Medical Laboratory Technology Journal
8 (2), 2022, 120-125
Received 2022-15-08; Revised 2022-08-09; Accepted 2022-30-09
Available online at : http://ejurnal-analiskesehatan.web.id

Effect of Diabetes Mellitus on Hypogonadism in Chronic Renal Failure

***Savas Karatas[1], Sennur Kose[2]**

[1]Endocrinology and Metabolism Department, Istanbul Research and Education Hospital,Turkey. [2]Nephrology Department, Istanbul Research And Education Hospital, Turkey. *Email: drsavaskaratas@yahoo.com
DOI: 10.31964/mltj.v8i1.467

Abstract: Hypogonadism in male patients with chronic renal failure and diabetes mellitus has been known separately; up to now, the effect of these two diseases together on testosterone deficiency and the impact of testosterone deficiency on metabolic values have not been known precisely, therefore in this study we aimed to investigate testosterone deficiency in patients with diabetes mellitus and chronic renal failure. Eighty-seven chronic renal failure patients and 45 control patients who were followed at endocrinology and nephrology clinics were included in the study. After exclusion criteria, the patients were divided into two groups according to diabetes mellitus status. Groups were compared according to testosterone levels. Testosterone deficiency and good groups were compared to blood glucose, Hba1c, and lipid profile levels. The mean age of 87 CRF patients and 45 people in the control group were similar (59.85 ± 9.99 and 56.67 ± 8.56, respectively, p= 0.16). Testosterone deficiency was 24.1% (21/87) in CRF group and 8.8% (4/45) in control group (p= 0.04). The total testosterone levels were notably lower in the diabetic-CRF patients, 3.44 ± 1.3 vs. 4.26 ± 1.46 mg/dl (p= 0.02). The testosterone deficient CRF group had higher blood glucose and HbA1c according to the testosterone sufficient group. (161.20 ± 61.24 mg/dl vs 133.25 ± 59.87 mg/dl blood glucose, p= 0.04 and 7.54 ± 1.46 vs 6.79 ± 1.14 % HbA1c, p= 0.04). Serum triglyceride and LDL levels did not significantly change between groups (p= 0.20 and 0.76, respectively). Testosterone deficiency in male CRF patients is not uncommon. Male patients with both T2DM and CRF have more common testosterone deficiency. In testosterone-sufficient patients, blood glucose regulation was better. Therefore, in these patients, it may be helpful not to neglect testosterone deficiency, which affects gonadal function, body metabolism, and cardiac and skeletal health.
Keywords: Diabetes; renal failure; testosterone

INTRODUCTION

Chronic renal failure (CRF), a progressive decline in kidney function, poses difficulties with its typical symptoms. However, it can also cause many hormonal imbalances, including dysfunction of the gonads, which can affect multiple systems in the body. Hypogonadism can affect 22-66% of patients with chronic kidney disease (Neuzillet et al., 2016). This phenomenon may be subtle and discreet in these patients.; However, its pathophysiology is complex, and its consequences are varied (Iglesias et al., 2012).

Diabetes mellitus, an ever-growing worldwide pandemic, can be an accompanying or causative part of chronic kidney failure. Hypogonadism complications can accompany diabetes due to insulin resistance and other unexplained mechanisms. Hypogonadism in these patients can lead to cardiovascular

Corresponding Author: Savas Karatas
Endocrinology Department..Istanbul Research and Education Hospital, Cerrahpaşa, Org. Abdurrahman Nafiz Gürman Cd. No:24, 34098 Fatih/İstanbul Turkey
Email: drsavaskaratas@yahoo.com

and musculoskeletal problems and even affect the composition of the body's adipose tissue (Dandona and Dhindsa, 2011). Previous studies have found increased hypogonadism in diabetes mellitus and CRF (Barrett-Connor et al., 1990; Oueslati et al., 2020), however, these studies did not investigate the effect of diabetes mellitus on hypogonadism in patients with CRF. Therefore we aimed to explore hypogonadism and its effect on CRF patients according to diabetes mellitus coexistence.

