

# Testosterone Replacement Therapy in the Aged Male: Monitoring Patients' Quality of Life Utilizing Scoring Systems

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**Abstract:** Hypogonadism has been associated with significant deterioration of well-being. In the aging male, late-onset hypogonadism affects sexual life, mental health, levels of energy, lower urinary tract symptoms and, therefore, quality of life may be found significantly deteriorated. Testosterone replacement or supplementation therapy has been found efficient to reverse the adverse effects of hypogonadism and improve quality of life. Scales and questionnaires assessing the general health, urinary symptoms, sexual health, and cognition can provide a thorough assessment of the clinical syndrome, optimize treatment, assist the follow-up, and facilitate referrals to other specialties depending on the chief complaint. A systematic assessment might combine several tools, but the optimal ones and the exact usage is unknown. In this narrative review, we are flipping through the literature presenting the available tools per domain for the assessment of quality of life in men on testosterone replacement therapy and we discuss the optimal usage.

**Keywords:** testosterone replacement treatment, quality of life, sexual health, well-being, mental health, lower urinary tract symptoms

## Introduction

Hypogonadism (HG), or testosterone (T) deficiency, is referred to as the syndrome of symptoms resulting from insufficient serum levels of testosterone, which results in inadequate action in sensitive tissues. Its role has been investigated for thousands of years, and the Romans are reported to have observed its impact on energy, erectile function, and urination.<sup>1</sup> The causes are several, but they can be categorized into two primary groups: primary hypogonadism or testicular failure, acquired or congenital and secondary hypogonadism, which implies the origin of the syndrome is found in the hypothalamus or the pituitary gland including complex mechanisms.<sup>2</sup> Klinefelter syndrome (KS) represents one of the commonest, congenital causes of primary hypogonadism.<sup>3</sup> Conversely, the aging of the testicles seems to be a natural phenomenon as men will experience roughly a 1–2% per year reduction of their circulating testosterone levels starting at the beginning of fifth decade, which eventually results in the development of the late-onset hypogonadism (LOH).<sup>4</sup> The timing of the manifestations varies according to the cause as congenital causes will manifest primarily as incomplete or delayed sexual development at childhood whereas late-onset or acquired hypogonadism will present more frequently as loss of libido, fatigue, mood disorders, and erectile dysfunction in older age.<sup>5,6</sup>

Hypogonadism presents as a clinical syndrome. This includes a combination of a variety of nonspecific signs and symptoms is present in addition to the hormonal imbalance. Incomplete sexual development, erectile and sexual dysfunction, decreased energy, mood disorders, muscle weakness, fatigue, sleeping difficulties, infertility, and chronic pain are the main manifestations of testosterone deficiency, which alone or in combination will affect significantly the quality of life of affected men.<sup>7–10</sup> In aged males, the condition warrants high suspicion as symptoms are not specific.

A combination of low energy, sleep disturbances, loss of libido, underperformed sexual activity, and emotional stress should trigger screening for hypogonadism in men above (but not limited to) the age of 40.<sup>7,11</sup>

Testosterone replacement therapy (TRT) or supplementation therapy (TST) has positive effects on body weight and metabolism, bone and liver health, cardiovascular status, sexual, and micturition health, and sarcopenia.<sup>12</sup> It has been offered in multiple pharmacological forms (oral administration, injections gel, transdermal patches, etc) for the restoration of normal testosterone levels in cases of both primary and secondary hypogonadism when clinically appropriate.<sup>1</sup> When hypogonadism is complicated by infertility, special hormonal manipulations are needed as low testosterone interferes with the spermatogenesis, but pure TRT may negatively affect the reproductive axis.<sup>13,14</sup> Testosterone replacement differs to treatment with human chorionic gonadotropin (HCG), which is used to treat secondary hypogonadism and improve spermatogenesis by stimulating the Leydig cells without the side effects on fertility seen in TRT.<sup>15</sup> Apart from the beneficial effect on the hormonal status, TRT has been found efficient to improve the quality of life in hypogonadic men as part of a multidisciplinary team approach as illustrated in subjective tools and metrics.<sup>16–18</sup> Various questionnaires and scoring systems have been proposed as assessors for the standardized evaluation of the effect on quality of life (QoL) along with the measurement of clinical parameters and should comprise the routine approach as QoL endpoints might elude.<sup>19,20</sup> Specific questionnaires such as the widespread used aging males' symptom rating scale (AMS) have been well-established as they assess several views of quality of life including sexual, somatic, and psychological aspects.<sup>18</sup> However, a more delicate and thorough tool might be needed in men where the chief complaint comes from the mental sphere, sexuality, or chronic pain.<sup>21,22</sup> Moreover, lower urinary tract symptoms are quite common in aging men with hypogonadism, affecting quality of life warranting follow-up.<sup>23</sup> However, a standard regime for monitoring the QoL in men on TRT is unknown and the optimal tools are yet to be established. So far, no specific tools affecting QoL in men on TRT has been suggested or included in international guidelines.<sup>24</sup> In this paper, we review the indications and the rationality of the available tools monitoring QoL in adult men with LOH on TRT, and we provide the evidence for their usage.

