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# randomized controlled trial of virtual reality-based exercise on bone mineral density in hypertensive prostate cancer patients undergoing androgen deprivation therapy

Ensayo controlado aleatorio de ejercicio basado en realidad virtual sobre la densidad mineral ósea en pacientes hipertensos con cáncer de próstata sometidos a terapia de privación androgénica

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Mohamed Maher Elkeblawy<sup>1</sup>, Walid Abouelnaga<sup>2</sup>, Amira H. Mohammed<sup>3</sup>, Abeer M. Yousef<sup>4</sup>, Nancy Aboelnour<sup>5</sup>

<sup>1</sup>Researcher, National Center of Research, Egypt. Email: Katyary@yahoo.com. <https://orcid.org/0000-0001-6001-1439>.

<sup>2</sup>Associate Professor, Department of Physical Therapy, Faculty of Allied Medical Science, Middle East University, Jordan; Associate Professor, Department of Physical Therapy for Surgery, Faculty of Physical Therapy, Cairo University, Egypt. <https://orcid.org/0000-0002-3050-351X>, Email: walidabolnaga@cu.edu.eg

<sup>3</sup>Department of Physical Therapy, College of Applied Medical Sciences, Qassim University, Buraydah 51452, P.O. Box 6666, Saudi Arabia. Department of Physical Therapy for Pediatrics, Faculty of Physical Therapy, Delta University for Science and Technology, Gamasa, Egypt. Email: Amira.hussien@deltauniv.edu.eg. <https://orcid.org/0000-0002-6018-9138>

<sup>4</sup>Department of Physical Therapy, College of Applied Medical Sciences, Qassim University, Buraydah 51452, P.O.Box 6666 Saudi Arabia. Basic Science Department, Faculty of Physical Therapy, Cairo University, Egypt. Email: a.aboelaish@qu.edu.sa; <https://orcid.org/0000-0002-2926-7660>;

<sup>5</sup>Professor of Physical Therapy, Faculty of Allied Medical Sciences, Aqaba University of Technology. Professor of Physical Therapy, Faculty of Physical Therapy, Cairo University, Egypt. Email: nancy.hassan@cu.edu.eg; <https://orcid.org/0000-0003-1643-0606>;

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**Abstract**

**A**ndrogen deprivation therapy (ADT) for prostate cancer, while life-prolonging, induces significant bone loss and frequently coincides with cardiovascular comorbidities such as hypertension, creating a complex management challenge. This randomized controlled trial investigated the efficacy of a 12-week, immersive virtual reality (VR) exercise program on bone mineral density (BMD) and cardiovascular parameters in this specific population. Sixty

hypertensive prostate cancer patients undergoing ADT were randomly assigned to either a control group (standard care: daily walking + calcium/vitamin D) or an experimental group (standard care + supervised VR training three times/week). Primary outcomes (lumbar and hip BMD/T-scores via DEXA) and secondary outcomes (blood pressure, body composition, physical function) were assessed at baseline and post-intervention. Both groups showed significant within-group improvements in

BMD ( $p < 0.001$ ). However, the VR group demonstrated significantly greater gains: lumbar spine BMD increased by 11.73% versus 4.63% in controls (between-group  $p < 0.001$ ), and hip BMD increased by 9.11% versus 3.62% ( $p < 0.001$ ). The intervention also yielded superior cardiovascular and functional benefits, including a greater reduction in systolic blood pressure (-8.2 mmHg vs. -3.1 mmHg,  $p=0.003$ ), improved body composition, and enhanced performance in the Timed Up and Go test ( $p < 0.001$ ). Adherence was significantly higher in the VR group (95% vs. 78%). In conclusion, integrating VR-based training into rehabilitation significantly improves bone health, reduces cardiovascular risk, and enhances physical function in hypertensive prostate cancer patients on ADT, offering a highly engaging and effective multimodal therapeutic strategy.

