EDITORIAL

Supervised exercise to reduce cardiovascular morbidity of androgen deprivation therapy for prostate cancer

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Prostate cancer (PA) is the most common cancer in men in the United States. With prostate-specific antigen (PSA) screening, most new cases are diagnosed at a localized stage with an excellent prognosis. As a result, the number of PA survivors has increased significantly. There were over 3.3 million PA survivors in the United States in 2016.[1] More than 64% of them were older than 70 years of age, and many of them had medical comorbidities. A study by Epstein et al[2] concluded that men with PA in the United States have a higher chance of dying from other causes than cancer.[2] Ischemic heart disease accounts for 24% of all deaths, compared to 16% from PA.

Androgen deprivation therapy (ADT) is the main treatment for metastatic PA. More recently, the use of ADT has been expanded to include patients with localized disease. The current National Comprehensive Cancer Network guidelines (version 1.2017) include the options of external beam radiation with 4 to 6 months of ADT for intermediate-risk PA, and with 2 to 3 years of ADT for high-risk PA. Randomized trials have also shown the benefit of adding ADT to salvage radiation therapy (RT) for patients with biochemical relapse of PA after surgery.[3] With the increased use of ADT, it is estimated that 45% of Medicare patients with PA have received ADT as part of their treatment.[4]

Unfortunately, ADT causes many side effects including vasomotor symptoms, sexual dysfunction, decrease in muscle mass and strength, increase in adiposity, decrease in bone density, metabolic syndrome, cardiovascular disease, diabetes, depression, and decline in cognitive function. In a cohort of patients aged 66 years or older, the use of gonadotropin-releasing hormone (GnRH) agonist was associated with a significantly increased risk of diabetes, coronary heart disease, myocardial infarction, and sudden cardiac death.[5] The increased risk of coronary heart disease and diabetes was seen in patients who received GnRH agonists for a period as short as 1 to 4 months. Patients with preexisting heart disease are at even higher risk of cardiac events after using ADT.[6] Despite the findings of these observational studies, there is controversy with regard to the cardiovascular effects of ADT on patient survival. Randomized trials using ADT with radiation have failed to show an increase in cardiovascular death among men randomized to receive GnRH agonists.[7]

Exercise can mitigate the cardiovascular and metabolic side effects of ADT. In a study by Corme el al,[8] 63 patients were randomized to either 3 months of supervised exercise or usual care at the time of initiation of ADT. At the end of the intervention, patients in the exercise group had better preservation of lean muscle mass, less gain in fat mass, and improved cardiovascular fitness. Gaskin et al[9] showed that a 12-week community-based exercise program was feasible. Patients in the exercise group achieved significantly better 6-minute walk test distance and other parameters of physical strength. In another randomized study, patients assigned to a 6-month dietary and physical activity intervention achieved a significant reduction in weight, body mass index, and percentage fat mass compared with the usual-care group.[10] A systematic review concluded that exercise training resulted in improvement in muscle strength, cardiorespiratory fitness, functional task performance, lean body mass, and fatigue.[11] However, most of the published studies have a relatively small number of patients and short duration of intervention as well as follow-up.

In this issue of the *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Hojan et al[12] reported the results of a randomized study to evaluate the effects of a 12-month exercise program on inflammatory and cardiometabolic factors as well as functional status on patients receiving ADT and

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RT for intermediate- and high-risk PA. Their hypothesis was that supervised exercise would improve inflammation and lipid status, cardiorespiratory capacity, reduce abdominal fat mass, and enhance quality of life (QoL). Patients received 3 to 5 months of ADT prior to RT, plus additional ADT during and after RT, for a total of 36 months. In the experimental arm, patients had supervised exercise in the rehabilitation department for 12 months. Patients in the usual-care arm were given printed instructions to perform moderate activity at home 5 d/wk. The outcome measure assessment was done at 3 time points: 1) baseline at 1 week before the onset of RT (assessment I); 2) 1 week after the end of RT (after 8 weeks of the program; assessment II); 3) final assessment after 10 months (12 months of the study time; assessment III). Serum levels of proinflammatory markers (interleukin [IL] 1β, IL-6, tumor necrosis factor α) and biochemical markers were assessed. Other measurements included anthropometric parameters, aerobic capacity, functional assessment using the FACT-F and QoL questionnaires of the European Organization for Research and Treatment of Cancer (EORTC).

