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SIMBOSPROST: Prevalence of metabolic syndrome and osteoporosis in prostate cancer patients treated with radiotherapy and androgen deprivation therapy: A multicentre, cross-sectional study

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ABSTRACT

Aim: To assess the prevalence of metabolic syndrome (MetS) and osteoporosis in patients with prostate cancer (PCa) treated with radical radiotherapy (RT) with or without androgen deprivation therapy (ADT).

Background: Worldwide, the prevalence of MetS is estimated to range from 20% to 25% of the adult population. However, prevalence rates are much higher in PCa patients (pts) who undergo ADT.

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Materials and methods: Multicentre cross-sectional study of 270 pts in Spain with PCa. Patients were divided into 3 groups based on the duration of ADT (6, 12–18, ≥24 months) and compared to a control group without ADT. MetS was defined according to NCEP ATP III criteria. Osteoporosis was assessed by DEXA.

Results: A total of 270 pts, treated from November 2011 to October 2012, were included. Of these, 122 pts (47%) fulfilled the criteria for MetS. The median age of this group was significantly higher (71.3 vs. 69.38 years, $p = 0.028$). MetS prevalence was 50% in the control group. In pts who received ADT, prevalence was 44.8% after 6 months of ADT, 45.3% after 12–18 months, and 50% after ≥24 months (pns). Most pts (168/270; 62%) underwent DEXA. Of those tested, 78 (46.4%) had osteopenia and only 11 (6.5%) had osteoporosis.

Conclusions: The prevalence of MetS in pts with PCa treated with radical RT was higher (47%) than in the general population. However, there were no significant differences in the duration of ADT administration. The prevalence of osteoporosis was low. These findings suggest that the prevalence of MetS in PCa patients may be higher than previously reported.

1. Background

Most patients diagnosed with prostate cancer (PCa) will be treated with surgery and/or radical radiotherapy. In many cases, these patients will also receive androgen deprivation therapy (ADT), which, when combined with radical radiotherapy, has been shown to modestly improve survival in locally advanced and high-risk disease.[1,2] However, despite its beneficial effects on survival, ADT may also induce numerous adverse effects, including sexual and cognitive dysfunction, bone mass loss, insulin resistance, dyslipidemia, and anaemia.[3]

Several of these adverse effects overlap with the metabolic syndrome (MetS), a combination of interrelated risk factors (hyperglycemia, hypertension, hypertriglyceridemia, low levels of high-density lipoproteins (HDL) cholesterol, and central obesity) for the development of cardiovascular disease (CVD) and type 2 diabetes. While the worldwide prevalence of MetS in the general population is estimated to range from 20% to 30%,[4] MetS prevalence is reported to be approximately 50% in PCa patients treated with ADT.[5] Rates of osteoporosis are also higher in this patient population (35.4–49.2%) versus the general population.[6,7]

In most cases of PCa, the disease progresses relatively slowly, even without treatment. As a consequence, a large percentage of these patients will ultimately die of causes unrelated to the cancer itself. In some cases, however, the cause of death has been attributed to the treatment itself,[8] particularly ADT, which has been linked to the development of MetS and diabetes.[6,9] Nevertheless, the question of whether ADT induces the development of MetS remains uncertain. A recent report[10] found that although ADT appears to induce changes in some of the components of MetS after 12 months of administration, it does not appear to increase rates of full MetS. However, other studies have reported that prevalence may increase as a function of the duration of ADT administration.[11–13] As a result, the long-term association between MetS, osteoporosis, and ADT remains controversial and poorly understood, as a recently reported meta-analysis found.[5]

2. Aim

Given the knowledge gap described above, the present study was carried out in a large cohort of PCa patients to determine the prevalence of MetS and osteoporosis after short-term (<6 months), medium-term (12–18 months), and long-term (≥24 months) administration of ADT. The main aim was to determine whether the prevalence of these conditions increases with duration of ADT administration. The data presented here provide an update to our interim analysis, reported in the year 2013.[14]

3. Materials and methods

This was a multicenter cross-sectional study of 270 patients diagnosed with localized intermediate or high risk PCa according to NCCN criteria. All patients were treated with radical RT without ADT (50 pts) or with ADT (220 pts). Patient characteristics at diagnosis are shown in Table 1.

