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Exercise-Based Interventions for Metabolic and Immune Modulation in Prostate Cancer: A Systematic Review and Meta-Analysis of RCTs

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ABSTRACT

Purpose: Prostate cancer is the most common malignancy in men and often leads to treatment-related morbidity, including metabolic alterations and chronic low-grade inflammation. Exercise has been proposed as a supportive strategy to mitigate treatment-related adverse effects. This study systematically reviews the impact of exercise on metabolic-, inflammatory-, hormonal- and tumour-related biomarkers in men with prostate cancer. A meta-analysis explored potential effects according to exercise type.

Methods: This systematic review followed PRISMA guidelines and included studies from PubMed, Scopus and Web of Science. Eligible studies involved prostate cancer patients, an exercise intervention and reported outcomes on metabolic, immune or tumour markers. Only randomised controlled trials with a control group were included. Twenty-five articles fulfilled the inclusion criteria. The methodological quality of the studies was assessed using the Cochrane Collaboration's tool.

Results: A total of 1,093 male participants were included across trials involving resistance, aerobic, combined exercise or yoga interventions. The meta-analysis showed a significant reduction in insulin levels within the combined exercise subgroup ($p = 0.03$). C-reactive protein was also significantly reduced in pooled analyses ($p = 0.001$). No consistent significant effects were observed for testosterone, glucose, IL-6 or prostate-specific antigen.

Conclusions: Exercise may induce modest changes in selected systemic biomarkers, particularly CRP, in men with prostate cancer undergoing treatment. However, effects were heterogeneous and generally small, and current evidence does not demonstrate consistent tumour-related modification. Exercise remains an important supportive strategy to enhance physiological resilience, but larger, high-quality trials are required to clarify clinical relevance.

1 | Introduction

Prostate cancer is the most frequently diagnosed malignancy among men worldwide and remains a leading cause of cancer-related morbidity [1, 2]. Although survival outcomes have improved, many patients experience substantial treatment-related adverse effects, particularly during androgen deprivation therapy (ADT), which remains a cornerstone of management in advanced and

recurrent disease [3]. ADT induces profound endocrine and metabolic alterations, including testosterone suppression, sarcopenia, increased fat mass, insulin resistance, dyslipidaemia and elevated cardiovascular risk [3, 4]. In parallel, oncological treatments may promote chronic low-grade systemic inflammation and immune perturbations [5].

These systemic alterations are clinically relevant not only because they affect symptom burden and quality of life [6] but also because they shape the physiological environment in which tumour progression occurs [7]. Structured exercise interventions have been proposed as a nonpharmacological strategy to mitigate ADT-related side effects and improve functional capacity [8]. Exercise modulates metabolic pathways, endocrine axes and inflammatory signalling networks through skeletal muscle–derived myokines and systemic adaptations [9]. However, the biological significance of these changes depends on the specific domain of the biomarker assessed.

These biomarkers investigated in exercise oncology can be organised into three hierarchical domains: (i) metabolic markers (e.g., insulin, glucose, IGF-1), reflecting systemic metabolic regulation; (ii) inflammatory mediators (e.g., C-reactive protein (CRP), IL-6), reflecting systemic inflammatory tone and immune signalling; and (iii) tumour-related endpoints (e.g., prostate-specific antigen or PSA), reflecting disease activity [10–12]. While metabolic and inflammatory markers may influence the systemic milieu, they do not constitute direct measures of tumour burden or disease modification [11].

Recent molecular frameworks in prostate cancer research emphasise the complexity of tumour–immune interactions and cytokine signalling pathways within the tumour microenvironment [13]. These models highlight how inflammatory signalling networks and immune regulatory pathways contribute to tumour behaviour and therapeutic responsiveness. Nevertheless, systemic biomarker modulation does not necessarily translate into clinically meaningful oncological outcomes.

Although individual trials have reported exercise-induced changes in selected biomarkers—including PSA [14], inflammatory mediators [15] and components of the insulin–IGF axis [16]—the evidence remains heterogeneous and fragmented. Variability in exercise modality, treatment phase and outcome reporting has limited the ability to draw consistent conclusions regarding biological effects in men undergoing active prostate cancer treatment.

To our knowledge, no comprehensive synthesis has systematically evaluated the effects of resistance, aerobic and combined exercise modalities across metabolic-, inflammatory-, hormonal- and tumour-related biomarker domains in this population. Therefore, the present study aimed to systematically review and meta-analyse the impact of structured exercise interventions on selected circulating markers in men with prostate cancer receiving oncological treatment. Rather than presuming a uniform biological benefit, this review seeks to clarify the magnitude, consistency and domain-specific relevance of exercise-induced biomarker changes within the treatment context.

2 | Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [17] guidelines were followed to conduct the current systematic review and meta-analysis. The protocol for this systematic review and meta-analysis was registered on PROSPERO (number of registers: CRD42024620154).

