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ARTICLE

Impact of leuprolide and goserelin on androgen suppression and adverse events in patients with prostate cancer

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Background: *Androgen deprivation therapy (ADT) is widely employed in the management of advanced prostate cancer, with luteinizing hormone-releasing hormone (LHRH) agonists such as leuprolide and goserelin being common options. However, pharmacological and metabolic differences between these agents may affect the efficacy of hormonal suppression and adverse event profiles. This study compared the effects of leuprolide (22.5 and 45 mg) and goserelin (10.8 mg) on prostate-specific antigen (PSA) and testosterone reduction, as well as their metabolic and cardiovascular impacts and the influence of genetic variants on therapeutic response.*

Methods: *A prospective, randomized, controlled study was conducted with 174 patients diagnosed with prostate cancer and treated with ADT for 12 months. Serum PSA and testosterone levels, lipid and glycemic profiles, and adverse events were monitored. Genetic analyses were performed to identify mutations in the TP53, BRCA1, BRCA2, and ATM genes.*

Results: *All treatment groups exhibited significant reductions in PSA and testosterone levels. Leuprolide 22.5 mg achieved the most pronounced PSA reduction, whereas goserelin 10.8 mg demonstrated greater variability in testosterone during the early months of therapy. Hot flashes were the most frequent adverse event, reported in 90% of patients treated with leuprolide 22.5 mg, while cardiovascular events were more prevalent in the goserelin 10.8 mg group. The TP53 gene was the most frequently altered (20.4%), followed by BRCA2 (7.4%) and ATM (6.5%), though these mutations did not significantly affect treatment response.*

Conclusion*: ADT effectively achieves hormonal suppression in prostate cancer; however, differences between LHRH agonists influence clinical and metabolic outcomes. Leuprolide 22.5 mg showed superior PSA reduction but higher rates of vasomotor symptoms and weight gain, while goserelin 10.8 mg was associated with hormonal instability and cardiovascular risk. Genetic findings suggest that BRCA2 variants may affect lipid metabolism, reinforcing the need for personalized ADT strategies integrating metabolic and genetic profiles.*

Key Words: prostate cancer, androgen deprivation therapy, luteinizing hormone-releasing hormone (LHRH) agonists, adverse events, genetic profile

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Introduction

Prostate cancer (PCa) is one of the most prevalent neoplasms among men and represents a significant challenge to global public health.[1,2] The progression of the disease is closely related to the presence of androgens, with testosterone being an essential factor for tumor maintenance and growth.[3] Androgen deprivation therapy (ADT) has been widely used as a therapeutic approach in the management of advanced PCa, aiming to reduce serum testosterone levels to slow disease progression and improve patient survival.[4,5]

Luteinizing hormone-releasing hormone (LHRH) analogs, such as Leuprolide and Goserelin, are the primary agents used in ADT. These drugs act by inhibiting the secretion of luteinizing hormone (LH) and, consequently, suppressing testicular testosterone production. Although effective in reducing hormone levels and controlling tumor progression, prolonged use of these agonists is associated with a range of adverse effects, including metabolic alterations, cardiovascular events, and impacts on patients' quality of life.[6,7] Recent studies indicate that treatment response may vary depending on the genetic profile of patients. Polymorphisms in genes related to hormonal metabolism and DNA repair, such as TP53, BRCA1, BRCA2, and ATM, may influence the efficacy of ADT and predisposition to adverse effects.[8–10] Therefore, assessing the genetic profile of patients may contribute to the personalization of therapeutic approaches, optimizing the benefits of ADT while minimizing its negative impacts.

Given this context, the present study aims to compare the effects of Leuprolide and Goserelin on prostate-specific antigen (PSA) and testosterone reduction, as well as to evaluate the incidence of adverse events and the relationship between genetic profile and therapeutic response in patients with PCa.

Methods

This prospective, randomized, and controlled study was conducted with 174 patients diagnosed with PCa, aged between 40 and 90 years, who were treated with ADT. The study was approved by Research Ethics Committee of the Faculty of Health, Santa Casa BH (CAAE: 42638620.3.0000.5138) and followed the principles established in the Declaration of Helsinki. All participants signed the Informed Consent Form (ICF) before the study began.

Participants

Participants were randomly assigned to three treatment groups: leuprolide 22.5 mg (every three months), leuprolide 45 mg (every six months), and goserelin 10.8 mg (every three months). Leuprolide was administered as a solid slow-release depot formulation, while goserelin was delivered as a slow-release implant. All drugs were administered subcutaneously at a 90° angle in the lower abdominal wall, avoiding areas with excessive pigmentation, nodules, lesions, or hair. The injections were performed by a qualified oncology nursing team, specifically trained and following the manufacturer's recommendations rigorously.

Patients included in the study had a confirmed diagnosis of prostate adenocarcinoma by prostate biopsy and were indicated for ADT due to locally advanced or metastatic disease, with an Eastern Cooperative Oncology Group (ECOG) performance status of $\leq$2. Exclusion criteria included patients with a history of recent severe cardiovascular diseases (myocardial infarction, stroke, or class III–IV heart failure in the last six months), previous use of ADT or chemotherapy, active concomitant malignant neoplasm, known hypersensitivity to LHRH agonists, or severe hepatic or renal insufficiency.

Procedures

This was a 12-month prospective follow-up study. Patients were monitored at predefined time points to assess treatment efficacy and safety. Assessments were conducted at baseline (T0), 3 months (T3), 6 months (T6), 9 months (T9), and 12 months (T12). Patients receiving quarterly administrations (Leuprolide 22.5 mg or Goserelin 10.8 mg) underwent evaluations at all five time points (T0, T3, T6, T9, and T12), whereas patients receiving semiannual administrations (Leuprolide 45 mg) were evaluated at three time points (T0, T6, and T12).

