Is erectile dysfunction an early clinical symptom of chronic kidney disease?

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ABSTRACT
Objectives: Erectile dysfunction (ED) is the persistent inability to attain and/or maintain erection sufficient for satisfactory sexual performance. Chronic kidney disease (CKD) is a problem with increasing incidence every day which disrupts quality of life significantly. We aimed to research whether ED is a warning symptom for the early stages of CKD or not.

Materials and methods: The records of 639 patients attending Ordu University due to ED were retrospectively investigated. According to International Index of Erectile Function (IIEF) scores and degree of ED, patients were compared in terms of GFR values.

Results: In 92.8% of patients, serum creatinine values were within normal limits (<1 mg/dL), while 30.5% of patients were observed to have GFR below 80. While stage 2 CKD was identified in 1% of the control group, this rate was calculated as 8% in the group with severe ED. In stage 1 and stage 2 CKD, IIEF scores were identified to be low by clear degree.

Conclusions: Results confirm that it was identified that the incidence of stage 1 and stage 2 CKD was higher among patients attending with ED compared to the control group. Just as ED may be an early clinical marker of coronary artery disease, it may be early warning symptom for CKD.

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Objectives
Erectile dysfunction (ED) disrupts quality of life in males to a severe degree, and as such, is an important pathology requiring treatment [1–3]. Studies generally mention mean incidence of 25–30 new cases per 1000 people, and it is expected that by 2025 it will be observed in an estimated 322 million people in the world in general [4]. When the causes of ED are examined, there are a broad spectrum of significant causes from factors like sedentary lifestyle and diet to metabolic and hormonal factors [5]. Endothelial dysfunction and vasculopathy are encountered as the most important hypotheses [6]. Additionally, as in uremic patients, vascular pathologies in addition to falls in libido developing due to hormonal changes and variations like reduced incidence of sexual union appear to be important factors. Especially renal functions have recently been associated with hormonal and erectile problems. ED has also become an important problem in uremic patients with low renal functions. Hormonal and erectile findings overlap with kidney functions such as cardiovascular system [7]. As a result, ED may be observed in the early period of some systemic diseases and if it can be considered an early-warning symptom, it may provide an advantage for diagnosis of these diseases in the early stage.

Chronic kidney disease (CKD) is a cause of significant mortality and morbidity and is a problem involving serious load on health budgets due to the increasing numbers of patients with each passing day [8]. In spite of the onset of the CKD process, our most commonly used marker for screening purposes of serum creatinine level may not give warning in the early stages due to the high tolerability of kidneys. Additionally, even when the creatinine levels begin to rise, generally patients are not observed to have the pronounced classic symptoms linked to uremia before kidney function reaches 20–30% levels in kidney function studies [9]. If diagnosis can be made in the early period, disease progression can be stopped to a significant degree with simple precautions. As a result, there is a need for clinical markers in order to...
diagnose CKD patients in the early period and prevent progression to advanced stage disease.

The aim of this study is to investigate whether ED is a possible clinical marker for early period CKD or not. Patients attending with ED are assessed in terms of CKD in order to evaluate whether ED is a warning symptom, with the aim of preventing or slowing the progression to end-stage renal failure in these patients.

Materials and methods

Data from 639 patients who attended Ordu University Faculty of Medicine Urology clinic from July 2015 to May 2019 with ED complaint and accessible records were retrospectively assessed. The serum creatinine values and International Index of Erectile Function (IIEF) 15 form used for routine assessment of patients were recorded. Patient survey forms and records were applied and recorded by a single doctor in our clinic. This study received permission from the relevant local ethics committee. According to total responses to items 1–5 and 15 on the IIEF-15 survey, ED was grouped as normal for points from 26 to 30, mild for 22 to 25 points, mild–moderate for 17 to 21 points, moderate for 11 to 16 points and severe for 0 to 10 points. The glomerular filtration rate (GFR) is currently considered the best overall index of renal function. GFR was calculated by using the Cockcroft–Gault equation. In this equation, the age, body weight, and serum creatinine level of the harvest are used to calculate the GFR. Validation studies have shown that the Cockcroft–Gault formula is equivalent or superior to various other measurements of GFR (e.g. clearances of insulin, iothalamate, Cr51-ethylendiaminetetraacetic acid, diethylenetriaminepentaacetic acid, Mag3, iohexol) [10]. According to GFR values, patients with CKD were classified according to CKD stage as defined in the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines. The correlation between the calculated GFR values and IIEF scores was analyzed. Due to the use of patients in the early stage, patients with stage 3 and stage 4 CKD according to GFR values were not included in statistical assessments. Patients with diabetes mellitus and endocrine problems that may cause ED, with heart failure or other cardiac pathologies, with neurological problems and with poor general status were not included in the study.