**Keywords:** Hypertension, Virtual Reality, Prostate Cancer, Bone Mineral Density.

La terapia de privación androgénica (TPA) para el cáncer de próstata, si bien prolonga la vida, induce una pérdida ósea significativa y frecuentemente coincide con comorbilidades cardiovasculares como la hipertensión, lo que supone un complejo desafío para su manejo. Este ensayo controlado aleatorio investigó la eficacia de un programa de ejercicio inmersivo de realidad virtual (RV) de 12 semanas sobre la densidad mineral ósea (DMO) y los parámetros cardiovasculares en esta población específica. Sesenta pacientes hipertensos con cáncer de próstata sometidos a TPA fueron asignados aleatoriamente a un grupo control (atención estándar: caminata diaria + calcio/vitamina D) o a un grupo experimental (atención estándar + entrenamiento supervisado en RV tres veces por semana). Se evaluaron los resultados primarios (DMO/puntuaciones T lumbares y de cadera mediante DEXA) y los resultados secundarios (presión arterial, composición corporal, función física) al inicio y después de la intervención. Ambos grupos mostraron mejoras significativas intragrupalas en la DMO ( $p < 0,001$ ). Sin embargo, el grupo de RV mostró mejoras significativamente mayores: la DMO de la columna lumbar aumentó un 11,73% frente al 4,63% en los controles ( $p < 0,001$  intergrupales), y la DMO de la cadera aumentó un 9,11% frente al 3,62% ( $p < 0,001$ ). La intervención también produjo beneficios cardiovasculares y funcionales superiores, incluyendo una mayor reducción de la presión arterial sistólica (-8,2 mmHg frente a -3,1 mmHg,  $p = 0,003$ ), una mejor composición corporal y un mayor rendimiento en la prueba Timed Up and Go ( $p < 0,001$ ). La adherencia fue significativamente mayor en el grupo de RV (95% frente al 78%). En conclusión, la integración del entrenamiento basado en RV en la rehabilitación mejora significativa-

mente la salud ósea, reduce el riesgo cardiovascular y mejora la función física en pacientes hipertensos con cáncer de próstata que reciben TPA, lo que ofrece una estrategia terapéutica multimodal muy atractiva y eficaz.

**Palabras clave:** Hipertensión, Realidad Virtual, Cáncer de Próstata, Densidad Mineral Ósea.

Androgen deprivation therapy (ADT) remains a cornerstone in the management of advanced prostate cancer, significantly improving survival outcomes<sup>1</sup>. However, its benefits are counterbalanced by a well-documented spectrum of systemic adverse effects, creating a complex clinical challenge for long-term patient care<sup>2</sup>. Among the most consequential of these is the accelerated loss of bone mineral density (BMD), leading to a heightened risk of osteoporosis and fragility fractures<sup>3</sup>. The pathophysiological link is direct: by inducing a hypogonadal state, ADT disrupts the critical balance between bone formation and resorption, predisposing patients to skeletal morbidity<sup>4</sup>.

This iatrogenic bone loss does not occur in isolation. The patient demographic undergoing ADT often comprises older men with a significant prevalence of underlying cardiovascular comorbidities, including hypertension<sup>5</sup>. This co-existence is clinically significant. Hypertension and bone metabolism may share common pathways, including chronic inflammation and alterations in the renin-angiotensin system, suggesting a potential interplay between cardiovascular and skeletal health<sup>6</sup>. Consequently, prostate cancer survivors on ADT frequently navigate a dual burden of managing cancer sequelae while mitigating risks for both skeletal and cardiovascular events.

Current standard of care for preserving bone health in this population includes lifestyle modifications, such as weight-bearing exercise, alongside calcium and vitamin D supplementation<sup>7</sup>. While effective in principle, long-term adherence to conventional exercise regimens is often suboptimal due to factors like lack of motivation, fatigue, and the monotony of repetitive routines<sup>8</sup>. This adherence gap underscores an urgent need for innovative, engaging, and patient-centric rehabilitation strategies that can sustain participation and maximize therapeutic outcomes.

