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Testosterone: A Missing Biological Link in Morbidity and Mortality Among U.S. Veterans

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ABSTRACT

Background: Testosterone deficiency is common among U.S. veterans but remains underrecognized and undertreated within the Veterans Health Administration. Traditional clinical focus has emphasized sarcopenia and sexual dysfunction, potentially overlooking broader systemic effects relevant to morbidity, mortality, and healthcare utilization.

Objective: To evaluate the role of testosterone deficiency as a unifying biological factor linking cardiovascular, psychiatric, and inflammatory conditions in veteran populations, and to assess the impact of testosterone restoration on clinical outcomes.

Methods: A narrative review of observational and interventional studies was conducted, focusing on associations between testosterone levels and cardiovascular health, psychiatric conditions, inflammation, and mortality. The review also evaluated evidence on outcomes after testosterone levels were restored to physiologic ranges.

Findings: Low testosterone is consistently associated with increased all-cause mortality; in one veteran cohort, men with low levels had an 88% higher risk of death compared to those with normal levels. Depression incidence reaches 21.7% over two years in hypogonadal men, compared to 7.1% in eugonadal men. These conditions share overlapping pathways involving interleukin-6, tumor necrosis factor-alpha, and C-reactive protein, markers that actively drive both cardiovascular and neuropsychiatric disease. In a large retrospective cohort, men whose testosterone reached the mid-normal range had lower rates of myocardial infarction, stroke, and death compared with untreated hypogonadal men. Restoration of physiologic testosterone levels is also associated with improvements in mood, metabolic function, and inflammatory burden. Early evidence suggests associations between low testosterone and increased suicide risk in veteran populations.

Conclusion: Testosterone deficiency is better understood as a central element of a broader neuro-immune-endocrine dysregulation than as a standalone hormonal problem. A structured approach to screening, diagnosis, and longitudinal management within the Veterans Health Administration may offer a high-impact strategy to improve clinical outcomes and reduce healthcare utilization.

Keywords: testosterone deficiency; veterans; cardiovascular mortality; neuro-immune-endocrine dysregulation; testosterone replacement therapy; systemic inflammation

Introduction

Compared to the general population, U.S. veterans face a greater prevalence of chronic diseases, mental health conditions, and early death. The increased risk stems from a complicated mix of combat exposure, ongoing stress, environmental elements, and co-occurring medical issues. Clinical focus has predominantly been on post-traumatic stress disorder (PTSD), major depressive disorder, and cardiovascular disease as the main causes. But these conditions often happen together and share significant biological links, hinting that they might not be separate diseases but instead linked signs of a shared systemic disruption.[1–4] The common thread may be more straightforward than it appears. Autonomic imbalance, neuroendocrine disruption, and persistent low-grade inflammation cut across every one of these conditions.

Testosterone's physiologic role extends well beyond reproduction. It contributes to mitochondrial energy production and neurotransmitter signaling, and it participates in inflammatory regulation across multiple organ systems.[5,6] Androgen receptors are distributed broadly, present in the brain, vasculature, skeletal muscle, and immune cells in addition to reproductive tissues.[7,8] At the vascular level, testosterone supports nitric oxide-mediated vasodilation and endothelial repair.[5] It is also a key regulator of skeletal muscle protein synthesis and mitochondrial efficiency.[6,7] Its central nervous system effects include modulation of serotonergic pathways and neuroplasticity, with downstream influence on mood and cognition.[9]

Age-related declines in testosterone are well described in the general population, but in veterans these changes are often accelerated or amplified by cumulative stress exposure, sleep disruption, opioid use, traumatic brain injury, and chronic systemic illness.[10,11] All of these exposures converge on the hypothalamic-pituitary-gonadal (HPG) axis, the hypothalamic-pituitary-adrenal (HPA) axis, or both. They also feed into inflammatory signaling that compounds the endocrine damage.[12–14] When the stress response stays activated, cortisol and catecholamines remain elevated. This suppresses gonadotropin-releasing hormone (GnRH) pulsatility and, with it, testosterone production.[12,15] Inflammatory cytokines, particularly interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha), independently suppress gonadal function and worsen metabolic dysfunction.[14]

A growing body of evidence suggests hypogonadism may function as a biological integrator. Rather than existing alongside cardiovascular disease, mood disorders, and systemic inflammation, testosterone deficiency appears to be a common thread connecting them.[5,16,17] Low testosterone tracks with higher rates of atherosclerosis, insulin resistance, sarcopenia, depressive symptoms, and all-cause mortality, a pattern more consistent with shared pathophysiology than coincidence.[5,6,18,19] From this perspective, testosterone deficiency may not simply coexist with these conditions but actively contribute to their development and progression. The relationship runs in both directions. Chronic stress and inflammation suppress testosterone production, while falling testosterone levels amplify inflammatory and metabolic dysfunction.[12,13] The result is a self-reinforcing cycle of neuro-immune-endocrine disruption.

