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ANDROPAUSE AND THE EFFECTS OF HORMONE REPLACEMENT THERAPY: RECENT RESEARCH TRENDS

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ABSTRACT

This study aimed to systematically analyze research trends over the past decade (2014–2024) concerning andropause and the effects of hormone replacement therapy (HRT). A scoping review methodology was employed to identify and select relevant articles published in domestic and international academic journals. A total of 17 studies were analyzed. The majority of studies (76.5%) were preclinical animal experiments, reporting positive effects such as increased testosterone levels, and enhanced muscle mass, reduced body fat, and improved sperm quality. Clinical studies involving human subjects (23.5%) demonstrated that HRT had beneficial effects in alleviating andropause symptoms and improving quality of life and sexual function. The review identified inconsistencies among study findings and limitations in clinical evidence, highlighting the need for long-term and systematic follow-up studies. This research provides foundational data for developing treatment strategies for andropause and emphasizes the need for more rigorous clinical research and policy support.

KEYWORDS: Andropause, Hormone Replacement Therapy (HRT), Testosterone, Male Menopause, Scoping Review.

1. INTRODUCTION

Andropause refers to a condition in middle-aged men characterized by physical and psychological symptoms resulting from a decline in testosterone levels [1]. In general, testosterone levels in men begin to decline by approximately 1% per year starting in their late 20s. Although individual variations exist, many men experience andropause symptoms between the ages of 40 and 60 [2]. The main symptoms include psychological issues such as fatigue, depression, and anxiety, as well as physical changes such as hot flashes, erectile dysfunction, decreased muscle mass, increased body fat, and reduced body hair [3]. Andropause symptoms are known to affect approximately 57% of men over the age of 40 [4], and domestic studies have reported that around 70% of middle-aged men aged 40 and above experience these symptoms [3]. In addition, decreased testosterone levels are also associated with chronic conditions such as cardiovascular disease, type 2 diabetes, osteoporosis, and obesity [1]. In particular, men with low testosterone levels are at increased risk of developing metabolic syndrome, which often leads to a higher likelihood of cardiovascular complications [5]. Andropause has implications beyond personal health, influencing family life and social connections. In the absence of proper intervention, it can contribute to the development of chronic conditions and psychological difficulties [6]. Therefore, appropriate treatment and management of andropause are essential. Current approaches include hormone replacement therapy, lifestyle modifications, and psychological counseling, all of which may help alleviate andropause symptoms [6].

Hormone replacement therapy (HRT) is one of the most effective treatment options for andropause, with testosterone replacement therapy (TRT) being the primary method used. The World Health Organization (WHO) defines TRT as a medical intervention for treating testosterone deficiency and reports that it is effective in alleviating andropause symptoms such as decreased bone density, reduced muscle mass, depression, fatigue, and diminished sexual function [7]. Moreover, TRT has demonstrated beneficial outcomes in men experiencing andropause, notably by improving bone density, increasing muscle mass, and enhancing sexual function [8]. According to the Endocrine Society Clinical Practice Guideline (2018), TRT is indicated for men with consistent symptoms of testosterone deficiency and morning serum total testosterone below 264 ng/dL (9.2 nmol/L). Before initiation, clinicians should obtain baseline measurements of

hematocrit, prostate-specific antigen (PSA), lipid profile, and perform a digital rectal examination, with follow-up monitoring of hematocrit and PSA at three- to six-month intervals to detect hematologic or prostate-related adverse events. Treatment typically starts with intramuscular testosterone enanthate or cypionate (50–100 mg weekly) or equivalent transdermal formulations, titrating doses to maintain mid-normal serum testosterone levels (400–600 ng/dL). These guidelines emphasize individualized risk-benefit discussions to avoid overtreatment particularly in men with comorbid thromboembolic or cardiovascular risk factors. Generally, men with total serum testosterone levels below 3.0–3.5 ng/mL have been considered primary candidates for TRT [11]. However, recent studies have argued for more flexible criteria, suggesting that men with higher testosterone levels may also be eligible for TRT if they present with specific clinical symptoms [11]. Although several studies have reported that TRT has beneficial effects such as increasing bone density, preserving muscle mass, and improving metabolic syndrome the absence of standardized guidelines on patient eligibility, optimal dosage, and appropriate treatment duration has created uncertainty in clinical practice [12]. In addition, it has been reported that 9% to 70% of men worldwide use complementary and alternative medicine (CAM), including acupuncture, nutrition therapy, herbal medicine, or supplements, which may be linked to a lack of confidence in conventional treatments [13]. Therefore, it is essential to systematically evaluate the efficacy and safety of TRT and to establish scientific evidence based on the latest research findings.

