

FATIGUE AND MUSCLE FUNCTION IN PROSTATE CANCER SURVIVORS RECEIVING DIFFERENT TREATMENT REGIMENS



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FADIGA E FUNÇÃO MUSCULAR EM SOBREVIVENTES DE CÂNCER DE PRÓSTATA EM DIFERENTES TRATAMENTOS

FATIGA Y FUNCIÓN MUSCULAR EN SOBREVIVIENTES DE CÁNCER DE PRÓSTATA EN DIFERENTES TRATAMIENTOS

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ABSTRACT

Introduction: Prostate cancer is the most prevalent neoplastic disease in men. After diagnosis, different treatment regimens are proposed based on the stage of the cancer. These treatments affect physical and muscle function, quality of life, and prognosis differently. **Objectives:** To assess fatigue, muscle strength, muscle thickness, and muscle quality in prostate cancer survivors undergoing androgen deprivation therapy (ADT). **Methods:** Ten ADT patients, eight non-ADT patients and 18 healthy control subjects were enrolled in this study. Perceived fatigue was assessed through the 20-item Multidimensional Fatigue Inventory. Muscle thickness and quality (e.g., echo intensity) were assessed through B-mode ultrasound. Muscle strength and work capacity were assessed using an isokinetic dynamometer. The groups were compared with one-way ANOVA and Bonferroni adjustment. **Results:** Muscle thickness, peak torque, and work capacity were lower in ADT than in the control group (CON) ($p = 0.021$; $p = 0.005$; $p < 0.001$, respectively). ADT showed greater echo intensity than CON ($p = 0.005$) and N-ADT ($p = 0.046$). There were no differences between N-ADT and CON in terms of muscle thickness, peak torque, work capacity, and echo intensity ($p > 0.05$). General fatigue was greater in both ADT ($p = 0.030$) and N-ADT ($p = 0.047$) compared to CON. Physical fatigue was greater in ADT than CON ($p = 0.006$). **Conclusion:** ADT patients showed lower levels of muscle function and greater levels of perceived fatigue than healthy control subjects. It appears that muscle function remains lower in ADT patients, even several years after treatment initiation, although this does not apply to non-ADT patients. **Level of evidence II; Diagnostic Studies - Investigating a Diagnostic Test.**

Keywords: Prostatic neoplasms; Fatigue; Muscle strength; Physical fitness.

RESUMO

Introdução: O câncer de próstata é a doença neoplásica mais frequente nos homens. Após seu diagnóstico, diferentes métodos de tratamento são propostos baseados no estágio do câncer. Esses tratamentos afetam diferentemente a função física e muscular, qualidade de vida e o prognóstico. **Objetivos:** Avaliar a fadiga, força muscular, espessura muscular e a qualidade muscular dos sobreviventes ao câncer de próstata que foram submetidos a terapia de privação androgênica (ADT). **Métodos:** Dez pacientes ADT, oito não ADT (N-ADT) e 18 indivíduos saudáveis no grupo controle (CON) foram inscritos neste estudo. A fadiga percebida foi avaliada através do Multidimensional Fatigue Inventory composto por 20 itens. A espessura e qualidade musculares (eco-intensidade) foram avaliadas através de um aparelho de ultrassom B-mode. A força muscular e a capacidade de trabalho foram avaliadas utilizando um dinamômetro isocinético. Os grupos foram comparados através de ANOVA de um fator e ajuste de Bonferroni. **Resultados:** O grupo ADT apresentou menor espessura muscular, pico de torque e capacidade de trabalho do que o grupo controle ($p = 0,021$; $p = 0,005$; $p < 0,001$, respectivamente). O grupo ADT demonstrou maior eco-intensidade que o grupo controle ($p = 0,005$) e N-ADT ($p = 0,046$). Não foram encontradas diferenças entre o grupo N-ADT e CON quanto à espessura muscular, pico de torque, capacidade de trabalho e eco-intensidade ($p > 0,05$). A fadiga geral foi maior tanto no grupo ADT ($p = 0,030$) quanto no grupo N-ADT ($p = 0,047$) quando comparada ao grupo CON. A fadiga física foi maior no grupo ADT do que no grupo CON ($p = 0,006$). **Conclusão:** Os pacientes submetidos à terapia de privação androgênica demonstraram menores níveis de função muscular e maiores níveis de fadiga percebida do que os indivíduos saudáveis do grupo controle. Parece que a função muscular permanece menor em pacientes submetidos à ADT vários anos após o início do tratamento, o que não ocorre com os pacientes N-ADT. **Nível de evidência II; Estudos diagnósticos - Investigação de um exame para diagnóstico.**

Descritores: Neoplasias da próstata; Fadiga; Força muscular; Aptidão física.