Yet testosterone deficiency remains underrecognized and undertreated in veteran care. Fatigue, depression, poor sleep, diminished exercise tolerance, and cognitive slowing are common in this population, but clinicians often attribute them to aging, stress, or psychiatric illness rather than considering an endocrine cause.[15] This misattribution may delay diagnosis and contribute to fragmented care, where underlying biological drivers remain unaddressed. Clinical guidelines vary, safety concerns persist, and screening practices differ enough that some providers test routinely while others never consider it.[20,21]

The Department of Veterans Affairs (VA) healthcare system, with its integrated care model and capacity for longitudinal monitoring, may be uniquely positioned to address this gap. As the largest integrated healthcare system in the United States, serving over nine million veterans,[22] the VA offers the infrastructure for population-level screening, standardized treatment protocols, and long-term outcome tracking that this clinical problem requires.[21]

Aim

This narrative review synthesizes currently available evidence linking testosterone deficiency to morbidity and mortality in male U.S. veterans and evaluates the clinical impact of restoring testosterone to physiologic levels. Six clinical domains are examined: cardiovascular outcomes, metabolic dysfunction, neuropsychiatric illness, systemic inflammation, suicide risk and behavioral outcomes, and healthcare utilization. Female veterans were excluded because testosterone physiology, reference ranges, and clinical presentation differ substantially by sex; the literature specific to female veterans also remains limited. The review concludes with a proposed systems-based framework for identification and longitudinal management of testosterone deficiency within the VA healthcare system.

Methods

Design and scope. A narrative review of the relationship between testosterone deficiency and clinical outcomes relevant to U.S. veterans was conducted. The review covered the six outcome domains described above. Consistent with the scope described above, the review focused on male populations.

Sources and search strategy. PubMed/MEDLINE and Google Scholar were searched using combinations of controlled vocabulary and free-text keywords related to testosterone deficiency, hypogonadism, and veteran health outcomes. Searches were limited to English-language publications. The search covered January 1990 through April 2025, with particular emphasis on studies published between 2022 and 2025. References published after the initial search window that met inclusion criteria and were identified during the revision process were also incorporated. The PubMed strategy used the following field-tagged query:
(("Testosterone"[MeSH Terms] OR testosterone[tiab] OR "Hypogonadism"[MeSH Terms] OR hypogonadism[tiab]

OR hypogonadal[tiab] OR "testosterone deficiency"[tiab] OR "low testosterone"[tiab] OR "androgen deficiency"[tiab]) AND ("Veterans"[MeSH Terms] OR veteran*[tiab] OR "military personnel"[tiab] OR "Veterans Health"[MeSH Terms] OR "United States Department of Veterans Affairs"[MeSH Terms]) AND ("Mortality"[MeSH Terms] OR mortality[tiab] OR "Cardiovascular Diseases"[MeSH Terms] OR cardiovascular[tiab] OR "Depressive Disorder"[MeSH Terms] OR depression[tiab] OR "Inflammation"[MeSH Terms] OR inflammation[tiab] OR "Suicide"[MeSH Terms] OR suicide[tiab] OR "testosterone replacement therapy"[tiab] OR "Testosterone/therapeutic use"[MeSH Terms])) AND english[lang] (exta spaces)

A secondary, broader search omitting the veteran-specific terms was performed to capture pathophysiological and interventional studies from the general male population. Reference lists of included articles and relevant systematic reviews were also hand-searched.

Eligibility criteria. Included sources comprised randomized controlled trials, large observational cohort studies, systematic reviews, meta-analyses, and clinical practice guidelines reporting on associations between testosterone levels and cardiovascular, metabolic, neuropsychiatric, inflammatory, or mortality outcomes. Narrative reviews were included when they offered biological interpretation not available in primary studies. Case reports ($n < 5$), conference abstracts without a corresponding full article, non-peer-reviewed sources, and animal-only studies were excluded, unless experimental data directly informed a biological mechanism discussed in the review.

