Prevalence of Hand Joint Symptoms in Androgen Deprivation Therapy among Japanese Patients with Prostate Cancer

Shogo Inoue*, Tetsutaro Hayashi, Jun Teishima, Akio Matsubara
Department of Urology, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan

Abstract

Purpose: The current trends in favor of androgen deprivation therapy (ADT) for nonmetastatic prostate cancer at the stage of biochemical recurrence or increasing prostate-specific antigen levels raise the issue of exposing asymptomatic patients to potential adverse effects over the longer term. The aim of this study is to assess the hand joint symptoms caused by ADT in Japanese patients with prostate cancer. Materials and Methods: We retrospectively reviewed and performed a cross-sectional survey of hand joint symptoms in patients receiving ADT for prostate cancer. The results were compared with a control group of patients with prostate cancer that was hormone-naïve group. In total, there were 279 Japanese patients with prostate cancer, of whom 150 patients were ADT treated and 129 patients were hormone naïve. Patients completed a three-item self-administered questionnaire assessing the presence of hand joint symptoms that started or worsened after initiating ADT. Results: A statistically significant difference was found between the incidence rates of hand joint symptoms of both groups (P = 0.0056). There was a statistically significant difference in the incidence rates of hand joint pain (P = 0.0273). However, the incidence rates of hand numbness (P = 0.0576) and hand muscle weakness (P = 0.1098) between both groups were not significantly different. Conclusion: Our cross-sectional study demonstrated that patients receiving ADT for prostate cancer show significant hand joint symptoms compared to hormone-naïve patients. Consequently, for patients receiving ADT who suffer from hand joint symptoms, we must consider the adverse effects of ADT.

Keywords: Androgen deprivation therapy, hand joint symptoms, prostate cancer, quality of life

Introduction

Prostate cancer was the most frequently diagnosed malignancy and the second leading estimated cause of cancer death in 2012 in men in the United States.[1] Androgen deprivation therapy (ADT) is commonly adopted in the case of lymph node involvement, metastatic disease, and adjuvant use with radiation.[2-4] In patients with locally advanced disease, ADT in combination with external beam radiation or as an adjuvant therapy has been shown to improve the chances of survival.[5,6] In patients with distant metastases, ADT improves the quality of life (QOL).[3,7] Although ADT is beneficial in these populations, it is often used as a primary therapy when cancer is localized and in cases of biochemical recurrence[8] without any evidence of survival advantage. The overall use of ADT has increased in the past two decades.[4]
and its use in cases of localized cancer and biochemical recurrence accounts for a great deal for this increase. As most prostate cancer patients die of conditions other than their primary malignancy, recognition and management of the known adverse and long-term unfavorable effects of ADT is important.\[9\]

ADT is associated with numerous adverse effects, including poorer QOL, sexual dysfunction, fatigue, loss of bone density, and muscle atrophy.\[2,10,11\] These adverse effects may lead to loss of physical function.\[12\] Several cross-sectional studies have described the effects of ADT on self-reported physical function. These studies consistently found that ADT users reported decreased physical function in comparison to nonusers.\[13,14\] We have found that ADT used for the treatment of prostate cancer has caused adverse effects such as hand joint symptoms in patients in our hospital. Aromatase inhibitors (AIs) are the standard therapy for postmenopausal women with hormone-sensitive breast cancer, although they can cause joint pain and stiffness. Adverse effects such as joint symptoms in breast cancer patients have frequently been reported,\[15,16\] but the ADT-related hand joint symptoms in patients with prostate cancer have rarely been reported until now. This indicates that hand joint symptoms have not been recognized as important adverse effects in prostate cancer patients.

We aimed to assess hand joint symptoms caused by ADT in Japanese prostate cancer patients and to clarify the factors that may be associated with an increased risk of ADT-related hand joint symptoms.