2.1 | Data Sources and Searches

The initial literature search was conducted in November 2024, with an updated search performed in April 2025, employing three electronic databases: PubMed (MEDLINE), Scopus and the Web of Science (WOS). The search strategy involved various combinations of the following terms: ('prostate cancer' OR PCA OR adenocarcinoma) AND (lactate OR glucose OR epinephrine OR norepinephrine OR MIF OR testosterone OR IGF1 OR B cell OR IL1B OR IL10 OR TNFA OR CRP OR 'C-reactive protein' OR 'natural killers' OR NK OR IL6 OR IL8 OR T cell OR vitamin D OR PSA OR 'tumour hypoxia' OR cortisol OR ROS OR 'reactive oxygen species' OR cytokines) AND (exercise OR 'physical activity' OR 'physical fitness' OR Pilates OR yoga) AND ('randomised controlled trial' OR 'control trial'). The exact search strategy for each database is reported in the Supporting information 1. No restrictions were applied regarding language or publication date.

The articles were included if they meet the following inclusion criteria: (a) participants had prostate cancer, (b) the intervention included any kind of exercise intervention, (c) the article reported effects on catecholamines, metabolic and/or tumour markers and/or natural killer (NK) cells and/or NK cell activity (NKCA) and/or interleukins and/or cortisol and/or vitamin D, (d) the design included a control group and (e) participants were randomly assigned to exercise and control groups. The following exclusion criteria were set: (a) the article was not written in English; (b) the article was a consensus, review, guideline, conference abstract and/or a study protocol or design; (c) prostate cancer patients' results were not reported separately; (d) the article was an acute intervention; (e) the article had duplicate data from another included article; (f) the article was not available; (g) the article had an intervention for cancer prevention; and (h) the article had a healthy men control group. The search was independently carried out by AMS and SV. In the event of any discrepancies, a consensus discussion was held under the supervision of J.L.L.-L. Similarly, the risk of bias assessment was conducted by AMS and SV, with any potential disagreements resolved through a consensus process led by J.L.L.-L. However, no disagreements arose during either the search or the risk of bias assessment.

2.2 | Quality Assessment

The authors AMS and SV conducted the risk of bias analyses. The assessment was performed using the Cochrane Risk-of-Bias Tool for Randomised Trials (RoB 2.9) [18], which evaluates bias across five domains: (i) the randomisation process, (ii) deviations from intended interventions, (iii) missing outcome data, (iv) measurement of the outcome and (v) selection of the reported result. Subsequently, traffic light and weighted summary risk-of-bias plots for the included randomised studies were generated using the risk-of-bias visualisation (robvis) online tool [19].

2.3 | Data Extraction

In accordance with PRISMA guidelines, data were extracted based on methodology, including participants, intervention, comparisons, outcomes and study design (PICOS). For

participants, baseline characteristics such as sample size, mean age, disease stage, type of treatment and intervention timing were recorded. Intervention details included programme duration, session length, weekly frequency, exercise description and intensity. Additionally, information on the intervention characteristics of the comparison group and exercise session attendance rates were collected. The outcomes assessed in this systematic review included testosterone (ng/dl, pmol and nmol/L), insulin (mU/L, pmol/L), glucose (nmol/l; mg/dL; %), IGF-1 (ng/mL), cortisol (nmol/L), PSA (ng/ml; ng/dL; μg/L; %), CRP (ng/dl; mg/L), tumour necrosis factor-alpha (TNF-α) (ft/mL; pg/mL), interleukin 6 (IL-6) (ft/mL; pg/mL), interleukin 1-beta (IL-1β) (ft/mL), interleukin 8 (IL-8) (pg/mL) and NK of tumours and healthy cells (cells/mm). Testosterone, insulin, glucose, PSA, CRP and IL-6 data were also used for a meta-analysis.

Data, including mean, standard deviation (SD) and the number of participants, were extracted for both the control group and the exercise intervention groups. If the required data were not readily available, the corresponding authors were contacted via email to request the relevant information. Articles were excluded from the meta-analysis if the authors did not attend to our request.

2.4 | Statistical Analysis

The participants' characteristics were presented as descriptive data, including mean values and SDs.

Meta-analysis statistics were conducted using Review Manager Software (RevMan) version (5.4) [20]. Five separate analyses were performed, each corresponding to one of the review variables, including those studies that evaluated oncology patients during the treatment process: testosterone, insulin, glucose, PSA and CRP.

Due to expected clinical and methodological heterogeneity, and following the Cochrane Guidelines for meta-analysis [21], the inverse variance method with random effects and a 95% confidence interval (CI) was applied. The standardised mean difference (SMD) was chosen to account for differences in outcome scales and measurement methods. All pooled estimates were calculated using postintervention endpoint values (mean, SD, n). Change-from-baseline values were not pooled. Statistical significance was set at $p < 0.05$, with SMD values interpreted as follows: small (< 0.4), moderate (0.4–0.7) and large (> 0.75).

Subgroup analyses were conducted, where possible, according to exercise modality: (a) resistance exercise, (b) combined exercise and (c) cardiovascular exercise.

Furthermore, to explore potential sources of clinical heterogeneity, stratified subgroup analyses were conducted based on disease stage (metastatic vs nonmetastatic) when sufficient studies were available within each outcome.

To assess the robustness of pooled estimates, sensitivity analyses were performed by excluding trials at a high risk of bias.