Selection process. Titles and abstracts were screened for relevance to the review's clinical and biological questions. Full-text review followed for records deemed eligible or uncertain on initial screening. Studies were assessed for internal consistency, sample size, and methodological quality.

Data extraction and synthesis. From each source, information was extracted on study design, population characteristics, testosterone measurement methods, clinical endpoints, and reported effect sizes where available. Because study populations, testosterone assays, intervention protocols, and outcome definitions varied considerably across the literature, a qualitative synthesis was used rather than formal meta-analysis. Evidence was organized thematically by outcome domain: cardiovascular and mortality, metabolic, neuropsychiatric, inflammatory, behavioral, and healthcare utilization. Study selection, data extraction, and synthesis were performed by the author.

Findings

Mortality and Cardiovascular Outcomes

Low testosterone levels are consistently associated with increased all-cause mortality and elevated risk of myocardial infarction and stroke.[16,18] In a longitudinal VA cohort, men with low serum testosterone had an 88% higher risk of death from any cause.[18] The association appears especially strong in veterans, where metabolic syndrome, smoking, and chronic stress already elevate baseline cardiovascular risk.[1] In these populations, testosterone deficiency may be more than a biomarker of disease burden. It may actively contribute to vascular pathology.

Can restoring testosterone change this trajectory? Several analyses suggest it can, at least when physiologic rather than supraphysiologic levels are targeted.[23,24] In a large retrospective cohort, men whose testosterone reached the mid-normal range had lower rates of myocardial infarction, stroke, and death compared with untreated hypogonadal men.[23] The data are consistent with testosterone exerting protective effects on vascular integrity, lipid metabolism, and endothelial function.

At the molecular level, testosterone activates endothelial nitric oxide synthase (eNOS), which promotes vasodilation and improves arterial compliance.[5] When testosterone is low, endothelial dysfunction, arterial stiffness, and atherosclerotic progression tend to follow.[5] Testosterone also modulates lipid metabolism. Deficiency is linked to higher low-density lipoprotein cholesterol (LDL), lower high-density lipoprotein cholesterol (HDL), and elevated triglycerides.[6] Chronic inflammation further amplifies these effects, creating a pro-atherogenic environment.[13]

Work published between 2022 and 2025 adds a further layer: testosterone appears to interact directly with plaque biology and vascular inflammation. The TRAVERSE trial ("Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men" trial), a landmark randomized controlled trial enrolling 5,246 men with hypogonadism and high cardiovascular risk, demonstrated that testosterone replacement therapy was noninferior to placebo with respect to major adverse cardiovascular events. The trial also identified higher rates of atrial fibrillation and acute kidney injury in the testosterone group, though no increase in prostate cancer was observed.[25] In a separate imaging substudy from the earlier Testosterone Trials, physiologic testosterone replacement was associated with changes in atherosclerotic plaque composition, though the clinical significance of observed increases in noncalcified plaque volume remains uncertain.[26]

Metabolic and Vascular Effects

Testosterone deficiency is strongly associated with insulin resistance, increased visceral adiposity, and metabolic syndrome.[17,27] The connection is not incidental. Testosterone is involved in glucose metabolism, fat cell differentiation, and cellular energy utilization. Low testosterone promotes visceral fat accumulation. Visceral fat, in turn, drives up inflammatory cytokine production and worsens insulin resistance, setting up a metabolic cycle that feeds on itself.[13,27]

At the cellular level, testosterone improves mitochondrial efficiency in skeletal muscle and increases glucose uptake, while restraining fat cell proliferation.[7] In hypogonadal states, mitochondrial output drops, oxidative stress rises, and the body loses metabolic flexibility.[7] Clinically, this manifests as central obesity, loss of lean muscle, and declining physical performance.[27]