Blood samples were collected via venipuncture in the morning after a 12-h fast and analyzed in a certified laboratory. Serum PSA was quantified by chemiluminescence, while total testosterone was measured using radioimmunoassay (RIA) or electrochemiluminescence immunoassay (ECLIA). The lipid profile, including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides, was assessed using an enzymatic colorimetric method, and fasting blood glucose was measured by the glucose oxidase method. All analyses were performed in triplicate to ensure result reliability.

Clinical and anthropometric evaluations included the measurement of weight and height using a precision digital scale and stadiometer for body mass index (BMI) calculation. Abdominal and hip circumference were measured using a non-elastic measuring tape positioned at the umbilical line and hip region, following World Health Organization (WHO) guidelines. Blood pressure was obtained using a validated sphygmomanometer, after five minutes of rest with the patient seated, and heart rate and respiratory rate were recorded using a pulse oximeter and multiparameter monitor. Adverse events were assessed and classified according to the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0). At each consultation, patients were questioned about possible symptoms and clinically examined to identify adverse reactions, which were categorized as mild (grade 1), moderate (grade 2), or severe (grades 3–4). The primary monitored events included hot flashes, metabolic alterations (hyperglycemia, dyslipidemia), cardiovascular events (hypertension, arrhythmias, thrombosis), musculoskeletal impacts (bone mass loss, muscle fatigue), and quality-of-life repercussions (insomnia, erectile dysfunction, depression).

Genetic analysis was conducted to identify polymorphisms and germline mutations in prostate cancer-related genes. DNA was extracted from peripheral blood samples collected in EDTA tubes and stored at −80°C until extraction. DNA extraction was performed using the silica column method with the QIAamp DNA Blood Mini Kit (Qiagen, Germany). The genetic material was amplified by Polymerase Chain Reaction (PCR) and sequenced using Next-Generation Sequencing (NGS). Variants in the TP53, BRCA1, BRCA2, and ATM genes were analyzed, and results were interpreted following the guidelines of the American College of Medical Genetics and Genomics (ACMG).

Statistical analysis

Statistical analysis was performed using R software (version 4.2.2). Comparisons of continuous variables between groups were conducted using analysis of variance (ANOVA), followed by Tukey's post-hoc tests for multiple comparisons. For categorical variables, the chi-square test or Fisher's exact test was applied. Additionally, logistic regression analyses were used to assess the association between genetic mutations and treatment response. The significance level adopted was $p < 0.05$.

Results

The baseline characteristics by study group

Baseline demographic and clinical features of the participants are displayed in Table 1. The mean age was similar across groups (73–74 years; $p = 0.964$), with a predominance of patients aged 70–79 years, followed by those aged ≥80 years. Most patients were classified as non-white ($p = 0.109$) and married ($p = 0.539$). The only significant difference was observed in educational level ($p = 0.044$), with a predominance of elementary education in all groups and a higher proportion of illiterate patients in the Leuprorelin 22.5 mg group, highlighting the overall low educational level of the sample. No significant differences were found regarding cancer history, smoking, alcohol consumption, clinical staging, or TNM classification, with T2 tumors, N0, and M0 predominating. Overall, the groups presented homogeneous demographic and clinical characteristics, reinforcing their comparability for outcome analysis.

Reduction in PSA and testosterone levels

A significant reduction in PSA and testosterone levels was observed over the course of the study in all groups at 6 months and 12 months ($p < 0.001$) (Table 2). Leuprolide 22.5 mg demonstrated the highest efficacy in PSA reduction at six months (mean reduction of 89.3%, 95% CI: 86.1–92.4). Leuprolide 45 mg and Goserelin 10.8 mg showed reductions of 86.7% and 84.5%, respectively. By the end of 12 months, PSA levels remained lower in the Leuprolide 22.5 mg group compared to the other groups ($p = 0.020$).

Testosterone levels declined rapidly in all groups, reaching castration values (<50 ng/dL) within four weeks. Considering the more restrictive cutoff (<20 ng/dL), at 3 months, the proportion of patients was 90.0% (54/60) with Leuprorelin 22.5 mg and 77.6% (33/42) with Goserelin 10.8 mg; this difference was not statistically significant ($p = 0.187$). At 6 months, the proportions were 88.3% (53/60), 78.3% (47/60), and 88.9% (37/42) for Leuprorelin 22.5 mg, Leuprorelin 45 mg, and Goserelin 10.8 mg, respectively, again without a significant difference ($p = 0.242$). At 12 months, the suppression rates remained high, 91.7% (55/60), 91.7% (55/60), and 85.7% (36/42), respectively ($p = 0.538$), indicating that although Goserelin showed more pronounced early fluctuations, the overall effectiveness of the three regimens in achieving testosterone <20 ng/dL was comparable (Figure 1).