**Materials and Methods**

We retrospectively reviewed and performed a cross-sectional study of consecutive patients receiving ADT for prostate cancer at Hiroshima University Hospital. The present study was conducted between April 2000 and November 2011 for a total of 279 Japanese patients with prostate cancer, of whom 150 patients were ADT treated and 129 patients were hormone naïve. In the ADT-treated group, all patients presented with clinical stage B, and in the hormone-naïve group, the number of patients with clinical stage B was 110 (73.3%), clinical stage C was 20 (13.3%), and clinical stage D was 20 (13.3%). Besides, there were 14 patients (5%) with bone metastasis and no patient with medications of bone-targeted agents in our cohort. These patients were recruited through mail. The Institutional Review Board approval was obtained before the commencement of the study.

The study protocol was approved by the institutional review board of Hiroshima University Hospital (IRB No. 107). Informed consent was confirmed by the IRB.

The self-administered Stanford Health Assessment Questionnaire (HAQ)\[17\] was developed in 1980 to assess the functional disability in rheumatoid arthritis and has been established as a reliable instrument. The HAQ is widely used and has been translated into many languages. It was recently translated and validated for effectiveness in Japanese.\[18\] Patients completed a three-item self-administered questionnaire assessing the presence of hand joint symptoms that had either started or worsened after initiating ADT. Hand joint symptoms were defined with one of the three symptoms that consist of hand joint pain, numbness, and muscle weakness in the Japanese version of the HAQ.

Demographic and medical data were collected from the medical records. Medical data included age, serum pretreatment prostate-specific antigen (PSA) values, body mass index (BMI), date and stage of prostate cancer diagnosis, previous diseases, i.e., diabetes mellitus (DM), spinal, cerebral vascular, and cardiovascular diseases, and prior/current cancer treatment, i.e., prostatectomy, radiation therapy, watchful waiting, and ADT. In principle, the patients who reported hand joint symptoms consulted specialists in neurology to investigate the association of ADT and their hand joint symptoms. If the specialists in neurology diagnosed the patients’ hand joint symptoms as having no association with ADT, these patients were excluded from the hand joint symptom group.

The differences in age, serum PSA value, BMI, and previous diseases between ADT-treated and hormone naïve groups were statistically analyzed using a Chi-square test. The analysis of the prevalence of hand joint symptoms between both groups was also evaluated using the Chi-square test. A logistic regression model was applied to calculate the odds’ ratio of hand joint symptoms among the groups. Analyses were performed using the JMP version 10 Statistical Software Package (SAS Institute Inc., Cary, NC, USA).

**Results**

There were significant differences between both groups in age and serum PSA values, as listed in Table 1. There were no significant differences in previous diseases, including DM and spinal, cerebral vascular, and cardiovascular diseases. Mean follow-up periods were 46.1 months in the hormone naïve group and 45.8 months in the ADT-treated group, and there were no significant differences between both groups ($P = 0.9331$).

The prevalence of hand joint symptoms between ADT-treated and hormone naïve patients is listed in Table 2. Of the total sample, 33 patients (11.8%) reported having hand joint symptoms. Of those who reported such symptoms, 25 patients (16.7%) were receiving ADT and 8 patients (6.2%) were hormone naïve; the incidence rates of hand joint symptoms showed a statistically significant difference between both groups ($P = 0.0056$). We classified the results of hand joint symptoms by various risk factors, including age, serum PSA value, BMI, and previous diseases, but there were no significant differences in the prevalence of hand joint symptoms for any of the classified risk factors except for treatment [Table 2]. The number of patients with hand joint symptoms for any of the classified risk factors except for treatment [Table 2]. The number of patients with hand joint symptoms for any of the classified risk factors except for treatment [Table 2].
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Table 1: Patient characteristics

