

Review

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Review

Myosteatorsis and Sarcopenic Obesity in Men Receiving Androgen Deprivation Therapy for Prostate Cancer: Rationale for Mechanism-Driven Multimodal Intervention

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Simple Summary

Androgen deprivation therapy (ADT) is a cornerstone of prostate cancer treatment but is associated with significant adverse effects on body composition and metabolic health. These include loss of skeletal muscle, increased fat mass, and development of sarcopenic obesity, a condition linked to functional decline, metabolic syndrome, and potentially adverse oncologic outcomes. An important and underrecognized component of this phenotype is myosteatorsis, defined as fatty infiltration of skeletal muscle, which reflects impaired muscle quality and underlying metabolic dysfunction. This review synthesizes current evidence on interventions aimed at mitigating sarcopenic obesity in men receiving ADT. While exercise and nutrition-based strategies have shown benefits in improving muscle strength and body composition, most studies are limited by small sample sizes, short durations, and lack of assessment of muscle quality. Notably, myosteatorsis has rarely been incorporated as a biomarker or endpoint in these trials. We propose a mechanism-driven framework in which ADT-induced metabolic and inflammatory changes promote myosteatorsis, which in turn contributes to sarcopenic obesity and associated clinical outcomes. Future interventions should incorporate multimodal strategies and include imaging-based measures of muscle quality to better guide clinical management and improve survivorship outcomes.

Abstract

Background: Androgen deprivation therapy (ADT) is widely used in the management of prostate cancer (PCa) and remains a cornerstone of treatment across multiple disease settings. Although ADT contributes substantially to disease control, it also induces significant adverse metabolic and body composition changes. These alterations include loss of lean mass, increased fat mass, and deterioration in muscle quality, together contributing to a clinical phenotype consistent with sarcopenic obesity (SO). Importantly, ADT-induced SO is characterized not only by reductions in skeletal muscle mass but also by impaired muscle quality, particularly fatty infiltration of skeletal muscle, or myosteatorsis, an underrecognized but defining feature of this syndrome. **Methods:** This narrative review examines current evidence regarding interventions aimed at mitigating sarcopenic obesity in men treated with ADT for prostate cancer, identifies key gaps in the literature, and proposes a mechanism-driven path forward for intervention development. **Results:** Several exercise- and nutrition-based interventions have been evaluated in men receiving ADT and demonstrate improvements in selected outcomes such as muscle strength, body composition, and metabolic

parameters. However, most studies have been limited by small sample sizes, short intervention durations, and a focus on isolated intervention components. Importantly, muscle quality and intramuscular fat infiltration (myosteatorsis), a central component of sarcopenic obesity, have rarely been incorporated as biomarkers or endpoints in intervention trials targeting men re-receiving ADT. Conclusion: Future interventions designed to mitigate SO and its associated metabolic abnormalities should evaluate comprehensive, bundled strategies initiated early during ADT and sustained long enough to capture clinically meaningful changes. Outcomes should include biomarkers of muscle mass, strength, and quality, including imaging-based measures of myosteatorsis, along with metabolic syndrome markers, inflammatory mediators, functional outcomes, adherence, and quality of life. These changes should be correlated with underlying biological mechanisms such as NF- κ B signaling and pro-inflammatory cytokines. Such data may inform future phase III trials and ultimately support clinical strategies to mitigate ADT-related sarcopenic obesity and its downstream cardiometabolic and oncologic consequences.

Keywords: prostate cancer; androgen deprivation therapy; sarcopenic obesity; myosteatorsis; muscle quality; metabolic abnormalities; inflammatory markers; multimodal intervention

1. Introduction

In 2026, an estimated 333,830 new cases of prostate cancer will be diagnosed in the United States, and 36,320 men will die from the disease [1]. Because prostate cancer is androgen dependent [2], androgen deprivation therapy (ADT) has become a mainstay of treatment for men with metastatic disease [3] and is also used in conjunction with radiotherapy for selected patients with localized or locally advanced disease [4]. It is estimated that more than 45% of men with prostate cancer receive ADT during the course of treatment [3].

ADT includes several classes of agents, including luteinizing hormone-releasing hormone agonists and antagonists such as leuprolide, goserelin, and degarelix; antiandrogens such as bicalutamide and flutamide; androgen synthesis inhibitors such as abiraterone; and other agents such as ketoconazole. The duration of treatment varies by disease risk group, treatment intent, and concomitant therapies, ranging from 4–6 months to several years. Men with high-risk disease may receive long-term ADT for 18–36 months, whereas those with intermediate-risk disease may receive shorter courses of 4–6 months. Men with metastatic disease may remain on ADT indefinitely [5].

Although ADT has improved disease control and survival, treatment-related adverse effects continue to compromise long-term health and quality of survival. The hormonal shifts associated with ADT induce substantial changes in body composition and metabolism, including increased fat mass, reduced lean body mass, altered lipid profiles, hyperglycemia, decreased insulin sensitivity, osteoporosis, and metabolic syndrome [5,6,10,16,20,21]. These changes may culminate in a clinical phenotype consistent with sarcopenic obesity (SO), characterized by the coexistence of sarcopenia and excess adiposity [6,8,10,11,17]. ADT-induced testosterone depletion contributes to reduced muscle protein synthesis and increased muscle catabolism, while also promoting visceral adiposity and metabolic dysfunction [5,10,16,20].