## Materials and Methods

A nonsystematic search in PubMed/Medline, Google Scholar, Web of Science, and Embase was performed using the terms “testosterone replacement therapy” and “quality of life”, “chronic pain”, “lower urinary tract symptoms”, “general health”, “well-being”, “sexual health”, “questionnaire”. Outstanding studies escaped from engine search were selected through the full texts of the reviewed papers. Exclusion criteria were non-English, animal, and retracted studies. We select the evidence related to the specialism of tools in the below domains: general health assessment, lower urinary tract symptoms, sexual health assessment, mental health, in men treated with TRT for LOH.

## General Health Assessment

The aging males' symptoms (AMS) scale was developed in 1999 as a tool to aid assessment of andropause including evaluation of symptoms, severity, and response to TRT. It consists of 17 questions of somatic, psychological, and sexual symptoms and the score varies from 17 (minimal significance) to 85 (severe symptoms consistent to TD).<sup>25</sup> It has been one of the most extensively used assessors of quality of life in men treated with hypogonadism and reduction of the score indicates treatment success in terms of quality of life improvements.<sup>26</sup> Domains of the questionnaires can also be used separately for the assessment of the chief complaint such as sleep disturbance/apnoea which is not an uncommon manifestation of HG.<sup>7</sup> Furthermore, it seems that the tool follows reliably the severity of the symptoms and the complexity of HG. Jeong et al reported that men with metabolic syndrome showed less improvement in the AMS scale reflecting directly the effect of the complications on quality of life.<sup>27</sup> Similarly, the androgen deficiency in the aging male (ADAM) questionnaire is another used tool initially designed for the screening of low testosterone. This questionnaire is shorter and consists of 10 questions with a binary response (yes/no) assessing sexual life, energy levels, mood, and activities performance. It has been used, but less frequently compared to AMS, for the assessment of the response to TRT and reduction in the score indicates improvement in quality of life.<sup>28</sup> Similarly to AMS, the questionnaire can be used for the assessment of single complaints such as the psychological aspects and for the monitoring of men with chronic pain.<sup>22,29</sup> Short-form health survey (SF) questionnaires have been developed for monitoring the QoL in patients with chronic

conditions and other stressful circumstances.<sup>30</sup> They assess aspects of general health, physical functioning, role physical, bodily pain, vitality, social functioning, mental health, and emotional status.<sup>31</sup> The original questionnaire consisted of 36 questions (SF36) has been used in young male cancer survivors treated for hypogonadism. This study did not reveal any changes in QoL but the outcome might be the result of selection bias.<sup>32</sup> A shorter version of eight questions, the SF-8 has also been reported to assess the response to individual symptoms and the treatment effect of testosterone.<sup>19</sup>