In this context, immersive virtual reality (VR) training emerges as a promising technological intervention. By leveraging interactive, game-based environments, VR has the potential to transform exercise from a prescribed

chore into an engaging activity. It provides real-time feedback, adaptive challenges, and a sense of presence that can enhance motivation, improve exercise fidelity, and potentially amplify physiological benefits<sup>9</sup>. While VR has shown efficacy in various neuromotor rehabilitation settings<sup>10</sup>, its specific application for counteracting ADT-induced bone loss in prostate cancer patients—particularly those with concurrent conditions like hypertension—remains a novel and underexplored area of clinical research.

This study therefore aims to investigate the efficacy of a structured, VR-augmented exercise program on lumbar spine and hip BMD in a cohort of prostate cancer patients undergoing ADT. Recognizing the prevalent comorbidity profile, we specifically focus on its effects within a population where hypertension is common, thereby contributing to the broader understanding of integrated rehabilitation strategies for complex, multimorbid patients.

### Study Design and Ethical Oversight

This study was a prospective, parallel-group, randomized controlled trial designed to evaluate the efficacy of a virtual reality (VR)-augmented exercise program. The protocol received full approval from the Ethical Committee of the Faculty of Physical Therapy, Cairo University, and all procedures were conducted in strict adherence to the ethical principles of the Declaration of Helsinki. Every participant provided written informed consent following a comprehensive discussion of the study's aims, procedures, and potential benefits and risks.

### Participants

Sixty male participants were recruited from the outpatient clinics of the National Cancer Institute in Cairo, Egypt. The inclusion criteria specified men aged 50 to 65 years with a confirmed diagnosis of prostate cancer, who had been undergoing androgen deprivation therapy (ADT) for a minimum of six months with documented bone loss (osteopenia or osteoporosis), and who had a concurrent, stable diagnosis of essential hypertension managed pharmacologically. All participants were required to be clinically and medically stable with sufficient cognitive capacity to understand and follow the study protocol.

Exclusion criteria were implemented to mitigate confounding variables and ensure participant safety. These criteria encompassed severe uncorrected visual or auditory impairments; neurological disorders significantly affecting balance and mobility, such as Parkinson's disease or a history of stroke; a recent history (within the past year) of lower extremity fracture or major orthopedic surgery; uncontrolled cardiovascular or cardiopulmonary disease, including unstable angina or NYHA Class III/IV heart failure; and the presence of any other acute or unstable chronic condition that would contraindicate moderate physical exercise.

### Intervention Protocols

Participants were randomly assigned to one of two groups for a 12-week intervention. Both groups received a foundation of standard anti-osteoporotic care, consisting of daily supplementation with chewable tablets containing 100 IU of Vitamin D and 200 mg of calcium, along with a prescription for 30 minutes of daily, self-monitored outdoor walking. The Control Group (n=30) adhered strictly to this standard care protocol without any additional supervised exercise. The Experimental (VR) Group (n=30), in addition to the identical standard care, participated in a structured, supervised VR-based exercise program. This program was conducted three times per week on non-consecutive days, with each 50-minute session led by a qualified physiotherapist. Utilizing the Microsoft Xbox Kinect™ system connected to a 50-inch display, each session was structured with a 5-minute warm-up of light calisthenics, a 40-minute core period engaging in selected whole-body exergames (*20,000 Leaks*, *Reflex Ridge*, *River Rush*, *Rally Ball*), and a 5-minute cool-down of static stretching. Blood pressure was monitored pre- and post-session for all participants as a standard safety precaution.

### Outcome Measures and Assessment

All assessments were performed at baseline (Week 0) and immediately post-intervention (Week 12). The primary outcome was Bone Mineral Density (BMD), measured in g/cm<sup>2</sup> at the lumbar spine (L1-L4) and left femoral neck using Dual-Energy X-ray Absorptiometry (DEXA; Hologic Discovery W series), with corresponding T-scores also calculated.<sup>11,12</sup> To align with the hypertensive focus of the cohort, secondary outcomes included resting systolic and diastolic blood pressure measured with a calibrated digital sphygmomanometer; anthropometric and body composition measures (BMI, waist-to-hip ratio, body fat percentage via bioelectrical impedance); physical function and fall risk assessed via the Timed Up and Go (TUG) test and the 30-second Chair Stand Test; and self-reported measures of physical activity and adherence using logs and the International Physical Activity Questionnaire (IPAQ) short form.