Statistics

Statistical analysis used the SPSS 22 (IBM Co., Armonk, NY) program. The analyses were performed using the Kolmogorov–Smirnov test, analysis of variance, and Student’s t-test, chi-square test, one-way ANOVA, and one-way ANCOVA test. Categorical data were studied with the Pearson correlation analysis, whereas discrete data were evaluated with the Spearman correlation analysis. In all statistical analyses, a p value less than .05 was accepted as statistically significant.

Results

The study used data from a total of 639 patients attending the urology clinic with ED complaint. Analysis identified 86 patients without ED and this patient group was used as a control group.

Mean age of patients was 62.02 ± 9.52 years. Mean creatinine value was found to be 0.89 ± 0.2, with mean GFR calculated as 100.52 ± 35.84. Among patients, 92.8% were observed to have serum creatinine values within normal limits (<1 mg/dL). However, when GFR values were calculated, 30.5% of patients with normal creatinine values had GFR of 80 or below. Mean creatinine and GFR values according to CKD stage of patients and mean IIEF scores according to these values are summarized in Table 1.

The chi-square test was used to check whether degree of ED varied according to CKD stage or not. Patients were found to have median IIEF scores of 42 ± 36. When the degree of ED is investigated according to the CKD stage identified in patients, the IIEF score of patients without CKD was clearly high, while a statistically significant fall was identified for IIEF scores in stage 1 and stage 2 CKD (p<.001). The degree of correlation between CKD stages and ED degree was calculated as 24.5%.

When the assessment of CKD according to ED degrees is examined, the distribution of CKD stage among those without ED included in the control group was 81.9% without CKD, 17.1% with first stage

| CKD Stage | Number of patients (n = 639) | Age (years) | Creatinine (mg/dL) | GFR (mL/min) | IIEF |
|-----------|----------------------------|-------------|-------------------|-------------|------|
| 0         | 444                        | 58.69 ± 8.15| 0.84 ± 0.12       | 112.10 ± 27.47| 47 ± 31|
| 1         | 167                        | 68.62 ± 7.7 | 1.0 ± 0.16        | 74.68 ± 12.62| 31 ± 42|
| 2         | 28                         | 75.18 ± 7.67| 1.23 ± 0.43       | 47.99 ± 9.71 | 15 ± 34|
CKD, and 1% with second stage CKD. For patients with severe ED, these rates were calculated as 54.0%, 38.0%, and 8.0%. Compared to CKD rates in the control group, the group with severe ED was observed to have a twofold increase in stage 1 CKD and an eightfold increase in stage 2 CKD. The distribution of CKD incidence according to ED groups is shown in Table 2.

When the one-way ANOVA test is examined, there was a significant difference found between mean age in the control group, stage 1 CKD and stage 2 CKD groups (p<.001). As CKD stage increased, there was a significant increase in age. As a result, age was noted as a covariate factor in the comparison of patient creatinine and GFR levels with IIEF scoring according to CKD stage. With the aim of performing healthy statistical comparisons due to the severely low number of stage 2 CKD patients compared to stage 1 CKD and the control groups, the stage 1 and stage 2 CKD groups were combined to form a single group with CKD. Taking age as a covariate factor, the control group and CKD groups were compared in terms of IIEF scores with one-way ANCOVA. As a result of ANCOVA, IIEF score was found to be statistically significantly low among patients with CKD (p<.001). Results are summarized in Table 3.

