

Testosterone deficiency in adults and corresponding treatment patterns across the globe

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Abstract: The global prevalence of testosterone deficiency (TD) ranges from 10–40%. The actual diagnosis of TD is controversial, as a wide range of total testosterone (TT) thresholds are used for diagnosis (200–400 ng/dL), and physicians differ in their emphasis placed on clinical symptoms. There are also significant global differences in the prescription patterns of testosterone replacement therapy (TRT). In the United States, prescription of TRT is significantly higher than the rest of the world, increasing 3-fold over the last 10 years and more so in eugonadal men. The majority of treating physicians emphasizes clinical symptomatology of TD over laboratory values, and up to one-fourth of their patients do not even have serum testosterone levels. There are significant inter-physician differences in willingness to prescribe TRT in the setting of prostate cancer. Data is scarce on testosterone prescribing patterns in Africa, Asia, and the Middle East. More literature is needed to better characterize how physicians from different regions diagnose TD.

Keywords: Testosterone deficiency (TD); testosterone replacement therapy (TRT); global health; hypogonadism (HG)

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Introduction

Driven by an increasingly aging population, the treatment of testosterone deficiency (TD) is experiencing a more frequent focus in sexual medicine. The prevalence of TD varies between 10–40% (1-4), and is known to increase with age, with an abrupt rise in men aged 45–50 years (4). Specifically, TD coincides with the presence of comorbidities, reaching as high as 80% in patients with multiple comorbidities (5-9). Although highly prevalent, the symptoms of TD are often successfully managed with testosterone replacement therapy (TRT), making the accurate diagnosis and appropriate treatment of TD an important topic of clinical interest.

TD is most commonly seen as a component of male hypogonadism (HG), which is a clinical syndrome related to the inadequate production of testosterone (androgen deficiency) and reduced spermatogenesis. Male HG

represents biochemical HG and/or symptomatic androgen deficiency. Biochemical HG is defined as a serum total testosterone (TT) level below a pre-determined threshold value, with several variations existing in the literature, usually between 200 and 400 ng/dL (10-12). Unfortunately, there is no commonly agreed upon and universally used TT-calibration laboratory standard, introducing added variability when defining a TT cut-off (13). The prevalence of biochemical HG increases with age, ranging from 12% among men in their 50s to 49% among those 80 years and older (14). Symptomatic androgen deficiency, on the other hand, is the presence of at least three signs or symptoms consistent with androgen deficiency and confirmed by a serum TT or free testosterone (FT) below the normal cut-off value. Symptomatic androgen deficiency is significantly less prevalent (6% only) than biochemical HG (15). Symptoms of androgen deficiency are often nonspecific

and include diminished libido and erectile dysfunction, weight gain, fatigue, poor concentration and depressed mood (6,10). There are significant differences in practice patterns regarding the diagnosis of HG, with some physicians placing more emphasis on biochemical HG, others on patient-reported symptoms, and most settling on a combination of the two. For example, it has been previously recommended by the International Society for Sexual Medicine (ISSM) that those with TT <200 ng/dL definitely have HG and should be treated; those with TT >400 definitely do not have TD; and those with TT between 200 and 400 should be treated based on their clinical symptoms, if they are symptomatic (12). No universal consensus has been reached, making the diagnosis and treatment of HG a controversial topic.

Fortunately, TRT has been shown to improve the symptoms of HG, as well as overall quality of life (QOL) (16-24), albeit at the cost of a low but potentially significant risk of adverse events (AEs). An increase in serum hematocrit is the most common AE (25), which in extreme cases can lead to serum hyperviscosity, which has been associated with vascular thromboembolic events such as stroke, myocardial infarction, and deep vein thrombosis.

Although it is clear that the clinical burden of TD is significant, and its treatment has the potential to improve QOL, many questions remain surrounding testosterone prescribing patterns around the world. This article discusses the incidence and prevalence of primary TD and male HG and the corresponding patterns of TRT across the globe. The clinical manifestations and laboratory diagnosis of male HG, and the evaluation and management of secondary male HG are not the subject of this review.