MATERIALS AND METHODS

The study included 87 patients referred to the Departments of Endocrinology and Metabolism of Nephrology of the Istanbul Research and Education Hospital between December 2021 and May 2022. Inclusion criteria were at least six months of chronic renal failure diagnosis, ages 18 to 70, and patients with thyroid disease, pituitary insufficiency, hyperprolactinemia, and liver failure were excluded from the study. Forty-five healthy controls who met the above inclusion criteria participated in the study.

A biochemical evaluation was performed in the morning after a 12-hour fast. It included the following parameters: blood sugar, HbA1c, urea, creatinine, total cholesterol, triglycerides, HDLc LDL cholesterol, total testosterone, prolactin, follicle-stimulating hormone (FSH), and luteinizing hormone (LH). FSH, LH, and total testosterone were calculated using the enzyme immunoassay method (Roche Cobas). Hypotestosteronemia is defined as low testosterone levels (<300 ng/dL) (Bhasin et al., 2010). Creatinine clearance was calculated using the Modification of Diet in Renal Disease (MDRD) study equation (MDRD) formula. The stages of chronic renal failure were determined according to the definitions of the National Kidney Foundation.

Data analysis was performed using SPSS 22.0 software. Where appropriate, the Chi-square test or Fisher's exact test was used for categorical variables to compare two groups. The student's t-test was used to compare normality distributed continuous variables of two groups. The Mann-Whitney U-test was used to compare continuous variables that were not generally distributed between two groups. The significance level was <0.05. Ethical approval was taken from the Istanbul Research and Education Hospital (2022/1987). The Helsinki guidelines were followed.

RESULTS AND DISCUSSION

The mean ages of 87 CRF patients and 47 control subjects were similar (59.85 ± 9.99 and 56.67 ± 8.56, respectively, p= 0.16). Testosterone, FSH, LH, and prolactin levels were similar in both groups. Testosterone levels were also lower in the CRF group; the difference between the CRF group and the control group was not significant (35.42 ± 1.31 in the CRF group vs. 41.02 ± 1.29 in the control group, p = 0.22) (Table 1) Testosterone deficiency was 24.1% (21/87) in the CRF group and 8.8% (4/45) in the control group (p= 0.04).

Although blood glucose levels were higher in the CRF group, we tried to look for a difference between diabetic CRF and non-diabetic CRF patients. Of the 76 patients with CRF, 46 had type 2 diabetes, and 30 had no diabetes. The properties of these two groups are presented in Table 2. Plasma glucose levels were higher in the CRF group (143.79 ± 59.16) than in the control group (94.93 ± 5.16), and the difference between the two groups was statistically significant (p<0.001). Total testosterone levels were significantly lower in people with diabetes with CRF (p= 0.02).

The effects of testosterone deficiency are presented in Table 3. 21 CRF patients were testosterone-deficient. Blood glucose and HbA1c levels were significantly higher

in the testosterone-deficient CRF group (p= 0.04 for both). This indicates that testosterone deficiency is more pronounced in CRF patients with diabetes.

Table 1. Study Population Properties

	CRF (n= 87)	Control (n= 45)	p-value
Age (years)	59.85±9.99	56.67±8.56	0.16
Creatinin (mg/dl)	1.86±1.15	0.63±0.23	**<0.01***
GFR (ml/min)	50.21±20.16	103.47±9.40	**<0.01***
Glucose (mg/dl)	143.79±59.16	94.93±5.16	**<0.01***
FSH (mıU/ml)	9.67±8.11	7.55±3.21	0.56
LH (mıu/ml)	9.98±1.01	4.46±0.42	0.14
Testesterone (ng/dl)	35.42±1.31	41.02±1.29	0.22
Prolactine (µg/l)	20.4±34.71	5.6±4.72	0.46