RESUMEN

Introducción: El cáncer de próstata es la enfermedad neoplásica más frecuente en los hombres. Después de su diagnóstico, diferentes métodos de tratamiento son propuestos basados en la etapa del cáncer. Estos tratamientos afectan de forma diferente la función física y muscular, la calidad de vida y el pronóstico. **Objetivos:** Evaluar la fatiga, fuerza muscular, espesor muscular, y la calidad muscular de sobrevivientes al cáncer de próstata que fueron sometidos a la terapia de privación de andrógenos (ADT). **Métodos:** Diez pacientes ADT, ocho no ADT (N-ADT) y 18 individuos sanos en el grupo control (CON) fueron inscritos en este estudio. La fatiga percibida fue evaluada a través del Multidimensional Fatigue Inventory compuesto por 20 ítems. El espesor y calidad muscular (eco intensidad) fueron evaluadas a través de un aparato de ultrasonido B-mode. La fuerza muscular y la capacidad de trabajo fueron evaluadas en un dinamómetro isocinético. Los grupos fueron comparados a través de ANOVA de un factor y ajuste de



Bonferroni. Resultados: El grupo ADT demostró menor espesor muscular, pico de torque y capacidad de trabajo que el grupo control ($p = 0,021$; $p = 0,005$; $p < 0,001$, respectivamente). El grupo ADT demostró mayor eco intensidad que el grupo control ($p = 0,005$) y N-ADT ($p = 0,046$). No se encontraron diferencias entre el grupo N-ADT y el grupo CON, con respecto al espesor muscular, pico de torque, capacidad de trabajo y eco intensidad ($p > 0,05$). La fatiga general fue mayor tanto en el grupo ADT ($p = 0,030$) como en el grupo N-ADT ($p = 0,047$), cuando comparada al grupo CON. La fatiga física fue mayor en el grupo ADT que en el grupo CON ($p = 0,006$). Conclusión: Los pacientes sometidos a la terapia de privación de andrógenos demostraron menores niveles de función muscular y mayores niveles de fatiga percibida que los individuos saludables del grupo control. Parece que la función muscular permanece menor en pacientes sometidos a ADT varios años después del inicio del tratamiento, lo que no ocurre con los pacientes N-ADT.

Nivel de evidencia II; Estudios de diagnóstico - Investigación de un examen de diagnóstico.

Descriptor: Neoplasias de la próstata; Fatiga; Fuerza muscular; Aptitud Física.

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INTRODUCTION

Prostate cancer (PC) is classified as a global burden issue by the World Health Organization, since it is the most prevalent neoplastic disease in men.¹ Only in United States, PC is responsible for 20% of new cancer diagnoses in men.² The rises in PC's incidence is related to population ageing and to the exposure to risk factors, such as unhealthy lifestyles.³ Although aging could be considered the main risk factor, lifestyle and ethnicity also affects PC's incidence.^{3,4}

After diagnosis, several interventions could be applied to treat PC. The most prevalent treatment regimens in early stages of PC are radiotherapy, radical prostatectomy, or the combination between them.^{5,6} However, in progressive stages of PC, androgen deprivation therapy (ADT) is widely used in order to reduce testosterone levels and attenuate PC's progression, leading to fall in 90% of prostatic specific antigen.

Although all regimens of treatment aim to defeat PC, they could affect distinctly quality of life and physical function.⁷ Therefore, both cancer and therapy could induce late side effects directly related to severity of such therapy and disease.^{5,8} PC survivors submitted to radiotherapy and radical prostatectomy usually report urinary dysfunction, sexual impotence, and intestinal disorders.⁹ Otherwise, PC survivors submitted to ADT could report cardiovascular impairments, depression, anemia, osteoporosis, and loss of muscle tissue. Recent studies showed the effect of ADT after only three months of treatment, leading to lower strength and functionality, and greater fatigue than non-ADT PC survivors.¹⁰ Furthermore, long-term ADT could deteriorate physical function and increase the risk of cardiovascular disease, insulin resistance and metabolic syndrome.^{11,12}

