American Journal of Men's Health
May-June 2020: 1–7

DOI: 10.1177/1557988320917258
journals.sagepub.com/home/jmh
SAGE

Effects of Testosterone Treatment on Quality of Life in Patients With Chronic Kidney Disease

Jeong Kyun Yeo[1], Ho Seok Koo[2], Jihyeong Yu[3], and Min Gu Park[1]

Abstract

Testosterone deficiency (TD) is common and impairs quality of life (QoL) in patients with chronic kidney disease (CKD). However, there are no studies about whether testosterone replacement therapy (TRT) can improve QoL in patients with CKD. Therefore, we investigated the effect of TRT on the QoL of patients with CKD and confirmed the safety of TRT. Twenty-five male patients with stages III–IV CKD whose serum testosterone levels were <350 ng/dl (TD) were enrolled and treated with testosterone gel for 3 months (group II). Age-matched controls with stages III–IV CKD and TD (group I) were recommended to exercise for the same period. Before and after the treatment, the BMI and handgrip strength were checked, serological tests were performed, and questionnaires were administered in both groups. Compared to baseline, there was no significant difference in serum testosterone levels, scores of the 36-Item Short Form Health Survey (SF-36), Aging Males' Symptoms Scale (AMS), and International Prostate Symptom Score (IPSS), and grip strength in group I after 3 months. In group II, a significant increase in testosterone, hemoglobin (Hb), and hematocrit (Hct) was observed, and grip strength significantly increased after TRT. Significant improvement in scores of SF-36, AMS, and IPSS was also confirmed after TRT in group II. There was a significant difference in testosterone, Hb, Hct, grip strength, and scores of SF-36, AMS, and IPSS between the two groups after 3 months. The patients in group II showed positive results and continued with TRT. Therefore, we conclude that TRT safely improves the QoL and TD symptoms in patients with moderate-to-severe CKD.

Keywords

Chronic kidney disease, testosterone, hypogonadism, quality of life, testosterone replacement therapy

Received November 4, 2019; revised February 27, 2020; accepted February 28, 2020

The prevalence of testosterone deficiency (TD) is reported to be 6%–9% in men in general, and it increases in men with diabetes or obesity (Hackett, 2019; Tostain, 2008). The prevalence further increases to as high as 44% in patients with severe renal function impairment, which corresponds to stage V chronic kidney disease (CKD; Carrero, 2011). According to a study conducted by the authors in 2013, TD prevalence among stage V CKD patients was up to 95% (Park et al., 2013), and patients undergoing hemodialysis presented with much more severe climacteric symptoms and lower serum testosterone levels (Park et al., 2013). The pathophysiological mechanism by which TD prevalence increases in CKD patients has not yet been clearly identified. However, it is speculated that TD may be induced by inadequate production and distribution of testosterone due to a dysfunctional hypothalamic–pituitary–gonadal axis, as CKD progresses (Dunkel et al., 1997; Schmidt et al., 2002).

Since TD prevalence is high in CKD patients in particular and symptom severity increases in accordance with the extent of renal dysfunction, as already mentioned, it is

[1]Department of Urology, Inje University, Seoul Paik Hospital, Seoul, Korea
[2]Department of Nephrology, Inje University, Seoul Paik Hospital, Seoul, Korea
[3]Department of Urology, Inje University, Sanggye Paik Hospital, Seoul, Korea

Corresponding Author:
Min Gu Park, Department of Urology, Inje University, Seoul Paik Hospital, Seoul 04551, Korea.
Email: uromgpark@gmail.com

highly likely that stages III–IV CKD patients show more severe climacteric symptoms than other TD patients in general (Park et al., 2013). Moreover, because CKD can be neither cured nor improved but typically worsens over the long term, TD symptoms, too, may gradually worsen and affect quality of life (QoL) in most CKD patients. However, few attempts have been made in the past to focus on and enhance the QoL of CKD patients. Some studies have reported that regular exercise could increase QoL and physical function of CKD patients (Aoike et al., 2018; Tang & Yang, 2017); however, an attempt to improve QoL through testosterone replacement therapy (TRT) has not been tried, other than in studies in which TRT was administered for the purpose of improving hypogonadal symptoms (Inoue, 2018) or sexual function (Canguven, 2010).