***p<0.05 (significant), the p-value has a significant effect with marks, t-test.**

Table 2: Characteristics Of CRF Groups

	CRF-T2DM(+) (n= 46)	CRF- T2DM (-) (n= 30)	P-value
Age (years)	57.4±11.1	61.3±8.4	0.10
Weight (kg)	88.5±11.5	80.3±12.588	0.11
Creatinine (mg/dl)	1.80±0.98	2.12±1.36	0.10
GFR (ml/min)	47.03±23.01	52.26±18.05	0.26
Glucose (mg/dl)	171.5±60.2	91.9±8.8	**<0.01***
LDL (mg/dl)	116.3±121.5	123.51±50.45	0.53
Triglyceride (mg/dl)	168.33±171.65	218.80±138.03	0.11
FSH (mıU/ml)	9.81±10.9	9.24±5.1	0.26
LH ((mıU/ml)	10.19±2.25	9.51±9.86	0.70
Testosterone (ng/dl)	3.44±1.30	4.26±1.46	**0.02***

***p-value has a significant effect with marks, t-test**

Table 3: Effects Of Testosterone Deficiency

	Testosterone Def CRF (n= 21)	Testosterone Suf CRF (n= 66)	p-value
Age (years)	59.73±10.29	58.82±9.79	0.71
Glucose (mg/dl)	161.20±61.24	133.25±59.87	**0.04***
HbA1c (%)	7.54±1.46	6.79±1.14	**0.04***
LDL (mg/dl)	127.11±32.14	121.12±52.21	0.76
Triglyceride (mg/dl)	229.09±139.96	186.65±121.02	0.20
25 (OH) D (mg/dl)	19.85±9.24	22.89±20.15	0.46

***p<0.05 (significant, Student's t-test)**

The current study showed that testosterone deficiency is common in CRF patients and more common in patients with T2DM and CRF, and in deficient patients, mean glucose and HbA1c levels were higher.

It has been known that diabetes mellitus and CRF are chronic diseases that can facilitate hypogonadism in men. Barrett-Connor et al. found that 21% of men with T2DM had lower serum testosterone below 3.5 ng/ml, whereas 13% had lower testosterone in healthy subjects. (Barrett-Connor et al., 1990). According to a meta-analysis, diabetes patients have lower testosterone, and this significant relationship remained constant even when adjusted with BMI and age. (Ding et al., 2006) There

are several mechanisms proposed for testosterone deficiency in T2DM. First is a resistance to leptin in obese patients, which has been shown to promote testosterone stimulation in rat Leydig cells. (Caprio et al., 1999), Moreover, it has been demonstrated that increased insülin resistance slowed testosterone secretion in Leydig cells (Pitteloud et al., 2005), Furthermore, central insülin resistance in brain cells, which can impair testosterone and LH concentrations, was proposed as another mechanism (Brüning et al., 2000).

CRF itself is associated with hypogonadism (Oueslati et al., 2020). This was attributed to the suppressed gonadal axis in these patients (Handelsman, 1985). Uremia facilitated oxidative stress (Vaziri, 2004), malnutrition, and multiple deficiencies (Cavalli et al., 2010) could be the other reasons. Moreover, both T2DM and CRF accompanying atherosclerosis and hypertension can cause urologic problems (Isidori & Lenzi, 2005). CRF is associated with increased prolactin levels; in our study, we found non-significant prolactin elevation in CRF patients, but it was in a stage that could not be clinically taken into account (Vilar et al., 2019). Additionally, it has been shown that low serum testosterone level is detrimental to kidney function (van der Burgh et al., 2022).

These factors explained here could be related to the current study's findings, which found higher glucose and HbA1c in testosterone deficient patients (Table 3). Diabetes and CRF differently have been related to hypogonadism, and this cooccurrence increases the frequency of testosterone deficiency, according to our study (Table 2).

