

# Renal Function Improves After the Discontinuation of Androgen Deprivation Therapy in Japanese Patients With Prostate Cancer

HIROSHI MASUDA, AYUMI FUJIMOTO, MANATO KANESAKA, KYOKUSIN HOU,  
TAKAHITO SUYAMA, KAZUHIRO ARAKI, SATOKO KOJIMA and YUKIO NAYA

*Department of Urology, Teikyo University Chiba Medical Center, Chiba, Japan*

**Abstract.** *Background:* Androgen deprivation therapy (ADT) is one of the most effective treatments for advanced prostate cancer (PCa). However, it has been reported that the use of ADT is significantly associated with an increased risk of acute kidney injury (AKI) among patients with newly diagnosed non-metastatic PCa. We investigated changes in renal function that occurred in Japanese patients with PCa after ADT was discontinued. *Patients and Methods:* Among 121 patients who underwent prostate biopsies, were pathologically diagnosed with PCa, and received ADT for  $\geq 6$  months at our Institution between 2009 and 2014, 60 patients who underwent radiotherapy for stage B or C PCa were eligible for inclusion in this retrospective study. Renal function was assessed using the estimated glomerular filtration rate (eGFR) before treatment and at 1, 3, 6, 9, and 12 months after the initiation of ADT and the rate of change in the eGFR ( $\Delta$ eGFR) during ADT and after the discontinuation of ADT was investigated. We divided patients into two groups: Group 1 received ADT for 6 months, and group 2 received ADT for 12 months. Age;  $\Delta$ eGFR; prostate-specific antigen, testosterone and hemoglobin levels; clinical stage; Gleason score; comorbidities; body mass index; heart rate; and the cardiothoracic ratio were analyzed. *Results:* A total of 60 patients (group 1:  $n=23$ , group 2:  $n=37$ ) were analyzed. The Gleason score of group 2 was higher than that of group 1 ( $p=0.0011$ ). Regarding clinical stage, group 1 had more patients with stage B disease, and group 2 had more with stage C ( $p<0.0001$ ). The eGFR decreased with the duration of

ADT treatment. At 12 months, renal function had started to recover in group 1, while it had continued to decrease in group 2. *Conclusion:* Discontinuation of ADT tended to result in improvements in renal function. Furthermore, this study indicated that renal dysfunction caused by 6 months of ADT is transient. Normalization of the serum testosterone level seen after the discontinuation of ADT may be associated with improvements in renal function. Thus, intermittent ADT may be a useful treatment for PCa, as it would help to preserve renal function.

Androgen deprivation therapy (ADT) is a mainstay of treatment for advanced prostate cancer (PCa). In randomized trials, ADT has been shown to improve overall survival in cases of locally advanced (1, 2) and lymph node-positive PCa (3), and after surgery for lymph node-positive PCa (4).

Although ADT has been shown to have beneficial effects against PCa progression, various adverse events, such as metabolic syndrome, sexual dysfunction, gynecomastia, fatigue, hot flashes, cardiovascular events, and acute kidney injury (AKI), can occur during treatment (5, 6). It was reported that the use of ADT was significantly associated with an increased risk of AKI among patients with newly diagnosed non-metastatic PCa (7, 8). We have previously reported that in Japanese patients with PCa, ADT-associated renal dysfunction occurs relatively early during ADT (9). In the renal system, hyperglycemia and dyslipidemia may disrupt glomerular function by expanding and thickening the interstitial tubular membrane (10). Furthermore, by lowering the testosterone level to a level similar to those seen after castration, ADT may antagonize the vasodilatory effects of testosterone on renal blood vessels (11) while also creating estrogen deficiency, which can negatively affect renal tubular function (12). Thus, ADT may increase the risk of AKI through these mechanisms. However, there are few reports on the changes in renal function seen after the discontinuation of ADT.

We hypothesized that if ADT were administered for a long period, a temporary deterioration of renal function would be seen but renal function would recover after the discontinuation of ADT. In the present study, we investigated the changes in

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*Correspondence to:* Hiroshi Masuda, MD, Ph.D., Department of Urology, Teikyo University Chiba Medical Center, 3426-3 Anesaki, Ichihara, Chiba, 299-0111, Japan. Tel: +81 436621211, Fax: +81 436614773, e-mail: hrsmasuda@yahoo.co.jp

**Key Words:** Renal dysfunction, discontinuation of androgen deprivation therapy, ADT, prostate cancer, estimated glomerular filtration rate.

Table I. Patient characteristics.