Sensitivity analyses by ADT exposure were planned. However, most trials contributing to each meta-analysis were conducted in men receiving ADT or androgen suppression, and the number of non-ADT trials per outcome was insufficient to allow meaningful subgroup comparisons. Therefore, formal ADT vs non-ADT subgroup analyses were not feasible.

Heterogeneity among studies was evaluated using Tau^2, I^2 and Chi^2 tests.

3 | Results

3.1 | Description of the Study Selection Procedure

A total of 311 articles were initially identified. After removing duplicates, 233 articles remained as potentially relevant from our literature search. Following the screening of titles and abstracts, 177 research articles were excluded for the following reasons: reviews and meta-analyses ($n = 77$), studies not involving prostate cancer patients ($n = 35$), nonexercise intervention ($n = 26$), protocols or study designs ($n = 22$), guidelines or conference abstracts ($n = 11$), grants ($n = 4$), intervention in animals ($n = 1$) and non-English articles ($n = 1$).

This left 55 articles for eligibility assessment, of which 33 were further excluded due to various reasons: not assessing study variables ($n = 8$), not reporting prostate cancer patient results separately ($n = 7$), absence of a control group ($n = 6$), involving acute exercise interventions ($n = 4$), study designs other than RCT ($n = 3$), data duplication from another study ($n = 2$), unavailability ($n = 1$), focus on exercise intervention for cancer prevention ($n = 1$) and using a control group of healthy men ($n = 1$). In addition, one article was identified through the reference list of one of the articles included in the search. Another article was incorporated via other sources. These articles were not retrieved through the conducted searches, as the terms 'randomised controlled trial' or 'control trial' did not appear in either the title or the keywords.

Ultimately, 25 articles met the inclusion criteria and were included in the systematic review and meta-analysis (Figure 1). No studies were founded with vitamin D data. Therefore, this variable was excluded from the systematic review and meta-analysis.

3.2 | Quality and Risk of Bias Assessment

Supporting information 2 shows a summary of the risk of bias assessment for the randomised controlled trials included in this systematic review. The analysis revealed that seven studies had a low risk of bias [7, 22–27], nine studies exhibited some concerns [15, 28–35] and nine studies had a high risk of bias [14, 16, 36–42].

3.3 | Participants' Characteristics

Table S1 in Supporting information 3 (SM3) provides an overview of the participant characteristics across the included studies. A total of 1093 male participants were analysed [7, 14–16, 22–42], with study sample sizes ranging from 18 [24] to 121 [28] individuals. The range of participants' age varied between 56 and 77 years old. Regarding prostate cancer stages, nine studies included patients in Stages I and II [14, 16, 23, 24, 27, 30, 34, 35, 39], two studies covered Stages I–III [22, 32], five studies focused on Stages I–IV without metastases [7, 15, 28, 31, 37] and six studies included patients in Stage I–IV with metastases [25, 29, 33, 36, 38, 40]. Additionally, two studies did not restrict the cancer stage for the research [26, 42].

In terms of exercise interventions based on treatment timing, three studies were conducted before any type of therapy

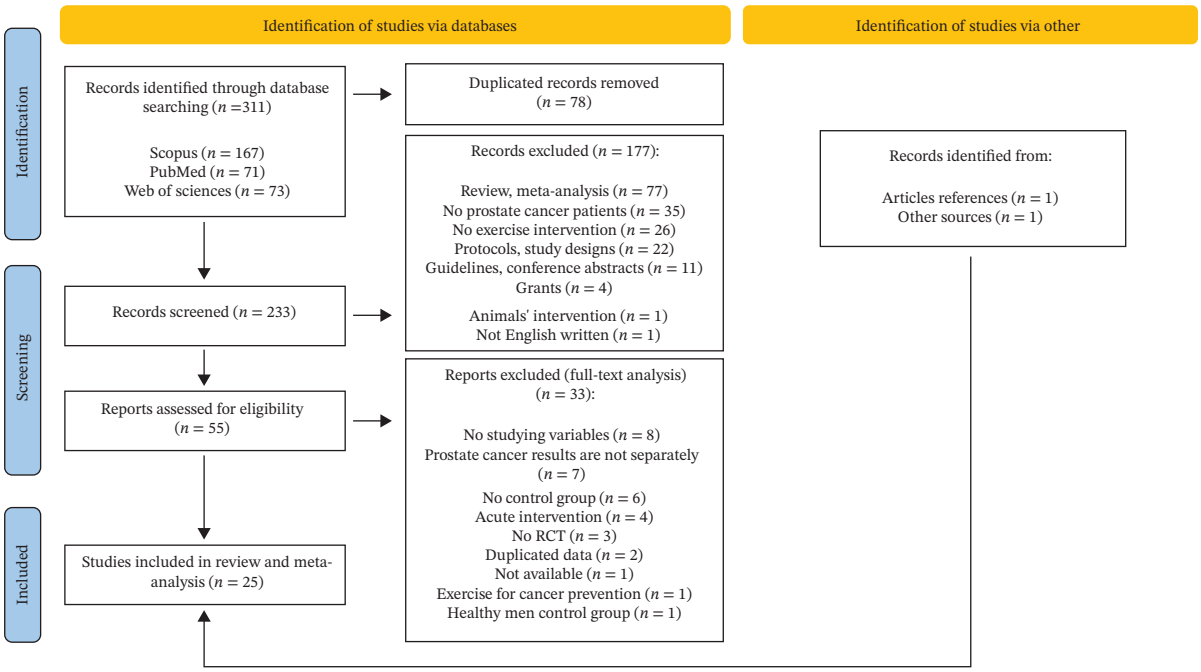

FIGURE 1 | Flowchart depicting the article selection process for inclusion in the systematic review and meta-analysis.