The inclusion criteria were as follows: (1) histologically confirmed PCa, (2) localized intermediate or high-risk PCa according to NCCN criteria, (3) scheduled for treatment with radical RT. Patients with nodal involvement, metastasis, or previous prostatectomy with adjuvant RT were excluded. The 270 patients who met the inclusion criteria during the study period (November 2011 to October 2012) were included.

The patient cohort was divided into four groups according to the duration of ADT administration, as follows: group 1, no ADT (50 pts); group 2, 6 months of ADT (60 pts); group 3, 12–18 months of ADT (99 pts); and group 4, ≥24 months ADT (61 pts).

All patients were interviewed to obtain detailed information regarding family and personal history of hypertension, hyperglycemia, hypercholesterolemia, hypertriglyceridemia and specific treatment for those conditions. Waist circumference, blood pressure, weight, and height were measured and levels of glucose, total and HDL-cholesterol, triglycerides and testosterone were assessed and monitored.

The presence of MetS was defined according to the updated NCEP ATP III[4] by the presence of 3 or more of the following

Table 1 – Characteristic of prostate cancer and treatment.

		No ADT	ADT
N	270	50	220
Median age (range)	71 years (51–89)	68 years	71 years
Median PSA (range)	10.5 ng/ml (2.53–268.20)	13.38 ng/ml	24.9 ng/ml
Tumour stage			
• T1c-T2a	85 (31.5%)	24 (8.8%)	61 (22.5%)
• T2b-T2c	136 (50.3%)	20 (7.4%)	116 (42.9%)
• T3a	31 (11.5%)	6 (2.2%)	25 (9.25%)
• T3b	18 (6.6%)	0	18 (6.6%)
Gleason			
• ≤6	69 (25.6%)	12 (4.4%)	57 (21.1%)
• 7	94 (34.8%)	28 (10.3%)	66 (24.4%)
• ≥8	105 (38.9%)	8 (2.9%)	97 (35.9%)
• Unknown	2 (0.7%)	2 (0.7%)	0
Risk group			
• Intermediate	100 (33.3%)	31 (11.4%)	59 (21.8%)
• High	161 (59.6%)	19 (7%)	142 (52.5%)
• Very high	19 (7%)	0	19 (7%)
Median dose EBRT	78 Gy (66.6–80.0)		

five risk factors: (1) waist circumference ≥102 cm, (2) fasting glucose ≥110 mg/dL or previously diagnosed type 2 diabetes, (3) serum triglyceride level ≥150 mg/dL or pharmacological treatment for it, (4) systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or previously diagnosed hypertension, and (5) high-density lipoprotein (cHDL) cholesterol <40 mg/dL.

Osteoporosis was diagnosed by dual energy X-ray absorptiometry (DEXA) and considered to be present when the T score at the hip or spine was ≤2.5. Sixty-two percent (168/270) pts underwent DEXA testing, as follows: 22/50 pts in group 1, 27/60 pts in group 2, 70/99 in group 3, and 49/61 pts in group 4.

The study was approved by all the Clinical Research Ethics Committees at each of the participating hospitals. All patients were required to sign an informed consent form to participate.

4. Results

4.1. *Metabolic health*

Height (cm), weight (kg), waist circumference (cm), systolic and diastolic blood pressure (mm Hg), glycemia (mg/dL), total cholesterol (mg/dL), HDL-cholesterol (mg/dL), triglyceride (mg/dL), testosterone in ng/ml, and body mass index (BMI) are shown in Table 2.

As Table 2 shows, the only significant differences between the four groups were as follows: diastolic blood pressure ($p = 0.004$) and testosterone levels ($p = 0.000$) (both of which were higher in the control group), and BMI, which was higher in group 4 (patients with ≥24 m ADT) ($p = 0.029$).

The majority of pts (232 out of 270; 86%) were overweight. By group, the percentage of overweight pts was as follows: group 1 (78%), group 2 (80%), group 3 (88%), and group 4 (95%) (Fig. 1). Obesity correlated with lower levels of HDL cholesterol ($p = 0.020$) and testosterone levels ($p = 0.007$).