Variable		Group 1 (n=23)	Group 2 (n=37)	p-Value
Age, years	Median (IQR)	71 (56-84)	69 (59-77)	0.2317
PSA, ng/ml	Median (IQR)	11.7 (3.99-41.4)	12.2 (3.45-489)	0.8141
Testosterone, ng/ml	Median (IQR)	4.13 (2.76-6.94)	4.17 (1.64-8.99)	0.6203
Hemoglobin, g/dl	Median (IQR)	14.2 (10.8-17.1)	14.8 (12.6-16.8)	0.0664
GS, n (%)	6	2 (9)	1 (3)	0.0011
	7	17 (77)	12 (32)	
	≥8	3 (14)	24 (65)	
Clinical stage, n (%)	B	22 (95)	13 (35)	<0.0001
	C	1(5)	24 (65)	
Median ΔeGFR (IQR), %	1 Month	0 (−13.7-37.0)	0 (−26.9-36.8)	0.5015
	3 Months	−0.36 (−16.6-21.7)	−0.31 (−24.1-15.8)	0.5121
	6 Months	−0.36 (−32.3-36.6)	−0.40 (−22.1-31.5)	0.8383
	9 Months	−0.35 (−18.4-13.4)	−0.38 (−22.1-31.2)	0.7499
	12 Months	−0.32 (−18.6-31.1)	−0.42 (−13.9-18.0)	0.1538
BMI, kg/m2		22.5 (16.4-36.5)	24.3 (20.8-32.8)	0.0714
Comorbidities, n (%)	Hypertension	9 (37)	15 (41)	0.9778
	Diabetes mellitus	4 (18)	8 (22)	0.7495
	Dyslipidemia	4 (18)	7 (19)	0.9439
Heart rate, beats/min	Median (IQR)	63 (52-85)	66 (52-106)	0.8629
Cardiothoracic ratio, %	Median (IQR)	45.3 (38.3-57.9)	47.5 (38.6-58.9)	0.4377

BMI: Body mass index; ΔeGFR: change estimated glomerular filtration rate at timepoint; GS: Gleason score; IQR: interquartile range; PSA: prostate-specific antigen.

renal function seen after the discontinuation of ADT in Japanese patients with PCa.

## Patients and Methods

**Study subjects.** This was a retrospective study that used data extracted from electronic records. Of the 121 patients that underwent a prostate biopsy, were pathologically diagnosed with PCa, and treated with ADT for ≥6 months at the Department of Urology, Teikyo University Chiba Medical Center (Ichihara, Japan) between April 2009 and August 2014, 60 who received radiotherapy for stage B or C PCa were included in this study. The prostate biopsies were performed transrectally under ultrasound sonography and local anesthesia. They were conducted routinely using a 14-region template in all patients. The biopsy specimens were examined by a dedicated histopathologist at our hospital.

**Clinical and laboratory assessments.** The rate of change in the estimated glomerular filtration rate (ΔeGFR) was used to evaluate renal function. ΔeGFR was calculated using the following formula: (eGFR<sub>t</sub> – pretreatment eGFR)/pretreatment eGFR×100, where eGFR<sub>t</sub> was the eGFR at the 1-, 3-, 6-, 9- and 12-month timepoints. The patients were divided into two groups: Group 1 received ADT for 6 months, and group 2 received ADT for 12 months.

We evaluated the following factors in each group in order to identify risk factors for renal dysfunction after ADT: Age; prostate-specific antigen (PSA), testosterone, and hemoglobin levels; ΔeGFR at 1, 3, 6, 9, and 12 months after ADT was initiated; Gleason score; presence/absence of hypertension; presence/absence of diabetes mellitus; presence/absence of dyslipidemia; body mass index; heart rate; and cardiothoracic ratio.

**Statistical analysis.** The results are shown as median and interquartile range (IQR). The Mann–Whitney U-test and chi-squared test were used for the statistical analyses. All analyses were performed with JMP version 10 (SAS Institute Inc., Cary, NC, USA). Probability values of less than 0.05 were considered statistically significant.

**Ethical approval.** The Institutional Review Board of Teikyo University approved this study (TUIC-COI 19-1407).

## Results

Out of 121 eligible patients, 60 were evaluated in this study. There were 23 patients in group 1 and 37 patients in group 2. Combined androgen blockade was employed in all cases, and after 6 months of this treatment, radiotherapy was performed. Univariate analyses showed statistically significant differences in the Gleason score and clinical stage between the groups (Table I). The Gleason score of group 2 was higher than that of group 1 ( $p=0.0011$ ). Regarding clinical stage, group 1 had more patients with stage B, and group 2 had more with stage C ( $p<0.0001$ ). In group 1, the median ΔeGFR values at 1, 3, 6, 9, and 12 months were 0%, −0.36%, −0.36%, −0.35%, and −0.32%, respectively ( $p=0.5640$ ). In group 2, the corresponding median ΔeGFR values were 0%, −0.31%, −0.40%, −0.38%, and −0.42%, respectively ( $p=0.6851$ ) (Figure 1). Although there was no statistically significant difference, renal function tended to be slightly better at 12 months than at 3 or 6 months in group 1.