Recent interventional studies have demonstrated that testosterone replacement improves glycemic control, reduces waist circumference, and favorably alters body composition in men with hypogonadism and type 2 diabetes.[28,29] Enhanced insulin sensitivity and reduced visceral fat appear to account for much of the benefit. In the T4DM trial, a randomized, placebo-controlled study of 1,007 men aged 50 to 74 with central obesity and impaired glucose tolerance, two years of intramuscular testosterone undecanoate combined with a lifestyle program reduced progression to type 2 diabetes by 40% compared with placebo.[30] However, a prespecified substudy of the TRAVERSE trial found no significant difference in diabetes progression between testosterone and placebo groups in the absence of a structured lifestyle intervention, suggesting the metabolic benefit may depend on concurrent behavioral change.[31]

For veterans, among whom obesity, diabetes, and physical inactivity are common, testosterone deficiency may be a correctable driver sitting upstream of much of this metabolic dysfunction.[32]

Neuropsychiatric Outcomes

The link between low testosterone and depression is well documented. Hypogonadism has been associated with depressive symptoms, reduced motivation, anhedonia, and cognitive impairment.[19,33,34] In one cohort, the two-year incidence of depression was 21.7% in hypogonadal older men, compared to 7.1% in eugonadal men.[34] Both observational and trial data support these associations, though effect sizes differ depending on the population studied and how outcomes were measured.

Testosterone interacts directly with serotonergic signaling, affecting mood and executive function.[9] The biology is consistent: androgen receptors are concentrated in the amygdala, hippocampus, and prefrontal cortex, all of which are involved in emotional processing and executive control.[8,9]

Recent work from 2024 and 2025 strengthens the case that inflammation mediates the relationship between endocrine dysfunction and depression. Elevated cytokine levels, including IL-6 and TNF-alpha, disrupt neurotransmitter metabolism, weaken synaptic plasticity, and impair neurogenesis.[9,35,36] Testosterone appears to dampen neuroinflammation. Without it, the inflammatory processes that contribute to depression and cognitive decline may intensify.

In veterans, these interactions may be amplified by coexisting PTSD and chronic stress exposure. The overlap between hypogonadism, neuroinflammation, and dysregulated stress circuitry suggests testosterone deficiency may worsen and prolong neuropsychiatric illness in this population. A recent genetic analysis strengthens this interpretation: an inverse correlation between testosterone levels and PTSD risk in males suggests the association may reflect shared biological pathways rather than coincidence.[37]

Inflammatory Pathways

If there is a single mechanism that ties testosterone deficiency to disease across organ systems, inflammation is the strongest candidate. Low testosterone is consistently associated with elevated levels of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), and C-reactive protein (CRP).[13,14] These are not passive markers. They actively drive endothelial dysfunction, insulin resistance, and neuropsychiatric impairment.[5,36]

Recent data confirm that testosterone deficiency fuels chronic inflammatory signaling across vascular, metabolic, and neural tissue.[13,35,38] Testosterone inhibits Th1 and Th17 differentiation and restrains macrophage activation and cytokine output, effects that are lost in hypogonadal states.[35,39]

Testosterone replacement reduces inflammatory markers in hypogonadal men, with parallel improvements in metabolic and cardiovascular measures.[28,38] Work from 2022 to 2025 shows these effects are not limited to the periphery; they extend into the central nervous system, pointing to a role in dampening neuroinflammation as well.[35]

Testosterone, in this view, sits within a neuro-immune-endocrine axis where it both responds to and regulates inflammatory tone. When it falls, inflammation rises. Rising inflammation, in turn, pushes testosterone lower still.

Suicide Risk and Behavioral Outcomes

A smaller but growing body of evidence links low testosterone and inflammation to suicidal behavior.[40] Suicide has many causes, but these findings suggest endocrine and immune dysregulation may be among the biological contributors, especially in chronically stressed populations like veterans.

Low testosterone has been linked to suicidal behavior, reduced stress tolerance, and difficulty regulating emotion.[40] Inflammatory cytokines, meanwhile, alter serotonin and glutamate signaling, both of which are implicated in mood instability and impulsive behavior.[41]

Recent studies (2023-2025) suggest that the interaction between endocrine dysfunction and inflammation may create a neurobiological environment that increases vulnerability to suicidal ideation and behavior.[40,41] In veterans, where suicide rates remain high and biological and psychosocial risk factors overlap, this is more than an academic observation.[42]