### Discussion

According to the results, in patients evaluated for ED, those with low IIEF scores were found to have a higher incidence of CKD. The CKD findings identified according to degree of ED diagnosed in patients found that those with severe ED were identified to have eight times the rate of stage 2 CKD compared to those with mild ED and 17 times the rate of stage 2 CKD compared to the control group (p<.001). The median IIEF score was calculated as 47±31 for the group without CKD, while the median IIEF score for those with stage 2 CKD was 15±34. IIEF score was found to be statistically significantly low in those with CKD (p<.001).

ED currently affects more than 150 million people, and is a pathology disrupting quality of life to a severe degree. In a variety of countries, the prevalence of ED is stated to be 52–62% [11]. When the underlying causes of ED are examined, currently attention is paid to organic causes and the literature includes a variety of studies stating that ED may be a warning symptom of generally systematic diseases in the early period. The association of ED with atherosclerotic heart disease is an accepted situation [12]. Endothelial dysfunction explains the connection between systemic diseases especially and ED. As a result, ED may be an important early marker of endothelial dysfunction and may provide advantages for early diagnosis in terms of vascular pathologies due to being a sign which brings the patient to the doctor in the early stage [13]. One of the side effects most frequently encountered with renal failure is known to be ED. ED may be identified at rates of 40% in male patients entering dialysis [14]. Different to what is known, study group included patients with no CKD diagnosis who were identified to experience problems related to erection. In addition, the data showed concurrent reduction in GFR in patients with reduced erectile capacity.

The GFR value calculated with the Cockcroft–Gault formula was used when scanning CKD in ED patients [10]. GFR is currently considered the best overall index of renal function. Validation studies have shown that the Cockcroft–Gault formula is equivalent to or superior than various other measurements of GFR (e.g. clearances of insulin, iothalamate, Cr51-ethylenediaminetetraacetic acid, diethylenetriaminepentaacetic acid, Mag3, iohexol) [15]. Therefore, we used GFR to evaluate renal function and calculated it with this formula.

It was observed that 93% of the patients whose blood creatinine levels were measured had normal

### Table 2. Distribution of CKD frequency in ED groups.

| Erectile dysfunction | CKD stage | 0 | 1 | 2 | p Value |
|---------------------|-----------|---|---|---|---------|
| None                |           | 86 (81.9) | 18 (17.1) | 1 (1.0) | .000*** (χ²=41.172) CC = 0.245 |
| Mild                |           | 83 (78.3) | 21 (19.8) | 2 (1.9) | |
| Mild–moderate       |           | 79 (76.7) | 21 (20.4) | 3 (2.9) | |
| Moderate            |           | 80 (72.1) | 26 (23.4) | 5 (4.5) | |
| Severe              |           | 115 (54.0) | 81 (38.0) | 17 (8.0) | |

χ²: likelihood ratio chi-square; CC: contingency coefficient. ***Statistically significant (p<.001).

### Table 3. Comparison with one-way ANCOVA of IIEF scores taking age as covariate in CKD and control groups.

| Variables | CKD | N  | Mean | SD  | Minimum | Maximum | p Value |
|-----------|-----|----|------|-----|---------|---------|---------|
| Age       | No  | 443| 58.83| 8.00| 40.00   | 82.00   | .000*** |
|           | Yes | 195| 69.56| 8.01| 44.00   | 92.00   | .000*** |
| IIEF      | No  | 443| 16.79| 8.53| 1.00    | 30.00   |         |
|           | Yes | 195| 12.17| 8.99| 1.00    | 29.00   |         |

***Statistically significant (one-way ANCOVA, p<.001).
***Statistically significant (Student’s t-test, p<.001).
results. In daily practice, CKD generally does not come to mind for patients attending with mild or moderate ED complaints who have normal creatinine value. Early diagnosis of CKD is very important for patients. In Turkey, the incidence of end-stage CKD is reported to increase 12% annually [16]. When CKD is identified in the early period and necessary precautions are taken, the advance to end-stage renal failure can be prevented; and in this way, there will be a 50% reduction in patient numbers requiring dialysis [16]. As a result, it is very important that in daily practice patients attending all clinics, not just urology, focus on CKD to protect patients against health problems they may experience later. Just as patients attending with ED complaints are assessed in cardiac terms, it will be beneficial to patient health and the country's economy to assess them in terms of CKD.