Considering that both incidence and survivorship are rising due to aging population, unhealthy habits and screening improvement, the growing population of survivors requires specialized follow-up and care.¹³ Only two studies have examined physical functions in PC survivors submitted do ADT and non-ADT.¹⁰ However, both studies only assessed survivors up to 12 months after the treatment beginning. Also, both studies used non-gold standard field tests to assess muscle function. Therefore, it is mandatory to understand the effects of different regimens of treatment for prostate cancer in order to provide a better long-term care and to clarify the magnitude of late side effects, even several years after the beginning of therapy. So, the purpose of the present study was to assess muscle strength, muscle thickness and muscle quality in prostate cancer survivors submitted to androgen deprivation therapy. Therefore, prostate cancer survivors submitted to ADT were compared to prostate cancer survivors submitted to non-ADT and to control healthy subjects.

METHODS

Subjects

All participants were volunteers recruited from community, by word of mouth and advertisements on Internet. Prostate cancer survivors were

also recruited from public and private local hospitals. The participants were informed of the purpose, procedures and risks of the study prior to signing an informed consent. The procedures were approved by the University Institutional Review Board. Ten PC survivors were included in ADT group, eight PC survivors that undergone non-ADT therapies, such as radical prostatectomy and/or radiotherapy, were included in N-ADT group, and eighteen control healthy subjects matched by age were included in control group (CON). Patients were included in ADT and N-ADT groups if they were diagnosed with non-metastatic prostate cancer through a prostate biopsy. Additionally, participants included in ADT group must have been performing androgen deprivation therapy for at least 12 months. Healthy control subjects included in CON were selected based on similar age and absence of cancer diagnosis. Participants were excluded of this study if they were diagnosed with hypertension, cardiovascular, metabolic and/or neuroendocrine disease, and/or had any orthopedic limitation. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research ethical committee (CAAE: 94882218.8.0000.0023) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Experimental procedures

After signing the informed consent form, the participants reported to the Strength Training Research Laboratory for testing. All groups performed the following tests and evaluations in the same sequence: 1) self-perceived fatigue, 2) anthropometrics measurements, 3) muscle thickness and echo intensity, and 4) strength and work capacity. All evaluations were performed at the same period of the day (afternoon), by the same researcher, in a controlled temperature room, from January to April 2018. All participants were asked to follow pre-assessment guidelines before reporting to the laboratory including: avoid physical exertion for at least 48 hours prior to the evaluations.

Self-perceived fatigue

Self-perceived fatigue was measured through MFI-20. This questionnaire was designed to assess different levels of fatigue between different subjects, groups and/or different conditions, as well as various populations. Several dimensions comprise the questionnaire, which measure fatigue experienced in previous days. In this study, general fatigue and physical fatigue were used as markers of self-perceived fatigue.

Muscle thickness and quality

Muscle thickness (MT) was measured using B-mode ultrasound (Philips, VMI, Brazil). A 7.5-MHz scanning probe was placed on the skin perpendicular to the tissue interface. The scanning probe was coated with a water-soluble transmission gel to provide acoustic contact without

depressing the dermal surface. No additional pressure was applied to standardize the compression on the dermal surface. Before measurement, all volunteers rested for 10 minutes in order to guarantee the rest condition and to avoid the influence of any body fluids disordered by walking. The MT images were determined in lower-body muscles including the rectus femoris and vastus intermedius. The measurement was taken at 60% of the distance from the greater trochanter to the lateral epicondyle and 3 cm lateral to the midline of the anterior thigh. Once the examiner found a satisfactory image, it was frozen, stored and analyzed using the software Image-J (National Institute of Health, USA, version 1.49). The distance between subcutaneous adipose tissue-rectus femoris interface and vastus intermedius-bone interface was designated as MT. All measurements and analyses were performed three times by the same researcher and the mean value was used for analysis.

Muscle quality was assessed by echo intensity (EI). The EI was determined by gray-scale analysis using the standard histogram function Image-J. In order to assess EI in the rectus femoris, a region of interest was selected in muscle without any bone or surrounding fascia, with a depth limit of 5 cm. When this setting was insufficient to display the entire muscle, only the superficial part was used for analysis. A reliable measurement of EI is extracted from a minimum of 15% of muscle area.¹⁴ The EI was expressed in values between 0 (black) and 256 (white). The increase in EI value represents a decrease in muscle quality. In our laboratory, the ultrasound intra-rater reliability was 0.94 and the coefficient of variation was 2.4%.