## Lower Urinary Tract Symptoms

Evaluation of the QoL related to lower urinary tract symptoms (LUTS) in men treated for HG is clinically relevant as there is a theoretical effect of testosterone on prostate growth. A 12% significant increase on prostate volume in hypogonadic men (with no bothering urinary tract symptoms) treated with TRT has been reported.<sup>33</sup> Moreover, LUTS are reported quite common in aging men treated for hypogonadism, likely the result of concurrent BPH.<sup>23</sup> Although the association of hypogonadism and LUTS is weak, men with obstructive symptoms due for surgery and international prostate symptoms score IPSS >19 have been reported with higher testosterone concentrations compared with men with lower score.<sup>34</sup> In contrast, a meta-analysis has reported that alterations in IPSS for an average follow-up of three years were similar between men who received TRT versus those not treated. As a result and compared to the previous dogma, TRT should not be regarded an absolute, but rather a relative, contraindication in men with severe BPH.<sup>23,35</sup> However, a critical view in studies showing no deterioration in IPSS with TRT may reveal that relevant information regarding the anatomical risk factors (eg, prostate volume) were unreported, whereas in others, men with high IPSS were excluded.<sup>35</sup> Therefore, it is advisable that assessment of urinary tract symptoms be included in the follow-up of hypogonadic men treated with testosterone replacement. In that regard, the IPSS represents a well-reported, reliable tool in monitoring and can facilitate as an indirect measure of quality of life.<sup>35</sup> Using IPSS, changes in both voiding and storage type of symptoms can be detected promptly in men on moderate to severe scale, in the very early follow-up of treatment at three months and even if TRT is used as monotherapy without addition of BPH drugs.<sup>36–38</sup> Furthermore and of interest, alterations in urinary symptoms have been reported not to be linked with similar effects of testosterone on general body health such as weight loss and sexual health; thus, IPSS looks sensible to remain during follow-up and not to be substituted by other markers of clinical response.<sup>39</sup>

## Sexual Health

Hypogonadism has been a well-documented cause of loss of libido and reduction of sexual activity affecting the quality of life significantly and independently.<sup>40,41</sup> TRT compared with placebo has been shown to achieve a significant improvement in sexual health in men with no comorbidities treated for over 30 weeks.<sup>42</sup> For the assessment of the response and monitoring of QoL several questionnaires have been proposed. The International Index of Erectile Function (IIEF) is a validated assessment tool for the evaluation of the severity of sexual illness in the concept of hypogonadic men under treatment. It is the more widespread used tool for the assessment of sexual health outcomes.<sup>42</sup> It is a self-reported questionnaire of 15 questions, which in its original form assess erectile function, orgasm, desire, intercourse satisfaction, and overall satisfaction. The lower the score, the higher the severity of the symptoms.<sup>43</sup> A shorter version (IIEF-5) includes a series of five questions which has been used for the assessment of sexual health in men treated with TRT.<sup>20</sup> Replacement therapy has been found to improve all domains of IIEFF over a timespan of several weeks following improvements in quality of life.<sup>44</sup> Derogatis interview for sexual functioning (DISF-SRII) - scored to 100, where 100 indicates better sexual function – is a self-reporting tool which can also be used as an alternative for men in TRT.<sup>45</sup> The psychosexual daily questionnaire (PDQ) is a six-question tool providing a useful aspect of the psychosexuality of men with hypogonadism.<sup>46</sup> The limitation of the tool is the need of daily completion for a standard period of time, which may vary but should reflect the past period. However, the domains of the questionnaire (desire, pleasure, mood etc) can be used for the assessment of the response to TRT with adequate reproducibility.<sup>45</sup> The brief male Sexual function inventory (BMSFI) is a similar questionnaire of 11 questions which include erectile function, ejaculation, personal view of the sexual problem, and overall satisfaction. It has been reported useful for the monitoring of QoL in terms of sexual health in men undergoing TRT.<sup>47</sup> Other validated tools such as the men's sexual health questionnaire score could be potentially

used, but they are infrequently reported in men on TRT. One study has assessed the usage of the tool in men with testosterone deficiency and profound ejaculatory dysfunction.<sup>48</sup>