Accordingly, the present study was conducted to explore the effect of TRT on QoL and investigate the safety of the therapy in patients with impaired renal function, by administering hormone therapy using testosterone gel over a relatively short term of 3 months to stages III–IV CKD patients who were diagnosed with TD.

Material and Methods

Subjects

Twenty-five male patients with stages III–IV CKD whose serum total testosterone (TT) levels were lower than 350 ng/dl with more than 1 TD symptom were consecutively enrolled in this study. The cutoff level for TT was set according to the European Association of Urology (EAU) guidelines for TD (Dohle et al., 2018). Stage III–IV CKD was defined as Modification of Diet in Renal Disease (MDRD) Study glomerular filtration rate (GFR) of 15–59 ml/min/1.73 m^2. Then, age-matched 25 male CKD patients with same conditions (TD) were consecutively enrolled as controls (group I). Patients who met any of the following exclusion criteria were excluded from the study: having undergone TRT using testosterone in any form within the past 3–6 months, having been diagnosed with or treated for prostate cancer or breast cancer, a serum prostate-specific antigen (PSA) >3.0, hepatic dysfunction, thyroid dysfunction, a hematocrit (Hct) level of 50% or more, and severe sleep apnea. Patients received a full explanation of the content and purpose of the study before the trial and were enrolled after signing informed consent. Group I patients were recommended to exercise regularly and group II patients were treated with 2% testosterone gel at 60 mg/day for 3 months. Before and after treatment, body mass index (BMI), vital signs (blood pressure, heart rate, and body temperature), and hand grip strength were checked, and serological tests including hemoglobin (Hb), Hct, PSA, blood urea nitrogen (BUN), creatinine (Cr), GFR, glucose, total cholesterol, triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and TT were also carried out. Self-administered questionnaires such as the 36-Item Short Form Health Survey (SF-36), Aging Males' Symptoms Scale (AMS), International Prostate Symptom Score (IPSS), and Center for Epidemiologic Studies Depression Scale (CES-D) were also administered to the participants. SF-36, which has been widely used as the tool for estimating the QoL of CKD and hypogonadal patients (Katznelson, 2006; Lausevic et al., 2007; Santos, 2008), consisted of a total of 36 items across the following 8 sections: (a) Physical Functioning, (b) Physical Role, (c) Bodily Pain, (d) General Health, (e) Vitality, (f) Social Functioning, (g) Emotional Role, and (h) Mental Health. Two summary measures—physical and mental component summary scores—were computed based on the 36 items. Each of the summary scores was transformed into a linear scale ranging from 0 to 100 points, with higher scores indicating better QoL. For group II patients, a global assessment question (GAQ; "Do you want to continue testosterone treatment?") was additionally asked. Electrocardiogram (EKG) was recorded before and after the testosterone treatment and side effects related to testosterone treatment were investigated.

Ethics Statement

The present study protocol was reviewed and approved by the Institutional Review Board of Seoul Paik Hospital and it complied with the Declaration of Helsinki.

Statistical Analyses

To conduct statistical analysis to examine changes in the parameters in the pre and posttreatment period and to compare between groups, Kolmogorov–Smirnov test was first performed to test for normality in distributions. Continuous variables that were confirmed to follow a normal distribution were then subjected to paired *t* test, independent *t* test, or chi-square test to test for pre- and posttreatment changes and between-group differences. Statistical significance was determined if a *p* value was less than .05.

Results

Twenty-three patients in group I and 22 patients in group II completed the 3-month-long therapy. Three patients who dropped out from testosterone treatment were not related to the side effects of testosterone gel. The mean age of patients was 68.54 years (55–84) in group I and 69.72 (58–86) in group II. The continuous variables among the assessment items were confirmed to follow a

Table 1. Comparison Between the Parameters in the Two Groups at Baseline.