Although extensive research has been conducted on the treatment and management of menopause in women, studies focusing on andropause and hormone replacement therapy (HRT) in men remain comparatively limited. Several studies have highlighted the positive effects of testosterone replacement therapy (TRT), including increased muscle mass, enhanced bone density, and improved sexual function [7]. However, some research has raised concerns about potential adverse effects on cardiovascular health and prostate function [14]. In contrast, other studies have suggested that TRT may lower the risk of metabolic syndrome and contribute to better cardiovascular outcomes [15]. Similarly, while certain findings indicate that TRT may support cognitive function, others report no significant correlation [16]. These inconsistencies may be attributed to variations in study populations, durations, administration methods, and dosage levels. Given these divergent findings, a

comprehensive review of the existing literature is essential. Accordingly, this study aims to systematically examine recent research trends related to andropause and HRT and to provide foundational evidence for the development of effective treatment strategies.

2. RESEARCH METHODOLOGY

2.1. Study Design

This study is a scoping review conducted to identify recent trends in research on andropause and the effects of hormone replacement therapy (HRT) published in South Korea between 2014 and 2024.

2.2. Study Subjects

This study was conducted in accordance with the scoping review framework proposed by Arksey and O'Malley [17], focusing on research articles addressing the effects of andropause and hormone replacement therapy (HRT) in men. Studies published in domestic academic journals between January 2014 and December 2024 were included and subjected to content analysis.

2.3. Analysis Methods

This review followed the six-stage framework proposed by Arksey and O'Malley [17], with additional refinements based on expert consultation [18]. **The six stages are as follows**

2.3.1. Formulating the Research Questions

Clearly defined research questions are essential in scoping reviews, as they guide the scope and focus of literature analysis. This study sought to examine recent research trends on hormone replacement therapy (HRT) for andropause, **with the following research questions**

What are the recent research trends regarding hormone replacement therapy for andropause in men?

What are the reported effects of hormone replacement therapy (HRT) on andropause symptoms?

What major treatment approaches have been proposed in previous studies, and what are their limitations?

2.3.2. Identifying Relevant Studies

The literature search was conducted to identify studies published between January 2014 and December 2024 that evaluated the effects of hormone replacement therapy on andropause. Searches were performed in the domestic databases RISS, NDSL, KMBASE, KoreaMed, and the National Assembly Library. Articles published in either Korean or English were eligible for inclusion. Three independent reviewers screened titles, abstracts, and full texts. **The search**

strategy employed the following terms 남성 갱년기 증후군 (Male Andropause Syndrome), 갱년기 호르몬 대체 요법 (Menopausal Hormone Replacement Therapy), Andropause, Male Menopause, Hormone Replacement Therapy, Testosterone Therapy, aging male, late-onset hypogonadism, and testosterone therapy in elderly, and age-related testosterone decline. This study was conducted as a scoping review following the Arksey and O'Malley framework; therefore, no formal critical appraisal of individual study quality was undertaken. Consequently, the methodological rigor of the included studies varies, and the overall evidence base is heterogeneous in strength and weakness.

2.3.3. Selecting Studies

To ensure consistent application of inclusion and exclusion criteria, two meetings were held. Four researchers independently reviewed article titles and abstracts. A total of 174 articles were initially identified: 83 from RISS, 18 from KMBASE, 2 from KoreaMed, and 71 from NDSL.

After applying exclusion criteria such as irrelevance to andropause ($n = 89$), lack of clinical context ($n = 5$), and misalignment with the study objectives ($n = 45$) 139 articles were excluded. Ultimately, 17 peer-reviewed articles were included in the final analysis. The selection process is illustrated in <Figure 1>.

2.3.4. Development of the Analytical Framework

To systematically analyze the selected studies, an analytical framework was developed based on the criteria proposed by Armstrong et al. [19] and previous literature. **The framework comprised two main components**

- 1) General study characteristics (author(s), year, population, study design, journal source, analysis method, and research focus)
- 2) Key findings and reported outcomes related to andropause and HRT.