## Mental Health

Mental health disorders such as depression or mood fluctuations are one of the principal manifestations of hypogonadism.<sup>49</sup> Older and andropause men may see their QoL decline as part of the syndrome.<sup>50</sup> Younger men with congenital HG may experience more severe mental disorders (eg, alienation, shame) due to disrupted puberty, infertility issues, or delay to the final diagnosis.<sup>51</sup> Much of this dysfunction in hypogonadism can be reversed or improved when appropriate with TRT.<sup>52</sup> The domains from the short-form health survey (SF) questionnaires can be used for monitoring mental health in men under treatment.<sup>9</sup> The symptom checklist 90 revised (SCL-90-R) is a sum of 90 questions which is used for the assessment of psychological well-being in patients with mental diseases or coming from traumatic situations.<sup>53</sup> The questionnaire is quite analytic including questions related to feeling of guilt, agoraphobia, anger, etc. It has been used to assess the magnitude of psychological distress in men with Klinefelter syndrome. Fabrazzo et al reported that men with KS at their 40s experience significantly higher presence of obsessions, compulsions phobias and psychoticism compared to healthy controls based on the analysis by SCL-90-R.<sup>16</sup> Domains of the AMS questionnaire (No. 4) can also be used for the assessment of mental health in periodical visits,<sup>54</sup> whereas QoL associated with mental health has been found to remain significantly impaired in those with a high AMS score.<sup>19</sup> When the chief complaint is depression, questionnaires such as the Hamilton depression rating scale (HAM-D) and the Endicott quality of life enjoyment and satisfaction scale (Q-LES-Q) can be used at diagnosis, follow-up and to alert for relapse.<sup>21</sup> The first one assesses the short-term (past three days) anxiety and tension, fears, muscular tension and difficulty in concentration.<sup>55</sup> Q-LES-Q comes in a long a short form; the latter one consists of 16 questions assessing the level of satisfaction of the past week related to general activities, feeling of strength and sociality, sexual drive, and others similar parameters. It has been reported to carry the highest specificity.<sup>56</sup> It also exists in a pediatric form, which might make it attractive in young-onset hypogonadic patients for the assessment of depressive disorders.<sup>57</sup> Finally, AMS and SF questionnaires include questions assessing mental health and well-being.<sup>32,58</sup>

## Discussion

Quality of life and the entity of hypogonadism are strongly related. Regardless of age of presentation and exact cause, hypogonadic men experience significant deterioration in their well-being. Therefore, both the assessment of the QoL at diagnosis and the re-evaluation during treatment should be regarded integral part of the management. Although all aspects of HG may affect QoL by causing disease-related symptoms, in this paper we focused on the four main domains.

The questionnaires are the cornerstone of the assessment of HG and response to TRT in terms of QoL as holding several advantages. They can be conducted quickly, with low-cost, can be easily repeated and can facilitate research. In contrast, it should be noted that they carry the risk of reporting bias, which may occur due to defensiveness, education, feeling of guilt, and may range from the underreporting edge up to the extreme response bias.<sup>59</sup> Also, they lack specificity for HG and therefore, should be utilized after the diagnosis of HG through measurement of testosterone has been established.<sup>8</sup> In that regard, if symptoms persist during follow-up other pathologies must be evaluated.

The optimal tool for the assessment of QoL is unknown as no comparison has been reported amongst questionnaires. The sum of the fundamental tools per domain is illustrated in Table 1. The AMS scale and the short-form health survey questionnaires look a wise choice for monitoring as they assess general, social, and mental health; AMS also assess sexual health, but SF does not. The AMS scale can provide rapidly the magnitude and the extent of the effects of HG and the course of TRT.<sup>60</sup> Further on, specific tools could be selected according to patients' main complaint. In men with profound erectile dysfunction, IIEF score should be used for the assessment of sexual health and repeated during treatment.<sup>20</sup> If mental health is mostly impaired, the likelihood of a severe underlying mental condition should be considered. Questionnaires such as the HAM-D scale should be used to assess the possibility of depressive disorder within or additional to the spectrum of HG.<sup>21</sup> Although the usage of such questionnaires is quite useful to the urologist, a referral to a specialized clinician should be considered prudent if any signs of mental illness. It is of outmost importance that an indisputable linkage of mental illness to HG be avoided and rather, further investigated. Finally, the presence of LUTS in men with HG is not uncommon, especially in older men. As aforesaid, the old dogma that TRT