4.2. *Metabolic syndrome*

The number and percentage of patients who fulfilled the criteria for each of the five NCEP components of MetS were as follows: waist circumference ≥102 cm (158/267 pts; 59.2%); HDL-cholesterol ≤40 mg/dL (25/259 pts; 10%); triglyceride levels ≥150 mg/dL or receiving pharmacological treatment for hypertriglyceridemia (86/261pts; 33%); blood pressure > 130/85 mm Hg or receiving pharmacological treatment for hypertension (221/270 pts; 81.9%); and fasting glucose ≥110 mg/dL, previously diagnosed type 2 diabetes, or pharmacological treatment for diabetes (100/270 pts; 37%). No statistically significant differences in any of these parameters were observed between the four groups (data not shown).

MetS was assessed in 259 out of 270 patients (11 pts were not evaluable for MetS due to missing data), as follows: 46/50 pts in group 1; 58/60 in group 2; 97/99 in group 3; and 58/61 in group 4. Based on the NCEP ATP III criteria, 122 pts (47%) fulfilled the diagnostic criteria for MetS.

Patients with MetS were significantly older (median age, 71.3 vs. 69.38 years, $p = 0.028$). Risk factors found to be significantly correlated with MetS included a family history of diabetes (57.6% vs. 44%, $p = 0.045$), and a personal history of obesity (70% vs. 45.5%, $p = 0.039$), hypertension (59% vs. 21.9%,

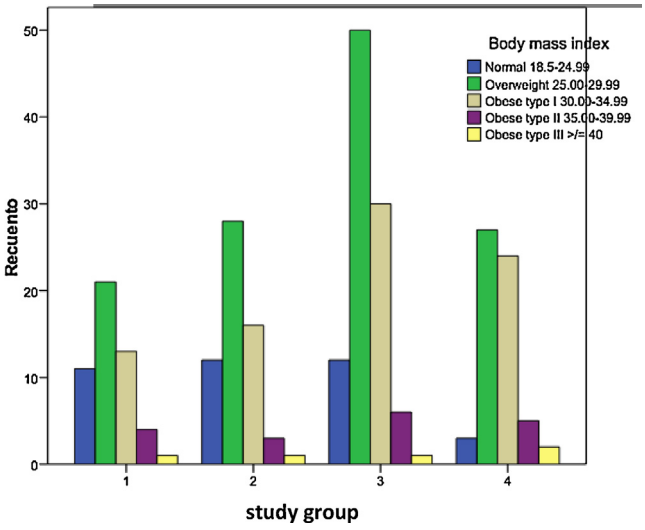

Fig. 1 – Body mass index by study group.

Table 2 – Metabolic Health according to the study group.

	N	Total	Group 1 (no ADT)	Group 2 (6 m ADT)	Group 3 (12–18 m ADT)	Group 4 (>24 m ADT)	p
N		270	50	60	99	61	
Height (cm)	270	167.31 ± 6.4	168.56 ± 6.11	167.18 ± 7.2	167.3 ± 6.2	166.44 ± 6.1	0.31
Weight (kg)	270	81.52 ± 12.8	80.7 ± 12.9	79.3 ± 12.4	81.4 ± 12.2	84.4 ± 13.6	0.176
Waist circumference (cm)	267	104.82 ± 10.9	104.1 ± 10.8	102.4 ± 9.5	105.4 ± 10.2	106.5 ± 12.9	0.242
Systolic blood pressure	270	140.69 ± 18.941	140.9 ± 17.2	134.9 ± 17.1	142.2 ± 20.5	143.6 ± 18.5	0.054
Diastolic blood pressure	270	76.66 ± 10.958	81.54 ± 11.3	75.13 ± 9.4	76.2 ± 10.3	74.7 ± 12.3	0.004
Glycemia (mg/dL)	263	112.3 ± 28.5	113.5 ± 36.4	108.1 ± 19.1	111.6 ± 28.1	116.9 ± 30.4	0.389
Total cholesterol (mg/dL)	263	202.7 ± 38.5	200.4 ± 38.3	202.1 ± 37.1	207.12 ± 40.9	198.1 ± 36.2	0.515
HDL cholesterol (mg/dL)	247	56.4 ± 17	51.3 ± 14.65	56.7 ± 16.5	58.1 ± 18.5	56.9 ± 15.9	0.196
Triglyceride (mg/dL)	259	132.1 ± 77.3	128.39 ± 76.37	133.21 ± 79.82	137.32 ± 87.73	125.34 ± 54.83	0.800
Testosterone (ng/ml)	240	0.75 ± 1.73	4.04 ± 3.18	0.27 ± 0.39	0.28 ± 0.45	0.22 ± 0.12	0.000
Body mass index	270	29.10 ± 4.11	28.45 ± 4.50	28.41 ± 4.18	29.05 ± 3.7	30.39 ± 4.07	0.029

$p = 0.000$), or diabetes (76.4% vs. 39.2%, $p = 0.000$). The metabolic profile of pts according to the presence or not of MetS is shown in Table 3. The patients with MetS showed a non-significant trend towards lower testosterone levels.