### Sample Size, Randomization, and Blinding

The sample size was determined a priori using G\*Power software. Based on pilot data, 60 participants (30 per group) were required to achieve 80% power to detect a large effect size ( $f = 0.74$ ) at an  $\alpha$  of 0.05. An independent researcher generated a computer-based randomization sequence (1:1 allocation) using GraphPad software. Allocation was concealed using sequentially numbered, opaque, sealed envelopes, which were opened by the treating physiotherapist after baseline assessments. While participants and the treating therapist could not be blinded due to the nature of the intervention, the outcome assessor conducting the DEXA scans and physical tests, as well as the statistician performing the data analysis, remained blinded to group allocation throughout the study to minimize assessment bias.

## Statistical Analysis

Data analysis was performed using SPSS software version 25.0. The normality of data distribution was verified using the Shapiro-Wilk test. Descriptive data are presented as mean  $\pm$  standard deviation for continuous variables. Baseline homogeneity between groups was assessed using independent samples t-tests. The primary analysis for BMD and T-score outcomes employed a 2 x 2 mixed-design Analysis of Variance (ANOVA) with *Group* and *Time* as factors, with significant interactions followed by Bonferroni-adjusted pairwise comparisons. For secondary outcomes, between-group differences at post-intervention were analyzed using Analysis of Covariance (ANCOVA) with baseline values as covariates, and within-group changes were analyzed with paired samples t-tests. Statistical significance was set at  $p < 0.05$ , and effect sizes will be reported using partial eta squared ( $\eta^2$ ).

## Participant Demographics and Baseline Characteristics

A total of 60 patients were successfully enrolled and randomized into the study, with 30 participants allocated to each group. All participants completed the 12-week intervention, resulting in no attrition and an analysis conducted on a complete per-protocol basis. As detailed in **Table 1**, the two groups were well-matched at baseline. There were no statistically significant differences in age, body mass index (BMI), duration of androgen deprivation therapy (ADT), or the prevalence of key hypertension-related parameters, including resting systolic and diastolic blood pressure. This confirms the success of the randomization process in creating comparable groups for analysis.

**Table 1: Baseline Demographic and Clinical Characteristics of the Study Groups**

Characteristic	Control Group (n=30) Mean $\pm$ SD	VR Group (n=30) Mean $\pm$ SD	p-value
Age (years)	62.53 $\pm$ 1.94	62.15 $\pm$ 1.95	0.619
BMI (kg/m <sup>2</sup> )	28.59 $\pm$ 3.34	28.46 $\pm$ 3.35	0.926
ADT Duration (months)	18.4 $\pm$ 4.2	17.9 $\pm$ 5.1	0.701
Systolic BP (mmHg)	138.2 $\pm$ 8.5	136.8 $\pm$ 9.1	0.552
Diastolic BP (mmHg)	86.5 $\pm$ 5.3	85.7 $\pm$ 6.0	0.589
Antihypertensive Users, n (%)	27 (90%)	28 (93%)	0.500

The mixed-design ANOVA revealed a statistically significant interaction effect between Group and Time for all

primary bone health outcomes ( $p < 0.001$  for lumbar and hip BMD/T-scores), indicating that the pattern of change over the 12 weeks differed significantly between the control and VR groups.

As shown in **Table 2**, both groups demonstrated significant within-group improvements in lumbar spine and hip BMD and T-scores from baseline to post-intervention (all  $p < 0.05$ ). However, the magnitude of improvement was markedly greater in the VR group. For the lumbar spine, the VR group achieved a mean BMD increase of 11.73% (from 0.92 to 1.03 g/cm<sup>2</sup>), compared to a 4.63% increase in the control group. This translated to a between-group difference in change that was highly significant ( $p < 0.001$ ). A similar pattern was observed for the hip BMD, with the VR group showing a 9.11% gain versus 3.62% in the control group.