[32, 39, 42], 15 studies took place during treatments (hormonotherapy with ADP [7, 15, 22, 25, 26, 28, 29, 31, 33, 36–38, 40], radiotherapy [7, 22, 26, 28, 31, 36], chemotherapy, prostatectomy and/or others [14, 16, 22, 25, 26, 30, 36, 40, 42]), two were implemented before and after patients had completed their treatments [7, 42], seven studies took place during active surveillance [16, 23, 24, 27, 34, 35, 41] and one study did not report information about the treatments of the patients [35]. Further details on study characteristics, including specific types of treatments and intervention and control groups, are provided in Table S1 on SM3.

3.4 | Characteristics of Exercise Interventions

The exercise intervention programmes implemented in the studies varied in duration, ranging from 2 [39] to 96 [16] weeks (see Table S2 in SM3). While most interventions maintained a fixed length, some were adjusted to align with concurrent medical treatments such as surgery or radiotherapy. The exercise frequency ranged from two to seven sessions per week. In terms of exercise modality, six studies focused on resistance training (some with dietary control) [24, 28, 33, 36–38], nine implemented combined training [7, 15, 22, 25, 26, 29, 31, 40, 41] and finally, 12 studies incorporated cardiovascular training (aerobic, HIIT or yoga) [14, 16, 23, 24, 27, 28, 30, 32, 34, 35, 39, 42].

Aerobic training was conducted using various methods and equipment, including treadmill running, ergometer, walking, yoga or cross-training exercises. The duration of aerobic sessions varied from 12 to 90 min over a period of 2–96 weeks. Training intensity was determined based on different physiological markers, such as a percentage of maximal workload derived from VO_2 peak (30%–95%), a percentage of maximal workload derived from power peak (30%–120%), age-predicted maximum heart rate (65%–85%), or the rate of perceived exertion (RPE), which ranged from 11 to 17.

For resistance training, session durations ranged between 45 and 60 min, with intervention periods lasting between 6 and 52 weeks. The intensity of resistance exercises was determined based on one-repetition maximum (1RM), typically ranging from 30% to 100% of 1RM.

Additionally, there were nine studies with combined exercise interventions lasting from 12 to 58 weeks and including resistance, aerobic and flexibility exercises. Most interventions included a structured warm-up and cool-down period lasting between 5 and 15 min.

Participant adherence was generally high, with exercise session attendance exceedingly more than 75% in studies that reported compliance data. Further details for each training protocol can be found in Table S2 on SM3.

3.5 | Effects of the Interventions on Metabolic, Tumour-Related, Inflammatory and Hormonal Biomarkers

The included trials reported the effects of exercise interventions on metabolic, tumour-related, inflammatory and hormonal biomarkers. A comprehensive summary of individual study findings, including reported intra- and intergroup effects for each variable, is provided in Table S3 and S4 of the SM3. When sufficient data were available, pooled effect estimates were calculated using random-effects meta-analyses based on postintervention endpoint values. An overview of pooled results, heterogeneity and sensitivity analyses is presented in Table 1. Forest plots for the principal clinically relevant outcomes (insulin, PSA and CRP) are included in the main manuscript, with additional subgroup and sensitivity analyses provided in the Supporting Information.

3.6 | Effects of Exercise on Metabolic Biomarkers

Six studies ($n = 287$ participants) contributed to the insulin meta-analysis (Figure 2). The overall pooled effect was not statistically significant (SMD = −0.35 [95% CI: −1.00 to 0.31]), and heterogeneity was substantial ($I^2 = 85\%$). Although the combined

TABLE 1 | Summary of pooled effects of exercise on metabolic, tumour-related and inflammatory biomarkers.

Outcome	Studies	N	Pooled SMD (95% CI)	I^2 (%)	Statistically significant	Robust after sensitivity analyses*
Metabolic markers						
Insulin	6	287	−0.35 (−1.00, 0.31)	85	No	No (attenuated; heterogeneity remained)
Glucose	5	264	−0.13 (−0.38, 0.12)	7	No	Yes (unchanged)
Tumour-related marker						
PSA	10	653	−0.11 (−0.30, 0.08)	25	No	Yes (effect attenuated to null)
Inflammatory markers						
CRP	3	247	−0.42 (−0.67, −0.16)	0	Yes	Yes (remained significant)
IL-6	3	149	−0.36 (−1.09, 0.38)	77	No	No (heterogeneity persisted)

*Sensitivity analyses included exclusion of a high risk of bias trials, stratification by disease stage and restriction to ADT-exposed trials where feasible.