TABLE 1. **Demographic and clinical characteristics of patients (n = 174)**

Variables	Medication			*p*-Value
	Leuprolide 22.5 mg (n = 60)	Leuprolide 45 mg (n = 60)	Goserelin 10.8 mg (n = 54)	
Age (years)	73.8 ± 8.3	74.3 ± 9.2	73.9 ± 7.8	0.964
Range age, n (%)				0.850
<60	4 (6.67%)	4 (6.67%)	3 (5.56%)	
60–69	14 (23.33%)	13 (21.67%)	11 (20.37%)	
70–79	29 (48.33%)	23 (38.33%)	26 (48.15%)	
≥80	13 (21.67%)	20 (33.33%)	14 (25.93%)	
Race, n (%)				0.109
Whites	16 (26.67%)	26 (43.33%)	23 (42.59%)	
Brown (mixed race)	44 (73.33%)	34 (56.67%)	31 (57.41%)	
Education†, n (%)				0.044*
Illiterate	12 (20.00%)	2 (3.51%)	7 (12.96%)	
Fundamental	45 (75.00%)	49 (85.96%)	39 (72.22%)	
Average	1 (1.67%)	5 (8.77%)	7 (12.96%)	
Superior	2 (3.33%)	1 (1.75%)	1 (1.85%)	
Marital status, n (%)				0.539
Married	41 (68.33%)	47 (78.33%)	35 (64.81%)	
Divorced	5 (8.33%)	1 (1.67%)	4 (7.41%)	
Single	10 (16.67%)	10 (16.67%)	12 (22.22%)	
Widower	4 (6.67%)	2 (3.33%)	3 (5.56%)	
History of cancer, n (%)				0.802
No	23 (38.33%)	25 (41.67%)	24 (44.44%)	
Yes	37 (61.67%)	35 (58.33%)	30 (55.56%)	
Smoking, n (%)				0.469
No	25 (41.67%)	29 (48.33%)	20 (37.04%)	
Yes	35 (58.33%)	31 (51.67%)	34 (62.92%)	
Alcoholism, n (%)				0.058
No	21 (35.00%)	34 (56.67%)	25 (46.30%)	
Yes	39 (65.00%)	26 (43.33%)	29 (53.70%)	
Staging††, n (%)				0.250
I	3 (5.00%)	4 (6.67%)	6 (11.32%)	
II	20 (33.33%)	24 (40.00%)	23 (43.40%)	
III	20 (33.33%)	22 (36.67%)	10 (18.87%)	
IV	17 (28.33%)	10 (16.67%)	14 (26.42%)	
T stage, n (%)				0.451
1	8 (13.33%)	6 (10.00%)	6 (11.11%)	
2	29 (48.33%)	24 (40.00%)	27 (50.00%)	
3	18 (30.00%)	26 (43.33%)	13 (24.07%)	
4	5 (8.33%)	4 (6.67%)	7 (12.96%)	
X	–	–	1 (1.85%)	
N stage, n (%)				0.586
0	33 (55.00%)	40 (66.67%)	36 (66.67%)	
1	17 (28.33%)	12 (20.00%)	11 (20.37%)	
2	2 (3.33%)	–	2 (3.70%)	
X	8 (13.33%)	8 (13.33%)	5 (9.26%)	

(Continued)

TABLE 1. **Continued**

Variables	Medication			*p*-Value
	Leuprolide 22.5 mg (n = 60)	Leuprolide 45 mg (n = 60)	Goserelin 10.8 mg (n = 54)	
M stage, n (%)				0.608
0	43 (71.67%)	47 (78.33%)	38 (70.37%)	
1	15 (25.00%)	9 (15.00%)	13 (24.07%)	
X	2 (3.33%)	4 (6.67%)	3 (5.56%)	

Note. [†]Education: 03 (three) No Information (medication 2, n = 57); [††]Staging: 01 (one) No Information (medication 3, n = 53). Education comparison was performed by grouping *illiterate* and *fundamental* vs. *average* and *superior* education levels, with a resulting *p*-value of 0.213. The *p*-values refer to the chi-square test via Monte Carlo simulation and ANOVA for comparing the variability. *significant at 5% significance level. "T = primary tumor size/extension; N = regional lymph node involvement; M = distant metastasis, according to the TNM classification. T-X, N-X, and M-X indicate that the primary tumor, regional lymph nodes, or distant metastases could not be assessed, respectively."

TABLE 2. **Longitudinal changes in PSA and testosterone levels in patients treated with different formulations of leuprolide and goserelin**

Variables	Drugs	n	Time					*p*-Value
			Baseline	3 Months	6 Months	9 Months	12 Months	
PSA	Leuprolide 22.5 mg	60	36.9 (10.8–113)[a]	0.86 (0.27–3.53)[b]	0.23 (0.06–1.30)[c]	0.07 (0.03–1.35)[c]	0.04 (0.02–1.10)[c]	<0.001*
	Leuprolide 45 mg	60	9.88 (3.52–32.4)[a]	–	0.09 (0.04–0.53)[b]	–	0.04 (0.02–0.11)[b]	<0.001*
	Goserelin 10.8 mg	42	13.9 (6.90–37)[a]	0.72 (0.21–3.25)[b]	0.22 (0.04–0.58)[c]	0.09 (0.03–0.36)[c]	0.07 (0.02–0.38)[c]	<0.001*
Testosterone	Leuprolide 22.5 mg	60	420 (274–613)[a]	13 (10–17)[b]	11.5 (8.75–15)[b]	13 (9–16)[b]	12 (8–15.2)[b]	<0.001*
	Leuprolide 45 mg	60	464 (317–616)[a]	–	12 (9–18)[b]	–	11.5 (8–17.2)[b]	<0.001*
	Goserelin 10.8 mg	42	502 (342–614)[a]	12.5 (9–20.4)[b]	11.5 (7.25–15.8)[b]	10.7 (8–16.5)[b]	12 (7.25–16)[b]	<0.001*

Note. Values are expressed as median (IQR) and were analyzed using the Friedman test. Different lowercase letters in the rows indicate statistically significant differences according to the Wilcoxon test ($p < 0.05$). *$p < 0.05$ considered statistically significant.

Metabolic alterations and adverse events

Lipid and glycemic parameters showed variations throughout the study. A significant increase in mean triglyceride levels was observed in all evaluated groups ($p < 0.05$). In terms of total cholesterol levels, an increase was noted only in the Leuprolide 45 mg group ($p = 0.047$). No significant changes were observed in glucose levels ($p > 0.05$). During the 12-month follow-up, a significant increase in abdominal circumference was observed across all treatment groups ($p = 0.006$ for leuprolide 22.5 mg, $p = 0.004$ for leuprolide 45 mg, and $p < 0.001$ for goserelin 10.8 mg), indicating progressive accumulation of visceral adiposity under ADT. Hip circumference also increased significantly in all arms, although to a lesser extent, suggesting preferential central fat deposition. BMI rose significantly in patients treated with leuprolide 22.5 mg and goserelin 10.8 mg (both $p < 0.001$), whereas no relevant change was detected with leuprolide 45 mg ($p = 0.933$). These findings highlight the adverse impact of ADT on body composition, with central adiposity being the predominant change, which may contribute to increased cardiometabolic risk (Table 3).