Global prevalence of TD and primary HG

Although the measurement of serum testosterone levels is commonly used in the diagnosis of male HG, the cut-off values for low testosterone are not well defined and vary throughout the literature, ranging from 200–400 ng/dL, with 300 ng/dL being the most commonly utilized in clinical practice. Other measurements such as FT may also be used. Although cut-off is an important component in diagnosing HG, guidelines from the United States Endocrine Society define HG as symptoms of HG with TT <300 ng/dL, which differs from the cut-off of 249 ng/dL recommended by the European Association for Urology (10,26).

A summary of the global prevalence of TD and HG can be seen in *Table 1*. The prevalence of TD in middle-aged to elderly men in the United States ranged from 24–39%—a

prevalence much higher than that observed in other parts of the world (4,15,27,28). This prevalence dropped to 6% when Araujo *et al.* evaluated HG by applying the combination of a TT threshold of 200 ng/dL and the presence of three patient-reported symptoms of HG (15), demonstrating that there is a significant difference between biochemical and clinical HG. The prevalence of diagnosed HG in Europe was significantly lower than in the US, ranging from 8–20% (9,29-31), but again appeared to be significantly lower when only diagnosed in patients with both low testosterone as well as symptoms of androgen deficiency (32). Studies in Asia and South America demonstrated a similar trend, with the prevalence of biochemical HG ranging from 17–33%, but dropping to just half of that (10–12%) when requiring the presence of relevant symptoms (3,9,33-35). HG data is lacking in Middle-Eastern populations, but studies from Jordan and Saudi Arabia (S-Arabia) showed a prevalence of 8–24% (29,36). Prevalence data in Africa was scarce, and the literature was clouded by the existence of comorbid diseases such as diabetes mellitus. Overall, although the United States seems to have a higher prevalence of diagnosed HG, prevalence rates are likely similar to other geographic locations.

It is clear that the major problem in estimating the prevalence of HG is the inconsistent data on what physicians emphasize most during diagnosis. Manifestations of male HG are often nonspecific and subclinical, and are influenced by several factors including patient's age and presence of comorbidities. The diagnosis of male HG is further complicated by significant variations in the laboratory tests for TT. This conflicting data leads to significant differences in reported prevalence and prescribing patterns.

Testosterone prescribing patterns

While many similarities exist in testosterone prescribing patterns, there are also important geographic differences in the frequency of laboratory testing and use of clinical symptoms to diagnose and treat TD and HG. This often leads to significant differences in the prevalence of testosterone prescriptions. A closer look at the literature available for each part of the world (*Table 2*) can shed light on these pertinent similarities and differences.

North America

The United States has the reputation of being one of the heaviest prescribers of testosterone (37). In a study of over

Table 1 Worldwide prevalence of testosterone deficiency: summary of key studies

Study	Country	N	Age (range) (years)	TT threshold (ng/dL)	Prevalence	Symptomatic ^a prevalence
North America						
Araujo <i>et al.</i> , 2004	USA	1,691	40–70	<200 or 200–400 + FT <8.91 ng/dL	25%	6%
Araujo <i>et al.</i> , 2007	USA	1,475	30–79	<300	24%	5.6%
Mulligan <i>et al.</i> , 2006	USA	2,162	45–96	<300	38.7%	
Europe						
Gooren <i>et al.</i> , 2012	Germany	1,568	72% of men >45	<282	8%	
	Spain	1,016	86% of men >45	<282	20%	
	UK	746	72% of men >45	<282	9%	
Tajar <i>et al.</i> 2012	Eight European countries ^b	2,966	40–79	<317		2.1%
Schneider <i>et al.</i> , 2009	Germany	2,719	59	<300	19.3%	
Asia						
Wong <i>et al.</i> , 2006	Hong Kong	252	45–64	<200 or 200–400 + FT <8.91 ng/dL		10%
Lin <i>et al.</i> , 2006	Taiwan	650	40–80	<317	19%	
				FT <6.63 ng/dL	33%	
Liu <i>et al.</i> , 2009	Taiwan	734	43–87	<300	24%	
				<300 + FT <5 ng/dL	17%	12%
South America						
Gooren <i>et al.</i> , 2012	Brazil	670	83% men >45	<253	24%	
Clapauch <i>et al.</i> , 2008	Brazil	106	50–84	<400 + AMS score >26	12%	
Nardoza <i>et al.</i> , 2011	Brazil	1,623	24–87	<300	20%	
Middle East						
Gooren <i>et al.</i> , 2012	Saudi Arabia	858	71% of men >45	<253	24%	
Africa						
Ogbera <i>et al.</i> , 2011	Nigeria	203 ^c , 90 ^d	30–86	<346	36% ^c , 47% ^d	
Asare <i>et al.</i> , 2014	Ghana	105, 105 ^c	30–60	<231	6.7%, 35% ^c	