Beyond reductions in muscle mass alone, a defining and increasingly recognized feature of sarcopenic obesity is impaired muscle quality, particularly the accumulation of fat within skeletal muscle, termed **myosteatorsis** [8,11,34,57]. Myosteatorsis reflects ectopic lipid deposition within and between muscle fibers and is associated with reduced muscle strength, impaired metabolic function, insulin resistance, and systemic inflammation [12,34,57]. Emerging evidence suggests that myosteatorsis may represent one of the most clinically informative manifestations of sarcopenic obesity because it captures deterioration in muscle quality rather than quantity alone [8,11,34,57]. However, despite its biological and clinical relevance, myosteatorsis has rarely been systematically evaluated in men with prostate cancer receiving ADT [8,10,11].

The adverse effects of SO in men receiving ADT extend beyond body composition alone. Compared with sarcopenia in isolation, SO appears to exacerbate metabolic dysregulation and has been associated with cardiovascular disease, insulin resistance, and diabetes mellitus [6–8,12–15]. These metabolic derangements may also adversely influence cancer outcomes, including biochemical recurrence, development of castration-resistant disease, metastatic progression, and prostate cancer-specific as well as all-cause mortality [14,16,18,19]. These risks may be compounded by age-related declines in muscle mass, bone mineral density, and metabolic resilience [17].

Consensus groups have emphasized that heterogeneity in definitions continues to limit comparability across studies and slow clinical translation [11]. Importantly, reliance on body mass index alone is inadequate, as it does not capture body composition, muscle function, or muscle quality, all of which are central to SO [11,17]. Recent work has highlighted myosteatorsis as an emerging biomarker of cancer prognosis across multiple malignancies. In men receiving androgen deprivation therapy, this phenotype may represent a central manifestation of treatment-related metabolic toxicity. We therefore propose that **myosteatorsis should be considered a key biomarker of ADT-induced sarcopenic obesity**, linking metabolic dysfunction, inflammation, and skeletal muscle deterioration in this population.

2. Materials and Methods

This manuscript was developed as a structured narrative review aimed at integrating current clinical and mechanistic evidence related to androgen deprivation therapy, myosteatorsis, and sarcopenic obesity. Relevant literature was identified through targeted searches of PubMed/MEDLINE and related databases, supplemented by review of key references and prior work in this area. Given the heterogeneity of study designs and emerging nature of this field, a narrative approach was used to synthesize findings and propose a conceptual framework to guide future research and intervention strategies. The search covered studies published from January 2000 through December 2025, reflecting the period during which imaging-based characterization of sarcopenic obesity emerged in oncology research. Search terms included combinations of Medical Subject Headings (MeSH) and keywords related to “androgen deprivation therapy”, “sarcopenia”, “obesity”, “myosteatorsis”, muscle quality,” AND “cancer,” “oncology,” “survival,” “treatment toxicity,” “metabolic abnormalities” and “body composition.” Reference lists of relevant reviews and primary articles were also manually screened to identify additional eligible studies. Studies included if they: evaluated ADT and related adverse events in prostate cancer patients; examined associations with clinical, functional, metabolic, or survival outcomes; or provided mechanistic or biological insights relevant to myosteatorsis and sarcopenic obesity. The review included observational cohort studies, retrospective imaging analyses, translational studies, and relevant mechanistic investigations. studies were excluded if they: focused exclusively on non-cancer populations without mechanistic relevance, examined sarcopenia without assessment of muscle quality or fat infiltration, were conference abstracts lacking sufficient methodological detail or were non-English publications.

Study Selection and Data Synthesis: Titles and abstracts were screened for relevance, followed by full-text review of eligible articles. Evidence was synthesized qualitatively, with emphasis on recurring findings across tumor types, methodological approaches, and biological pathways. Given heterogeneity in study design and outcome reporting, quantitative meta-analysis was not performed.

Assessment of evidence quality: As this review was narrative in nature, formal risk-of-bias scoring was not conducted. However, study interpretation considered sample size, methodological rigor, imaging standardization, adjustment for confounding variables, and consistency of findings across independent cohorts.

3. Results

3.1. Biological Mechanisms Linking ADT to Myosteatorsis and Sarcopenic Obesity

The biological mechanisms underlying SO in men on chronic ADT likely involve a complex cascade of hormonal, inflammatory, and metabolic events. Both skeletal muscle and visceral adipose tissue contribute to this process [22,24,25,33,54,55,75–79]. Experimental evidence suggests that activation of the ubiquitin-proteasome pathway, mediated in part through upregulation of NF- κ B, contributes substantially to skeletal muscle degradation and is stimulated by pro-inflammatory cytokines including TNF- α and IL-6 [27–32]. These pathways have long been implicated in muscle wasting and cachexia and are also relevant to the development of sarcopenic obesity [22,24,25,51,53,55,75–79].

