certain levels may have bad outcomes like exacerbation of coronary or cerebrovascular disease or at least peripheral vascular circulation. The mechanism by which it causes these bad outcomes is the direct effect of high haemoglobin on increasing blood viscosity, particularly in those with secondary erythrocytosis [64-66]. If the route of administration is the injection route, the development of polycythemia is easier than in administration by topical route [8]. This usually occurs in the first 3 months of scrotal transdermal preparations in more than 5% of cases [67]. Polycythemia incidence usually correlates positively with the dose of androgen taken [9]. Some authors reported that the frequency of polycythemia is much related to supra-physiological levels of testosterone [8]. An initial treatment for erythrocytosis and other conditions like marked cardiac failure or occlusive sleep apnea is a must before trials of TRT [36, 52, 68]. In the current study, the use of the suggested dose and the duration of IM testosterone therapy did not cause any significant changes in the levels of haemoglobin, haematocrit or counts of RBCs and platelets. Testosterone deficiency as mentioned causes decline in haemoglobin levels by about 10 to 20% [69, 70]. The principal mechanism of enhancing haematopoiesis could be stimulating the kidney directly to produce the hormone erythropoietin and androgen might also act directly on erythropoietic stem cells [70].

The differences in hematological parameters among various studies could be explained by differences in study design, age of cases, duration of therapy and the route of androgen administration. As

mentioned before, the current dosage in TRT did not lead to any significant change in the platelets count and this is a very important point that means that the currently used dose and its route of administration could not develop undesirable thromboembolic sequelae related to thrombocytes count.

In the current evaluation for quality of life questionnaire, there was some improvement in physical problems (33%) and in the cognitive problems also (22%) in the aged men. There was no detectable improvement in the affective problems related to aging. Also, in comparing means of scores given for physical activities and for cognitive aspects before and after treatment, significant differences were found p <0.05, but no difference was found for affective aspects after therapy. The improvement in physical activities could be related to increased skeletal muscle protein synthesis and strength which in turn could be mediated by stimulation of intramuscular IGF-1 system [71]. The absence of clear changes on the affective level in the current study could be explained by the fact that testosterone effect on the central nervous system could not be clarified well as human behaviors are influenced by confounding effects of social learning, psychological aspects and educational levels.

It is well known that the strength of any muscle correlates with its mass and from the biochemical point of view, T can act directly on cells of muscles and stimulate expression of IGF-1 either directly or indirectly. This could enhance protein synthesis in muscle and leads to more growth of muscle. No obvious association between T levels and grip strength was recorded but a positive correlation was recorded between fat free mass and bioavailable T [72-75].

There is conflicting data about the mechanism by which T improves physical activity. Is it an actual direct improvement of physical activity or it is just a decrease in incidence of fractures and disabilities rate? In cases with induced T deficiency, there was reduction of sensation of well being with slight changes in mood that accompanied reduction in libido too. The TRT corrected the depression in those studied cases. A non linear relationship was shown between depression and concentration of T [76-78]. The relationship between testosterone level and depression was nonlinear relationship [78]. The TRT has conflicting and inconsistent results as regards its effects on quality of life, physical activity and mood [79-81]. Some other studies recorded insignificant effects on mood when testosterone was given at physiological doses to eugonadal males with no depression [82, 83]. In hypogonadal men, TRT was associated with improved mood and sense of well-being, and also reduced fatigue and irritability. On the other side, supraphysiologic TRT in male subjects who were eugonadal was accompanied by mania in some cases. In contrast, other TRT researches denied any significant changes in mood between placebo groups and the groups that had received TRT [79, 84-91].

In agreement to the current work, there was improvement in cognitive functions in other researches. This improvement was mainly represented in the processing capacity, mathematical reasoning and spatial capabilities in middle aged and elderly men. This improvement was related mainly to both free and bioavailable testosterone but not the total one [92-96]. However, there were some other findings that recorded absence of association between some cognitive functions such as attention, memory and speed on one side and the concentration of androgens on the other side. The interaction between androgen concentration and other factors like the presence of systemic disorders and genotyping of apolipoprotein E4 might be responsible for this discrepancy in their results [97, 98-101]. The previous trials had found that TRT for short periods could correct partially some cognitive problems although it had no effects on cognitive functions in Alzheimer cases in spite of improving quality of life in them [92, 100-103].

