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.¹-³ Simultaneously, androgen deprivation therapy (ADT) has also been increasingly used in PCa patients in recent years.¹-³ 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).¹-³ 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.⁸ 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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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.

**COMPETING INTERESTS**

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

**REFERENCES**

1. Suzuki H, Kamiya N, Imamoto T, Kawamura K, Yano M, et al. Current topics and perspectives relating to hormone therapy for prostate cancer. Int J Clin Oncol 2008; 13: 401–10.
2. Imamoto T, Suzuki H, Utsumi T, Endo T, Takano M, et al. Association between serum sex hormone levels and prostate cancer: effect of prostate cancer on serum testosterone levels. Future Oncol 2009; 5: 1005–13.
3. Hou WH, Huang CY, Wang CC, Lin KH, Chen CH, et al. Impact of androgen-deprivation therapy on the outcome of dose-escalation prostate cancer radiotherapy without elective pelvic irradiation. Asian J Androl 2017; 19: 596–601.
4. Kao LT, Lin HC, Chung SD, Huang CY. No increased risk of dementia in patients receiving androgen deprivation therapy for prostate cancer: a 5-year follow-up study. Asian J Androl 2017; 19: 414–7.
5. Wang Y, Dai B, Ye DW. Serum testosterone level predicts the effective time of androgen deprivation therapy in metastatic prostate cancer patients. Asian J Androl 2017; 19: 178–83.
6. Chen QJ, Lai HM, Chen BD, Li XM, Zhai H, et al. Appropriate LDL-C-to-HDL-C ratio cutoffs for categorization of cardiovascular disease risk factors among Uygur adults in Xinjiang, China. Int J Environ Res Public Health 2016; 13: 235.
7. Oka R, Utsumi T, Endo T, Yano M, Kamiyama S, et al. Effect of androgen deprivation therapy on arterial stiffness and serum lipid profile changes in patients with prostate cancer: a prospective study of initial 6-month follow-up. Int J Clin Oncol 2016; 21: 389–96.
8. Kameda S, Sakata T, Kubo Y, Mitsuguro M, Okamoto A, et al. Association of platelet aggregation with lipid levels in the Japanese population: the Suita study. J Atheroscler Thromb 2011; 18: 850–7.
Jeon JC, Park J, Park S, Moon KH, Cheon SH, et al. Hypercholesterolemia is associated with a shorter time to castration-resistant prostate cancer in patients who have undergone androgen deprivation therapy. World J Mens Health 2016; 34: 28-33.

Di Lorenzo G, Sonpavde G, Pond G, Lucarelli G, Rossetti S, et al. Statin use and survival in patients with metastatic castration-resistant prostate cancer treated with abiraterone acetate. Eur Urol Focus 2017. pii: S2405-4569 (17) 30083-4.

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SUPPLEMENTARY MATERIALS AND METHODS

Data collection

The data of 100 patients were analyzed. The following agents were used as ADT at the discretion of each urologist: 47 patients received goserelin subcutaneously in combination with oral bicalutamide 80 mg daily; 40 patients received leuprorelin subcutaneously in combination with oral bicalutamide 80 mg daily; and 13 patients received only degarelix subcutaneously.

The following baseline and follow-up variables were collected from medical records: age, body mass index (BMI), systolic, diastolic, and mean blood pressures (BPs), comorbidities, and clinical laboratory data. Comorbidities included hypertension, diabetes mellitus, dyslipidemia, and CVD. Clinical laboratory data included prostate-specific antigen (PSA), testosterone, HbA1c, triglycerides, total cholesterol (TC), HDL-C, LDL-C, L/H ratio, and C-reactive protein.

Statistical analysis

The results are reported as mean (± standard deviation). First, the changes in serum lipid profiles and testosterone among baseline and 3 and 6 months of follow-up measurements were compared in all patients using ANOVA and Tukey's or Games–Howell tests (Figure 1). Second, the patients were divided into three groups: (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); or (III) baseline L/H ratio of <2.5 without medical treatment for dyslipidemia (n = 49). The changes in serum lipid profiles were compared in each group using the paired t-test or the Wilcoxon signed-rank test between baseline and 6 months of follow-up. Finally, in Group III patients, univariate analyses were performed to assess the associations between an increased L/H ratio and baseline variables. Continuous parametric variables were compared using t-tests. Nonparametric variables were compared using Mann–Whitney U-tests. Categorical variables were compared using Chi-square tests or Fisher's exact test. After significant candidate variables were selected on univariate analyses, multivariate logistic regression analysis was carried out to identify clinical predictors associated with an increased L/H ratio. Significance was defined at the level of P < 0.05. All statistical analyses were carried out using SPSS Statistics 23 (IBM, Chicago, IL, USA).

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 NO M0                                    | 61 (61.0)          |
| T3-4 NO 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 |
|---------------------------------|---------------------------|-------------------------------------------|
|                                 | Baseline | 6 months | P    | Baseline | 6 months | P    |
|                                 | Baseline | 6 months | P    | Baseline | 6 months | P    |
| L/H ratio <2.5 (n=49)           |          |          |      |          |          |      |
| L/H ratio ≥2.5 (n=22)           |          |          |      |          |          |      |
| Triglycerides, mg dl⁻¹          | 158.3±67.4 | 166.8±115.1 | 0.770 | 129.6±74.5 | 131.8±60.4 | 0.373 |
| 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 |
| 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 |
| 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 |
| L/H ratio                       | 2.0±0.6 | 2.0±0.7 | 0.784 | 1.9±0.5 | 1.9±0.6 | 0.004 |

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