Obesity and truncal adiposity further amplify these effects. Pro-inflammatory cytokines are upregulated by leptin and adiposity-related signaling, thereby exacerbating muscle catabolism [22,33,54–57]. Elevated TNF- α may suppress adiponectin production, impair mitochondrial function, and inhibit muscle protein synthesis [32]. Obesity has also been shown to induce leptin resistance, promoting reduced muscle fatty acid oxidation and ectopic lipid deposition within skeletal muscle [33,34,56]. These processes contribute directly to myosteatorsis, representing pathological lipid accumulation within skeletal muscle and a central component of sarcopenic obesity [34,57].

While sarcopenic obesity is often described as a body composition phenotype defined by the coexistence of reduced muscle mass and increased adiposity, myosteatorsis represents a distinct pathological alteration in muscle quality characterized by ectopic lipid accumulation within skeletal muscle. In this context, myosteatorsis should not be viewed merely as a body phenotype, but rather as a metabolic and structural alteration in skeletal muscle that reflects underlying inflammatory and metabolic dysregulation.

3.2. Conceptual Framework (Figure 1)

Although sarcopenic obesity is commonly described as a body composition phenotype defined by the coexistence of reduced skeletal muscle mass and excess adiposity, this framework may not fully capture the underlying biological processes occurring in men receiving ADT. We propose a conceptual model in which myosteatorsis represents a central pathological alteration in skeletal muscle quality that precedes and drives the clinical phenotype of sarcopenic obesity. In this model, ADT-induced testosterone depletion promotes metabolic dysregulation, adipose tissue expansion, and inflammatory signaling pathways involving NF- κ B and pro-inflammatory cytokines. These processes contribute to ectopic lipid accumulation within skeletal muscle, resulting in myosteatorsis, impaired muscle function, and progressive loss of metabolic resilience. Sarcopenic obesity therefore emerges as the clinical manifestation of these underlying alterations in muscle quality and systemic metabolism. Recognizing myosteatorsis as a central component of this pathway may improve risk stratification and guide the development of targeted, mechanism-driven interventions aimed at preserving muscle quality and metabolic health in men receiving ADT.

Figure 1. Conceptual framework linking androgen deprivation therapy to myosteatorsis and sarcopenic obesity and potential intervention targets.