Peak torque and work capacity

Isokinetic muscle strength (peak torque (PT)) and work capacity (WC) was measured using an isokinetic Biodex System 3 (Biodex Medical, Inc., Shirley NY, USA) dynamometer. Subjects were positioned on the dynamometer seat with safety belts fastened to the trunk, pelvis and thigh to avoid extraneous body movements. The lateral epicondyle of the femur was used to align the knee rotation axis and the dynamometer rotation axis, allowing free knee extension and flexion from 85° flexion to full extension. Gravity correction was obtained by measuring the torque exerted by the lever arm and the participant's leg at 30° flexion as well as in a relaxed position. The values of the isokinetic variables were automatically adjusted for gravity with the software Biodex Advantage (Biodex Medical, Inc., Shirley NY, USA). The calibration of dynamometer was carried out according to the specifications provided by the manufacture. For the test, participants were asked to cross their arms across the chest. The same researcher carried out the test procedures for all participants and provided verbal encouragement.

As part of warm-up and familiarization with isokinetic knee extension and warm-up, subjects performed one set of 10 submaximal knee isokinetic extension at 120°/s.¹ Two minutes after familiarization/warm-up session, volunteers performed two sets of four maximal isokinetic knee extension at 60°/s.¹⁵ The greatest torque achieved in both sets was considered (PT). WC was also measured on the right knee extensors. Three minutes after strength protocol, volunteers performed 30 maximal isokinetic knee extensions at 120°/s for WC evaluation. Work capacity was calculated as the amount of torque produced throughout the entire range of motion of all repetitions. Test-retest reliability coefficient (ICC) value for knee extensor peak torque was 0.91 in our laboratory.

Statistical Analysis

Data are presented as mean ± standard deviation. Normal distribution parameters were checked with Shapiro-Wilk test. To compare anthropometric characteristics, muscle strength, muscle quality and perceived fatigue between all groups, one-way analyses of variance were used. The Bonferroni adjustment was applied as post-hoc analysis. The Statistical Package for Social Sciences (SPSS), version 21.0 (IBM, USA) was used for all analyses. The alpha level was set at 5% ($p \leq 0.05$).

RESULTS

Ten PC survivors composed ADT group, eight PC survivors composed N-ADT group, and 18 apparently healthy men composed CON group. ADT and N-ADT clinical characteristics are reported in Table 1.

Descriptive and comparative data analysis of ADT, N-ADT and CON are reported in Table 2. No significant differences in any physical characteristics between ADT, N-ADT and CON were observed ($p > 0.05$).

Muscle function, muscle quality and fatigue variables are presented in Figure 1. The one-way analyses of variance showed a significant effect between groups on muscle thickness ($F = 4.158$; $p = 0.025$), peak torque ($F = 5.983$; $p = 0.006$), work capacity ($F = 9.529$; $p = 0.001$), echo

Table 1. Clinical Characteristics of ADT and N-ADT, expressed as mean ± SD.

Clinical Characteristics	ADT (n = 10)	N-ADT (n = 8)
Sessions of CT	3.90 ± 1.29	0
Sessions of RT	2.50 ± 4.08	4.63 ± 4.69
Years from treatment begins	5.10 ± 3.12	5.60 ± 3.53
Age at diagnosis	69.80 ± 5.57	64.75 ± 4.58

CT: chemotherapy; RT: radiotherapy; ADT: androgen deprivation therapy group; N-ADT: non-androgen deprivation therapy.

Table 2. Descriptive and comparative data of all groups, expressed in mean ± standard deviation.

Variable	ADT (n = 10)	N-ADT (n = 08)	CON (n = 18)
Age (years)	74.40 ± 5.76	69.75 ± 5.92	72.17 ± 6.54
Weight (kg)	77.44 ± 14.75	82.25 ± 9.20	77.94 ± 9.47
Height (m)	1.63 ± 0.07	1.70 ± 0.07	1.69 ± 0.07
BMI (kg.m ⁻²)	28.87 ± 4.42	28.68 ± 3.41	27.40 ± 2.91

ADT: androgen deprivation therapy group; N-ADT: non-androgen deprivation therapy; CON: control group; BMI: body mass index.

