LETTER TO THE EDITOR

Prostate Cancer

Worsening of the low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio in patients with prostate cancer after androgen deprivation therapy

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Dear Editor,

Prostate cancer (PCa) is the most frequently diagnosed male cancer in Western countries, and the number of PCa patients is also rapidly increasing in Japan.[1,2] Simultaneously, androgen deprivation therapy (ADT) has also been increasingly used in PCa patients in recent years.[3–5] However, the long-term use of ADT is associated with a variety of pivotal adverse events, including diabetes, anemia, osteoporosis, serum lipid profile changes, and cardiovascular disease (CVD).[1,2] Higher low-density lipoprotein cholesterol (LDL-C) and/or lower high-density lipoprotein cholesterol (HDL-C) are well-established risk factors for CVD, and control of their levels has been an important goal in the treatment and prevention of CVD.[6,7] Recently, another alternative parameter, the LDL-C to HDL-C (L/H) ratio, has been reported to be strongly associated with CVD and is thought to be a better predictor of future CVD than LDL-C alone. Closely monitoring serum lipid profile, including the L/H ratio changes affected by ADT, is a key to preventing CVD in PCa patients. Moreover, we previously suggested that a higher L/H ratio might have an impact on the development of arterial stiffness after ADT administration.[7] Although some cutoff points of the L/H ratio have been reported in clinical use, it has been suggested that thrombosis can occur when the L/H ratio increases to around 2.5 or more in East Asian populations.[6] The aim of the present study was to investigate the changes in serum lipid profile and to identify the clinical factors associated with an increased L/H ratio in PCa patients who received ADT.

This was a retrospective study approved by the institutional review board of Toho University Sakura Medical Center (No. 2012-008). All patients enrolled in the study gave their written informed consent. One hundred patients with pathologically confirmed PCa scheduled to receive ADT for more than 6 months between March 2012 and August 2015 were analyzed. Patients and the statistical analysis methods are minutely described in the

Supplementary Materials and Methods. Briefly, the patients were divided into three groups for assessment: (I) receiving medical treatment for dyslipidemia (*n* = 29); (II) baseline L/H ratio of 2.5 or more without medical treatment for dyslipidemia (*n* = 22); and (III) baseline L/H ratio of <2.5 without medical treatment for dyslipidemia (*n* = 49). Group III patients were also assessed using uni- and multivariate analyses to determine the associations between an increased L/H ratio and baseline variables.

Supplementary Table 1 shows the baseline characteristics of the patients in this study. **Figure 1** shows the changes in serum lipid profiles and testosterone at baseline and after 3 and 6 months of follow-up in all enrolled patients. ADT significantly lowered testosterone levels. After 3 months of follow-up, total cholesterol (TC, *P*<0.001), HDL-C (*P*=0.010), and LDL-C (*P*=0.007) were significantly increased, while triglycerides and L/H ratio did not show significant changes in all patients. **Supplementary Table 2** shows the results of patients in each group. TC, HDL-C, and LDL-C increased significantly after 6 months of ADT administration in each group of patients. The L/H ratio (mean±s.d.) increased significantly from 1.8±0.5 to 1.9±0.6 (*P* = 0.004) in Group III patients, while it did not change significantly in Group I and II patients. The L/H ratio increased to 2.5 or more in 7 of the 49 patients in Group III after 6 months of follow-up. The clinical predictors associated with an increased L/H ratio of 2.5 or more on uni- and multivariate analyses are summarized in **Table 1**. Multivariate analysis revealed that HDL-C was an independent predictor of an increased L/H ratio of 2.5 or more after 6 months of follow-up (odds ratio: 1.13, *P* = 0.013).