The study demonstrated benefits of the supervised exercise program over usual care with regard to the anthropometric parameters (weight control, change in body mass index, waist-to-hip ratio) and functional parameters. There was also an improvement in numerous QoL measurements. These findings were generally consistent with other published studies evaluating the effects of exercise on patients receiving ADT.

No significant change in the lipid profile with exercise was found in the study. The changes in the level of proinflammatory markers at different assessment points were more difficult to interpret. There was an increase in all 3 markers at assessment II as compared with the baseline, which could be a response of the body to RT injury. Although the authors reported in the Results section that the highest level of TNF-α was seen in assessment II, data in table 2 showed that the highest level actually occurred at assessment III. The same was true for IL-1β. Presumably, the inflammatory effect of RT would have subsided by 12 months, yet only the IL-6 level declined at assessment III as compared with assessment II. The increase in the cytokine level in the exercise group was lower than in the usual-care group, and the authors attributed that to the positive effect of exercise on anti-inflammatory factors. In contrary to IL-1β and TNF-α, IL-6 levels declined at assessment III. Only the levels of IL-6 showed a significant change ($P < 0.001$). No significant correlation between the cytokine levels and lipid and anthropometric parameters in both groups of patients was found. The data did not allow a definitive conclusion to be made with regard to the level of these cytokines in relationship to the extent of cardiovascular toxicity from ADT. A shortcoming of the study was the timing of the baseline assessment. It was performed 1 week before the start of RT, which meant that patients had already received about 3 to 5 months of ADT. The detrimental effects of ADT could be present even after 1 to 4 months of the treatment.[5] The baseline levels of cytokines and other biochemical markers were obtained when these patients were already in a hypogonadal state, which would confound the interpretation of the data. By changing the baseline assessment to before ADT was initiated and adding another measurement after patients had completed ADT, the result might provide a clearer picture of the kinetics of cytokine levels in response to ADT and exercise.

To enroll 72 participants for this study, 826 patients were screened. A relevant question is whether participants in the study are representative of the general population of patients with PA, many of whom are elderly patients with comorbidities. Participants in the study might be healthier than the general population of patients seen in routine clinical practice. In order to include most of the patients receiving ADT, an exercise program would need to be tailored and individualized to increase the chance of patient compliance.

One strength of the study was the use of 12 months of supervised exercise, which was among the longest durations used in similar studies. There was an impressive retention rate of the participants to complete the program, likely a result of the effort of the study staff. It demonstrated that such a program would be feasible in an outpatient rehabilitation department. This study adds to the existing literature supporting the use of exercise program for patients treated with ADT.

The best way to minimize the detrimental effects of ADT on patients is by limiting its use only in patients for whom the benefits clearly outweigh the side effects. There is significant heterogeneity in both high-risk and intermediate-risk PA. For instance, a patient with a clinical stage T1c, PSA 5 ng/ml, and 1 of 12 biopsy cores showing Gleason 3+4 PA is likely to have a better prognosis than another patient with clinical stage T2c, PSA 16 ng/ml, and 9 of 12 biopsy cores showing Gleason 4+3 cancer, yet both would be categorized as having intermediate-risk disease, and ADT would be routinely recommended to both patients. Future studies should recognize the heterogeneity of risk groups with the goal to identify subgroups of disease that would benefit the most by adding ADT, while avoiding its use in subgroups that derive minimal benefits. Larger studies on the effect of exercise with long-term follow-up would be needed to evaluate whether the intervention would translate into better survival. Analogous to cardiac rehabilitation program for patients after a cardiac event, lifestyle intervention, including exercise program and dietary modification, should be routinely offered as part of the PA survivorship care.

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