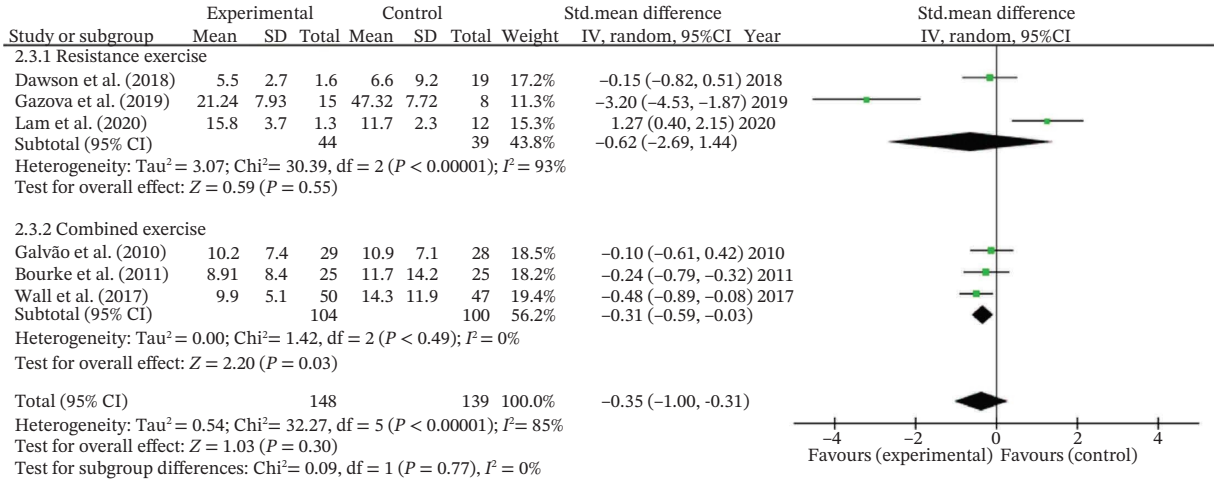

FIGURE 2 | Meta-analysis results of insulin in resistance and combined exercises comparing with control group data.

exercise subgroup showed a statistically significant reduction in insulin levels, no significant subgroup differences were detected, and the overall estimate remained nonsignificant.

Stratified analyses by disease stage (metastatic vs nonmetastatic) did not demonstrate significant differences between strata. Moreover, sensitivity analyses excluding trials at a high risk of bias attenuated the pooled effect towards null values (SMD = 0.02 [95% CI: −0.56 to 0.60]), while heterogeneity remained elevated (see Figures S1 and S2 on SM3). These findings indicate that the observed insulin effects were not robust.

Five studies ($n = 264$ participants) evaluated glucose levels (Figure S7). The pooled analysis showed no statistically significant effect of exercise (SMD = −0.13 [95% CI: −0.38 to 0.12]), with low heterogeneity ($I^2 = 7\%$). Restricting analyses to ADT-exposed trials yielded a slightly larger but still nonsignificant effect (SMD = −0.25 [95% CI: −0.51 to 0.02]), and exclusion of trials at a high risk of bias did not materially alter results (SMD = −0.14 [95% CI: −0.46 to 0.18]) (see Figures S3, S4, S5 on SM3.

3.7 | Effects of Exercise on Tumour-Related Biomarker

Individual study findings for PSA are summarised in Table S4 on SM3. After exclusion of one study reporting model-based estimates to ensure metric consistency [40], 10 trials ($n = 608$ participants) were included in the meta-analysis.

The overall pooled effect was small and not statistically significant (SMD = −0.11 [95% CI: −0.30 to 0.08]), with low-to-moderate heterogeneity ($I^2 = 25\%$). Although pooled estimates varied across exercise modalities, no significant subgroup differences were detected, and none of the modality-specific effects reached statistical significance (see Figure S6 on SM3).

Stratified analyses by disease stage (metastatic vs nonmetastatic) and restriction to ADT-exposed trials did not materially alter pooled estimates. Furthermore, sensitivity analyses excluding trials at a high risk of bias attenuated the pooled effect towards null values (SMD = −0.01 [95% CI: −0.22 to 0.19]; $I^2 = 11\%$) (see SM3 Figures S7, S8, S9).

3.8 | Effects of Exercise on Inflammatory Biomarkers

Individual study findings for inflammatory and immune-related markers are summarised in SM3 Table S4.

Three studies ($n = 247$ participants) contributed to the CRP meta-analysis (Figure 3). Exercise was associated with a statistically significant reduction in CRP levels (SMD = −0.42 [95% CI: −0.67 to −0.16]), with no observed heterogeneity ($I^2 = 0\%$).

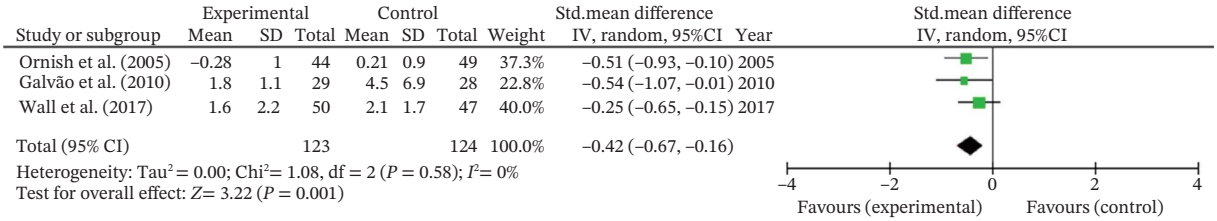

FIGURE 3 | Meta-analysis results of CRP comparing exercise with control group data.