LDL-C levels increased significantly in this study, even in patients who took lipid-lowering drugs, while HDL-C levels also increased significantly (**Supplementary Table 2**). In our study, enrolled patients did not have new-onset CVD within 6 months of follow-up. Although the duration of follow-up might have been too short to investigate new-onset CVD after ADT, increased HDL-C levels might have offset the cardiovascular risk caused by increased LDL-C levels. The L/H ratio is considered to be a clinically useful marker of cardiovascular events, and an increased L/H ratio is associated with an increased risk of cardiovascular events; in particular, baseline L/H ratios above

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Table 1: Uni- and multivariate analyses of the clinical variables at baseline for new-onset of low-density lipoprotein/high-density lipoprotein cholesterol ratio ≥2.5 after androgen deprivation therapy

Variables	Univariate			Multivariate		
	L/H ratio ≥2.5 (n=7)	L/H ratio <2.5 (n=42)	P	Odds ratio	95% CI	P
Age (year)	69.1±12.7	73.6±5.8	0.399	-	-	-
BMI (kg m⁻²)	23.4±3.9	23.2±2.9	0.812	-	-	-
Systolic BP (mmHg)	125.6±6.0	136.1±15.7	0.090	-	-	-
Diastolic BP (mmHg)	70.0±5.5	79.8±11.2	0.029	-	-	-
Mean BP (mmHg)	88.5±3.7	98.6±10.4	0.016	-	-	-
Clinical laboratory values				-	-	-
HbA1c (%)	5.8±0.6	5.3±1.6	0.278	-	-	-
Triglycerides (mg dl⁻¹)	127.1±73.9	130±75.5	0.967	-	-	-
Total cholesterol (mg dl⁻¹)	177.7±35.7	186±30.6	0.521	-	-	-
HDL-C (mg dl⁻¹)	47.4±9.4	59.7±10.7	0.007	1.13	1.03–1.24	0.013
LDL-C (mg dl⁻¹)	108.3±22.2	100.5±24.3	0.431	-	-	-
CRP (mg dl⁻¹)	0.3±0.6	0.5±2.0	0.475	-	-	-

Data are presented as mean±s.d. CI: confidence internal; BMI: body mass index; BP: blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; L/H ratio: low-density lipoprotein/high-density lipoprotein cholesterol ratio; CRP: C-reactive protein; s.d.: standard deviation; HbA1c: glycated hemoglobin
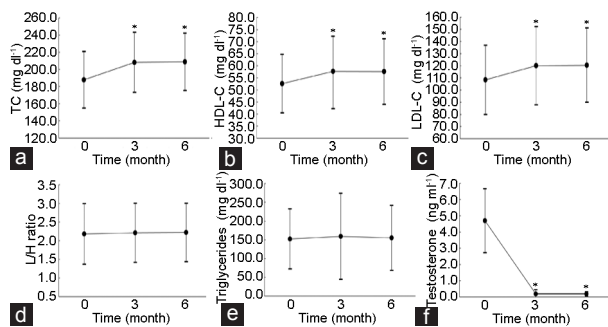
Figure 1: Changes in serum lipid profile and testosterone at baseline and after 3 and 6 months of follow-up in prostate cancer patients after ADT; (**a**) TC, (**b**) HDL-C, (**c**) LDL-C, (**d**) L/H, (**e**) triglycerides, and (**f**) testosterone. *$P < 0.05$. TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; L/H: ratio of LDL-C to HDL-C; ADT: androgen deprivation therapy.

2.5 are associated with an increased risk of cardiovascular events.[8] In this study, the L/H ratio showed a significant increase in Group III. This study is the first to show that there exist a group of patients who have a higher risk of a worsening L/H ratio within the initial 6-month follow-up period after ADT despite having favorable baseline serum lipid profiles. Moreover, this study is the first to suggest that HDL-C is an independent predictor of an increased L/H ratio of 2.5 or more after 6 months of follow-up. Although these relationships still remain controversial, hypercholesterolemia is reported to be associated with a shorter time to castration-resistant PCa (CRPC) after ADT and survival after treatment for CRPC.[9,10] From the viewpoint of not only cardiovascular risk but also cancer management, it seems to be very important to aggressively manage dyslipidemia with the use of statins after initiation of ADT in patients with PCa.