2.3.5. Data Charting and Analysis

Data charting was conducted using the developed analytical framework. Microsoft Excel 2020 was used for data entry and coding. Frequency analysis and descriptive statistics were performed to summarize study characteristics and findings.

3. RESULTS

3.1. Search and Selection of Relevant Literature

The step-by-step process of literature selection is illustrated in Figure 1. A total of 174 articles were

initially retrieved through searches across five academic databases. After applying the inclusion criteria, 139 studies were excluded, resulting in 35 articles being selected for the first round of screening.

Two researchers then independently reviewed the titles and abstracts of the 35 articles, applying both inclusion and exclusion criteria with a focus on

relevant keywords. As a result, 18 studies were excluded, including 1 duplicate, 8 cellular studies, 4 studies unrelated to hormone replacement therapy, 3 review articles, and 2 studies for which the full text could not be obtained. Ultimately, 17 studies were included in the final analysis.

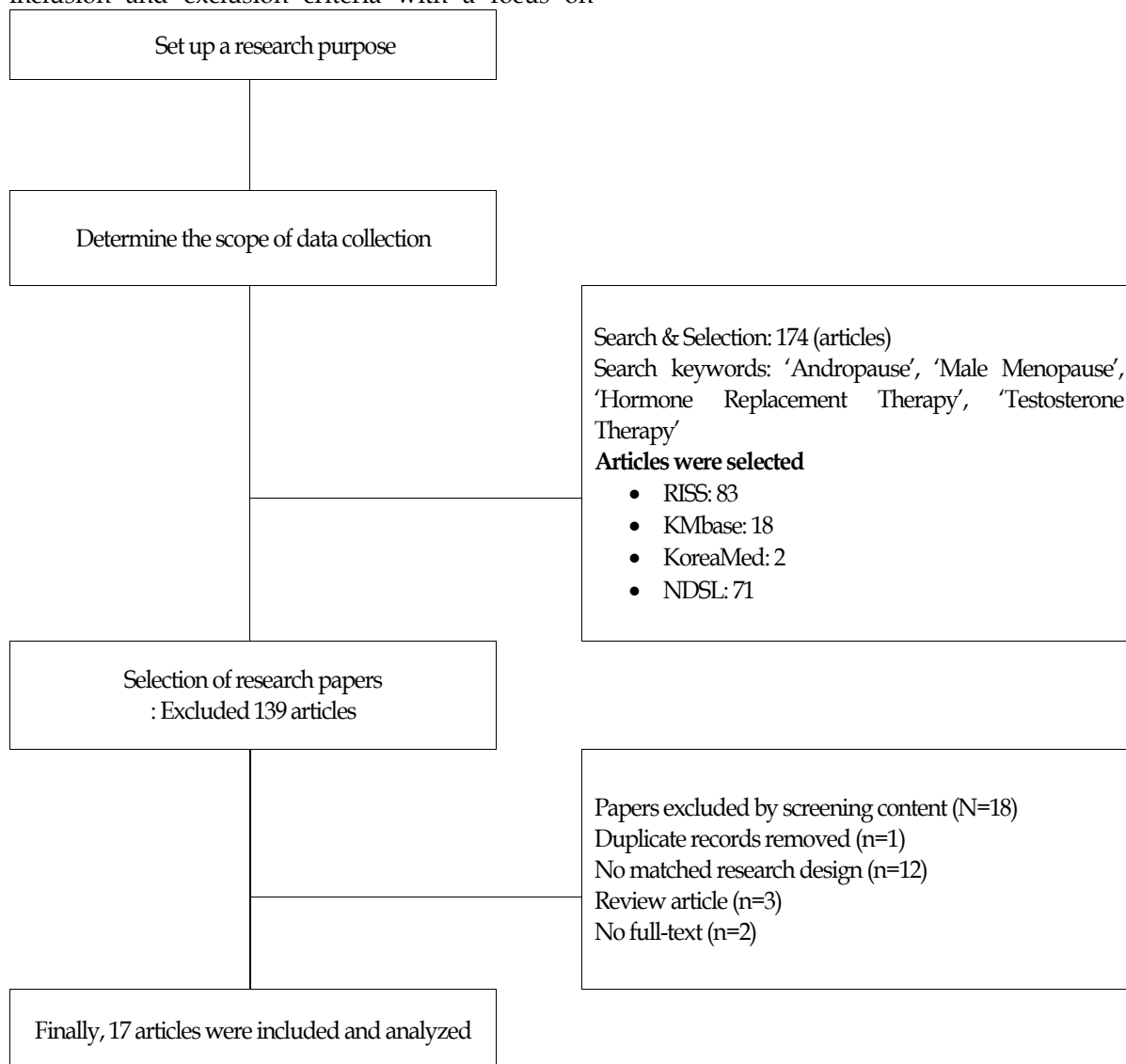


Figure 1. Flowchart of Included Studies through Database Search and Selection Process.

4. GENERAL CHARACTERISTICS OF THE INCLUDED STUDIES

This scoping review systematically analyzed 17 studies published between 2014 and 2024 that examined the effects of hormone replacement therapy (HRT) on andropause. The general characteristics of the selected studies were categorized and analyzed based on publication year, journal of publication, country of origin, study design, and characteristics of the study population (Table 1). Among the 17 studies included in the final analysis, 9 studies (52.9%) were published

between 2015 and 2020, while 8 studies (47.1%) were published between 2021 and 2024. The 17 selected studies were published across 15 different academic journals. Nutrients had the highest number of publications, with 3 articles (17.6%). This was followed by Journal of the Korea Society of Food Science and Nutrition and The Pharmaceutical Society of Korea, each with 2 articles (11.8%). The remaining journals Journal of Life Science, Journal of Medicinal Food, Food Science and Biotechnology, Chung-Ang Journal of Medicine, Oxidative Medicine and Cellular Longevity,