Restricting analyses to trials conducted during ADT exposure did not materially alter the pooled estimate, and exclusion of trials at a high risk of bias yielded comparable results (SMD = −0.36 [95% CI: −0.68 to −0.04]), indicating a modest but consistent anti-inflammatory effect (SM3 Figures 10 and 11).

In contrast, three studies ($n = 149$ participants) assessed IL-6 levels. The pooled effect was not statistically significant (SMD = −0.36 [95% CI: −1.09 to 0.38]), and substantial heterogeneity was observed ($I^2 = 77\%$). Sensitivity analyses excluding trials at a high risk of bias did not materially change the results, and the effect remained nonsignificant. These findings indicate inconsistent evidence regarding exercise-induced modulation of IL-6 (SM3 Figures S12 and S13).

Additional inflammatory and immune markers, including cortisol, TNF-α, IL-1β, IL-5, IL-8, IL-12 and NK cell activity, were reported in individual trials. The number of studies per outcome was limited, and reporting formats varied across studies; therefore, no meta-analyses were performed for these variables. Reported findings included both statistically significant and nonsignificant within- and between-group differences across trials.

3.9 | Effects of Exercise on Hormonal Biomarkers

Individual study findings for testosterone are summarised in SM3 Table S3. Seven studies ($n = 482$ participants) were included in the meta-analysis.

The overall pooled effect was small and not statistically significant (SMD = 0.16 [95% CI: −0.08 to 0.39]), with low-to-moderate heterogeneity ($I^2 = 38\%$) (see SM3 Figure 14). Although resistance exercise showed a numerically larger pooled estimate compared with other modalities, no statistically significant subgroup differences were detected, and none of the modality-specific effects reached statistical significance.

Stratified analyses by disease stage and sensitivity analyses excluding trials at a high risk of bias did not materially alter the pooled estimates (see SM3 Figures 15, 16, 17). Overall, current evidence does not support a consistent or robust effect of exercise interventions on circulating testosterone levels in men with prostate cancer.

IGF-1 was evaluated in six trials. Most studies reported not statistically significant between-group differences following the intervention. One study observed a significant increase in IGF-1 within the exercise group, while another reported a significant between-group difference favouring high-intensity exercise. Due to variability in reporting formats and limited study numbers, no meta-analysis was performed.

3.10 | Adverse Effects on Interventions

Four studies reported adverse effects based on the exercise intervention. Firstly, one study reported three overuse injuries affecting the lower extremities in the exercise group, including muscle pain and stiffness [7]. In another trial [28], three participants experienced exercise-related adverse events, with only one classified as serious. In the resistance group, one individual reported chest pain during exercise, but cardiologic evaluations revealed no abnormalities. In the aerobic group, one participant experienced a brief episode of syncope before a treadmill test, with no cause identified, and later completed testing without issues. The single serious adverse event occurred in the aerobic group, where a participant suffered an acute myocardial infarction on the third day of training. He collapsed 15 min postsession due to ventricular fibrillation, was resuscitated and fully recovered but did not continue the intervention. Electrocardiogram findings confirmed an anterior wall myocardial infarction, despite no prior cardiac history. Another study reported a tendinopathy resulting from the strength training intervention [33]. Finally, eight participants experienced a worsening of pre-existing conditions potentially linked to high-interval intensity training (HIIT), including joint pain ($n = 6$), chest discomfort ($n = 1$) and light headedness ($n = 1$) [23].

Nine studies reported no adverse events related to the exercise intervention, while another 10 did not provide any information regarding adverse events or participant dropouts.

4 | Discussion

This systematic review and meta-analysis evaluated the effects of structured exercise interventions on metabolic, inflammatory, tumour-related and hormonal biomarkers in men with prostate cancer. Overall, pooled analyses did not demonstrate consistent effects on insulin, glucose, testosterone, IL-6 or PSA levels. In contrast, exercise was associated with a modest but statistically significant reduction in CRP, although this finding was derived from a limited number of studies.

The biomarkers included in this review reflect distinct biological domains. Metabolic markers (insulin, glucose, IGF-1) primarily represent systemic metabolic regulation, which is profoundly altered during ADT [3, 4]. Inflammatory mediators such as CRP and IL-6 reflect systemic inflammatory tone, which may be influenced by both cancer progression and treatment-related immune dysregulation [5]. PSA represents tumour-related biological activity but is not a direct surrogate of survival or disease modification [43]. Therefore, while exercise-induced biomarker modulation may support biological plausibility, it does not, by itself, establish clinically meaningful oncological benefit.

4.1 | Metabolic and Hormonal Biomarkers

Regarding metabolic outcomes, pooled analyses did not confirm a consistent effect of exercise on insulin or glucose regulation. Although several individual trials reported favourable metabolic changes following combined or high-intensity training [15, 22, 27], these effects were not robust at the pooled level. The insulin meta-analysis was characterised by substantial heterogeneity, which persisted after exclusion of high-risk-of-bias studies, suggesting genuine variability in intervention characteristics, supervision intensity, baseline metabolic status and treatment phase.