Clinicians should pay attention not only to patients receiving medical treatment for dyslipidemia or with an L/H ratio of 2.5 or more but also to patients with an L/H ratio of <2.5. This study shows that patients with a baseline L/H ratio of <2.5 have a risk of worsening L/H ratio, although they seem to be "good lipid metabolism patients." Clinicians can identify and manage PCa patients with a greater risk of worsening serum lipid profiles after ADT more effectively.

AUTHOR CONTRIBUTIONS

RO recruited patients, conducted this project, drafted the manuscript, and performed the statistical analyses; TU recruited patients, planned this project, performed the statistical analyses, and proofread the manuscript; TE, MY, and SK recruited patients and proofread the manuscript; NK recruited patients, proofread the manuscript, and participated in this project design and coordination; HS recruited patients, proofread the manuscript, participated in this project design and coordination, and obtained the grant for this project. All authors read and approved the final manuscript.

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Supplementary information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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636

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Supplementary Table 1: Demographic and baseline characteristics of the study patients

Variable	Value
Age, year	72.5±6.9
BMI, kg m^{-2}	23.6±3.0
Systolic BP, mmHg	133.5±16.6
Diastolic BP, mmHg	76.3±11.0
Mean BP, mmHg	95.4±11.0
Comorbidities, n (%)	
Hypertension	50 (50.0)
Diabetes mellitus	20 (20.0)
Dyslipidemia	29 (29.0)
CVD	16 (16.0)
PSA, ng ml^{-1}	83.8±366.1
Testosterone, ng ml^{-1}	4.6±1.9
HbA1c, %	5.9±0.7
TNM classification at diagnosis, n (%)	
T1-2 N0 M0	61 (61.0)
T3-4 N0 M0	23 (23.0)
T1-4 N1 M0	2 (2.0)
T1-4 N1 M1	14 (14.0)
Gleason score at diagnosis, n (%)	
6 or less	3 (3.0)
7	59 (59.0)
8–10	38 (38.0)
Treatment	
ADT alone	52 (52.0)
Before radiotherapy	40 (40.0)
Biochemical recurrence after RP	8 (8.0)

BMI: body mass index; BP: blood pressure; PSA: prostate-specific antigen; ADT: androgen deprivation therapy; RP: radical prostatectomy; HbA1c: glycated hemoglobin; TNM: tumor, node, and metastasis; CVD: cardiovascular disease

Supplementary Table 2: Comparison of serum lipid profiles between baseline and 6 months of follow-up

Variable	With dyslipidemia (n=27)			Without medical treatment for dyslipidemia					
				L/H ratio <2.5 (n=49)			L/H ratio ≥2.5 (n=22)		
	Baseline	6 months	P	Baseline	6 months	P	Baseline	6 months	P
Triglycerides, mg dl^{-1}	158.3±67.4	166.8±115.1	0.770	129.6±74.5	131.8±60.4	0.373	195.5±90.3	192.1±79.6	0.910
Total cholesterol, mg dl^{-1}	174.6±25.3	194.3±29.7	<0.001	184.8±31.1	206.6±28.1	<0.001	211.6±34.3	232.7±36.8	0.002
HDL-C, mg dl^{-1}	50.9±11.4	57.1±12.6	0.002	57.9±11.3	62.4±13.9	0.003	43.0±7.3	47.6±8.1	0.001
LDL-C, mg dl^{-1}	98.9±20.5	107.3±26.2	0.003	101.6±24.0	115.6±26.1	<0.001	138.9±26.3	149±27.9	0.045
L/H ratio	2.0±0.6	2.0±0.7	0.784	1.8±0.5	1.9±0.6	0.004	3.3±0.6	3.2±0.6	0.277

HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; L/H ratio: low-density lipoprotein/high-density lipoprotein cholesterol ratio