In the current evaluation of sexual activity questionnaire (Massachusetts Male Aging Study Sexual Activity Questionnaire), 30% and 33% of men got improvement in getting erection and keeping it respectively, but lower percentages got improved sexual activity frequency, getting full hard erection and being awaken with erection (4%, 7% and 7% respectively). On comparing scores for the previously mentioned sexual parameters before and after TRT, there was significant increase in scoring for getting erection and keeping it (p= 0.003 and 0.001 respectively). As regards the items used for evaluating sexual satisfaction, 23% of cases had got improvement in satisfaction with frequency of activity, 41% had got satisfaction with sex life, 41% for both satisfaction with partner and partner satisfaction after TRT. On comparing the scores of the previously mentioned satisfaction parameters before and after TRT, highly significant increase was shown in all parameters (p values were; 0.006, 0.001, 0.002 and 0.002 respectively). Sexual satisfaction is a subjective evaluation of the degree to which partners are satisfied with the sexual life and it is related to sexual excitability, libido, orgasmic ability and ejaculate amount. Testosterone could affect orgasm through a central effect on higher centres and through peripheral anabolic effects and it may affect orgasm as a consequence to improved libido and ejaculatory volume. Low desire in both genders, arousal disorders in women, premature ejaculation and erectile dysfunction were the categories most strongly associated with sexual dissatisfaction. The history of

patients in the current study showed that the positive cases for nocturnal erection increased from 24 cases (44%) to 30 (56%) after TRT, but no effect on sexual desire, orgasm and successful vaginal penetration was shown. Only 2 cases out of 54 patients were suffering from low desire, unsuccessful penetration and inadequate orgasm before therapy. The currently used form and dose of testosterone could not be blamed for absence of better response as regards these 3 categories as the number of these cases is very low and a conclusion based on this very little number (two) could not be accepted except after doing further studies that should include greater number of cases suffering from these symptoms. In a study made by Schiavi [104], it was reported that exogenous TRT had increased significantly the frequency of masturbation, sexual activity and early morning erection in eugonadal men. It was suggested that nocturnal penile tumescence (NPT) might be androgen dependent, while erectile responses to audiovisual sexual stimulation is androgen independent. He did not observe any correlation between NPT and erectile problems in elderly suggesting that the erectile problems were largely non hormonal in origin. Also, he observed a significant association between the levels of bioavailable T and the duration of NPT in men aged 55-64 years [104].

A lot of authors recorded an obvious relationship between sexual activities and the levels of free and bioavailable testosterone. They studied their cases as regards orgasm, libido and erection. They found that there is an essential need for aged cases to raise their blood testosterone, but the presence of other diseases or administration of some medications related to that age could be responsible for the reduced libido and erectile disorders (ED) [105-109]. However, this kind of cases would get too much improvement if received adequate TRT that would correct the vascular problem in corpus cavernosum. The presence of a lot of benefits in these cases should not keep researches away from future work done for old males with normal testosterone levels suffering from ED. However, hypogonadal men with low sexual activities will get much improvement than others [110-115].

Some authors suggested a level for testosterone, above which, there will be no more improvement in sexual activity, while others had reported imprecise reports [9, 67,116].

Hydroalcoholic testosterone (1%) gel as one of the effective transdermal preparations had been proved to be a successful safe line of treatment in some research work done for cases with ED. Future research work on the effect of TRT on old ED cases that have normal T is needed in order to accurately evaluate possible fruitful benefits of TRT [111, 117,118]

4. Conclusion

Although the evidence from a lot of research work is not consistent in this hot evolving area, the suggested testosterone intervention is thought to be accompanied by many benefits at the level of physical and some important sexual functions as it improved most sexual satisfaction parameters and some sexual performance like getting and keeping erection. At the same time, it has no detectable risks on lipid profile, liver function tests or haematological parameters. No cases had developed polycythemia or cancer prostate which are the most debated conditions as regards this therapy. Also, there is evidence that many etiological factors in addition to Testosterone level are responsible for the occurrence of andropause.

Recommendations

- A placebo-controlled well designed study on TRT for more evaluation of other possible benefits and other potential risks is needed and it should be done on a larger scale for both cases with low and normal testosterone.
- The TRT alone can't replace required healthy lifestyle needed in aged people and it should be done for those with obvious annoying symptoms.
- Regular monitoring of the clinical response to TRT and potential side effects is recommended in long term but not short term therapies.
- Considering contraindications of TRT specially cases with prostatic carcinoma, benign prostatic hyperplasia or erythrocytosis before giving TRT.

Limitations

For generalization of this line of therapy, a greater number of cases should be included in future large scale and long term studies. No data on effects of TRT on osteoporosis and bone fracture rates and no detailed data on cardiovascular morbidity and mortality.

Conflict of Interests:

Authors have declared that no conflict of interest could exist.

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