4.3. *Analysis by study group (Table 4)*

The groups did not differ significantly in terms of MetS prevalence: 50% in group 1, 44.8% in group 2, 45.3% in group 3, and 50% in group 4. The only pts with normal testosterone levels were those in group 1 (no ADT) who did not develop MetS.

A diagnosis of MetS was significantly correlated with the following factors: personal history of hypertension and antihypertensive treatment (groups 1, 2, 3); family history of diabetes (group 2); and personal history of diabetes and antidiabetic treatment (groups 3 and 4)

4.4. *MetS in high-risk prostate cancer*

The presence of MetS did not correlate with any of the following parameters: NCCN risk group ($p = 0.892$), Gleason score ($p = 0.820$), or tumour stage ($p = 0.934$).

4.5. *Bone health*

Of the 168 pts who underwent DEXA testing, 78 (46.4%) presented osteopenia. By study group, osteopenia rates were as follows: group 1, 11/22 pts (50%); group 2, 13/27 pts (48.1%); group 3, 29/70 pts (41.4%); and group 4, 25/49 (51%). These differences were not significant. Osteoporosis was present in only 11 patients (6.5%), by group (1, 2, 3, 4, respectively) as follow: 2 pts (9.1%); 1 pt (3.7%); 6 pts (8.6%); and 2 pts (4.1%). No fractures were observed. None of these small differences were significant.

Neither osteopenia nor osteoporosis were significantly correlated with age. Patients with normal bone mineral density (BMD) had testosterone levels of 0.66 ± 1.46 ng/ml while patients with osteopenia had marginally (non-significant) higher levels (0.71 ± 1.48 ng/ml). In contrast, patients with osteoporosis presented significantly higher levels of testosterone (2.16 ± 4.44 ng/ml; $p = 0.036$).

4.6. *Discussion*

In this study, our primary aim was to assess the prevalence rates of MetS and osteoporosis in patients treated with RT and ADT. As our results show, there were no significant differences in the prevalence rates for either MetS or osteoporosis, regardless of the duration of ADT. Moreover, we found no significant differences in the prevalence of these conditions, regardless of whether ADT was administered or not. These findings suggest that ADT does not increase rates of MetS or osteoporosis, even after long-term administration.

In men, low testosterone levels are associated with increased insulin resistance, type 2 diabetes and MetS. Since ADT reduces testosterone levels, pts with PCa who receive ADT are, at least theoretically, at a higher risk of developing MetS. Androgen suppression also induces other metabolic alterations, particularly insulin resistance,[15,16] and several studies have shown that ADT increases abdominal fat

Table 3 – Metabolic profile according to the presence or not of MetS.

Evaluable patients: $n = 259$	MetS	No MetS	p
N	122 (47%)	137 (52.8%)	
Waist circumference (cm)	110.21	100.36	0.000
Systolic blood pressure (mm Hg)	145.52	136.80	0.000
Diastolic blood pressure (mm Hg)	78.50	74.94	0.010
Glycemia (mg/dL)	122.83	103.08	0.000
Triglyceride (mg/dL)	167.38	102.91	0.000
HDL-cholesterol HDL (mg/dL)	50.89	61.24	0.000
Total cholesterol total (mg/dL)	201.43	205.51	0.397
Testosterone (ng/ml)	0.58	0.89	0.407

and triglycerides while lowering insulin sensitivity,[3,17] thus increasing the probability of developing MetS.