These findings should be interpreted within the endocrine context of prostate cancer management. ADT is known to induce insulin resistance, adverse lipid profiles and increased abdominal adiposity [3], potentially attenuating or masking exercise-induced metabolic adaptations. While exercise is recognised as an effective strategy to mitigate ADT-related side effects and preserve functional capacity [8], current pooled biomarker evidence does not demonstrate consistent metabolic normalisation at the systemic level.

Similarly, no statistically significant pooled effect was observed for testosterone. Although resistance training has been proposed as a countermeasure against ADT-induced sarcopenia [44], circulating testosterone levels are pharmacologically suppressed during treatment. Consequently, functional and body composition improvements associated with exercise likely occur independently of systemic testosterone restoration. Furthermore, the complex relationship between endogenous testosterone and long-term outcomes in men [45] underscores the need for caution when interpreting hormonal modulation as a surrogate of clinical benefit.

4.2 | Inflammatory and Immune Modulation

In contrast to metabolic and tumour-related markers, exercise was associated with a statistically significant reduction in CRP levels. This finding is consistent with broader oncology literature indicating that regular physical activity may attenuate chronic low-grade systemic inflammation in cancer survivors [5]. Given that ADT and other oncological treatments are associated with persistent inflammatory activation and metabolic dysregulation [4], reductions in CRP may reflect partial mitigation of treatment-related inflammatory burden. Nevertheless, this result was derived from only three trials, and although heterogeneity was low, the limited number of studies restricts generalisability and precludes definitive conclusions regarding clinical impact.

Pooled analysis did not demonstrate a significant effect on IL-6, and substantial heterogeneity was observed. This discrepancy between CRP and IL-6 may reflect the complex and context-dependent role of IL-6 in exercise physiology. As both a pro-inflammatory cytokine and an exercise-induced myokine [9], IL-6 responses vary according to timing and physiological context. Consequently, changes in IL-6 levels cannot be interpreted straightforwardly as beneficial or detrimental in this clinical setting.

Other inflammatory and immune-related markers—including TNF-α, IL-1β, IL-5, IL-8, IL-12, cortisol, IGF-1 and NK cell activity—were reported in isolated trials but lacked sufficient consistency for pooled analysis. Some studies suggested reductions in pro-inflammatory cytokines [7, 15], while others observed improvements in immune cell function or tumour-infiltrating NK cell dynamics [39]. However, most of these findings were derived from within-group comparisons and remain heterogeneous in magnitude and direction. Consequently, current evidence does not allow firm conclusions regarding exercise-induced immune remodelling in prostate cancer.

From a mechanistic perspective, exercise-induced modulation of systemic inflammation may intersect with contemporary models of tumour–immune interaction. Recent molecular evidence has highlighted the role of specific cytokine signalling axes and immune regulatory pathways—such as IL-6/JAK-STAT, TNF/NF-κB and immune checkpoint–related signalling—in shaping the prostate tumour microenvironment and influencing immune surveillance [13]. These frameworks emphasise that inflammatory signalling nodes are not merely epiphenomena but active regulators of tumour–immune crosstalk and potential therapeutic targets in immunotherapy strategies.

Within this context, reductions in systemic inflammatory tone—such as the CRP decrease observed in the present analysis—may be biologically relevant, as systemic cytokine gradients can influence immune cell trafficking and activation states. However, immune checkpoint inhibitors have demonstrated limited efficacy in unselected metastatic castration-resistant prostate cancer (mCRPC) populations, with low objective response rates reported in phase II trials [46, 47]. Clinical benefit appears largely restricted to molecularly defined subgroups, such as mismatch repair–deficient tumours [48]. To date, no clinical evidence indicates that exercise-induced biomarker modulation enhances immunotherapy responsiveness, delays tumour progression, or improves survival in prostate cancer.

Therefore, while exercise may contribute to systemic inflammatory regulation, the clinical significance of these biomarker changes within the context of tumour control or immunotherapy outcomes remains to be established.

4.3 | Tumour-Related Marker (PSA)

Furthermore, pooled analyses did not demonstrate a statistically significant effect of exercise on PSA levels. Although individual trials reported reductions following certain exercise modalities [14, 40, 49], these findings were not confirmed at the pooled level. After exclusion of a study reporting model-based estimates, heterogeneity decreased and the overall effect remained nonsignificant.

PSA is a clinically established marker of tumour activity; however, in the context of ADT, pharmacological androgen suppression may dominate PSA dynamics. Therefore, current evidence does not support a direct tumour-modifying effect of exercise as reflected by PSA changes.

4.4 | Clinical and Translational Implications

Although exercise did not demonstrate consistent effects across all biomarkers, it appears safe and may confer modest benefits in systemic inflammatory regulation, particularly with respect to CRP. Importantly, biomarker modulation should not be interpreted as direct evidence of tumour control or survival benefit.

Exercise remains an important supportive component of prostate cancer care, particularly for maintaining physical function and overall health. However, biomarker findings alone should not guide prescription decisions without careful consideration of patient-specific clinical context, treatment phase and safety monitoring.