Healthcare Utilization

Beyond mortality and psychiatric risk, testosterone deficiency also imposes a burden through its less dramatic but more pervasive effects on daily function. Fatigue, disrupted sleep, declining physical capacity, and vague somatic complaints are common in testosterone-deficient men, and all of them generate healthcare visits.[20,21] These symptoms often lead to repeated clinical encounters, diagnostic testing, and pharmacologic interventions without addressing underlying endocrine dysfunction. In the only

large VA cohort study of testosterone prescribing practices, just 2.2% of male veterans received testosterone therapy despite prevalence estimates of hypogonadism ranging from 5% to over 30% in this population, suggesting a substantial gap between disease burden and clinical recognition.[11,21,43]

Treatment of hypogonadism has been linked to improved functional status and lower symptom burden,[20,28] which may in turn reduce healthcare utilization. When energy, mood, and physical capacity improve, patients tend to need fewer visits and less symptomatic medication.

For a system that spends heavily on repeated visits for nonspecific complaints, identifying and treating an underlying endocrine driver could produce real cost savings. Integrating endocrine assessment into routine care pathways may allow for earlier identification of reversible contributors to chronic symptoms, improving both patient outcomes and healthcare efficiency.[21]

Discussion

Testosterone is not an isolated endocrine variable. The evidence reviewed here supports its role as a regulator operating across interrelated biological systems. In veterans, where chronic stress exposure, sleep disruption, and comorbid disease are highly prevalent, this regulatory role becomes particularly relevant and clinically actionable. Testosterone is better understood as a systems-level regulator, one that shapes neuroendocrine signaling, immune tone, metabolic efficiency, and vascular health, than as a reproductive hormone with limited clinical reach.[5,12,27,35]

Across all six domains reviewed here, the pattern is the same: testosterone deficiency pushes the body toward a pro-inflammatory, catabolic, metabolically unstable state that is not confined to one organ system. Low testosterone tracks with elevated inflammatory markers. It also correlates with adverse lipid profiles, insulin resistance, and endothelial dysfunction.[5,6,14,17] Depression, cardiovascular disease, sarcopenia, and fatigue may all be surface expressions of one deeper neuro-immune-endocrine disturbance.

At the neuropsychiatric level, testosterone plays a critical role in modulating mood and cognitive function. Androgen receptors are concentrated in brain regions that govern mood and executive function.[9] Low testosterone states have been associated with increased risk of depressive symptoms, anhedonia, and reduced executive function.[19] For veterans who carry trauma histories and live under chronic stress, this interaction matters clinically. Hypogonadism may make mood disorders harder to recover from. Impaired serotonergic signaling and reduced neuroplasticity are the probable pathways.[9]

What makes this particularly difficult to treat is that the relationship runs in both directions. Chronic stress, inflammation, and systemic illness suppress testosterone production through effects on the HPG axis. Elevated cortisol, inflammatory cytokines, and autonomic dysregulation all inhibit GnRH pulsatility and suppress luteinizing hormone (LH) secretion. The result is lower testosterone production.[12,13] Low testosterone then amplifies the same processes. Inflammatory signaling increases, mitochondrial function declines, and physiological resilience erodes. This creates a self-reinforcing cycle in which endocrine dysfunction both reflects and perpetuates disease.

The process amounts to a neuro-immune-endocrine loop (Figure 1). Stress drives up sympathetic tone and HPA output, raising cortisol and inflammatory mediators. Both suppress testosterone, removing one of the body's own brakes on inflammation and metabolic decline.[13,15] The result is a persistent state of low-grade inflammation, weakened anabolic drive, and poor recovery capacity. Over time, this state contributes to accelerated biological aging, increased cardiovascular risk, and progressive functional decline.[16]