**Table I** Tools for Monitoring QoL

<b>General Health</b>
Aging male symptoms (AMS) scale
Short-form health survey (SF) questionnaires
Androgen deficiency in the aging male (ADAM) questionnaire
<b>Urinary Symptoms</b>
International prostate symptoms score (IPSS)
<b>Sexual Health</b>
International index of erectile function (IIEF)
Derogatis interview for sexual functioning (DISF-SRII)
Psychosexual daily questionnaire (PDQ)
Brief male sexual function inventory (BMSFI)
Aging male symptoms (AMS) scale
<b>Mental Health</b>
Symptom checklist 90 revised (SCL-90-R)
Hamilton depression rating scale (HAM-D)
Endicott quality of life enjoyment and satisfaction scale (Q-LES-Q)
Aging male symptoms (AMS) scale
Short-form health survey (SF) questionnaires

is contraindicated in men with BPH has been revoked. However, possible selection bias in the reported studies warrants a close follow-up in men with BPH until the safety of TRT is confirmed.<sup>35</sup> In that regard, the IPSS should be regarded a great tool for the risk stratification of men on TRT. Furthermore, clinical assessment through biochemical markers (eg, serum testosterone, lipid markers, hematocrit, etc) should also be considered as indirect prognostic assessors of QoL as disease-related symptoms from untreatable disease may affect well-being significantly.<sup>61</sup> The optimal schedule of re-evaluating QoL endpoints is not defined, but it would be sensible to be re-evaluated every 3–6 months as the routine assessment for men on TRT.<sup>24</sup>

Moreover, a special mention should be made regarding the association between TRT and prostate cancer. That diagnosis of prostatic malignancy is frequent in the male population might be a significant reason for QoL changes.<sup>62</sup> It has been reported TRT may neither have an impact on decision-making nor undermine early diagnosis of prostate cancer as the effect on prostate specific antigen (PSA) readings is minimal.<sup>63</sup> No effect on overall and specific mortality, and eventually in QoL is expected in selected men having received successful surgical treatment for prostate cancer who receive TRT.<sup>64</sup> The findings are consistent with the so-called “saturation model” which supports that in normal and high testosterone levels prostate growth is insensitive; however, other authors advise that the available evidence should be critically reviewed and any decision-making in that concept should not be based on the model alone.<sup>65</sup> Specific guidelines for the management of these patients are still under consideration.<sup>66</sup> Given the limitations of our study, a suggested algorithm is illustrated in Table 2. Finally, the peculiarities regarding administration methods (gel, injections, patches, etc) needs to be appreciated as they may be related to patient experience, but the actual effect is unclear as recommendations may be guided by the clinicians.<sup>67</sup> Cost and convenience may have an impact on choice, but satisfaction has been reported similar among gels, injections, and implantable pellets.<sup>67</sup>



**Table 2** Suggestion for Monitoring QoL in Men on TRT

Suggested Tool	Rationality
Aging male symptoms scale (AMS)	Assess general well-being, sexual health, mental health – should be performed at baseline and follow-up in all men on TRT – domains can be used separately
International prostate symptoms score (IPSS)	Assessment of LUTS – should be performed in men on TRT with at risk of BPE and when clinically relevant
International index of erectile function (IIEF-5)	Assess sexual and erectile function – should be performed in all men on TRT and when clinically relevant
Symptom checklist 90 revised (SCL-90-R)	Specific for mental health, depressive disorders, sociality, phobias, etc – should be performed in men on TRT with profound mental symptoms, if symptoms persist or deteriorate and upon any suspicion of co-existent mental illness – ideal for communication of the referral to the specialists
Hamilton depression rating scale (HAM-D)	
Endicott quality of life enjoyment and satisfaction scale (Q-LES-Q)	

**Abbreviation:** BPE, benign prostate enlargement.

We appreciate some limitations in our study. We performed a narrative review, not a systematic one, and the selection of the discussed score systems and questionnaires was based on the panel's judgment. Our goal was to present the strategy regarding the utilization of these tools and not to perform a comparative, qualitative, or quantitative analysis. Moreover, it must be noted that our research was focused on the clinical concept of LOH and the treatment with testosterone supplementation in the aging male. Our results may, or may not, have reproducibility in infertile men with secondary hypogonadism treated with HCG.<sup>15</sup>

## Conclusions

Monitoring the QoL in men on TRT warrants a deep insight of the clinical spectrum of HG and thus, a cautious selection of surveillance tools. Questionnaires are the cornerstone, but the optimal tool is unknown. A tool assessing several domains of QoL should be selected. However, in order that all aspects of well-being are monitored, a clinician may need to combine the tools and target the chief complaint. Finally, as the clinical spectrum of HG is not specific, questionnaires can be used to unmask coexistent mental illness. In cases of high suspicion, a specialist referral must be considered.

## Disclosure

The authors report no conflicts of interest in this work.

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