An animal experiment investigating the correlation between ED and CKD showed that erection problems in rats occurred with disruption of nitric oxide (NO) synthase gene expression, which led to endothelial function forming the infrastructure for chronic renal failure [17]. In older men, renal hemodynamics are directly connected to the NO system. When NO synthase inhibitors are administered, GFR and renal plasma perfusion reduces by a large proportion in elderly men compared to young men and glomerular capillary pressure was shown to increase by nearly twofold [18]. NO is also known to be the primary neurotransmitter to initiate erection. As a result, this appears to be a common point in the origin of kidney functions and ED. Additionally, testosterone levels fall due to Leydig cell dysfunction in chronic renal failure [19]. Stimulation of the pituitary linked to the reduction in testosterone levels will increase LH levels. Simultaneously, the reduced renal clearance of LH is another cause of elevated plasma LH level [20]. Injury to seminiferous tubules and Sertoli cells is present in CKD patients. Linked to this, FSH levels may rise in CKD patients due to secretion from Sertoli cells and disruption of inhibin secretion controlling FSH release [21]. Studies have generally shown an inverse relationship between serum total testosterone (TT) and creatinine clearance. It has been reported that TT has beneficial effects on kidney functions and that renal functions are also associated with erectile complaints. Especially in CKD patients, low TT levels have been associated with the progression of CKD [22]. In this study plan, we tried to examine whether ED is an early marker in patients who have ED complaints and have not had a problem or diagnosis associated with CKD before. The mean TT value of our patients with ED diagnosis was found to be $4.22 \pm 1.38 \text{ng/mL}$. This presentation can be explained by the fact that we aim to use ED as an early marker in newly diagnosed CKD and that there are other common causes of CKD such as vascular factors in ED pathophysiology. These variations in androgen synthesis are reported to begin to be observed from the early period of CKD. Though our group was in the early stage of CKD, the observation of sexual function disorder appears to be compatible with these findings. When all these data are evaluated together, it can be interpreted that ED may be an early symptom of CKD as in coronary artery disease.

According to the results of the study, the incidence of CKD in those with ED was increased and it appears that ED may be a clinical marker in early period CKD patients. When evaluating patients attending with ED during routine clinical activities, it may be helpful to remember this for the early diagnosis of CKD. Though patients with ED complaint have normal blood creatinine values, CKD should be remembered and GFR values should be examined. Just as it is an accepted reality that ED may be an early symptom of CAD, it should be remembered that it may also be an early signal for CKD. There are some limitations to this study. To examine whether ED is an early symptom of CKD, the study group should have initially presented with and without CKD, and patients with ED should have demonstrated a higher rate of CKD development over time. There is a need for larger prospective multicenter clinical studies on this topic.

**Conclusions**

As a result, as the disease stage of CKD patients increased, a significant fall was observed in the IIEF scores of patients. Unlike other studies in the literature, we evaluated patients diagnosed with ED in terms of early stage CKD. Patients attending with ED complaints were observed to have higher incidence of stage 1 and stage 2 CKD compared to the control group and the CKD rate was identified to increase as disease severity increased. Just as ED is an early finding of coronary artery diseases, it may be an early warning symptom for CKD. If CKD is identified early, it is a known reality that the progression to end-stage renal failure can be slowed or stopped. We believe it will be beneficial for both patient health and economic costs to examine the GFR value during assessment of patients attending the clinic with ED complaint.
Disclosure statement
No potential conflict of interest was reported by the author(s).

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