Hormone and Metabolic Research, Diabetes & Metabolic Syndrome, Korean Society of Food Science and Technology, Journal of Physiology & Pathology in Korean Medicine, and Medicine each contributed 1 article (5.9%). The majority of the studies (15 articles, 88.2%) were conducted in South Korea, followed by one study each from India (5.9%) and Türkiye (5.9%). An analysis of study designs revealed that 13 studies (76.5%) were preclinical animal experiments, while 4 studies (23.5%) were clinical trials involving human

participants. Notably, a higher proportion of the research employed animal models. The human studies primarily adopted randomized controlled trial designs or quasi-experimental approaches to evaluate clinical efficacy. Regarding the characteristics of study subjects, all 13 preclinical studies (76.5%) utilized rats, most commonly male Sprague-Dawley rats. In the clinical studies (4 articles, 23.5%), the participants were patients diagnosed with andropause.

Table 1: Characteristics of Included Studies.

Variable	Category	n	%
Publication Years	2016	3	17.6
	2017	2	11.8
	2018	1	5.9
	2019	3	17.6
	2021	1	5.9
	2022	3	17.6
	2023	3	17.6
	2024	1	5.9
Journals Published	Nutrients	3	17.6
	Journal Korea Society of Food Science and Nutrition	2	11.8
	The Pharmaceutical Society Of Korea	2	11.8
	Journal of Life Science	1	5.9
	Journal of Medicinal Food	1	5.9
	Food Science and Biotechnology	1	5.9
	Chung-Ang Journal of Medicine	1	5.9
	Oxidative Medicine and Cellular Longevity	1	5.9
	Hormone and Metabolic Research	1	5.9
	Diabetes & Metabolic Syndrome	1	5.9
	Korean Society of Food Science and Technology	1	5.9
	Journal Physiol & Pathol Korean Medicine	1	5.9
Countries Where Studies Were Conducted	South Korea	15	88.2
	India	1	5.9
	Turkey	1	5.9
Study Design	Preclinical animal study	13	76.5
	Clinical study in humans	4	23.5
Target Subjects	Rats	13	76.5
	Patients with andropause syndrome	4	23.5

5. METHODS OF THE EFFECTS OF HORMONE REPLACEMENT THERAPY

This study analyzed 17 articles that assessed the effects of hormone replacement therapy (HRT) or natural product-based complementary therapies on andropause. The evaluation methods employed in the studies were categorized into objective physiological indicators and subjective self-reported measures.