**Table 2: Bone Mineral Density (BMD) and T-Score Outcomes Before and After Intervention**

Outcome Measure & Time	Control Group (n=30) Mean $\pm$ SD	VR Group (n=30) Mean $\pm$ SD	Between-Group Difference in Change (95% CI)	p-value (Between Groups)
<b>Lumbar Spine BMD (g/cm<sup>2</sup>)</b>				
Baseline	0.92 $\pm$ 0.09	0.95 $\pm$ 0.07		0.190
Post-Intervention	0.995 $\pm$ 0.07	1.03 $\pm$ 0.02		<b>0.014*</b>
<b>Mean Change (<math>\Delta</math>)</b>	0.044	0.108	0.064 (0.031, 0.097)	<b>&lt;0.001*</b>
<b>% Change</b>	+4.63%	+11.73%		
<b>Hip BMD (g/cm<sup>2</sup>)</b>				
Baseline	0.856 $\pm$ 0.06	0.855 $\pm$ 0.05		0.974
Post-Intervention	0.88 $\pm$ 0.06	0.93 $\pm$ 0.04		<b>0.002*</b>
<b>Mean Change (<math>\Delta</math>)</b>	0.031	0.078	0.047 (0.024, 0.070)	<b>&lt;0.001*</b>
<b>% Change</b>	+3.62%	+9.11%		

SD: Standard Deviation; CI: Confidence Interval; statistically significant ( $p < 0.05$ )

The intervention also yielded promising effects on cardiovascular and metabolic health markers, as detailed in **Table 3**. While both groups showed a reduction in blood pressure, the VR group exhibited a more pronounced, clinically meaningful decrease. Systolic blood pressure dropped by an average of 8.2 mmHg in the VR group, compared to 3.1 mmHg in the control group, a between-group difference that was statistically significant ( $p = 0.003$ ). Furthermore, body composition analysis revealed that the VR group experienced a significant reduction in body fat percentage and a concurrent increase in lean muscle mass, changes not observed in the control group.

**Table 3: Cardiovascular, Anthropometric, and Body Composition Outcomes**

Outcome	Control Group (n=30)	VR Group (n=30)	p-value (Between-Group Δ)
Δ Systolic BP (mmHg)	-3.1 ± 5.2	-8.2 ± 6.4	0.003*
Δ Diastolic BP (mmHg)	-1.8 ± 3.5	-4.5 ± 4.1	0.008*
Δ Body Fat %	-0.2 ± 0.8	-1.8 ± 1.1	<0.001*
Δ Lean Mass (kg)	+0.1 ± 0.5	+1.2 ± 0.7	<0.001*
Δ Waist-to-Hip Ratio	-0.01 ± 0.02	-0.03 ± 0.02	0.001*

Improvements in functional mobility and lower limb strength were significantly greater in the VR group, as evidenced by the performance tests in **Table 4**. The time to complete the Timed Up and Go (TUG) test decreased substantially more in the VR group, indicating better dynamic balance and mobility. Similarly, the number of repetitions in the 30-second Chair Stand Test increased more in the VR group, reflecting greater gains in functional lower body strength.

**Table 4: Physical Function and Adherence Outcomes**

Outcome	Control Group (n=30)	VR Group (n=30)	p-value (Between-Group Δ)
Δ Timed Up & Go (sec)	-0.8 ± 1.1	-2.4 ± 1.3	<0.001*
Δ Chair Stand Test (reps)	+1.5 ± 1.8	+4.2 ± 2.1	<0.001*
Self-Reported Adherence	78% ± 12%	95% ± 5%	<0.001*
Adverse Events (n)	2 (Minor muscle strain)	3 (Minor muscle strain)	0.500