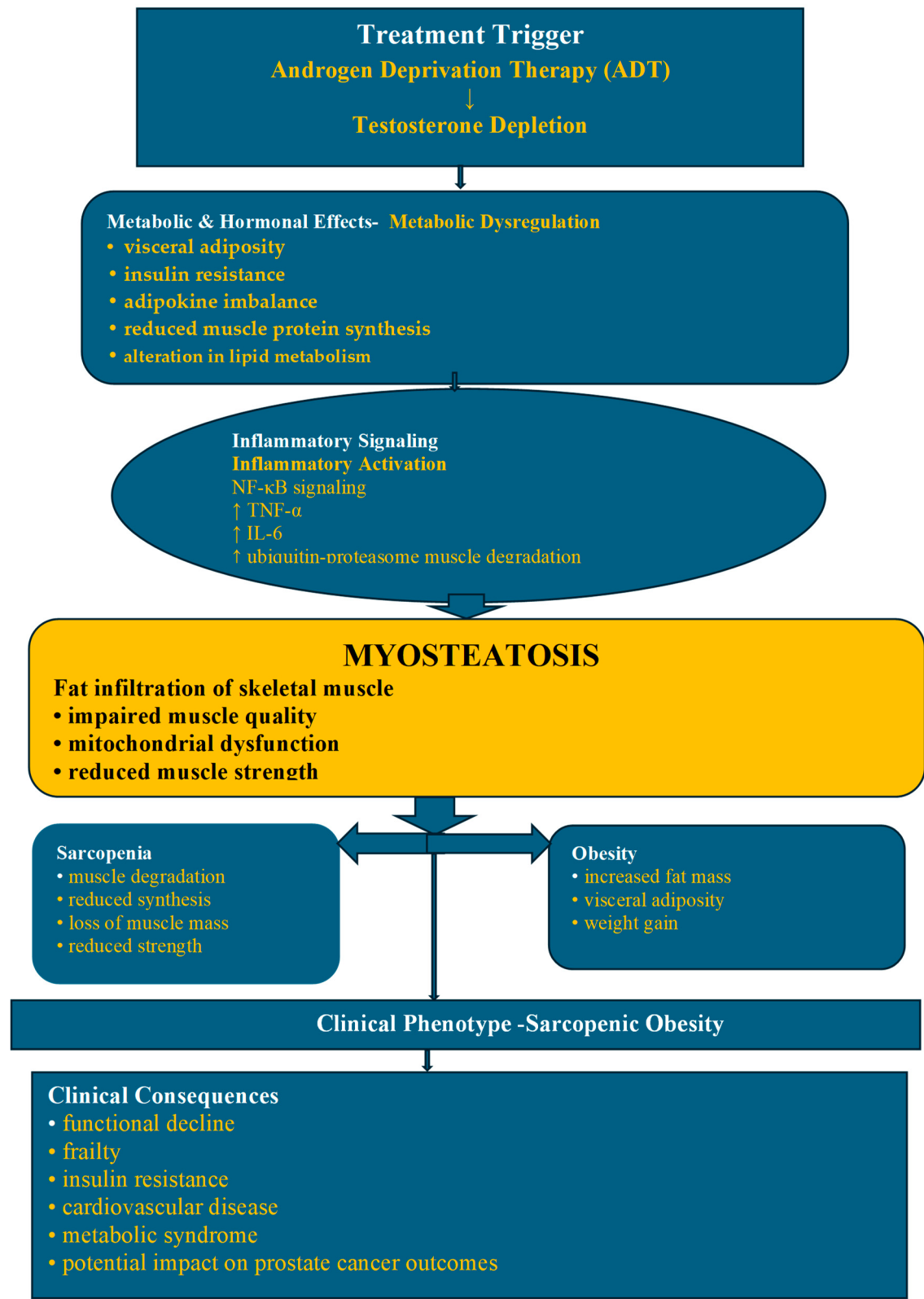


Figure 1. caption.

This framework positions myosteatorsis as both a biomarker and a potential therapeutic target in the prevention of ADT-related metabolic toxicity.

3.3. Current Strategies to Manage Sarcopenia, Obesity, and Other Metabolic Consequences of ADT

Although SO is well characterized in aging populations, it remains insufficiently defined in men with prostate cancer receiving ADT [10,11,17]. By contrast, several individual adverse effects of ADT, including obesity, sarcopenia, loss of bone mineral density, and vasomotor symptoms, are well documented [35–40]. Standard supportive therapies are therefore commonly used to manage selected toxicities. ADT has been shown to reduce bone mineral density measured by dual-energy X-ray absorptiometry by 8.5% within 6 months of initiation [35] and by as much as 17% within 2 years [36–38]. Bone protection agents, including bisphosphonates, monoclonal antibodies, and selective estrogen receptor modulators, are often used in conjunction with calcium and vitamin D supplementation, although calcium and vitamin D alone appear insufficient to halt ADT-related bone loss [35–40]. Vasomotor symptoms are commonly managed using hormonal therapies and non-hormonal agents [39].

In contrast, there are currently no standardized interventions specifically designed to prevent or reverse sarcopenia, obesity, SO, or the broader metabolic toxicities associated with ADT. Nonetheless, existing studies suggest that supervised exercise, including resistance training and nutritional counseling, can reduce fat mass and improve muscle mass and function in men treated with ADT [16,41–49]. In the IDEA-P trial, 32 PCa subjects on ADT were randomized to group mediated exercise and nutritional intervention for a period of 12 weeks resulting in improved muscle strength and mobility [47]. In a pilot trial (NCT04870515) researchers are evaluating diet and physical activity administered for 6 months targeting PCa patients treated with ADT and radiation therapy on changes in anthropometrics, metabolic abnormalities and treatment outcomes. In a trial using (NCT03880422) evaluating a nutrition and exercise intervention for 6 months in reducing ADT-induced obese frailty in PCA survivors. In 60 PCa patients, resistance exercise training for 20 weeks was observed to mitigate effects of ADT on body composition, muscle mass, strength, and aerobic capacity, with no additional benefits of protein supplementation [48]. An additional study is currently evaluating remotely monitored exercise interventions for 12 weeks in PCa patients on ADT, (NCT06429813, unpublished). Similarly, a 12-week feasibility trial is evaluating behavioral exercise training for men undergoing ADT for PCa (NCT06250751 unpublished). A 6-month intervention combining aerobic and resistance exercise program in 60 men on ADT has a significant favorable effect on cardiorespiratory capacity, resting fat oxidation, glucose, and body composition [50]. In a trial utilizing a 12-month internet-based lifestyle intervention (weight loss and resistance training) to eradicate obese frailty in PCa survivors (NCT06011499) is ongoing. These efforts underscore growing recognition that exercise and nutrition interventions are both feasible and clinically relevant in this population.

However, most intervention trials in men receiving ADT have been limited by small sample sizes, short intervention durations, and limited assessment of muscle quality or metabolic biomarkers [16,41–50]. Many studies have lasted only 12–16 weeks, even though clinically meaningful adverse changes in body composition and metabolism often evolve over 6–12 months after ADT initiation [5,10,16,20,114]. Additionally, with the occurrence of multiple/related adverse effects with SO in PCa patients on ADT, it may be relevant to integrate multiple evidence-based interventions in parallel by blending and bundling evidence-based strategies [50] administered simultaneously to overcome the limitations of siloed interventions. Although the prevalence of obesity and sarcopenia have been reported, to date, inter-muscle fat infiltration which is a cardinal feature of SO in PCa patients on ADT- has not been used as a biomarker nor as an outcome marker of an intervention. Importantly, there is a paucity of interventions that target the underlying mechanisms to mitigate the impact of ADT induced SO and its effects on metabolic abnormalities, PCa and all-cause mortality in this patient population. Most studies focus on body weight, lean mass, or strength while largely overlooking muscle quality and myosteatosis. Yet fatty infiltration of skeletal muscle may represent one of the most biologically and clinically informative features of ADT-induced sarcopenic obesity [8,34,57]. As a result, the true impact of ADT on skeletal muscle quality, and the potential reversibility of these changes through intervention, remains poorly understood.