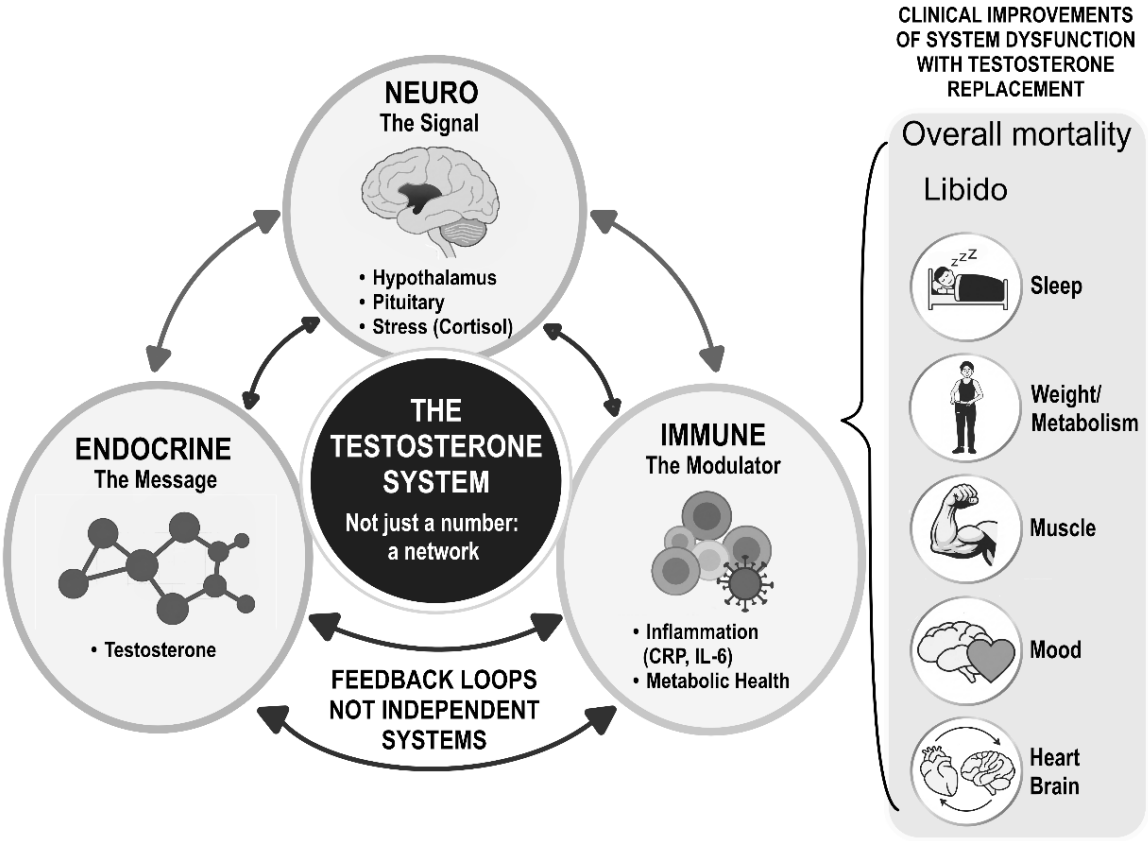

Figure 1. The neuro-immune-endocrine framework of testosterone deficiency. Testosterone functions within an interconnected network of neuroendocrine, immune, and hormonal signaling pathways. Dysregulation of this network contributes to clinical manifestations across multiple domains.

The mitochondrial data add a further dimension to this framework. Testosterone enhances mitochondrial biogenesis, improves oxidative phosphorylation efficiency, and reduces reactive oxygen species production.[7] When testosterone is low, mitochondrial dysfunction may be what produces the fatigue, exercise intolerance, and muscle loss so commonly reported by veterans and aging men. This offers a plausible explanation for the link between endocrine dysfunction and the clinical picture of low energy and physical fragility.

These considerations, from inflammatory signaling to mitochondrial dysfunction, converge on the cardiovascular system, where the relationship between testosterone and risk has historically been controversial. Earlier observational studies raised concerns about possible prothrombotic and cardiovascular harms from testosterone therapy.[44] As noted in the cardiovascular findings, the TRAVERSE trial demonstrated that testosterone replacement therapy was noninferior to placebo with respect to major adverse cardiovascular events in men with hypogonadism and pre-existing or high cardiovascular risk.[25] The Androgen Society has since concluded that testosterone therapy is not associated with increased risks of heart attack, stroke, or cardiovascular death.[45] Earlier observational data in older men receiving testosterone similarly showed no increased risk of myocardial infarction.[46] Low endogenous testosterone, on its own, tracks with higher rates of atherosclerosis, coronary artery disease, and all-cause mortality.[16] The weight of evidence now favors viewing testosterone deficiency as a contributor to cardiovascular risk, not a bystander.