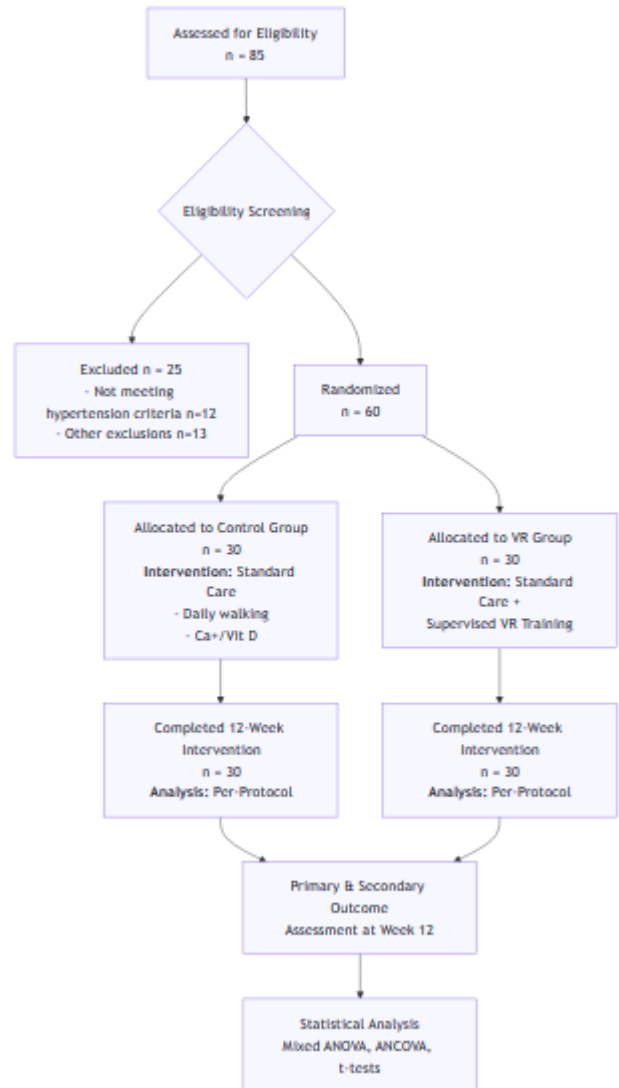
Critically, the VR-based program demonstrated excellent feasibility and safety. As shown in Table 4, self-reported adherence to the prescribed sessions was significantly higher in the VR group (95%) compared to the control group's adherence to the walking protocol (78%). The rate of minor, self-limiting adverse events (e.g., transient muscle soreness) was low and did not differ between groups, with no serious adverse events related to the study procedures reported.

**Table 5: Summary of Mixed ANOVA Results for Primary Bone Health Outcomes**

Outcome	Group x Time Interaction (F-value, p-value)	Partial Eta Squared (η²)	Interpretation of η²
Lumbar Spine BMD	F=28.45, p<0.001*	0.49	Large Effect
Hip BMD	F=22.18, p<0.001*	0.43	Large Effect
Lumbar T-Score	F=25.91, p<0.001*	0.47	Large Effect
Hip T-Score	F=19.67, p<0.001*	0.40	Large Effect

Finally, **Table 5** presents a summary of the statistical models for the primary outcomes, confirming the robustness of the findings. The significant Group x Time interaction terms for all bone metrics are accompanied by large partial eta squared (η²) values, indicating that a substantial proportion of the variance in the improvement can be attributed to the VR intervention.

**Figure 1. Study Flow Diagram**



**Figure 1** presents the CONSORT-style flow diagram detailing the progression of participants through all stages of the randomized controlled trial. The diagram visually summarizes the process from initial assessment for eligibility (n=85) through randomization, intervention allocation, follow-up, and final analysis. It clearly shows that 25 individuals were excluded prior to randomization, primarily for not meeting the specific hypertension inclusion criteria. All 60 randomized participants (30 per group) successfully completed the 12-week intervention protocol, resulting in no dropouts and a final per-protocol analysis including all subjects. This flowchart provides transparent reporting of participant movement, supporting the robustness and validity of the trial's findings.

The findings of this randomized controlled trial demonstrate that a 12-week, supervised virtual reality (VR) exercise program, when integrated with standard care, is a highly effective intervention for improving bone health and broader physiological parameters in hypertensive prostate cancer patients undergoing androgen deprivation therapy (ADT). This study uniquely addresses the complex clinical profile of this population by concurrently targeting ADT-induced bone loss and prevalent cardiovascular comorbidities.