5.1. Objective Physiological Evaluation Methods

Objective physiological indicators were the primary means of evaluating the effects of HRT or complementary therapies in most studies. These

indicators included serum hormone levels, sperm count and motility, changes in body composition, gene expression, and lipid profiles. The most commonly assessed parameter was the change in total testosterone levels, which was analyzed in all 17 studies (100%). Most reported a statistically significant increase following treatment. Sperm count and motility were evaluated in 11 studies (64.7%) [S1–2, S4–5, S7–10, S12, S16–17], with significant improvements observed, particularly in animal studies. Muscle mass gain and body fat reduction were assessed in 10 studies (58.8%)[S1, S2, S5–7, S9–10, S13–14, S17], where most reported increases in muscle mass and reductions in body fat in the HRT or complementary therapy groups. Changes in gene expression related to hormone

synthesis and degradation enzymes were examined in 9 studies (52.9%) [S2, S4, S7–10, S12, S16–17]. Significant alterations were observed in the expression levels of genes such as 3 β -HSD, CYP11A1, aromatase, and 5 α -reductase. Additionally, 6 studies (35.3%) [S1, S2, S5–6, S14–15] analyzed changes in sex hormone-binding globulin (SHBG) and cholesterol levels. These same studies reported decreased SHBG levels enhancing testosterone bioavailability and improvements in blood lipid profiles.

5.2 Subjective Evaluation Methods

In the four clinical studies involving human participants [S1, S6, S14–15], self-reported questionnaires were used to assess improvements in symptoms related to andropause. Three studies (17.6%) [S1, S14–15] employed the Aging Males' Symptoms (AMS) Scale and the Androgen Deficiency in the Aging Males (ADAM) Scale, all of which reported statistically significant reductions in symptom scores in the HRT treatment groups. One study (5.9%) [S6] utilized quality of life-related scales, including the Quality of Life (QoL) Scale, the International Index of Erectile Function-5 (IIEF-5), and the Short Form-12 (SF-12) mental health index. This study demonstrated overall improvements in quality of life and sexual function indicators following treatment.

6. DISCUSSION

6.1. Implications for Clinical Practice

This study was conducted using the scoping review methodology proposed by Armstrong et al.[19] to systematically examine recent research trends on andropause and the effects of hormone replacement therapy (HRT), with the aim of providing foundational data for developing future treatment strategies. A total of 17 relevant studies were identified through the review. The earliest among them was a clinical study conducted in Türkiye by Bayram (2016), which investigated the effects of gonadotropin replacement therapy (GRT) on metabolic indicators and body composition in men with idiopathic hypogonadotropic hypogonadism (IHH). In Korea, the earliest identified study was conducted by Lee (2016), who examined the effects of dandelion extract on menopausal symptoms in rats. Excluding these two early studies, only 3 of the remaining 15 focused on human participants. Among the domestic studies, Lee (2018) evaluated the efficacy and safety of Tadalafil, while Jung (2023) examined the effects of unripe *Rubus coreanus* extract on quality of life and urinary symptoms. Internationally, a 2023 study by Kant compared a testosterone-treated group with a

non-treated control group to assess the therapeutic effects of HRT. Notably, all of these studies involved participants with either clinically low testosterone levels or observable andropause symptoms. Clinical practice should align with international standards; for example, the Endocrine Society (2018) recommends baseline hematocrit, PSA, and lipid profiling before TRT initiation, with follow-up every 3–6 months to monitor efficacy and safety.

6.2 Research Gaps and Limitations

Most of the studies conducted in South Korea were preclinical experiments using rat models. These studies reported beneficial effects such as increased testosterone levels, improved testicular tissue structure, enhanced sperm quality, and elevated antioxidant activity through the use of plant-based extracts including dandelion, carob, fenugreek, centipede grass (*Aeginetia indica*), *Rubus coreanus* (Korean black raspberry), bitter melon, and *Acorus gramineus*. Some of these studies further explored mechanistic evidence by analyzing increased expression of androgen receptors and the regulation of hormone-related enzymes. In contrast, clinical studies involving human subjects primarily employed interventions such as testosterone replacement therapy (TRT), pharmacological agents like tadalafil, and functional health supplements derived from *Rubus coreanus* extract. These interventions demonstrated significant improvements not only in andropause symptoms but also in broader outcomes such as quality of life, urinary function, and sexual performance. Notably, a study conducted in India reported that testosterone supplementation had a positive effect on glycemic control, suggesting the potential of HRT as a therapeutic strategy from an endocrinological and metabolic perspective. While most domestic studies were focused on preclinical validation of functional ingredients or herbal extracts using animal models, some included clinical research involving human participants to assess the effects of pharmaceuticals or natural compounds. These efforts reflect an emerging interest not only in verifying physiological efficacy but also in exploring the practical applicability of such treatments. In contrast, international studies have expanded their scope beyond clinical outcomes to include qualitative and quantitative research on men's perceptions, lived experiences, and psychological impacts of andropause. This highlights a distinct research focus abroad more closely aligned with policy development and real-world treatment implementation compared to the predominantly