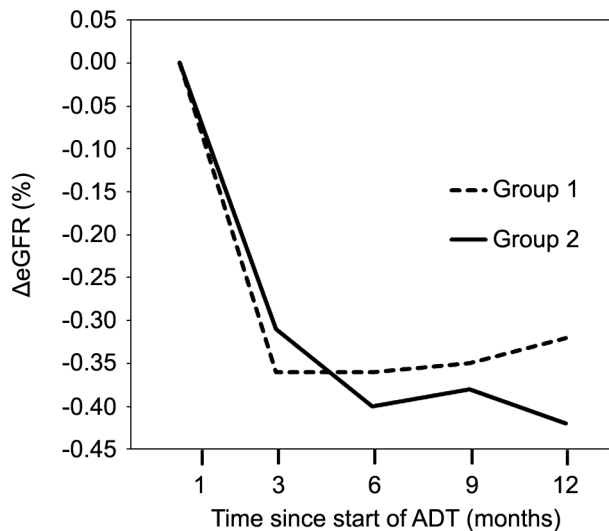


Figure 1. The rate of change in renal function during androgen deprivation therapy (ADT) in patients with prostate cancer. There was no statistically significant difference between the groups.

## Discussion

In the present study, it was revealed that renal function tended to improve after the discontinuation of ADT in Japanese patients with PCa. This finding supported our hypothesis. We previously reported that renal dysfunction due to ADT for PCa occurs early in the course of treatment (9). However, it was unclear whether ADT-induced renal dysfunction is temporary or permanent. The present study suggests that renal dysfunction induced by ADT is temporary.

Although ADT has been shown to have beneficial effects against PCa progression, serious adverse events can occur during such treatment (5). Specifically, ADT reduces the testosterone level, leading to a hypogonadal condition marked by metabolic changes, such as dyslipidemia (13), hyperglycemia (14), and an increase in fat mass (15).

Recently, it was reported that ADT has harmful effects on renal function. Specifically, it was found that administering ADT for newly diagnosed non-metastatic PCa significantly increased the risk of AKI (7). In addition, the latter study showed that when the ADT treatment period was split into tertiles, the highest risk of AKI occurred within the first third of the ADT treatment period (<386 days) (7). However, as far as we are aware, no previous studies have investigated early renal dysfunction induced by ADT. Although only one case report of bicalutamide-related AKI has been published to date (16), ADT and its hypogonadal effects have well-known consequences that our findings are consistent with. We speculate on how ADT affects renal function below.

In the renal system, hyperglycemia and dyslipidemia may disrupt glomerular function by expanding and thickening the interstitial tubular membrane (10). Furthermore, by lowering the testosterone level to a level similar to those seen after castration, ADT may antagonize the vasodilatory effects of testosterone on renal blood vessels (11), while also creating an estrogen deficiency, which can negatively affect renal tubular function (12). Thus, ADT may increase the risk of AKI through these mechanisms. It was reported that the serum testosterone level increased after the discontinuation of ADT (17), and these changes may be associated with improvements in renal function. As the normalization of serum testosterone level may influence ADT-associated renal dysfunction, it is suggested that intermittent ADT should be considered as an option for PCa therapy in order to prevent impairment of renal function.

We would like to emphasize several limitations of our study. Firstly, it was a retrospective cohort study which involved the extraction of electronically stored clinical data, and it had a small sample size. Thus, it will be necessary to validate the findings of this retrospective analysis in prospective studies, including a randomized study, with larger populations in future. Secondly, serum testosterone levels were not measured after the discontinuation of ADT. In order to verify the association between the recovery of renal function and the serum level of testosterone after the discontinuation of ADT, we should have measured the serum level of testosterone after the discontinuation of ADT and compared renal function by serum testosterone level. Unfortunately, the Japanese medical insurance system does not cover frequent serum testosterone examinations, and hence, it was difficult to perform such examinations in this study. The examination of the serum testosterone level in real-world clinical practice may be an important issue. Thirdly,  $\Delta eGFR$  was used to evaluate renal function in the present study. We considered that it was necessary to evaluate renal function after 6 months of ADT. The reason for using  $\Delta eGFR$  as a parameter of renal function was that we considered that it might also be used to evaluate patients with renal dysfunction. Hence,  $\Delta eGFR$  was used instead of  $eGFR$  to assess renal function.  $eGFR$  has been used to classify chronic kidney disease. However,  $\Delta eGFR$  seems to be a useful tool for monitoring changes in renal function over time, and its use is expected to become more widespread in the future. Finally, the impact of radiotherapy on renal function was not examined. The possibility of bladder function deteriorating due to radiotherapy cannot be excluded. As a result, it is possible that secondary deterioration of renal function occurred in this study.

## Conclusion

The findings of this study suggest that renal dysfunction seen in Japanese patients during ADT for PCa is temporary, *i.e.*, renal function tended to recover after the discontinuation of

ADT. Furthermore, this study indicated that renal dysfunction caused by 6 months of ADT is transient. The normalization of serum testosterone level observed after the discontinuation of ADT for PCa may be associated with improvements in renal function. Intermittent ADT might be considered as an endocrine therapy for PCa in order to preserve renal function.

## Conflicts of Interest

The Authors state that they have no conflicts of interest in relation to this study.

## Authors' Contributions

HM designed the study and acquired the data. HM prepared and edited the article. AF, KM, KH, TS, KA, SK, and YN were involved in the patient care and reviewed the electronic records. All of the Authors have read and approved the article.

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