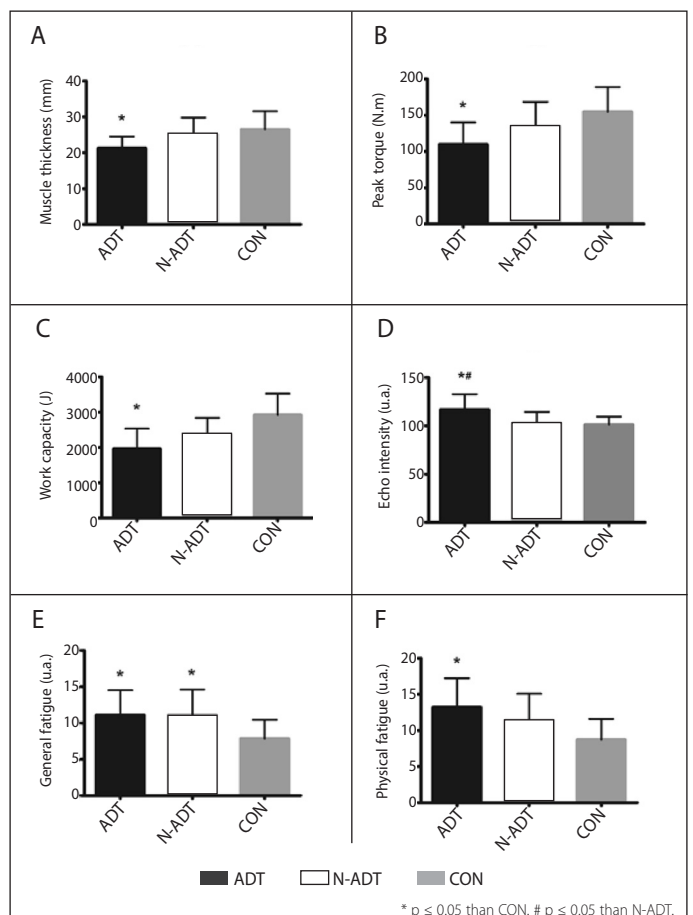


Figure 1. Variables of muscle function and fatigue in ADT, N-ADT and CON. (A) muscle thickness, (B) peak torque, (C) work capacity, (D) echo intensity, (E) general fatigue, (F) physical fatigue.

intensity ($F = 6.192$; $p = 0.005$), general fatigue ($F = 5.244$; $p = 0.011$), and physical fatigue ($F = 5.880$; $p = 0.007$). ADT group showed lower muscle thickness, peak torque, and work capacity than CON ($p = 0.021$; $p = 0.005$; $p < 0.001$, respectively). ADT showed greater echo intensity than CON ($p = 0.005$) and N-ADT ($p = 0.046$). There were no differences between N-ADT and CON on muscle thickness, peak torque, work capacity, and echo intensity ($p > 0.05$). General fatigue was greater in both ADT ($p = 0.030$) and N-ADT ($p = 0.047$) compared to CON. Physical fatigue was greater in ADT than CON ($p = 0.006$). There was no difference between N-ADT and CON on physical fatigue ($p = 0.797$).

DISCUSSION

The purpose of the present study was to assess muscle strength, thickness and quality in prostate cancer survivors submitted to androgen deprivation therapy, and to compare ADT patients to non-ADT patients and control healthy subjects. Therefore, the main results suggest that ADT patients showed lower muscle thickness and function, and greater perceived fatigue than control healthy subjects. Also, non-ADT prostate cancer survivors showed greater general fatigue than control healthy subjects, despite no differences in muscle function between them.

Testosterone inhibition in PC patients could affect skeletal muscle tissue due to upregulation of myostatin, imbalance between muscle protein breakdown and synthesis, and attenuation of hypertrophic pathways Akt/mTOR/P70S6K.^{16,17} Moreover, mitochondrial dysfunction induced by both disease and treatment could affect skeletal muscle tissue due to reductions in AMPK and PGC1- α expression, and reactive oxygen species overproduction.¹⁸ In this study PC patients submitted to ADT showed lower muscle thickness than CON, while no difference was observed between non-ADT patients and CON. Likewise, Chang et al. (2014)¹⁹ showed a substantial reduction in muscle tissue of PC survivors after 20 week of testosterone deprivation. Indeed, such reduction could last for several years after the treatment beginning, as suggested in this study.