	Group I	Group II	*p* value
BMI	24.54 ± 8.25	25.10 ± 7.85	.830
Grip strength			
Right	31.95 ± 11.05	32.05 ± 9.79	.530
Left	30.82 ± 5.30	31.57 ± 6.80	.330
SF-36			
Physical component score	51.48 ± 21.56	52.48 ± 19.56	.860
Mental component score	52.09 ± 20.32	54.09 ± 24.23	.320
IPSS (total)	16.21 ± 5.21	14.89 + 8.39	.087
IPSS (QoL)	4.01 ± 1.85	3.61 ± 2.03	.108
AMS (psychological)	14.12 ± 8.42	12.72 ± 7.43	.160
AMS (somatic)	18.23 ± 6.11	17.72 ± 8.11	.320
AMS (sexual)	16.13 ± 5.26	18.28 ± 6.26	.095
AMS (total)	49.45 ± 13.50	48.72 ± 17.9	.532
CES-D	19.45 ± 10.10	18.56 ± 12.39	.165
Hb	12.5 ± 2.82	13.2 ± 1.82	.320
Hct	37.52 ± 8.12	38.37 ± 5.12	.380
Glucose	129.47 ± 23.01	119.47 ± 39.33	.315
Total cholesterol	180.34 ± 20.89	167.71 ± 30.95	.106
Triglyceride	230.32± 100.0	206.56 ± 98.21	.098
HDL	46.01 ± 14.33	43.22 ± 10.84	.085
LDL	99.05 ± 35.23	91.17 ± 23.38	.189
PSA	1.34 ± 0.95	1.10 ± 0.63	.221
Testosterone	239.20 + 70.68	243.30 ± 65.68	.105
GFR	42.85 ± 14.15	43.35 ± 13.09	.756
Kidney function grade			.695
2	0	0	
3	14	15	
4	6	5	

Note. AMS = Aging Males' Symptoms Scale; BMI = body mass index; CES-D = Center for Epidemiologic Studies Depression Scale; GFR = glomerular filtration rate; Hb = hemoglobin; Hct = hematocrit; HDL = high-density lipoprotein; IPSS = International Prostate Symptom Score; LDL = low-density lipoprotein; PSA = prostate-specific antigen; SF-36 = 36-Item Short Form Health Survey.

normal distribution. There was no significant difference between the two groups in age, comorbidities, BMI, and vital signs at baseline. There were also no significant differences in hand grip strength, scores of SF-36, IPSS, AMS, and CES-D, Hb, Hct, GFR, glucose, total cholesterol, TG, LDL, HDL, PSA, TT, and stage of kidney function between the two groups at baseline (Table 1). Compared to baseline, there was no significant difference in serum testosterone,Hb, Hct, GFR, glucose, total cholesterol, TG, LDL, HDL, and PSA levels, scores of SF-36, AMS, IPSS, and CES-D, and hand grip strength in group I after 3 months.

In group II, testosterone level statistically significantly increased posttreatment with TRT, and hand grip strength also increased on both sides. The SF-36 score, a measure that assessed QoL, improved statistically significantly in both physical and mental components. Urinary function, assessed with IPSS, improved significantly after the 3-month-long treatment as well. The results of AMS, an assessment of hypogonadal symptoms, showed that prior to the treatment, the patients manifested moderate (AMS scores of 37–49) or severe symptoms, whereas after the treatment, mental, physical, and sexual functions all significantly improved, with the mean AMS score indicating mild symptoms (scores of 27–36). As shown in the CES-D score, depression also statistically significantly improved. Hb was also statistically significantly elevated. Regarding lipid profile, TG statistically significantly decreased, while blood glucose, PSA, GFR, and the severity of CKD did not show a statistically significant difference (Table 2).