The aetiology of MetS is not yet fully understood.[18] However, there are many interrelated factors that are thought to be important in the development of this syndrome. Most patients are old, obese, sedentary and have a certain degree of insulin resistance. Central abdominal obesity is a physical manifestation of this metabolic state. Insulin resistance in fat cells results in the hydrolysis of stored triglycerides, which raises the free fatty acids in the blood plasma. These free fatty acids are absorbed by the liver, leading to an increase in very low density lipoproteins (VLDL), a decrease in HDL, and a non-alcoholic fatty liver. Insulin resistance in the muscles and a reduction in its intake in the liver reduce the storage of glucose, which will raise the level of glucose.

To our knowledge, only three previous cross-sectional studies have assessed MetS prevalence in PCa patients undergoing ADT.[11,12,13] In one of those studies, Braga-Basaria et al.[12] reported a MetS prevalence of 20% in the control group vs. 22% in PCa patients without ADT and 55% in patients who underwent ADT. A more recent study by Cleffi et al.[13] compared two groups of PCa pts: in one group, pts received a mean of 15 months of ADT while the other group did not undergo ADT, reporting a significant difference in MetS prevalence (54% vs. 24%, respectively). The most recently published cross-sectional study was conducted by Morote et al.[11] who found a MetS prevalence of 32% in a control group (no PCa) vs. 36% in PCa patients without ADT treatment, and 51% in patients who received ADT. Relevant to our study, those authors observed that MetS prevalence increased progressively over time in the ADT group (44% vs. 57%, respectively, with <3 vs. >3 years of ADT). In contrast, we found no significant increase in rates of MetS over time. The reasons for these differences are not clear and more research is needed to clarify this.

Morote and colleagues[11] observed that the percentage of patients with waist circumference ≥102 cm and glucose ≥110 mg/dL was significantly higher in patients who had undergone ADT vs. the control group, while no significant differences were observed in the remaining components of MetS. In our study, we also assessed these factors individually; however, in contrast to those authors, we did not find any significant differences between the study groups. However, we did observe that in patients who received >12 months of ADT (groups 3 and 4), the development of MetS was significantly correlated with a personal history of diabetes or treatment thereof.

ADT increases fat mass and may, therefore, lead to obesity. Not surprisingly, the vast majority of pts in our study (86%) were overweight. Interestingly, in group 1, while just over three-quarters (78%) of patients were overweight, the corresponding figure was 95% in group 4, the group with the longest duration of ADT treatment. In fact, the prevalence of overweight in group 4 was significantly higher than in the other groups, suggesting that long-term use of ADT may play a role in promoting obesity. In addition, long-term use of ADT was associated with significantly lower HDL cholesterol and testosterone levels. Basaria et al.[16] found that patients on long-term ADT are at risk of developing insulin resistance and hyperglycemia. Our results seem to confirm that finding, as we found that hyperglycemia is more common among patients who receive long-term ADT (groups 3 and 4) and who fulfil the criteria for MetS.

One of the main differences between our findings and those reported by other authors is the relatively high percentage (50%) of pts in the control group with MetS. Even though these patients did not receive ADT, the percentage who met the criteria for a diagnosis of MetS was nearly double that of the general population. This finding may be partially age-related: the median age of these patients was 71 and testosterone levels are known to decrease with age. Indeed, in the non-ADT treatment group, we found that the patients with MetS had significantly lower levels of testosterone (2.7 vs. 5.1 ng/ml) than men without MetS. Another explanation may be related to the potential contribution of MetS to the subsequent development of PCa.[19] Conteduca et al.[19] reported that testosterone levels are inversely related to total cholesterol, LDL cholesterol, and triglycerides, and positively related to serum HDL cholesterol. This finding suggests that MetS may be an important aetiological factor in the development of prostate cancer, and may help explain why patients with PCa tend to have a higher prevalence of MetS, even without ADT.[20,21] Certainly, the data from our study, in which 50% of men without ADT fulfilled the criteria for MetS, appear to support this hypothesis, and several studies have correlated metabolic alterations with more advanced disease and with high-grade prostate cancer.[22,23] After definitive therapy for localized prostate, men with MetS might have a higher risk of developing PSA recurrence and metastases. The presence of obesity and other components of MetS have also been associated with an increased risk of PCa mortality.[6,9]

4.7. *Osteoporosis and osteopenia*

ADT is reported to cause a 3–5% annual decrease in BMD; as a result, PCa patients treated with ADT have a significantly lower BMD than non-treated patients.[24] The prevalence

Table 4 – Metabolic syndrome: analysis by study group.