Adverse events were recorded in all groups, with a higher frequency in the Leuprolide 22.5 mg group.

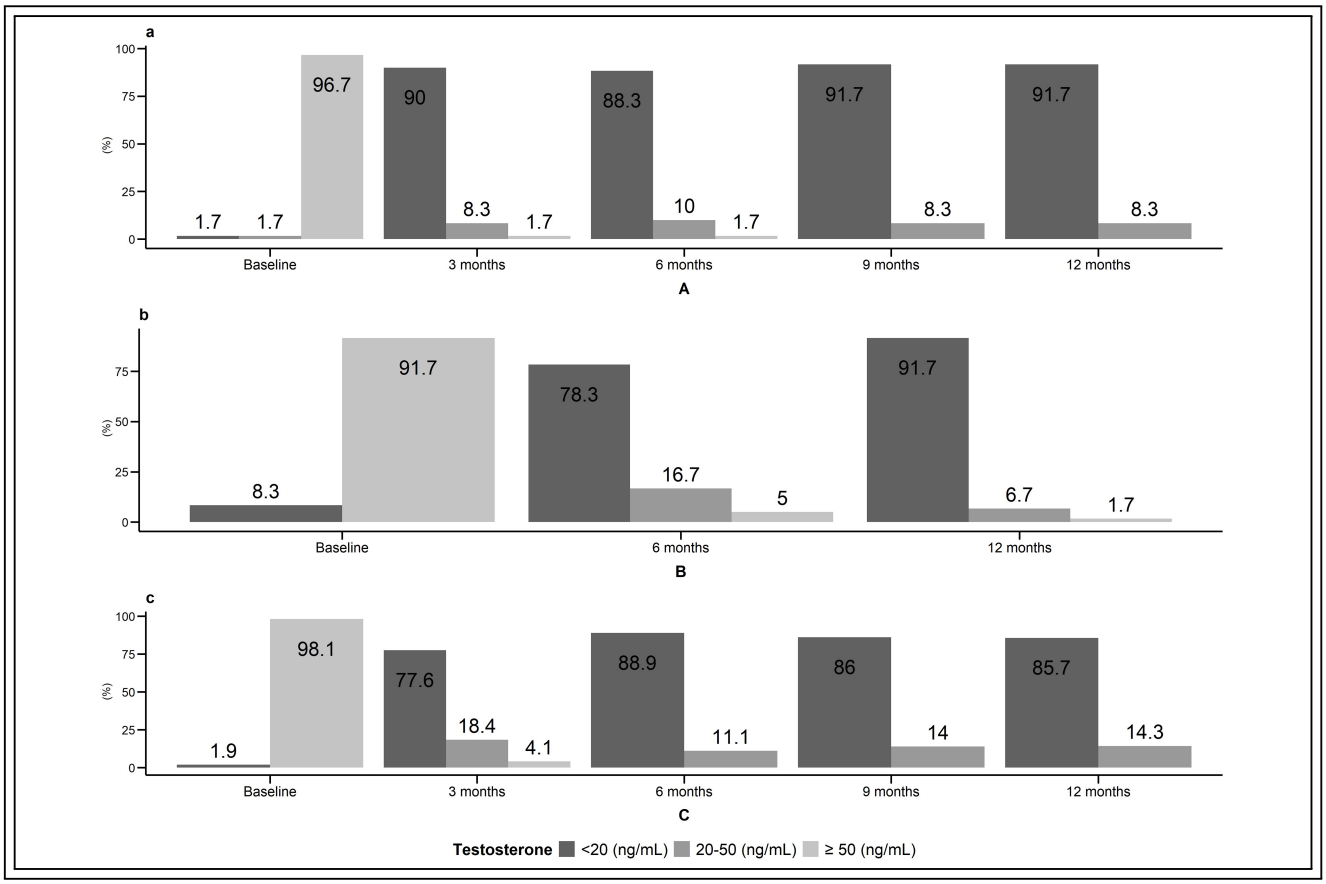

FIGURE 1. Distribution of reduction in testosterone levels in patients with prostate cancer. Treated with (A) Leuprolide 22.5 mg, (B) Leuprolide 45 mg, and (C) Goserelin 10.8 mg

Hot flashes were the most commonly reported side effect, occurring in 90% of patients in this group, followed by 83.33% in the Goserelin 10.8 mg group and 71.67% in the Leuprolide 45 mg group ($p = 0.033$). Weight gain was also more pronounced in the Leuprolide 22.5 mg group, with an average increase of 4.3 kg after 12 months, though the difference was not statistically significant ($p = 0.181$).

Systemic arterial hypertension (SAH) was the most prevalent comorbidity across all groups, with frequencies of 44.00%, 45.65%, and 40.54%, respectively. Dyslipidemia (DLP) and diabetes mellitus (DM) showed similar prevalence, ranging from 14.67% to 24.32%. The absence of comorbidities was observed in 16.22% to 22.67% of patients.

Additionally, metabolic syndrome was identified in 73.4% of patients (n = 116), while 26.6% (n = 42) did not present this condition. Analysis showed a significant association between metabolic syndrome and the type of GnRH analog used ($p = 0.040$). Leuprolide 22.5 mg was the most associated with metabolic syndrome (51.7% of cases), followed by Leuprolide 45 mg (32.8%) and Goserelin 10.8 mg (15.5%) (Figure 2).