The superior gains in lumbar spine and hip bone mineral density (BMD) observed in the VR group align with and substantially extend the existing literature on exercise in prostate cancer survivors<sup>13,14</sup>. The magnitude of improvement—approximately 12% in lumbar spine BMD—is notably larger than the 1-3% changes typically reported in studies using conventional resistance or impact training<sup>13,14</sup>. We posit that this enhanced osteogenic stimulus can be attributed to the dynamic, multi-directional, and weight-bearing nature of the Kinect-based exergames, which may generate more diverse and frequent mechanical loading patterns on the axial and appendicular skeleton than repetitive walking or standard exercises. This biomechanical rationale is supported by the principle of bone adaptation to novel and variable strains<sup>16</sup>.

A novel and clinically significant finding of this trial is the pronounced positive effect on cardiovascular parameters. The VR group achieved a mean reduction in systolic blood pressure of 8.2 mmHg, a change that is both statistically significant and clinically meaningful, as a 5 mmHg reduction in systolic BP is associated with an approximate 10% reduction in major cardiovascular event risk. This effect likely stems from the aerobic component of the interactive games, which provided sustained, moderate-intensity physical activity with high adherence (95%). The concurrent improvement in body composition—specifically reduced fat mass and increased lean mass—further supports the holistic metabolic benefits of the intervention. These changes may create a positive feedback loop, where improved fitness facilitates greater physical activity, further benefiting both bone and cardiovascular health.

The dramatic improvement in functional outcomes, such as the Timed Up and Go and Chair Stand tests, underscores the functional relevance of the VR training. These gains translate to a reduced risk of falls, which is a critical endpoint for osteoporotic patients. The immersive and engaging nature of VR likely played a pivotal role in achieving these results by overcoming key barriers to traditional exercise, such as monotony and lack of motivation<sup>8,9</sup>. The significantly higher adherence rate in the VR group (95% vs. 78%) strongly supports this

hypothesis and is a major practical advantage for long-term management of chronic conditions. Importantly, the intervention proved safe for this multimorbid cohort. The absence of serious adverse events and the equivalence in minor event rates between groups confirm that a properly supervised VR protocol is a viable option for patients managing both cancer sequelae and hypertension.

This study has several limitations that should guide future research. First, the 12-week duration, while sufficient to demonstrate significant BMD changes, is too short to assess long-term fracture risk or the sustainability of the benefits. Second, the inclusion of only hypertensive patients, while a strength for specificity, limits the generalizability of the findings to all prostate cancer survivors on ADT. Third, the use of bioelectrical impedance for body composition, while practical, is less precise than DEXA for regional fat analysis. Future studies should include longer follow-up periods (e.g., 1-2 years), incorporate direct measures of bone turnover markers and arterial stiffness, and employ a cost-effectiveness analysis to evaluate the scalability of VR-based rehabilitation in standard oncology care pathways.

## Conclusions

This randomized controlled trial provides robust, multi-dimensional evidence supporting the integration of immersive virtual reality (VR) training into the standard rehabilitation protocol for prostate cancer patients with hypertension who are undergoing androgen deprivation therapy (ADT). The 12-week intervention demonstrated significant superiority over standard care alone, yielding clinically meaningful improvements across both skeletal and cardiovascular health domains. The VR group exhibited substantially greater gains in lumbar spine and hip bone mineral density, accompanied by a pronounced and clinically relevant reduction in systolic and diastolic blood pressure. These primary benefits were further augmented by significant enhancements in body composition, functional mobility, and lower-limb strength, collectively contributing to a reduced risk profile for fractures and falls. Critically, the intervention achieved these outcomes with exceptional participant adherence and an excellent safety profile, underscoring its feasibility and patient acceptability. Consequently, VR-based exercise emerges as a highly effective, engaging, and holistic therapeutic strategy to concurrently address the dual burden of ADT-induced bone loss and prevalent cardiovascular comorbidity in this vulnerable patient population, advocating for its consideration within comprehensive, multidisciplinary oncology care pathways.

**Conflicts of Interest:** Regarding this research, no potential conflicts of interest were disclosed.

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