|                      | No. | ADT  | Hormone-naive | P  |
|----------------------|-----|------|---------------|----|
|                      | No. | %    | No. | %    |     |
| Total                | 279 | 150  | 129 |      | <0.0001 |
| Age, yr              |     |      |     |      |       |
| < 70                 | 121 | 47   | 74  | 61.2 |     |
| ≥ 70                 | 158 | 103  | 55  | 34.8 |     |
| PSA, ng/ml           |     |      |     |      | <0.0001 |
| < 10                 | 146 | 53   | 93  | 63.4 |     |
| ≥ 10                 | 133 | 97   | 36  | 27.1 |     |
| BMI, kg/m²           |     |      |     |      | 0.224  |
| < 25                 | 193 | 99   | 107 | 45.9 |     |
| ≥25                  | 55  | 30   | 25  | 45.4 |     |
| DM                   |     |      |     |      | 0.8131  |
| No                   | 233 | 126  | 107 | 45.9 |     |
| Yes                  | 46  | 24   | 22  | 47.8 |     |
| Spinal disease       |     |      |     |      | 0.4665  |
| No                   | 249 | 132  | 117 | 47   |     |
| Yes                  | 30  | 18   | 12  | 40   |     |
| Cerebral vascular disease | | | | | 0.4035  |
| No                   | 245 | 134  | 111 | 45.3 |     |
| Yes                  | 34  | 16   | 18  | 52.9 |     |
| Cardiovascular disease | | | | | 0.1799  |
| No                   | 148 | 74   | 50  | 50   |     |
| Yes                  | 131 | 76   | 55  | 42   |     |

Table 2: Prevalence of hand joint symptoms classified by risk factors

| Hand joint symptoms | No. | % |
|---------------------|-----|---|
|                      | No. |  |
| Treatment           | 279 | 11.8 |
| Hormone-naive       | 150 | 6.2 |
| ADT                 | 25  | 16.7 |
| Age, yr             | 121 | 9.1 |
| < 70                | 158 | 13.9 |
| ≥ 70                | 133 | 13.5 |
| PSA, ng/ml          |     |    |
| < 10                | 146 | 10.3 |
| ≥ 10                | 133 | 13.5 |
| BMI, kg/m²          |     |    |
| < 25                | 193 | 11.4 |
| ≥25                 | 55  | 14.6 |
| DM                  |     |    |
| No                   | 233 | 11.6 |
| Yes                  | 46  | 13  |
| Spinal disease       |     |    |
| No                   | 249 | 11.7 |
| Yes                  | 30  | 13.3 |
| Cerebral vascular disease | | | | | 0.4877  |
| No                   | 245 | 12.2 |
| Yes                  | 34  | 8.8 |
| Cardiovascular disease | | | | | 0.0915  |
| No                   | 148 | 14.9 |
| Yes                  | 131 | 8.4 |

symptoms was 2 (14.3%) with and 31 (11.7%) without bone metastasis; there were no significant difference ($P=0.7760$).
In particular, the patients who had previously had cerebral vascular or cardiovascular diseases were less likely to have hand joint symptoms compared with the patients who did not have these diseases.

We analyzed three items, including hand joint pain, numbness, and muscle weakness. Twelve patients (4.3%) reported hand joint pain, of them, ten patients (6.7%) were receiving ADT and two patients (1.6%) were hormone naïve. A total of 22 patients (7.9%) reported hand numbness, of which 16 of those patients (10.7%) were receiving ADT and 6 patients (4.7%) were hormone naïve. Fifteen patients (5.4%) reported hand muscle weakness, of which 11 patients were ADT patients (7.3%) and 4 (3.1%) patients were hormone naïve. There was a statistically significant difference in the incidence rates of hand joint pain ($P = 0.0273$), but there was no significant difference in the incidence rates of hand numbness ($P = 0.0576$) or hand muscle weakness ($P = 0.1098$) between the ADT and hormone-naive groups [Table 3]. These results suggest that hand joint pain is the most characteristic symptom associated with the ADT. The mean duration from the initiation of ADT was 23.7 (1–84) months until the onset of hand joint symptoms. Furthermore, by each symptom, the mean durations until the onset of each symptom were 21.6, 24.8, and 25.4 months in hand joint pain, numbness, and muscle weakness.

We excluded the factors of multivariate analysis because the ratio of hand joint symptoms was lower in the patients with vascular or cardiovascular diseases, and hence, we were concerned these diseases could not be influenced by the onset of hand joint symptoms. The results of logistic regression analysis showed that the risk of hand joint symptoms was higher in the ADT-treated patients than in the hormone-naïve patients ($P = 0.015$, odds’ ratio = 2.921, 95% confidence interval = 1.222–7.649). These results indicate that ADT contributed most significantly to triggering hand joint symptoms [Table 4].