In comparison of the two groups at 3 months, there was a significant difference in grip strength and scores of SF-36, IPSS, AMS, and CES-D. There were also significant differences in Hb, Hct, TG, and TT. No significant difference in GFR and grade of kidney function was observed between the two groups at 3 months (Table 3). All patients in group II were satisfied and wanted to

Table 2. Changes in Group II After 3 Months of Testosterone Treatment.

	Baseline	3 months	*p* value
BMI	25.10 ± 7.85	24.60 ± 8.23	.185
Grip strength			
Right	32.05 ± 9.79	36.03 ± 6.44	.042
Left	31.57 ± 6.80	33.14± 6.83	.009
SF-36			
Physical component score	52.48 ± 19.56	67.12 ± 19.18	.000
Mental component score	54.09 ± 24.23	69.05 ± 24.61	.000
IPSS (total)	14.89 ± 8.39	9.39 ± 6.75	.009
IPSS (QoL)	3.61 ± 2.03	2.00 ± 1.41	.002
AMS (psycho)	12.72 ± 7.43	7.89 ± 4.13	.002
AMS (somato)	17.72 ± 8.11	12.94 ± 5.40	.005
AMS (sexual)	18.28 ± 6.26	12.56 ± 4.97	.001
AMS (total)	48.72 ± 17.9	33.11 ± 12.49	.000
CES-D	18.56 ± 12.39	13.28 ± 8.84	.005
Hb	13.2 ± 1.82	13.88 ± 1.80	.012
Hct	38.37 ± 5.12	40.87 ± 5.43	.004
Glucose	119.47 ± 39.33	145.00 ± 72.16	.079
Total cholesterol	167.71 ± 30.95	162.50 ± 32.85	.574
Triglyceride	206.56 ± 98.21	143.22 ± 73.96	.047
HDL	43.22 ± 10.84	42.67 ± 9.00	.829
LDL	91.17 ± 23.38	81.83 ± 36.49	.589
PSA	1.10 ± 0.63	1.08 ± 0.72	.833
Testosterone	243.30 ± 65.68	771.00 ± 405.29	.000
GFR	43.35 ± 13.09	45.15 ± 14.53	.084
Kidney function grade			.595
2	0	1	
3	15	14	
4	5	5	

Note. AMS = Aging Males' Symptoms Scale; BMI = body mass index; CES-D = Center for Epidemiologic Studies Depression Scale; GFR = glomerular filtration rate; Hb = hemoglobin; Hct = hematocrit; HDL = high-density lipoprotein; IPSS = International Prostate Symptom Score; LDL = low-density lipoprotein; PSA = prostate-specific antigen; SF-36 = 36-Item Short Form Health Survey.

continue TRT. Five patients of group II complained of rashes or itching sensation where the testosterone gel was applied; however, they were all resolved by changing the gel application site and short-term treatment with antihistamine drugs. There was also no significant change in EKG and other cardiovascular events during the treatment.

Discussion

As predicted, the study findings show that stages III–IV CKD patients in the climacteric period manifested moderate-to-severe hypogonadal symptoms and experienced low QoL, but after 3-month-long TRT, scores indicative of mental and physical QoL improved significantly, and the patients expressed high satisfaction with the treatment. Moreover, male hypogonadal symptoms improved in all areas, and the level of severity decreased from moderate or severe to mild.

It is very common for CKD patients showing imbalance between protein synthesis and degradation to present with sarcopenia accompanying skeletal muscle atrophy, and sarcopenia is reported to be strongly linked to morbidity and mortality in CKD patients (Kalantar-Zadeh et al., 2013; Watanabe, 2019). Accordingly, the current study finding of significant enhancement in grip strength due to testosterone treatment suggests that from the standpoint of sarcopenia, TRT may be a useful solution in moderate-to-severe CKD patients.