Combined aerobic and resistance training is commonly implemented in the literature and appears feasible for many patients; nevertheless, optimal dose, intensity and supervision parameters remain insufficiently defined. Given variability in adherence, intervention reporting and safety documentation, exercise recommendations should be regarded as evidence-informed considerations rather than definitive clinical guidelines.

Although most trials reported few serious adverse events, isolated cardiovascular complications and symptom exacerbations were described, including during higher-intensity protocols. These findings highlight the importance of individual tailoring, appropriate supervision and adjustment according to comorbidity burden and treatment status, rather than suggesting that specific modalities are universally benign or universally contraindicated.

Future research should prioritise harmonised reporting of exercise protocols (e.g., using FITT principles), consistent biomarker measurement strategies [50, 51] and integration of clinically meaningful endpoints, including disease progression, treatment response and patient-centred outcomes.

4.5 | Limitations and Strengths

Several limitations of this systematic review and meta-analysis should be acknowledged. First, although comprehensive search strategies were applied, the inclusion of English-language publications only may have introduced language bias. Second, the number of trials available for several key outcomes—particularly CRP and IL-6—was limited, restricting statistical power and reducing the robustness and generalisability of pooled estimates. Many included trials were characterised by relatively small sample sizes and moderate risk of bias, which may have inflated effect estimates or limited causal inference. Third, substantial heterogeneity was observed in certain analyses, particularly for insulin. Although additional stratified and sensitivity analyses were performed (including by disease stage, ADT exposure and risk of bias), residual variability likely reflects genuine differences in exercise dose, supervision intensity, intervention duration, baseline metabolic status and control group design. The wide variation in control conditions (e.g., usual care, wait-list, stretching, lifestyle advice) may also have contributed to performance and contamination bias. Fourth, the use of SMDs allowed pooling across diverse measurement units but may reduce clinical interpretability of effect sizes. Furthermore, although a broad range of biomarkers was included in the review scope, only a subset could be quantitatively synthesised due to inconsistent reporting across studies. Finally, the timing of exercise relative to oncological treatment (e.g., during ADT, radiotherapy, active surveillance or postsurgery) varied substantially across trials and likely influenced metabolic and inflammatory responses. However, formal subgroup analyses by treatment phase were not feasible due to insufficient study numbers within each category. This limitation may contribute to residual heterogeneity and restrict causal interpretation.

Notwithstanding these limitations, this review provides, to our knowledge, the most comprehensive synthesis to date of exercise-induced modulation of metabolic-, inflammatory-, hormonal- and tumour-related biomarkers in men with prostate cancer undergoing active treatment. A key strength lies in the structured conceptual framework distinguishing systemic metabolic markers, inflammatory mediators, hormonal factors and tumour-related endpoints, which enhances interpretative clarity and reduces mechanistic overextension.

Methodologically, the review was restricted to randomised controlled trials, strengthening internal validity. Consistent endpoint-based extraction methods were applied across studies to minimise metric-related bias, and pooled analyses were complemented by multiple sensitivity approaches, including exclusion of high-risk-of-bias trials, stratification by disease stage (metastatic vs nonmetastatic) and restriction to ADT-exposed populations. These additional analyses enhance transparency and allow more cautious interpretation of heterogeneity.

Furthermore, by quantitatively synthesising data in a field characterised by heterogeneous reporting and fragmented biomarker selection, this review provides a structured overview of the current evidence base while explicitly distinguishing between systemic physiological adaptation and tumour-specific outcomes. This separation strengthens the clinical interpretability of findings and helps prevent over attribution of biomarker changes to disease modification.

5 | Conclusions

This systematic review and meta-analysis suggest that structured exercise interventions in men with prostate cancer are safe and may induce modest modulation of selected systemic biomarkers. While pooled analyses did not demonstrate consistent effects on metabolic markers (insulin, glucose), testosterone, IL-6 or PSA, a statistically significant reduction in CRP was observed, indicating a potential anti-inflammatory effect.

However, the magnitude of biomarker changes was generally modest, and evidence for several outcomes was limited by small sample sizes and heterogeneity. Therefore, although exercise represents an important supportive strategy during prostate cancer treatment—particularly for maintaining functional capacity and overall health—current evidence does not establish a direct tumour-modifying effect or clear clinical impact based on biomarker modulation alone.

Further large-scale, methodologically robust trials integrating biomarker outcomes with clinically meaningful endpoints are required to clarify the translational relevance of exercise-induced biological adaptations in this population.

Author Contributions

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writing–review and editing, Narcis Gusi, Francisco Javier Dominguez-Muñoz, Juan Luis Leon-Llamas and Santos Villafaina.

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Disclosure

All authors have read and agreed to the published version of the manuscript.

Ethics Statement

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in the supporting information of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Information 1. Supporting Information. Supporting Information file 1: search strategies and filters applied in the selected databases.

Supporting Information 2. Supporting Information file 2: summary of the risk of bias assessment for the randomised controlled trials included in this systematic review.

Supporting Information 3. Supporting Information file 3: characteristics of the participants, data extraction and meta-analysis included in the systematic review.