Genetic analysis and correlation with therapeutic response

Genetic analysis revealed a considerable prevalence of mutations in TP53, BRCA2 and ATM among the studied patients. P53 was the most frequently altered gene (20.37% of cases), followed by BRCA2 (7.41%) and ATM (6.48%), all of which are involved in DNA repair and tumor progression.

According to our analysis, the three groups were homogeneous with respect to the genetic data. Although TP53 showed the highest frequency of alterations, followed by BRCA2, ATM, and BRCA1, no statistically significant differences were observed among the groups. These findings indicate that, in this study, the evaluated genetic variations did not influence the distribution across treatment regimens,

TABLE 3. **Longitudinal evaluation of metabolic parameters in patients receiving leuprolide or goserelin therapy**

Variables	Drugs	n	Time					*p*-Value
			Baseline	3 Months	6 Months	9 Months	12 Months	
Total cholesterol	Leuprolide 22.5 mg	60	183.0 ± 40.3	196.0 ± 37.8	188.0 ± 34.2	192.0± 41.7	184.0 ± 38.2	0.679 (ns)
	Leuprolide 45 mg	60	186 (162–211)	–	186 (165–237)	–	190 (160–220)	0.047*
	Goserelin 10.8 mg	41	188 (156–214)	189 (156–229)	193 (165–226)	199 (157–219)	185 (160–215)	0.298 (ns)
Triglycerides	Leuprolide 22.5 mg	60	110 (85.2–159)^{a}	128 (96.2–165)^{b}	128 (102–178)^{b}	114 (85.8–168)^{ab}	122 (95.8–172)^{ab}	0.042*
	Leuprolide 45 mg	60	109 (87–155)^{a}	–	150 (83–202)^{b}	–	140 (96–181)^{b}	0.031*
	Goserelin 10.8 mg	42	112 (95.5–150)^{a}	140 (108–176)^{ab}	146 (99–183)^{b}	140 (106–200)^{b}	143 (101–187)^{b}	0.006*
Glycemia	Leuprolide 22.5 mg	60	104 (94–113)	102 (93–110)	103 (91–112)	97 (91.8–108)	96 (90–107)	0.290 (ns)
	Leuprolide 45 mg	59	101 (94.5–112)	–	100 (93–112)	–	101 (93.5–112)	0.223 (ns)
	Goserelin 10.8 mg	41	104 (95–118)	98 (90–108)	96 (85–110)	99 (87–121)	96 (89–111)	0.278 (ns)
BMC	Leuprolide 22.5 mg	60	24.8 (23.3–28.1)^{a}	25.3 (23.5–28.1)^{ab}	25.9 (21.4–28.4)^{b}	26 (23.9–28.7)^{b}	26.1 (24–28.8)^{b}	<0.001*
	Leuprolide 45 mg	55	27.5 ± 4.6	–	27.2 ± 4.3	–	27.8 ± 4.6	0.933 (ns)
	Goserelin 10.8 mg	42	24.6 (22.7–29.4)^{a}	25.9 (23–29.3)^{a}	26.5 (23.1–30.2)^{b}	27 (23.3–29.4)^{b}	26.2 (23.4–31.1)^{b}	<0.001*
Abdominal circunference	Leuprolide 22.5 mg	60	93.5 (88.8–100)^{a}	95 (89–100)^{b}	95 (91–102)^{b}	96.5 (91.8–102)^{b}	96.5 (92–102)^{b}	0.0056*
	Leuprolide 45 mg	58	97 (89.2–105)^{a}	–	101 (91–106)^{b}	–	102 (92.2–106)^{c}	0.004*
	Goserelin 10.8 mg	41	95 (85–106)^{a}	96 (88–108)^{ab}	100 (90–108)^{bc}	100 (92–107)^{c}	100 (92–105)^{bc}	<0.001*
Hip circunference	Leuprolide 22.5 mg	60	95 (92–102)^{a}	96.5 (92–100)^{ab}	98 (94–101)^{ab}	98.5 (94–104)^{b}	98 (94–104)^{ab}	0.005*
	Leuprolide 45 mg	58	98 (93–102)	–	98 (94–104)	–	98.5 (94–105)	0.043*
	Goserelin 10.8 mg	40	98 (90–102)^{a}	100 (94–105)^{b}	102 (94–108)^{b}	101 (95–106)^{b}	100 (94–105)^{ab}	<0.001*

Note: Values are expressed as median (interquartile range [IQR]) and were analyzed using the Friedman test; values are expressed as mean ± standard deviation (SD) and were analyzed using one-way repeated-measures ANOVA. Different lowercase letters in the rows indicate statistically significant differences according to the Wilcoxon test ($p < 0.05$). *$p < 0.05$ considered statistically significant; ns: not significant.