biological and intervention-based orientation of Korean studies. However, as a scoping review, we did not perform formal quality appraisal of individual studies, and the limited search terms may have excluded relevant work; consequently, the included studies vary in methodological rigor and carry different levels of evidence strength and weakness. These factors introduce potential bias and underscore the need for more rigorous systematic reviews.

6.3. Policy and Guideline Recommendations

Despite ongoing research, gaps remain in the diagnosis and treatment of andropause, and many men continue to experience a decline in quality of life. While hormone replacement therapy (HRT) has been reported to improve physical vitality, mood, and overall quality of life, its full range of effects has yet to be thoroughly explored. In response, international studies have begun to examine not only the physiological changes associated with andropause, but also men's identity, psychological shifts, and subjective experiences. Qualitative research approaches have been used to explore men's personal experiences with HRT, aiming to deepen understanding beyond biomedical perspectives. Some studies have attempted to distinguish whether testosterone decline is a direct result of aging or secondary to comorbid conditions [23], while others have investigated the associations between testosterone deficiency, falls, and depressive symptoms in older men [24], as well as the prevalence of testosterone deficiency among elderly male populations [25]. These diverse lines of inquiry, both domestic and international, highlight the potential for multidimensional intervention strategies targeting andropause symptoms. We recommend that Korea develop standardized HRT guidelines drawing on WHO's 2015 testosterone replacement recommendations and the Endocrine Society's 2018 clinical practice guideline to ensure consistency in patient selection, dosing, and monitoring.

6.4. Need for Qualitative Patient-Centered Research

However, this scoping review utilized a limited set of search terms such as "andropause," "male climacteric syndrome," and "hormone replacement therapy" which may have excluded relevant studies that did not explicitly include these terms. In

addition, as scoping reviews do not include an assessment of the methodological quality of evidence, there is a potential risk of bias in the selection process. Future research should adopt a more comprehensive search strategy and incorporate systematic reviews and meta-analyses to establish more precise and reliable evidence bases. Future research should expand qualitative methods to capture men's lived experiences of HRT, exploring psychosocial impacts, treatment preferences, and barriers to care, thereby informing truly patient-centered clinical guidelines.

Taken together, this scoping review highlights critical gaps in clinical validation of HRT for andropause and underscores the need for standardized diagnostic criteria, multicenter randomized trials, and patient-centered outcome measures. Implementation of harmonized guidelines drawing on both domestic data and international consensus will be pivotal to translating these findings into improved men's health outcomes.

7. CONCLUSION AND RECOMMENDATIONS

This scoping review demonstrates that most research on andropause and HRT over the past decade remains at the preclinical stage, with limited clinical validation. To translate these findings into practice and inform policy, **we recommend**

1. Establish standardized diagnostic criteria for testosterone deficiency and conduct multicenter randomized controlled trials with adequate sample sizes.
2. Implement long-term clinical studies in diverse, real-world populations, including patient-centered outcomes (e.g., quality of life, sexual function, metabolic endpoints).
3. Undertake systematic reviews and meta-analyses to consolidate existing evidence on both benefits (e.g., increased muscle mass, improved QoL) and risks (e.g., cardiovascular, thromboembolic).
4. Develop and disseminate evidence-based clinical guidelines, integrating international consensus (WHO, Endocrine Society) with domestic data to ensure consistent patient selection, dosing, and monitoring.

Such coordinated efforts will be pivotal in bridging the gap between preclinical insights and clinical practice, ultimately improving health outcomes for aging men.

Author Contribution: † These authors contributed equally as co-first authors.

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