The practical implication is straightforward. Treating depression, fatigue, or cardiovascular disease without checking whether endocrine dysfunction is driving them may explain why some patients never fully improve. Correcting testosterone deficiency, when present, may improve several of these conditions at once. Trial data show that testosterone replacement can improve mood, body composition, insulin sensitivity, and sexual function in hypogonadal men.[20,47] The size and reproducibility of these effects, however, differ considerably across studies. Notably, metabolic improvements may be most robust when testosterone therapy is combined with structured lifestyle modification, as suggested by the divergent outcomes of the T4DM and TRAVERSE diabetes substudies.[30,31]

These arguments have limits. Most of the evidence is observational. Consistent associations across studies are not the same as proven causation. Testosterone replacement therapy (TRT) trials have produced inconsistent results, largely because studies differ in patient selection, baseline hormone levels, dosing strategies, formulation, and duration of follow-up.[20] The inconsistency in how neuropsychiatric outcomes are measured makes direct comparison across studies difficult.

Safety concerns have slowed adoption. Polycythemia, fluid retention, and the possibility of worsening prostate disease are the main risks clinicians weigh when considering long-term therapy.[15] The TRAVERSE trial found higher rates of atrial fibrillation and acute kidney injury in the testosterone group, although no increase in prostate

cancer was observed.[25] More recent data suggest that these risks are manageable, provided therapy targets men with confirmed biochemical and symptomatic deficiency and stays within physiologic replacement ranges under regular monitoring.[15,48] Careful patient selection, dose adjustment, and ongoing monitoring remain non-negotiable.

The VA is one of the few healthcare systems where a structured, integrated approach to testosterone deficiency could realistically be implemented. Veterans frequently present with overlapping conditions, including PTSD, sleep disorders, metabolic syndrome, and chronic pain, that may share underlying neuro-immune-endocrine dysregulation. Yet endocrine, mental health, and primary care services usually run in parallel, not in coordination. That fragmentation makes it easy to miss conditions that cut across specialties, and easier still to treat symptoms without ever looking for the biology underneath.[21]

Adding testosterone evaluation to the workup of veterans who present with fatigue, depression, poor sleep, muscle loss, or metabolic disease could catch cases earlier and improve coordination across services. This would also align with the VA's broader push toward prevention, longitudinal management, and reducing high-cost utilization. Screening protocols could be incorporated into routine laboratory assessment in high-risk populations, with clear referral pathways for endocrine evaluation and treatment. This need may be most acute in high-risk subgroups, including veterans with PTSD, chronic opioid use, or metabolic syndrome, where testosterone deficiency appears more prevalent and its clinical impact more pronounced.[10,11] The VA's infrastructure for longitudinal monitoring and standardized care protocols provides a practical foundation for implementing such screening at scale. Recent international consensus recommendations have emphasized the importance of standardized diagnostic pathways and evidence-based management of testosterone deficiency across clinical settings.[48,49]

Testosterone assessment could also fit within a broader framework that addresses both autonomic and inflammatory regulation. Hypogonadism, chronic stress, and inflammation overlap extensively. Combining hormonal optimization with sleep restoration, stress reduction, and metabolic intervention is likely to produce better results than addressing any single element alone.

What is still missing is prospective trial data in veteran populations specifically, with hard endpoints: mortality, cardiovascular events, functional status, and validated mental health measures. Longitudinal studies tracking testosterone alongside inflammatory markers and autonomic function would sharpen the mechanistic picture. And without cost-effectiveness data, it will be hard to persuade health systems to adopt routine screening at scale.

Recognizing testosterone not as a single hormone but as a node in a complex adaptive system has implications that reach past endocrinology. It reinforces a paradigm in which chronic disease reflects dysregulated biological networks, not isolated organ failures. Within this paradigm, testosterone deficiency in veterans may serve as both a biomarker and a therapeutic target within a larger strategy aimed at restoring physiologic balance, improving resilience, and reducing long-term disease burden.

Conclusion

Testosterone deficiency is common among U.S. veterans and carries consequences for survival, cardiovascular and mental health, and the cost of their care.

The available evidence links testosterone optimization to better survival, lower cardiovascular risk, improved mood, and reduced inflammation. Most of this evidence is observational, and the size of the benefit differs by domain, but the consistency of associations across independent datasets and multiple organ systems supports the biological plausibility of the link. Yet testosterone deficiency is not systematically identified or managed within the VA system, partly because the symptoms it produces are nonspecific and rarely prompt endocrine testing.

A structured, systems-based approach to screening and longitudinal care may represent a high-impact intervention with the potential to improve outcomes and reduce costs at scale.

Conflicts of Interest

The author has no conflicts of interest to declare.

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