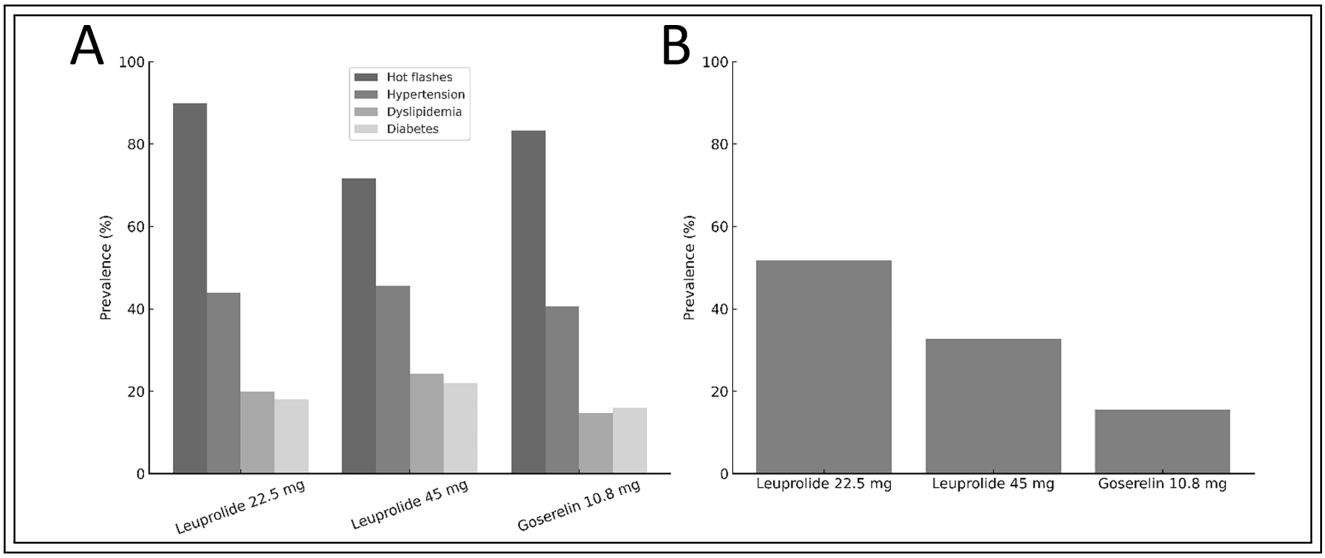

FIGURE 2. Frequency of adverse events and prevalence of metabolic syndrome according to treatment group. (**A**) Distribution of the main adverse events. (**B**) Prevalence of metabolic syndrome by treatment group

thereby reinforcing the comparability of the groups (Table 4).

In our study, the BRCA2 mutation was detected in 7.69% of patients under 70 years old and 1.45% of those aged 70 or older, with no statistically significant difference. No self-declared White patients presented this mutation, while 5.88% of non-White patients were carriers ($p = 0.294$).

TABLE 4. **Genetic profile according to the groups**

Gene	Category	Leuprolide 22.5 mg (n = 41)	Leuprolide 45 mg (n = 36)	Goserelin 10.8 mg (n = 31)	*p*-Value
ATM	Yes	4 (9.8%)	1 (2.8%)	2 (6.5%)	0.463
	No	37 (90.2%)	35 (97.2%)	29 (93.5%)	
BRCA1	Yes	1 (2.4%)	2 (5.6%)	1 (3.2%)	0.760
	No	40 (97.6%)	34 (94.4%)	30 (96.8%)	
BRCA2	Yes	1 (2.4%)	4 (11.1%)	3 (9.7%)	0.297
	No	40 (97.6%)	32 (88.9%)	28 (90.3%)	
TP53	Yes	5 (12.2%)	8 (22.2%)	9 (29.0%)	0.202
	No	36 (87.8%)	28 (77.8%)	22 (71.0%)	

Note. Fisher's Test.

Regarding the Gleason score, the mutation was identified in 3.51% of patients with Gleason <8 and 11.76% of those with Gleason ≥8, with no statistical significance. The mutation was observed in 5.71% of patients without metastases, while none of the patients with metastatic disease carried the mutation ($p = 0.448$). In terms of mortality, 7.62% of surviving patients had the mutation, whereas none of the deceased patients were carriers ($p > 0.99$) (Table 5).

Discussion

Efficacy in PSA and testosterone reduction

The results of this study reinforce the efficacy of ADT in reducing PSA and testosterone levels in patients with prostate cancer, corroborating previous findings.[4,5,7] Furthermore, they highlight differences between LHRH agonists regarding the magnitude of androgen suppression, stability of hormone levels over time, and the incidence of metabolic and cardiovascular adverse effects.

The significant reduction in PSA levels across all groups confirms the efficacy of LHRH agonists in controlling advanced prostate cancer, as reported in previous studies.[11,12] Leuprolide 22.5 mg demonstrated the greatest percentage reduction in PSA at six months, suggesting a faster and more sustained therapeutic response. These findings are consistent with studies indicating a relationship between the pharmacokinetics of Leuprolide and a more stable hormonal response compared to Goserelin.[13]

Consistent testosterone suppression to levels below 20 ng/dL was observed in all treatment groups has clinical relevance. Current evidence suggests that defining castration solely as testosterone <50 ng/dL may underestimate the therapeutic impact of ADT, as lower thresholds (<20 ng/dL) are associated with better clinical outcomes, including delayed disease progression and increased overall survival. In our study, both leuprolide (22.5 and 45 mg) and goserelin (10.8 mg) achieved and maintained testosterone concentrations well below this threshold throughout follow-up, demonstrating their efficacy in maintaining profound androgen suppression. These results reinforce recent recommendations advocating <20 ng/dL as the reference level for chemical castration and highlight the importance of reporting absolute values rather than only percentage reductions.[14] These findings are consistent with evidence showing that testosterone suppression below 20 ng/dL provides superior oncological outcomes compared with the traditional 50 ng/dL threshold, thereby supporting the clinical relevance of our results.[14–16]

While leuprolide 22.5 and 45 mg maintained more consistent chemical castration due to the use of system Atrigel® a biodegradable polymer and biocompatible solvent system that, when injected subcutaneously resulting in more stable plasma levels and lower interindividual variability, goserelin 10.8 mg is released more pulsatilely, potentially generating initial hormonal fluctuations and greater variability among patients. In this study, hormonal fluctuations were observed during the first three months, a phenomenon previously reported by Reis.[17] These fluctuations may be associated with the intermittent release profile of the drug, potentially influencing disease progression and requiring closer monitoring. Evidence suggests that testosterone oscillations may contribute to ADT resistance and negatively impact patient survival.[15]

TABLE 5. **Distribution of BRCA2 gene mutation according to demographic, clinical-pathological characteristics and clinical outcome**