Elevated serum testosterone level is known to enhance vitality, overall patient condition, and libido in a relatively early point in treatment (Ng Tang Fui & Hoermann, 2017; Park et al., 2019). A similar pattern of TRT effects was also found in patients with moderate-to-severe CKD, and the effect of TRT was confirmed in QoL improvement as well. Since CKD patients have high risk for cardiovascular events, adverse events due to this treatment should be closely observed. However, no major complications were

Table 3. Comparison Between the Parameters in the Two Groups at 3 Months.

	Group I	Group II	*p* value
BMI	24.35 + 7.85	24.60 ± 8.23	.935
Grip strength			
Right	31.75 + 7.79	36.03 ± 6.44	.025
Left	30.95 + 5.80	33.14 ± 6.83	.003
SF-36			
Physical component score	50.33 ± 19.23	67.12 ± 19.18	.000
Mental component score	50.09 ± 20.58	69.05 ± 24.61	.000
IPSS (total)	15.89 ± 9.39	9.39 ± 6.75	.010
IPSS (QoL)	3.83 ± 2.54	2.00 ± 1.41	.002
AMS (psychological)	13.98 ± 6.43	7.89 ± 4.13	.005
AMS (somatic)	17.88 ± 9.11	12.94 ± 5.40	.003
AMS (sexual)	19.21 ± 8.26	12.56 ± 4.97	.000
AMS (total)	49.98 ± 18.90	33.11 ± 12.49	.000
CES-D	18.85 ±14.35	13.28 ± 8.84	.003
Hb	12.60 ± 2.52	13.88 ± 1.80	.002
Hct	37.92 ± 7.12	40.87 ± 5.43	.003
Glucose	125.47 ± 21.89	145.00 ± 72.16	.070
Total cholesterol	183.12 ± 22.00	162.50 ± 32.85	.078
Triglyceride	231.52 ± 98.45	143.22 ± 73.96	.035
HDL	44.01 ± 17.93	42.67 ± 9.00	.265
LDL	89.00 ± 38.63	81.83 ± 36.49	.175
PSA	1.28 ± 0.85	1.08 ± 0.72	.135
Testosterone	245.10 ± 50.42	771.00 ± 405.29	.000
GFR	42.53 ± 15.05	45.15 ± 14.53	.075
Kidney function grade			.653
2	2	1	
3	12	14	
4	6	5	

Note. AMS = Aging Males' Symptoms Scale; BMI = body mass index; CES-D = Center for Epidemiologic Studies Depression Scale; GFR = glomerular filtration rate; Hb = hemoglobin; Hct = hematocrit; HDL = high-density lipoprotein; IPSS = International Prostate Symptom Score; LDL = low-density lipoprotein; PSA = prostate-specific antigen; SF-36 = 36-Item Short Form Health Survey.

reported in a recently conducted pilot study in which patients undergoing hemodialysis were treated with testosterone enanthate intramuscular injection, which has higher testosterone treatment–related risk (Inoue, 2018). In the present study too, major complications such as worsening renal function and cardiovascular events did not occur following TRT. With respect to renal function, there was no change in serum Cr level, GFR, and grade of renal function. No patients in group II showed significant abnormal elevation of PSA and Hct levels after testosterone treatment. Some patients only complained of mild skin rashes and itching sensation; however, none dropped out from the study due to side effects of testosterone gel. In addition, treatment compliance and satisfaction were excellent, a finding that confirms that TRT can be used to improve QoL of CKD patients.

Increased quality of physical and mental life was found to have a positive effect not only on overall male hypogonadal symptoms but also on urinary function and mood. With regard to lower urinary tract symptoms (LUTS) in CKD patients, Chen et al. (Chen, 2019) proposed bladder urothelial dysfunction, chronic inflammation, and change in sensory protein in the bladder urothelium as the mechanisms of bladder instability in patients with CKD and end-stage renal disease (ESRD). Some recent studies have reported that testosterone treatment improved LUTS (Okada et al., 2018; Yucel et al., 2017). Although more research is necessary on LUTS in CKD patients with TD, the opinion stated in the current guidelines is that in general, testosterone treatment does not greatly affect LUTS induced by BPH (Bhasin et al., 2018; Morgentaler et al., 2019).