3.4. Promising Approaches to Ameliorate SO and Other Metabolic Consequences of ADT

A stronger intervention framework for men receiving ADT should be grounded in the biology of SO and myosteatorsis. These observations suggest that interventions targeting inflammatory and muscle proteolysis pathways may be important [22–34,51–57,75–79][Figure 2].

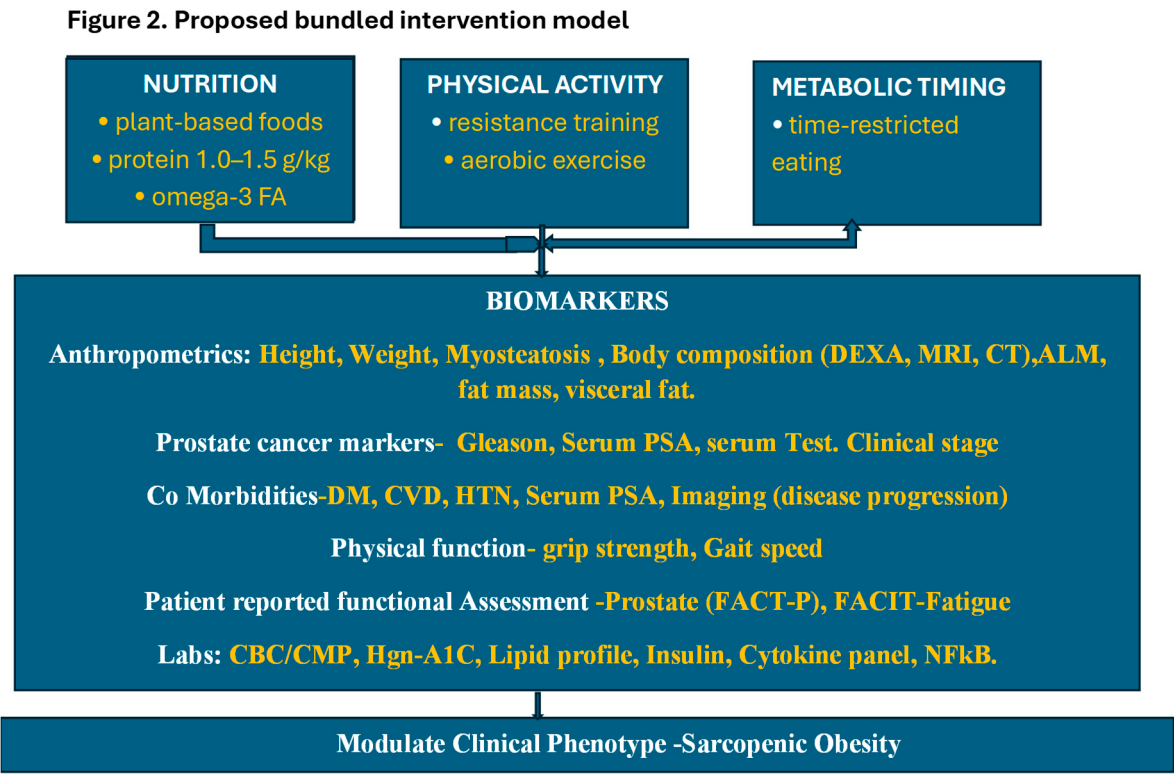


Figure 2. caption.

3.4.1. Exercise

Exercise remains the most evidence-based cornerstone of intervention. Resistance training is particularly important for preserving or restoring muscle mass and strength, while aerobic exercise improves cardiorespiratory fitness, insulin sensitivity, and fat oxidation [16,41–49,114]. Systematic reviews and network meta-analyses support the benefit of exercise-based strategies for improving body composition in men with prostate cancer [44,45]. Given the multidimensional metabolic effects associated with ADT, combining resistance and aerobic exercise appears especially relevant.

3.4.2. Protein and Micronutrient Support

Increased dietary protein intake in the range of 1.0–1.5 g/kg body weight has been shown to stimulate muscle protein synthesis, and distribution of protein intake across meals may further enhance the anabolic response [69–73]. High-protein diets combined with resistance training may help preserve appendicular lean mass during weight loss [73]. Furthermore, combining high-protein, essential amino-acid-rich diets with increased fiber intake can foster a healthy, balanced gut microbiome (eubiosis) by promoting the production of beneficial short-chain and branched-chain fatty acids. Recent studies have explored consuming high levels of fiber and protein to increase specific gut bacteria that boost metabolic health, improve satiety, and support protein synthesis [121,122]. This strategy could serve as a novel dietary approach to manage sarcopenic obesity. Nonetheless, additional human studies employing advanced metabolomic techniques are necessary to thoroughly understand how macronutrients, particularly protein, interact with the microbiome. On the other hand, others have shown that higher protein intake, specifically from animal food sources, is protective against sarcopenia but also linked to a higher obesity risk [123]. Thus, future

human studies evaluating leaner protein sources in this target population with increased fiber intake should be evaluated.