**DISCUSSION**

Currently, ADT is used for hormonal therapy in most patients with locally advanced and metastatic prostate cancer.[19] ADT includes various treatment modalities which reduce circulating androgen levels or block their effect on prostate cancer cells. Although several medical therapies exist to reduce androgen levels, the most commonly employed agents are luteinizing hormone-releasing hormone (LHRH) agonists, including leuprolide and goserelin.[20]

Given the prevalence of ADT, treating physicians should recognize the known adverse and long-term unfavorable effects and provide monitoring of patients undergoing treatment.[20] Well-known adverse effects of ADT include hot flushes, night sweats, erectile dysfunction, decreased
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libido, fatigue, depression, and gynecomastia. In addition, decreased hemoglobin levels, changes in fat and lean body mass, changes in plasma lipoproteins, increased insulin levels, and osteoporosis can occur.\[21\]

AIs improve survival chances in postmenopausal women with hormone-sensitive breast cancer. However, breast cancer patients receiving AIs have a higher incidence of osteoporosis, bone fractures, and musculoskeletal symptoms, particularly joint pain and stiffness.\[15\] Adverse effects such as joint symptoms in the patients with breast cancer were much reported, and medications such as nonsteroidal anti-inflammatory drugs and acetaminophen were effective for AI-related joint pain relief.\[15,16\] In fact, we have found that many patients receiving ADT for the treatment of prostate cancer have suffered from adverse effects such as hand joint symptoms. However, ADT-related hand joint symptoms in patients with prostate cancer have rarely been reported. Therefore, hand joint symptoms were not recognized as notable adverse effects in prostate cancer patients until now.

The exact mechanism of the relation between ADT and hand joint symptoms is unclear but is believed to be related to androgen deprivation. Total and free testosterone levels were very low in the men receiving ADT, and estradiol levels were also low because of reduced aromatizing of testosterone to estradiol. These lower levels reflected the efficacy of the ADT.\[19\] Testosterone has an important role in muscle strength and protecting muscle mass. Many studies have been done that support the beneficial effects, both direct and indirect, of testosterone on skeletal muscles.\[22,23\] It binds to the androgen receptor directly, and this complex translocates to the nucleus to increase muscle protein synthesis.\[24\] Testosterone affects muscle fiber by acting at multiple steps in the pathways that regulate muscle protein synthesis and breakdown as well as the commitment and differentiation of pluripotent stem cells.\[25,26\] Testosterone also has indirect effects on skeletal muscles, including increased concentrations of insulin-like growth factor-1 (IGF-1) and growth hormone.\[27\] Local IGF-1 stimulates muscle protein synthesis and induces skeletal muscle hypertrophy.\[28\]

Another relevant factor is the role of gonadal steroids in the development, organization, and ongoing dynamics of the nervous system. They affect brain functions by modulating the transmission of nerve impulses, and they facilitate the corticospinal pathway.\[19\] Motor neurons and skeletal muscles both have androgen receptors.\[29\] Testosterone increases the number of androgen receptors in motor neurons, as well as the size and number of motor neurons in the spinal cord. Gonadal steroids may modify the descending pathways that control voluntary movements of hand muscles.\[30\] Because of these effects of testosterone on the nerve system and also on muscle strength, we surmised that diminishing levels of