Testosterone deficiency in CRF patients could impose additional health damage. Testosterone deficiency causes more profound anemia because testosterone itself promotes erythropoiesis (Ballal et al., 1991). Testosterone promotes muscle anabolism and protein synthesis; without testosterone, sarcopenia can develop, and the neuromuscular and cardiovascular systems could harm significantly (Handelsman & Liu, 1998). Considerable evidence suggests that androgen deficiency was associated with all cardiovascular mortality (Khaw et al., 2007). Furthermore, these were supported by several studies focused on the cardiovascular benefits of testosterone, one of which stimulates nitric oxide synthesis or endothelial progenitor cells (Hotta et al., 2019; Gaba et al., 2018).

The limitations of this study are its cross-sectional design; however, a detailed analysis of all the patients was done meticulously.Therefore current study highlighted a critical and non-dismissable topic in CRF. A particular focus should be given to T2DM patients with CRF. Further studies should investigate the mechanism deeply behind these associations.

CONCLUSION

Testosterone deficiency in male CRF patients is not rare; male patients with T2DM and CRF have more common testosterone deficiency. Since this hormone plays an essential role not only in sexual health but also in cardiac, muscle, and other vital systems, it is necessary not to disregard this hormone in the follow-up of CRF, especially in patients with diabetes.

ACKNOWLEDGEMENT

Thanks to all contributors to this research to be done.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest regarding this study.

REFERENCES

Ballal, S. H., Domoto, D. T., Polack, D. C., Marciulonis, P., & Martin, K. J. (1991). Androgens potentiate the effects of erythropoietin in the treatment of anemia of end-stage renal disease. *American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation, 17*(1), 29–33. https://doi.org/10.1016/s0272-6386(12)80246-0

Barrett-Connor, E., Khaw, K. T., & Yen, S. S. (1990). Endogenous sex hormone levels in older adult men with diabetes mellitus. *American Journal of Epidemiology, 132*(5), 895–901. https://doi.org/10.1093/oxfordjournals.aje.a115732

Bhasin, S., Cunningham, G. R., Hayes, F. J., Matsumoto, A. M., Snyder, P. J., Swerdloff, R. S., Montori, V. M., & Task Force, Endocrine Society. (2010). Testosterone therapy in men with androgen deficiency syndromes: An Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology and Metabolism, 95*(6), 2536–2559. https://doi.org/10.1210/jc.2009-2354

Brüning, J. C., Gautam, D., Burks, D. J., Gillette, J., Schubert, M., Orban, P. C., Klein, R., Krone, W., Müller-Wieland, D., & Kahn, C. R. (2000). Role of the brain insulin receptor in control of body weight and reproduction. *Science (New York, N.Y.), 289*(5487), 2122–2125. https://doi.org/10.1126/science.289.5487.2122

Caprio, M., Isidori, A. M., Carta, A. R., Moretti, C., Dufau, M. L., & Fabbri, A. (1999). Expression of functional leptin receptors in rodent Leydig cells. *Endocrinology, 140*(11), 4939–4947. https://doi.org/10.1210/endo.140.11.7088

Cavalli, A., Del Vecchio, L., & Locatelli, F. (2010). Geriatric nephrology. *Journal of Nephrology, 23* Suppl 15, S11-15.

Dandona, P., & Dhindsa, S. (2011). Update: Hypogonadotropic hypogonadism in type 2 diabetes and obesity. *The Journal of Clinical Endocrinology and Metabolism, 96*(9), 2643–2651. https://doi.org/10.1210/jc.2010-2724

Ding, E. L., Song, Y., Malik, V. S., & Liu, S. (2006). Sex differences of endogenous sex hormones and risk of type 2 diabetes: A systematic review and meta-analysis. *JAMA, 295*(11), 1288–1299. https://doi.org/10.1001/jama.295.11.1288