Variable	BRCA2		*p*-Value
	No (n = 100)	Yes (n = 8)	
Age range, n (%)			0.393[a]
<60	11 (84.62%)	2 (15.38%)	
60–69	25 (96.15%)	1 (3.85%)	
≥70	64 (92.75%)	5 (7.25%)	
Race, n (%)			0.465[b]
White	36 (90.00%)	4 (10.00%)	
Not white	64 (94.12%)	4 (5.88%)	
Gleason, n (%)			0.145[b]
<8	55 (96.49%)	2 (3.51%)	
≥8	45 (88.24%)	6 (11.76%)	
Metastasis, n (%)			0.448[a]
No	66 (94.29%)	4 (5.71%)	
Yes	34 (89.47%)	4 (10.53%)	
Death, n (%)			>0.99[a]
No	97 (92.38%)	8 (7.62%)	
Yes	3 (100.00%)	0 (0.00%)	

Note. [a]Chi-square with Monte Carlo Simulation; [b]Fisher's exact test.

Metabolic impact and cardiovascular risk

ADT has been widely associated with the development of metabolic syndrome, including increased insulin resistance, dyslipidemia, and weight gain.[18,19] In the present study, a significant increase in triglyceride levels was observed in the Goserelin 10.8 mg group, a finding consistent with investigations linking this drug to a less favorable lipid profile.[20] Elevated serum triglycerides have been associated with an increased risk of PCa recurrence, while cholesterol, LDL, or HDL were not associated with recurrence risk among all men.[20]

Cardiovascular events, such as hypertension and arrhythmias, were more frequent in the Goserelin 10.8 mg group, a finding previously described.[21]

The relationship between ADT and cardiovascular risk is widely debated; however, evidence suggests that androgen deprivation can lead to endothelial dysfunction, increased vascular inflammation, and insulin resistance.[22,23] Several studies report that PCa patients have high rates of cardiovascular comorbidity, with up to 90% of men receiving ADT.[24] These complications are well documented in the literature, with evidence demonstrating that ADT can increase the risk of dyslipidemia, insulin resistance, and cardiovascular events.[25–28] Other studies show that obesity may influence PCa risk and outcomes, with excess adiposity increasing risk.[29,30] An association between obesity and higher PCa-specific mortality has been reported,[31] whereas an inverse relationship between BMI and survival has also been observed,[30] indicating conflicting results in the literature.

Fasting glucose levels increased slightly in the groups treated with Leuprolide; the differences were not statistically significant, suggesting that the metabolic impact of ADT may vary depending on individual patient characteristics. However, studies suggest increases in both dyslipidemia and glucose levels, regardless of the drug used.[20,23,26]

ADT contributes to increased body fat, particularly in the abdominal and hip regions, and reduction of lean mass. These changes promote an adverse metabolic profile that may increase cardiovascular risk and negatively influence prognosis[31] and survival.[30] However, heterogeneity of results may be related to methodological differences and the limitation of BMI as a single marker of adiposity, reinforcing the importance of assessing measures such as abdominais and hip circumference in PCa patients receiving ADT.

In countries with a large proportion of the population living under unfavorable socioeconomic and demographic conditions, such as Brazil, obesity has

become a significant public health problem. This condition contributes to the development of metabolic syndrome (MS), which tends to be exacerbated in PCa patients due to the adverse metabolic effects of ADT, including dyslipidemia and insulin resistance.

When modifications in MS treatment are required, patients are referred to specialists such as cardiologists and/or endocrinologists at Basic Health Units for management. However, real-life monitoring is far from ideal, as there is still no clear definition of which healthcare professionals are responsible for following these patients. This lack of structure places an additional burden on both public and private healthcare systems, rendering patient care inefficient and fragmented. In practice, patients are usually counseled by their oncologist regarding the adverse effects of ADT, since Brazil does not yet have a specific educational or monitoring program for this purpose.

In Brazil, patient counseling on ADT-related metabolic and cardiovascular risks is typically conducted during oncology appointments, with no nationally standardized framework for systematic education or multidisciplinary follow-up. The Programa Academia da Saúde (Health Academy Program), launched in 2011 under the National Health Promotion Policy, aims to promote physical activity and healthy lifestyle behaviors through public community hubs coordinated by the Unified Health System (Sistema Único de Saúde—SUS).[6,7] However, its implementation remains heterogeneous, and these hubs do not function as intended, nor do they specifically target prostate cancer patients or those undergoing ADT.

Recent evidence supports the role of multidisciplinary interventions, including supervised physical exercise, dietary counseling, and educational programs, in preventing metabolic syndrome and improving body composition in prostate cancer patients treated with ADT, reinforcing the importance of integrated management approaches.[32] Regular, supervised exercise has been shown to improve metabolic, cardiovascular, and musculoskeletal outcomes in men undergoing ADT, enhancing physical function, quality of life, and reducing fatigue.[33–35] Moreover, findings by Choi et al.[36] emphasize the importance of multilevel educational and behavioral strategies to promote adherence to healthy behaviors, demonstrating that structured exercise and preemptive education can improve self-management and reduce metabolic side effects associated with ADT.

These observations highlight that the findings of this study reinforce the need for strict metabolic and cardiovascular monitoring in patients undergoing ADT, particularly those with preexisting risk factors. Strategies to address these adverse effects should include lifestyle modification, frequent clinical monitoring, and, when necessary, adjunctive therapies for metabolic control. Developing structured, culturally adapted educational and physical activity programs in Brazil could therefore represent a key strategy to reduce treatment-related complications and improve long-term outcomes for men receiving ADT.[35–38]

Adverse events and quality of life

Hot flashes were the most frequently reported adverse events, affecting more than 75% of patients in all groups. This finding is consistent with the literature, which indicates that between 50% and 80% of patients undergoing ADT experience hot flashes, making it one of the primary factors negatively impacting quality of life.[23] The high frequency of this adverse effect highlights the need for management strategies, such as the use of SSRIs and non-hormonal therapies. Most men undergoing ADT experience hot flashes, which may cause discomfort and embarrassment, disrupt sleep, and serve as a recurring reminder of the prostate cancer diagnosis. Current treatments for ADT-induced hot flashes include antidepressants and transdermal estradiol.[30] Although transdermal estradiol represents a therapeutic option for controlling vasomotor symptoms in men receiving androgen deprivation therapy, this medication is not covered by the Brazilian Unified Health System (SUS), which limits its availability in routine clinical practice. Consequently, management of hot flashes in this population is often restricted to symptomatic measures or alternative pharmacologic approaches.