With respect to depression, a recent study by Agrawaal et al. (2019) reported that the prevalence of depression in stage V CKD patients undergoing hemodialysis was 78%, with helplessness (82%) being the most common symptom. The present study was conducted with stages III–IV CKD patients only. However, since it is well known that

depression and anxiety co-occur with TD in itself (Berglund et al., 2011), the likelihood for CKD patients with TD, like this study's subjects, to present with depression symptoms is sufficiently high. Significant improvement in CES-D score over a short treatment duration of 3 months suggests that testosterone treatment may be a useful therapy for CKD patients complaining of depression and anxiety.

It is a well-known fact that CKD patients and those undergoing hemodialysis in particular present with anemia due to erythropoietin deficiency (Palmer, 2017). Two mechanisms by which testosterone treatment corrects anemia have been proposed. One mechanism involves increased production of endogenous erythropoietin, and the other mechanism suggests that androgens may increase the sensitivity of erythroid progenitors to the effects of erythropoietin (Gaughan, 1997). In this study, Hb and Hct were significantly elevated in group II patients, who had TRT, in comparison to group I patients, who performed exercise only. This finding suggests that although, generally, increased Hct is an adverse effect of testosterone treatment that should be observed closely, in CKD patients, Hct may be elevated for the purpose of correcting anemia.

It is reported that it takes a minimum of 3 months to a maximum of 2 years for testosterone treatment to have a significant effect, depending on the hypogonadal symptoms or relevant parameters and that testosterone treatment has a positive impact on metabolic components as well (Lunenfeld et al., 2015). Ultimately, improvement in metabolic parameters will reduce the risk of cardiovascular disease and, hence, the mortality rate. In the present study, parameters that evaluate the components of metabolic syndrome, such as BMI, glucose, and lipid profile, were not significantly improved, with the exception of TG. Even glucose levels in the testosterone treatment group showed an insignificant increase at 3 months in some patients, with poorly controlled diabetes mellitus. It is speculated that a treatment duration of 3 months may not have been long enough for improving metabolic components. Indeed, in another study conducted by the current authors, in which TRT was administered to non-CKD patients for 3 months, BMI, blood glucose, and lipid profile did not significantly change either (Cho et al., 2017). Furthermore, in group I subjects who performed exercise, metabolic components did not show changes. However, in a study where supervised exercise and diet were performed for over 1 year, metabolic components were found to improve (Heufelder et al., 2009).

The present study was conducted as a pilot study and it has a few limitations such as the following: The target population was small, TRT was administered for a short time, and the observation period after TRT was short. Additionally, muscle mass was not measured to assess the extent of sarcopenia, aside from using grip strength. Uroflowmetry, which is an objective assessment of LUTS, and prostate volume measurement (which is closely linked to LUTS) were not performed. However, the present study provided evidence that TRT can effectively enhance QoL in moderate-to-severe CKD patients without notable safety problems. In the future, research should be conducted to investigate the effect of TRT in stage V CKD and patients undergoing hemodialysis.

Conclusions

Testosterone treatment safely improves QoL as well as TD symptoms in patients with moderate-to-severe CKD and it is also expected to have a good effect on the improvement of anemia, which is also a common condition in CKD. More studies will be needed in the future to elucidate the mechanisms that underlie this beneficial effect of testosterone.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Min Gu Park https://orcid.org/0000-0001-5704-5320

References

Agrawaal, K. K., Chhetri, P. K., Singh, P. M., Manandhar, D. N., Poudel, P., & Chhetri, A. (2019). Prevalence of depression in patients with chronic kidney disease stage 5 on. *Journal of the Nepal Medical Association*, *57*(217), 172–175.