Regarding muscle strength, ADT patients showed lower peak torque than CON, while no difference was observed between non-ADT patients and CON. Considering that muscle strength is directly related to muscle tissue amount,¹⁶ the lower peak torque in ADT compared to CON could be explained by the lower muscle thickness. Moreover, physiological dysfunctions induced by both treatment and disease, such as Warburg effect, acidosis and oxidative stress, could also reduce muscle strength.^{20,21} Therefore, several studies have already showed lower muscle strength in ADT patients compared to CON.²² However, this study showed that muscle strength remains lower in ADT patients compared to healthy subjects even several years after the treatment beginning.

Furthermore, physiological impairments induced by both cancer and treatment could also affect the ability of the muscle tissue to perform multiple repetitions or prolonged tasks, exposing fatigue objectively. Falls in work capacity occurs due to reduced glycogen content and impaired glucose transport in response to insulin.²³ Cancer survivors may show an increased systemic acidity due to Warburg effect and overproduction of hydrogen ions,²⁴ which affect glycogen's production and content. Otherwise, insulin sensibility could also affect glucose transportation and work capacity. The inflammatory imbalance in cancer survivors could play a role in insulin resistance, since an increased pro-inflammatory cytokines release reduces insulin sensibility.²⁵ Furthermore, insulin resistance is a well-established adverse effect of ADT, induced by gonadotropin-releasing hormone agonists.²⁶ Therefore, it is not unexpected that PC survivors submitted to ADT show lower work capacity, even several years after the treatment beginning.

Echo intensity is frequently used as an indicator of muscle quality because it represents the accumulation of intramuscular adipose and connective tissue. A decreased muscle quality has already been reported in diseases such as chronic obstructive pulmonary disease and diabetes.²⁷ However, in cancer survivors, de Lima FD, et al. (2018)¹⁵ showed no differences between physically active Hodgkin's lymphoma survivors and healthy subjects matched by age and gender. Apparently, active Hodgkin's lymphoma survivors recover their muscle characteristics and functions after treatment, and time since treatment completion seems to affect positively muscle function in Hodgkin's disease.¹⁵ In our study, PC survivors submitted to ADT showed worse muscle quality than both non-ADT patients and control healthy subjects, even several years after the treatment beginning. Such phenomenon could be justified by imbalance between protein breakdown and synthesis,^{16,17} and metabolic dysfunctions.²⁶

Another interesting finding of this study is the greater general fatigue reported by both ADT and non-ADT PC survivors, while only ADT patients showed a greater physical fatigue compared to control healthy subjects. An increased general fatigue is widely reported in cancer survivors and has been already described in several cancer types.^{28,29} According O'Higgins, et al. (2018)³⁰ a cascade of biochemical, physiological, and psychological dysregulation of important biological systems contribute to cancer-related fatigue. Actually, a greater general fatigue is reported by cancer survivors even when muscle functions are preserved,¹⁵ suggesting that disease may play a role in general fatigue more than treatment.

Otherwise, only ADT patients showed greater physical fatigue than control healthy subjects. The physical fatigue assessed in Multidimensional Fatigue Inventory 20-item is related to the perception of physical exhaustion and could be indeed related to muscle characteristics and functions. Consequently, the increased physical fatigue in ADT patients is explained by the worse muscle strength, muscle thickness, muscle quality and work capacity compared to control healthy subjects.

This cross-sectional study was not without limitations. An important limitation was the small size of the sample. Evidently, these statements above are simply speculations at this time and more research is needed to confirm or refute these possibilities. However, this study should be seen as a hypothesis-generating study, providing initial information about fatigue mechanisms and muscle function in prostate cancer survivors even several years after the treatment beginning. Also, to the best of our knowledge, this is the first study that applied both subjective and objective markers of fatigue together. For future research, it is recommended that a larger sample size and other cancer types be included.

CONCLUSION

In summary, a lower level of muscle function and a higher level of self-perceived fatigue were observed in prostate cancer survivors submitted to androgen deprivation therapy compared to control healthy subjects with matched age. It appears that muscle function remains lower in ADT patients even several years after the treatment beginning, which does not occur with non-ADT patients, since no differences were observed in muscle function between non-ADT patients and control healthy subjects. Further investigations are required to clarify if strategies, such as exercise, can attenuate or even reverse these debilitating side effects of androgen deprivation therapy.

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