Additionally, greater weight gain was observed in the Leuprolide 22.5 mg group, a finding aligned with studies demonstrating that patients undergoing ADT may experience an average weight increase of 2 to 5 kg in the first year of treatment. Although comparatively less toxic than chemotherapy, ADT presents a range of significant side effects. These effects result from severe sex steroid deficiency and, consistent with the widespread expression of sex steroid receptors, affect multiple somatic and psychosocial domains. Adverse effects generally increase with the duration of ADT, and individual susceptibility varies depending on age, baseline comorbidities, and other poorly understood factors.[39,40]

Relevance of genetic analysis

The presence of mutations in the TP53, BRCA2, and ATM genes was observed in a significant proportion of patients, but without a direct impact on the

hormonal treatment response, corroborating previous studies.[8,24] These genes are involved in DNA repair[40–42] through homologous recombination, and mutations in them may lead to significant genomic instability, contributing to tumor progression. However, a higher incidence of metabolic adverse events was observed in patients with BRCA2 mutations, particularly those treated with Leuprolide 22.5 mg. Recent studies suggest that BRCA2 variants may be associated with altered lipid metabolism and greater susceptibility to metabolic complications.[25] A family history of BRCA1/2 mutations should be considered in PCa screening decisions.[43,44] Confirmation of this hypothesis will require future investigations, including studies with larger patient cohorts and functional analyses of these mutations.

Importantly, the absence of significant differences in genetic alterations among treatment groups reinforces that the clinical and metabolic responses observed are more likely attributable to the pharmacological characteristics of the agents rather than to baseline genetic variability.

Clinical implications and future perspectives

The findings of this study have important clinical implications. First, the choice of LHRH agonist should consider not only efficacy in reducing PSA and testosterone but also the profile of adverse effects. Patients at higher cardiovascular risk may benefit from more rigorous monitoring or the selection of an atherapeutic regimen that minimizes hormonal fluctuations and metabolic impacts[45] Furthermore, genetic analysis may become a useful tool for individualizing ADT, enabling the identification of subgroups of patients more susceptible to specific adverse effects. The incorporation of genetic biomarkers into clinical practice could assist in decision-making and allow for more precise treatment adjustments.[46]

Finally, in the context of the Brazilian public health system (SUS), which restricts therapeutic alternatives, our results reflect real-world outcomes with the most widely available regimens. This reinforces the clinical applicability of our findings while underscoring the importance of tailoring ADT according to patient comorbidities, genetic background, and treatment-related toxicities.[47]

Limitations

This study has some limitations. First, the 12-month follow-up period may be insufficient to assess the long-term outcomes of ADT, particularly regarding cardiovascular events and overall survival impact. Additionally, although the sample is representative, it may not capture all genetic variations associated with treatment response, necessitating larger cohort analyses. Another important limitation is the absence of a control group without ADT, which could provide additional data on the absolute impact of androgen deprivation on the investigated parameters.

Conclusions

This study confirms the efficacy of ADT in reducing PSA and testosterone levels, highlighting differences among LHRH agonists in terms of hormonal stability and adverse effect profiles. Genetic analysis revealed a high frequency of TP53, BRCA2, and ATM mutations, with no direct impact on treatment response but with a possible influence on patients' metabolic profiles. These findings reinforce the need for an individualized approach when selecting ADT, considering both oncological efficacy and metabolic and cardiovascular impact.

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Author Contributions

Conceptualization: Carla Simone Moreira Freitas and Aleida Nazareth Soares were responsible for conceiving the study design and defining the main research objectives. Methodology: Fabiana Rocha-Silva and Thaís Almeida Marques-Silva contributed to the development of methodological strategies, including patient selection criteria and data collection procedures. Data Curation: Ana Carolina Ribeiro de Oliveira and Thaís Almeida Marques-Silva carried out data management, ensuring accuracy, completeness, and proper organization of the database. Formal Analysis: Aleida Nazareth Soares and Ana Carolina Ribeiro de Oliveira performed the statistical analyses, interpreted the results, and verified their consistency with the study objectives. Writing—Original Draft

Preparation: Aleida Nazareth Soares, Fabiana Rocha-Silva and Carla Simone Moreira Freitas drafted the initial version of the manuscript, including the structuring of results and discussion. Writing—Review and Editing: Carla Simone Moreira Freitas and Aleida Nazareth Soares revised the manuscript critically for intellectual content, improving clarity, scientific rigor, and coherence. Supervision: Fabrizio dos Santos Cardoso and Sérgio Gomes da Silva supervised the entire research process, providing guidance, oversight, and critical feedback throughout the study. All authors reviewed and approved the final version of the manuscript.

Availability of Data and Materials

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval

The study was reviewed and approved by Research Ethics Committee of the Faculty of Health, Santa Casa BH (CAAE: 42638620.3.0000.5138). All patients consented to participate in the study and signed an Informed Consent Form. Confidentiality of patient data was ensured, as stated in the consent form. Ethical procedures were followed in accordance with Resolution 466/2012 of the Brazilian National Health Council (CNS), which regulates research involving human subjects.

Conflicts of Interest

The authors declare no conflicts of interest.

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