Aoike, D. T., Baria, F., Kamimura, M. A., Ammirati, A., & Cuppari, L. (2018). Home-based versus center-based aerobic exercise on cardiopulmonary performance, physical function, quality of life and quality of sleep of overweight patients with chronic kidney disease. *Clinical and Experimental Nephrology*, *22*(1), 87–98. doi:10.1007/s10157-017-1429-2

Berglund, L. H., Prytz, H. S., Perski, A., & Svartberg, J. (2011). Testosterone levels and psychological health status in men from a general. *Aging Male*, *14*(1), 37–41. doi:10.3109/13685538.2010.522276

Bhasin, S., Brito, J. P., Cunningham, G. R., Hayes, F. J., Hodis, H. N., Matsumoto, A. M., Snyder, P. J., Swerdloff, R. S., Wu, F. C., & Yialamas, M. A. (2018). Testosterone therapy in men with Hypogonadism: An endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology and Metabolism*, *103*(5), 1715–1744. doi:10.1210/jc.2018-00229

Canguven, O. (2010). Efficacy of testosterone gel in the treatment of erectile dysfunction in hypogonadal hemodialysis patients: A pilot study. *International Journal of Impotence Research*, *22*(2), 140–145. doi:10.1038/ijir.2009.55

Carrero, J. J. (2011). Prevalence and clinical implications of testosterone deficiency in men with end-stage renal disease. *Nephrology, Dialysis, Transplantation: Official Publication of the European Dialysis and Transplant Association - European Renal Association*, *26*(1), 184–190. doi:10.1093/ndt/gfq397

Chen, S. F. (2019). Changes in sensory proteins in the bladder urothelium of patients with chronic kidney disease and end-stage renal disease. *Lower Urinary Tract Symptoms*, *11*(2), O202–O208. doi:10.1111/luts.12240

Cho, D. Y., Yeo, J. K., Cho, S. I., Jung, J. E., Yang, S. J., Kong, D. H., Ha, J. K., Kim, J. G., & Park, M. G. (2017). Exercise improves the effects of testosterone replacement therapy and the durability of response after cessation of treatment: A pilot randomized controlled trial. *Asian Journal of Andrology*, *19*(5), 602–607. doi:10.4103/1008-682x.184269

Dohle, G., Arver, S., Bettocchi, C., Jones, T., & Kliesch, S. (2018). EAU guidelines on male hypogonadism. http://uroweb.org/guideline/male-hypogonadism/

Dunkel, L., Raivio, T., Laine, J., & Holmberg, C. (1997). Circulating luteinizing hormone receptor inhibitor(s) in boys with chronic renal. *Kidney International*, *51*(3), 777–784. doi:10.1038/ki.1997.109

Gaughan, W. J. (1997). A 6-month study of low-dose recombinant human erythropoietin alone and in combination with androgens for the treatment of anemia in chronic hemodialysis patients. *American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation*, *30*(4), 495–500.

Hackett, G. (2019). Type 2 diabetes and testosterone therapy. *World J Men's Health*, *37*(1), 31–44. doi:10.5534/wjmh.180027

Heufelder, A. E., Saad, F., Bunck, M. C., & Gooren, L. (2009). Fifty-two-week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. *Journal of Andrology*, *30*(6), 726–733. doi:10.2164/jandrol.108.007005

Inoue, Y. (2018). Efficacy of testosterone treatment in hemodialysis patients as assessed by aging males' symptoms scores: A pilot study. *American Journal of Men's Health*, *12*(5), 1541–1547. doi:10.1177/1557988318772734

Kalantar-Zadeh, K., Rhee, C., Sim, J. J., Stenvinkel, P., Anker, S. D., & Kovesdy, C. P. (2013). Why cachexia kills: Examining the causality of poor outcomes in wasting. *Journal of Cachexia, Sarcopenia and Muscle*, *4*(2), 89–94. doi:10.1007/s13539-013-0111-0

Katznelson, L. (2006). Effects of modest testosterone supplementation and exercise for 12 weeks on body composition and quality of life in elderly men. *European Journal of Endocrinology / European Federation of Endocrine Societies*, *155*(6), 867–875.