Gaba, A., Mairhofer, M., Zhegu, Z., Leditznig, N., Szabo, L., Tschugguel, W., Schneeberger, C., & Yotova, I. (2018). Testosterone-induced downregulation of migration and proliferation in human Umbilical Vein Endothelial Cells by Androgen Receptor dependent and independent mechanisms. *Molecular and Cellular Endocrinology, 476*, 173–184. https://doi.org/10.1016/j.mce.2018.05.007

Handelsman, D. J. (1985). Hypothalamic-pituitary gonadal dysfunction in renal failure, dialysis, and renal transplantation. *Endocrine Reviews, 6*(2), 151–182. https://doi.org/10.1210/edrv-6-2-151

Handelsman, D. J., & Liu, P. Y. (1998). Androgen therapy in chronic renal failure. *Bailliere's Clinical Endocrinology and Metabolism, 12*(3), 485–500. https://doi.org/10.1016/s0950-351x(98)80248-6

Hotta, Y., Kataoka, T., & Kimura, K. (2019). Testosterone Deficiency and Endothelial Dysfunction: Nitric Oxide, Asymmetric Dimethylarginine, and Endothelial Progenitor Cells. *Sexual Medicine Reviews, 7*(4), 661–668. https://doi.org/10.1016/j.sxmr.2019.02.005

Iglesias, P., Carrero, J. J., & Díez, J. J. (2012). Gonadal dysfunction in men with chronic kidney disease: Clinical features, prognostic implications, and therapeutic options. *Journal of Nephrology, 25*(1), 31–42. https://doi.org/10.5301/JN.2011.8481

Isidori, A. M., & Lenzi, A. (2005). Risk factors for androgen decline in older males: Lifestyle, chronic diseases, and drugs. *Journal of Endocrinological Investigation, 28*(3 Suppl), 14–22.

Khaw, K.-T., Dowsett, M., Folkerd, E., Bingham, S., Wareham, N., Luben, R., Welch, A., & Day, N. (2007). Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. *Circulation, 116*(23), 2694–2701. https://doi.org/10.1161/CIRCULATIONAHA.107.719005

Neuzillet, Y., Thuret, R., Kleinclauss, F., & Timsit, M.-O. (2016). [Andrologic consequences of chronic renal failure: State of the art for the yearly scientific report of the French National Association of Urology]. Progres En Urologie: *Journal De l'Association Francaise D'urologie Et De La Societe Francaise D'urologie, 26*(15), 1088–1093. https://doi.org/10.1016/j.purol.2016.08.013

Oueslati, I., Ounissi, M., Talbi, E., Azaiez, S., Bacha, M. M., & Ben Abdallah, T. (2020). Prevalence and risk factors of hypogonadism in men with chronic renal failure. *La Tunisie Medicale, 98*(2), 138–143.

Pitteloud, N., Hardin, M., Dwyer, A. A., Valassi, E., Yialamas, M., Elahi, D., & Hayes, F. J. (2005). Increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men. *The Journal of Clinical Endocrinology and Metabolism, 90*(5), 2636–2641. https://doi.org/10.1210/jc.2004-2190

van der Burgh AC, Khan SR, Neggers SJCMM, Hoorn EJ, Chaker L. (2022). The role of serum testosterone and dehydroepiandrosterone sulfate in kidney function and clinical outcomes in chronic kidney disease: a systematic review and meta-analysis. *Endocr Connect*, *11*(6): e220061. Published 2022 Jun 23. doi:10.1530/EC-22-0061

Vaziri, N. D. (2004). Oxidative stress in uremia: Nature, mechanisms, and potential consequences. *Seminars in Nephrology, 24*(5), 469–473. https://doi.org/10.1016/j.semnephrol.2004.06.026

Vilar, L., Vilar, C. F., Lyra, R., & Freitas, M. da C. (2019). Pitfalls in the Diagnostic Evaluation of Hyperprolactinemia. *Neuroendocrinology, 109*(1), 7–19. https://doi.org/10.1159/000499694