Androgen deprivation therapy (ADT) significantly increases the risk of bone fractures in addition to loss of muscle in men, though it remains unclear if different types of ADT or varying schedules (continuous vs. intermittent) offer different risks for osteoporosis. ADT has also been shown to significantly increase osteoporosis-related fracture risk in prostate cancer patients. Besides direct treatment-induced bone loss, this risk is heightened by pre-existing factors such as older age, low bone mineral density (BMD) and increased falling, driven by muscle weakness, poor balance, and postural hypotension [124,125]. Vitamin D and calcium supplementation may also support muscle function and skeletal health, particularly in the setting of concomitant ADT-related bone loss [35–40,74]. Improving bone mineral density (BMD), decrease the fracture rate and improving muscle loss in these patients has not been explored in conjunction with interventions with exercise, smoking abstinence, adequate calcium, protein, and vitamin D intake, along with the use of bisphosphonates or calcitonin.

3.4.3. Omega-3 Fatty Acids

Dietary omega-3 fatty acids represent a promising strategy because of their anti-inflammatory and potential anti-catabolic effects. Experimental evidence has demonstrated that the ubiquitin proteasome pathway as indicated by upregulation of NF- κ B accounts for the majority of skeletal muscle degradation, stimulated by several proinflammatory cytokines including TNF α , IL-6 [51]. Pro-inflammatory cytokines (IL-6 and TNF) are upregulated by leptin, associated with truncal obesity which has been shown to exacerbate sarcopenia [52–55]. Obesity has been shown to induce leptin resistance, promoting reduced muscle fatty oxidation and ectopic fat deposition impacting muscle quality, a unique feature of SO [56,57].

The deleterious effects of inflammatory cytokine induced- myogenesis was inhibited with ω -3 fatty acids-rich diets [58,59]. Oral administration of fish oil-derived ω -3-FA EPA and/or DHA have been shown to attenuate tumor growth, weight loss, and/or muscle wasting in animal models of cancer [60,61]. In a cell culture model of myogenesis, EPA suppresses increases in the activities of NF- κ B, caspase 8, and proteasome in differentiating C2C12 myotubes induced by PIF or TNF α , thereby suppressing apoptosis and necrosis [62,63]. The deleterious effects of inflammatory cytokines on myogenesis have also been shown to be inhibited by EPA [43,63]. Several recent laboratory studies indicate that EPA may attenuate protein degradation by preventing NF- κ B translocation to the nucleus [41,42]. In a recent meta-analysis (2024), supplementation of ω -3 FA had a favorable effect on improving lipid levels, reducing pro-inflammatory cytokines among patients with metabolic syndrome and cardiovascular disease. [64] as well as improved clinical outcomes in cancer patients undergoing chemotherapy [65]. ω -3 FA has been shown to reduce proinflammatory cytokines even in cancer patient populations. [66,67]. In a preliminary clinical trial [25] using ω -3 FA supplement- 4 grams Lovaza® plus MA and nutritional supplements administered for 6 weeks to thirty-six (36), stage II-IV cancer patients, we observed stable anthropometrics, significant increase in serum albumin, functional status with no toxicity. Proteasome activity was inhibited in 9 out of 14 patients (64%) post treatment. Serum cytokines showed that both TNF α and IL-6 declined or remained stable with ω -3 FA. Our observations are provocative in that this improvement/stabilization of skeletal and visceral proteins and proinflammatory cytokines, improvement in functional status occurred after initial weight loss, diagnosis of cancer and while on active cytotoxic therapies. [25]. In our preliminary study, ω -3 fatty acid intake of all men diagnosed with PCa was significantly lower (75% lower) than the recommendations of the USRDA for optimal ω -3 fatty acid (11.2 grams per week) [120]. Although direct trials in men receiving ADT are needed, omega-3 fatty acids may represent a feasible adjunctive intervention targeting inflammation and muscle catabolism in this population.