	Group 1 (no ADT)			Group 2 (6 m ADT)			Group 3 (12–18 m ADT)			Group 4 (≥24 m ADT)		
	MetS	No MetS	p	MetS	No MetS	p	MetS	No MetS	p	MetS	No MetS	p
N	23	23		32	26		53	44		29	29	
Age	69.09	66.13	0.076	71.5	68.2	0.092	72.89	70.70	0.154	70.52	70.83	0.859
Weight (kg)	87.25	75.76	0.002	81.7	77.4	0.201	87.01	76.82	0.000	89.11	80.33	0.015
Waist circumference (cm)	110.21	98.9	0.000	107.3	98.85	0.001	111.30	100.53	0.000	111.17	102.79	0.013
Systolic blood pressure	145.7	136	0.058	136.6	134.2	0.597	149.64	136.45	0.001	147.03	140.90	0.208
Diastolic blood pressure	84.4	78.6	0.093	73.65	76.03	0.350	79.41	73.66	0.005	76.76	73.14	0.275
Glycemia (mg/dL)	120.3	106.7	0.224	112.7	104.3	0.10	124.64	100.87	0.000	130.93	102.90	0.000
Triglyceride (mg/dL)	168.3	91.9	0.000	166.2	109.0	0.006	179.34	102.96	0.000	148.93	104.83	0.002
HDL cholesterol (mg/dL)	44.5	56.6	0.007	49.38	62.45	0.003	53.49	62.33	0.021	52.33	61.68	0.030
Total cholesterol (mg/dL)	197.9	203.8	0.617	203.69	205.06	0.884	208.5	205.81	0.750	190.86	206.79	0.103
Testosterone (ng/ml)	2.7	5.1	0.044	0.23	0.31	0.46	0.30	0.27	0.795	0.22	0.23	0.752

of osteopenia and osteoporosis is known to increase with age, which in part explains the higher rates of these conditions in PCa patients, who tend to be older than the general population.[25] Baseline studies in patients with newly diagnosed PCa have shown a high prevalence (ranging from 60% to 80%) of osteopenia and osteoporosis, even without hormonal treatment.[26] One study[27] reported a 35% prevalence in hormone-naive patients; however, in pts undergoing ADT, the prevalence increased steadily, reaching 43% after 2 years, 60% after 6 years, and 81% after 10 or more years. In our study, 46.4% had osteopenia, while osteoporosis was present in only 11 patients (6.5%). This result was somewhat surprising, especially in the light of the aforementioned rates of osteoporosis.[28] While we are not sure of the explanation for this discrepancy, we hypothesize that lifestyle modification advice given by treating physicians (e.g., advice to lift weights, and to limit smoking, alcohol, and caffeine consumption, and the use of calcium and vitamin D supplementation) may have been implemented to prevent the development of osteoporosis. This seems especially likely given that the risks of developing osteoporosis and bone fractures are well-known.

4.8. *Study limitations*

The main limitation of this study is its cross-sectional design, which does not permit us to evaluate changes in patient characteristics over time. Another limitation is that we do not have data on any interventions that may have been implemented by treating physicians to mitigate any treatment-related alterations in the study variables, such as anti-hypertensive treatments. As a result, this could have impacted the study results. However, we believe that the large sample size and the presence of a control group may have minimized any biases of this nature.

5. Conclusions

This cross-sectional study confirms previous reports that the prevalence of MetS in patients with prostate cancer is significantly higher than in the general population. In contrast to previous reports, we did not find any increase in MetS prevalence even after medium-to-long term use of ADT. However, in this study, the prevalence of diabetes was higher in patients who underwent more than 12 months ADT and overweight was significantly greater in patients who received more than 2 years of androgen deprivation. The prevalence of osteoporosis was low in all the study groups. Taken together, these findings suggest that ADT does not appear to increase the rates of MetS. Nevertheless, given the contrasting findings from other studies, longer term prospective trials would help to clarify this issue.

Our data confirm previous reports of the association between ADT (particularly long-term administration) and metabolic alterations. For this reason, patients treated with ADT should be carefully monitored during treatment and steps should be taken to address any metabolic disturbances or changes in bone mineral density that arise.

Conflict of interest

None declared.

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