Lausevic, M., Nesic, V., Stojanovic, M., & Stefanovic, V. (2007). Health-related quality of life in patients on peritoneal dialysis in Serbia: Influence of comorbidity, age, and income. *Artificial Organs*, *31*(12), 901–910. doi:10.1111/j.1525-1594.2007.00483.x

Lunenfeld, B., Mskhalaya, G., Zitzmann, M., Arver, S., Kalinchenko, S., Tishova, Y., & Morgentaler, A. (2015). Recommendations on the diagnosis, treatment and monitoring of hypogonadism in men. *Aging Male*, *18*(1), 5–15. doi:10.3109/13685538.2015.1004049

Morgentaler, A, Traish, A., Hackett, G., Jones, T. H., & Ramasamy, R. (2019). Diagnosis and treatment of testosterone deficiency: Updated recommendations from the Lisbon 2018 international consultation for sexual medicine. *Sexual Medicine Reviews*, *7*(4), 636–649. doi:10.1016/j.sxmr.2019.06.003

Ng Tang Fui, M., & Hoermann, R. (2017). The effects of testosterone on body composition in obese men are not sustained after cessation of testosterone treatment. *Clinical Endocrinology*, *87*(4), 336–343. doi:10.1111/cen.13385

Okada, K., Miyake, H., Ishida, T., Sumii, K., Enatsu, N., Chiba, K., Matsushita, K., & Fujisawa, M. (2018). Improved lower urinary tract symptoms associated with testosterone replacement. *American Journal of Men's Health*, *12*(5), 1403–1408. doi:10.1177/1557988316652843

Palmer, B. F. (2017). Gonadal dysfunction in chronic kidney disease. *Reviews in Endocrine & Metabolic Disorders*, *18*(1), 117–130. doi:10.1007/s11154-016-9385-9

Park, M. G., Koo, H. S., & Lee, B. (2013). Characteristics of testosterone deficiency syndrome in men with chronic kidney disease and male renal transplant recipients: A cross-sectional study. *Transplantation Proceedings*, *45*(8), 2970–2974. doi:10.1016/j.transproceed.2013.08.087

Park, M. G., Yeo, J. K., Park, S. G., Na, W., & Moon, D. G. (2019). Predictive factors of efficacy maintenance after testosterone treatment cessation. *Journal of Clinical Medicine*, *8*(2), pii: E151. doi:10.3390/jcm8020151

Santos, P. R. (2008). Clinical and laboratory variables associated with quality of life in Brazilian. *Revista médica de Chile*, *136*(10), 1264–1271. doi:/s0034-98872008001000005

Schmidt, A., Luger, A., & Horl, W. H. (2002). Sexual hormone abnormalities in male patients with renal failure. *Nephrology, Dialysis, Transplantation : Official Publication of the European Dialysis and Transplant Association - European Renal Association*, *17*(3), 368–371. doi:10.1093/ndt/17.3.368

Tang, Q., & Yang, B. (2017). Effects of individualized exercise program on physical function, psychological dimensions, and health-related quality of life in patients with chronic kidney disease: A randomized controlled trial in China. *International Journal of Nursing Practice*, *23*(2), e12519. doi:10.1111/ijn.12519

Tostain, J. L. (2008). Testosterone deficiency: A common, unrecognized syndrome. *Nature Clinical Practice Urology*, *5*(7), 388–396. doi:10.1038/ncpuro1167

Watanabe, H. (2019). Sarcopenia in chronic kidney disease: Factors, mechanisms, and therapeutic interventions. *Biological & Pharmaceutical Bulletin*, *42*(9), 1437–1445. doi:10.1248/bpb.b19-00513

Yucel, C., Keskin, M. Z., & Peskircioglu, C. L. (2017). The effect of transdermal testosterone administration on lower urinary tract symptoms and erectile dysfunction: A prospective, randomized, placebo-controlled trial. *Current Urology*, *11*(1), 4–8. doi:10.1159/000447187