3.4.4. Plant-Rich, Phytochemical-Based Dietary Strategies

We and others have shown that plant-based phytochemicals are promiscuous in their targeting and have been shown to target several critical hallmarks of carcinogenesis, without toxicities and intolerances at these doses [81–86]. Flavonoids are polyphenolic phytochemical compounds found in several plant foods including fruit, vegetables and grains. Several in vitro, preclinical and a few early randomized clinical trials have demonstrated that the effects of flavonoids are mediated by inhibiting the NF- κ B pathway [87]. Genes regulated by the transcription factor NF- κ B have been shown to modulate inflammation, cellular transformation, tumor cell survival, proliferation, invasion, angiogenesis, and metastasis. Phytochemical containing flavonoids can suppress the proinflammatory cell signaling pathways [88]. Flavonoids such as quercetin, genistein, curcumin, indole-3 carbinol, sulforaphane, resveratrol, anthocyanins and epigallocatechin 3-gallate regulate the gene expression of several pro-inflammatory molecules such as NF- κ B and modulate the expression and activation of proinflammatory cytokines tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6), and interleukin-8 (IL-8) [89-93]. Our team reported that EGCG potently and selectively inhibits the proteasome activity in intact human cells leading to the accumulation of I κ B- α and p27 proteins resulting in growth arrest. [94,95]. Our findings in preclinical models and early trials provide additional evidence for the safety and chemopreventive effect of GTC in preventing progression of PCa with EGCG [96,97]. Phytochemicals found in pomegranate extract has been shown to target multiple signaling pathways, specific to PCa, including STAT3 phosphorylation, NF- κ B activation, inhibition of IGF-1/AKT/mTOR signaling, inhibit androgen biosynthesis enzymes such as 5 α -reductase type I and 3 β -hydroxysteroid dehydrogenase type II, [100] inhibit CYP1B enzyme activity/expression and decrease serum PSA levels [106–108]. Other botanicals including Indole-3-carbinol [101,102], curcumin [103,104] and sulforaphane [105,106] target NF- κ B. With the promising data evolving from laboratory and early clinical trials, the recommendation to increase plant foods rich in phytochemicals to prevent cancer and other metabolic disorders has been consistent worldwide. Although these studies have targeted men with or at high risk for prostate cancer, currently, there are no trials targeting men receiving ADT.

3.4.5. Time-Restricted Eating and Fasting-Based Approaches

Periodic fasting (PF), intermittent fasting (IF) and time restricted eating (TRE) have been used to refer to periods of fasting or fasting mimicking diets (FMD) that encompass eating patterns with little or no energy intake restriction over an extended period of time in a day. Studies of IF (e.g., 60% energy restriction on 2 days per week or every other day), PF (e.g., a 5day diet providing 750-1100 kcal) and time-restricted feeding (TRF; limiting the daily period of food intake to 8-12 hours or less/day) in normal, overweight subjects and cancer patients have shown efficacy for weight loss and improvements in multiple health indicators including body composition, insulin resistance and reductions in risk factors for cardiovascular disease [107,108]. Preclinical studies have consistently shown that FMD can significantly reduce blood glucose, IGF-1, leptin and insulin levels in mice, with increase ketone bodies and IGFBP-1 levels. , reduce neoplasia incidence by 45%, markers of inflammation and obesity [108,109]. Metabolic changes have been observed to remain even post ending FMD and refeeding. Similar to animal models, subjects on fasting mimicking diets (FMD) have reported a 11.3% decrease in blood glucose level, 24% reduction in circulating IGF-1 [109,110]. FMD reduced systolic BP, reduced body weight, waist circumference, total body fat and trunk fat by 3% and increase in lean body mass. Studies in humans report a reduction in inflammatory markers with FMD [109,110]. Based on the concept of circadian rhythms, TRE is a daily eating pattern in which all nutritional intake occurs within a few hours (12 hours or more) each day with no restriction of nutritional composition [108]. Time-restricted eating in humans for 2-6 months or more has demonstrated reduction in fat and improvement in markers of metabolic syndrome, cancer, cardiovascular, insulin-resistance and diabetes [107]. Fasting periods in TRE and other fasting based approaches has been shown to enable organisms to enter an alternate metabolic phase, which relies less of glucose and more on ketone body-like carbon sources [52]. TRE has been shown to be feasible

and adoptable in adult population including in cancer patients, with no adverse effects [109–113]. TRE is especially appealing because it is pragmatic and may be more sustainable than prolonged fasting. However, in men receiving ADT, these strategies must be carefully evaluated to ensure that weight loss does not exacerbate muscle loss or worsen frailty.

4. Conclusions

ADT remains essential in the management of prostate cancer, but its benefits are accompanied by substantial adverse effects on body composition, metabolic health, physical function, and quality of life [5,6,10,16,20,21,114]. Among these, sarcopenic obesity represents a particularly important and underrecognized phenotype. Importantly, myosteatorosis should be considered more than a body composition phenotype; rather, it represents a pathological alteration in skeletal muscle quality that integrates metabolic dysfunction, inflammatory signaling, and ectopic lipid deposition [8,11,34,57].

Although exercise and nutrition-based interventions have shown promise, the existing intervention literature is limited by short duration, modest sample size, and insufficient attention to biologic mechanisms and muscle quality [16,41–50]. Current approaches have also tended to be siloed rather than pragmatic and integrated, despite the fact that ADT produces multiple interconnected adverse effects. A more comprehensive strategy that combines evidence-based interventions in parallel may therefore be needed to address the complexity of ADT-induced SO.

Recognizing myosteatorosis as a central biomarker of sarcopenic obesity may help guide both risk stratification and targeted intervention strategies for men receiving androgen deprivation therapy.