### Table 3: Prevalence of hand joint pain, hand numbness, and hand muscle weakness classified by risk factors

| Variable     | No. | %  | P     | No. | %  | P     | No. | %  | P     |
|--------------|-----|----|-------|-----|----|-------|-----|----|-------|
| Total        | 12  | 4.3|       | 22  | 7.9|       | 15  | 5.4|       |
| Treatment    |     |    | 0.0273|     |    | 0.0576|     |    | 0.1098 |
| Hormone-naive| 2   | 1.6|       | 6   | 4.7|       | 4   | 3.1|       |
| ADT          | 10  | 6.7|       | 16  | 10.7|       | 11  | 7.3|       |
| Age, yr      |     |    | 0.6371|     |    | 0.1044|     |    | 0.0502 |
| < 70         | 6   | 5  |       | 6   | 5  |       | 3   | 2.5|       |
| ≥70          | 6   | 3.8|       | 16  | 10.1|       | 12  | 7.6|       |
| PSA, ng/ml   |     |    | 0.1754|     |    | 0.2634|     |    | 0.9362 |
| < 10         | 4   | 2.7|       | 9   | 6.2|       | 8   | 5.5|       |
| ≥10          | 8   | 6  |       | 13  | 9.8|       | 7   | 5.3|       |
| BMI, kg/m²   |     |    | 0.8733|     |    | 0.904 |     |    | 0.3798 |
| < 25         | 8   | 4.2|       | 15  | 7.8|       | 8   | 4.2|       |
| ≥25          | 3   | 5.5|       | 5   | 9.1|       | 5   | 9.1|       |
| DM           |     |    | 0.442 |     |    | 0.8255|     |    | 0.7131 |
| No           | 9   | 3.9|       | 18  | 7.7|       | 12  | 5.2|       |
| Yes          | 3   | 6.5|       | 4   | 8.7|       | 3   | 6.5|       |
| Spinal disease|    |    | 0.5263|     |    | 0.2766|     |    | 0.7477 |
| No           | 10  | 4  |       | 18  | 7.2|       | 13  | 5.2|       |
| Yes          | 2   | 6.7|       | 4   | 13.3|       | 2   | 6.7|       |

### Table 4: Multivariate analysis to identify the risk factors for hand joint symptoms

| Variables     | SE  | P     | OR   | 95% CI          |
|---------------|-----|-------|------|-----------------|
| Treatment, ADT| 0.232| 0.015| 2.921| 1.222-7.649     |
| Age, yr ≥70   | 0.206| 0.55  | 1.276| 0.579-2.938     |
| PSA, ng/ml ≥10| 0.203| 0.976| 1.012| 0.453-2.248     |
| BMI, kg/m² ≥25| 0.29 | 0.615| 1.263| 0.488-3.007     |
| DM            | 0.25 | 0.852| 1.098| 0.379-2.775     |
| Spinal disease| 0.297| 0.897| 1.081| 0.293-3.172     |
testosterone caused by the LHRH agonist might affect the motor coordination and dexterity of the hands.\textsuperscript{19} We found that ADT might influence hand dexterity. Testosterone has an important function in the nerve and muscle system; therefore, we aimed to examine the adverse effects of ADT, especially the hand joint symptoms in patients with prostate cancer.

We were very surprised to find an almost three-fold increased risk of hand joint symptoms in patients who received ADT. To the best of our knowledge, this is the first report that indicates the prevalence of the clear relation between ADT and hand joint symptoms in a practice setting and the potential risk factors associated with ADT-induced adverse effects. Additional research should assess the natural history and clinical characteristics of these ADT-related hand joint symptoms and interventions to alleviate the symptoms. The long-term effects of profound androgen suppression in prostate cancer patients taking ADT are unknown. Therefore, targeted interventions that relieve ADT-induced hand joint symptoms are needed. However, until interventions are identified, if the patients suffer adverse effects, finding an alternative therapy may be a reasonable solution. Besides, it is very important to ask patients detailed questions about hand joint symptoms before ADT and to give sufficient informed consent concerning the complications of hand joint symptoms. We would have an experience of the improvement with hand joint symptoms if ADT-related symptoms were detected early.

A potential limitation of this study is the cross-sectional design, which introduces the possibility of selection and recalls bias. Another limitation was a lack of knowledge as to whether patients experienced hand joint symptoms before they began receiving ADT. Measurements both before and after ADT would be a superior study design. For our primary outcome of hand joint symptoms, we relied on self-reported questionnaires. We must examine the objective findings using a neurological approach to conduct a more precise investigation of hand joint symptoms. Furthermore, a randomized controlled and multicenter trial is required to confirm the present conclusions.

**Conclusions**

Our cross-sectional study demonstrated that patients receiving ADT for prostate cancer show significant hand joint symptoms in comparison with hormone-naïve patients. These results will help clinicians in discussing the risks of ADT with patients exhibiting hand joint symptoms. For patients receiving ADT who suffer from hand joint symptoms, we must consider the adverse effects of ADT. To the best of our knowledge, this is the first study to demonstrate the prevalence of hand joint symptoms in both ADT-treated and hormone-naïve Japanese patients with prostate cancer.

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**Conflicts of interest**

There are no conflicts of interest.

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