5. Future Directions

Based on current evidence, future interventions designed to mitigate SO and associated metabolic abnormalities in men receiving ADT should evaluate comprehensive, bundled, evidence-based strategies initiated early in the course of treatment, ideally within 3 months of starting ADT. These bundled interventions should include:(a) a nutrition plan emphasizing low-glycemic, minimally processed foods, high intake of plant-based phytochemical-rich foods, and adequate protein intake;(b) omega-3 fatty acid supplementation and appropriate micronutrient support, including vitamin D and calcium when indicated;(c) structured aerobic exercise;(d) progressive resistance training; and (e) carefully monitored time-restricted eating or related metabolic timing strategies when feasible and safe. Future clinical trials should incorporate objective measures of muscle quality, including imaging-based assessment of myosteatorosis using CT or MRI, as core biomarkers of intervention efficacy. Because myosteatorosis reflects both metabolic dysfunction and inflammatory signaling within skeletal muscle, it may provide a more clinically meaningful endpoint than lean mass alone. Clinical trials should ideally extend for at least 12 months, reflecting the timeframe over which metabolic and body composition changes become most pronounced [5,10,16,20,114]. Key endpoints should include changes in muscle mass, muscle strength, muscle quality, fat mass, metabolic syndrome biomarkers, inflammatory mediators, functional performance, symptom burden, adherence, acceptability, and quality of life. Mechanistic endpoints evaluating NF- κ B signaling and pro-inflammatory cytokines may clarify the biological pathways through which these interventions exert their effects. If validated in future trials, mechanism-driven multimodal interventions may provide an effective strategy to mitigate ADT-related sarcopenic obesity, improve metabolic health and functional outcomes, and ultimately enhance survivorship in men with prostate cancer.

Table 1. Key Points.

What is already known ADT, a cornerstone treatment for prostate cancer, is associated with substantial metabolic and body composition changes, including loss of skeletal muscle mass, increased adiposity, insulin resistance, and metabolic syndrome [5,6,10,16,20,21]. These changes may culminate in a phenotype consistent with sarcopenic obesity, which is associated with functional decline, cardiometabolic morbidity, and potentially adverse oncologic outcomes [6–8,12–19]. What this review adds This review highlights myosteatorosis, defined as fatty infiltration within skeletal muscle, as a defining and underrecognized component of sarcopenic obesity in men receiving ADT [8,10,11,34,57]. We discuss biological mechanisms linking ADT-induced hormonal depletion, metabolic dysregulation, and inflammatory signaling pathways, including NF-κB and pro-inflammatory cytokines, to the development of myosteatorosis and sarcopenic obesity [22–34,51–57]. Implications for clinical practice and research Future intervention trials in men receiving ADT should incorporate imaging-based measures of muscle quality, including myosteatorosis, as key biomarkers and endpoints. Mechanism-informed multimodal interventions integrating resistance exercise, optimized nutrition, anti-inflammatory dietary strategies, and metabolic approaches may help mitigate sarcopenic obesity and improve survivorship outcomes in prostate cancer patients undergoing ADT [16,41–50,58–80,107–113].
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Table 2. Clinical Significance.

Androgen deprivation therapy remains a cornerstone of prostate cancer treatment but is associated with significant metabolic and body composition toxicities that can adversely affect long-term survivorship [5,6,16,20,21,114]. Sarcopenic obesity, characterized by the coexistence of reduced skeletal muscle mass and excess adiposity, is increasingly recognized in men receiving ADT [5,8,10,11]. Importantly, deterioration in muscle quality, particularly fatty infiltration of skeletal muscle (myosteatorosis), may represent a central manifestation of this phenotype and a potentially important biomarker of treatment-related metabolic dysfunction [8,11,34,57]. Current clinical management strategies primarily address individual complications such as bone loss or weight gain but rarely target the underlying metabolic and inflammatory mechanisms driving sarcopenic obesity. Recognizing myosteatorosis as a key component of ADT-related toxicity may improve risk stratification and help guide intervention strategies. Mechanism-informed multimodal approaches incorporating resistance exercise, optimized nutrition, anti-inflammatory dietary strategies, and metabolic interventions may help mitigate sarcopenic obesity, improve functional outcomes, and potentially influence long-term cardiometabolic and oncologic outcomes in men receiving ADT [16,41–50,58–80,107–114].

Patents: Pending.

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Abbreviations

The following abbreviations are used in this manuscript:

SO	Sarcopenic obesity
MYO	Myosteatorsis
CC	Cancer cachexia
BMD	Bone mineral density
PCa	Prostate cancer
IGF-1	Insulin-like Growth Factor 1
IGFBP-1	Insulin-like growth factor-binding protein 1
MTOR	Mammalian target of rapamycin
EGCG	Epigallocatechin gallate
PIF	Proteolytic inducing factor
TRE	Time restricted eating
FMD	Fasting Mimicking Diet
TRF	Time restricted feeding
Kcal	Kilocalories
BP	Blood pressure
EPA	Eicosapentaenoic acid
DHA	Docosahexaenoic acid
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
TNFα	Tumor necrosis factor-alpha
IL	Interleukins
CT	Computer Tomography
L3	Lumbar vertebrae 3
SMI	Skeletal muscle index (SMI)
SMD	Skeletal muscle radiodensity
ADT	Androgen deprivation therapy

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