^a, at least 3 signs/symptoms of androgen deficiency: loss of libido, erectile dysfunction, depression, lethargy, inability to concentrate, sleep disturbance, irritability, depressed mood; ^b, men from Italy, Belgium, Sweden, the United Kingdom, Spain, Poland, Hungary, and Estonia; ^c, patients had type 2 diabetes mellitus; ^d, 90/203 patients with type 2 diabetes mellitus who also presented with metabolic syndrome. TT, total testosterone; FT, free testosterone; AMS, aging male's symptoms.

ten million Americans (38), testosterone use in men older than 40 was shown to have increased by more than 3-fold between the years 2001 and 2011. While often prescribed, many patients do not have laboratory-documented TD. According to this study, the most predominant reasons for testosterone prescription were HG (51%), fatigue (35%),

erectile dysfunction (32%), and psychosexual dysfunction (12%). One-fifth of new users received treatment for less than 30 days, and only three-fourths had their testosterone level measured in the prior year. Moreover, it was unclear how many of those men actually had abnormal results, leading the authors to conclude that the reasons for

Table 2 Testosterone prescribing patterns worldwide—summary of key studies

Study	Years	N	Region	Significant findings
Baillargeon <i>et al.</i> , 2013	2001–2011	>11 million	USA	3-fold increase in TRT (0.81% to 2.91%); only 75% had TT measured before T was prescribed
Canup <i>et al.</i> , 2015	2007–2011	Unknown	USA military	2-fold increase in TRT use over study period (27%/year); largest increase (33%) in age range of 35–44
Jasuja <i>et al.</i> , 2015	2009–2012	111,631	USA Military	2-fold increase in TRT use over study period; only 3% of patients met criteria for “ideal” evaluation ^a ; often did not follow guidelines for TRT: did not check TT, PSA, or hematocrit in 17%, 24%, and 15%, respectively
		57	USA	100% of physicians would prescribe T to patients with PC, 94% if previous RP, 94% with history of PC, 92% after external beam therapy, 51% with previously untreated PC, and 50% to patients on active surveillance
Layton <i>et al.</i> , 2014	2000–2011	416,877	USA + Europe	TRT/10,000: 75.7 in USA vs. 4.5 in Europe; TRT despite normal TT level: 4–9% in USA vs. 1% in Europe; TRT initiated for low TT: 43% in USA vs. 10% in Europe
Hall <i>et al.</i> , 2014	1976–2008	11,521	Canada	TRT/1,000: 1.6 in 1976, to 4.6 in 2000; decrease in TRT from 2000 to 2006, unlike USA
Gan <i>et al.</i> , 2013	2001–2010	Unknown	Europe ^b	90% increase in TRT use over study period; five-fold increase in prescription of more expensive transdermal T, increasing cost by 267% to 11.7 million lbs/yr; 137% increase in patient requests for TRT
Bjerkeli <i>et al.</i> , 2016	2006–2014	234	Europe ^c	TRT/1,000: 3.3 in 2006, to 6.0 in 2014; TRT twice as common in highest income quintile when compared to lowest (0.68% vs. 0.25%); 89% of TRT users did not have a dx of HG
Gooren <i>et al.</i> , 2007	2007	353	Global ^d	73% of Europeans associated TRT with more risk than benefit, vs. 61% in other countries; 67% of Europeans put more weight on HG symptoms than lab values for dx, vs. 80% in other countries; 74% of physicians regularly measure TT, and 42% regularly measure FT; 56% of physicians choose short- or medium-term T treatment instead of long-term
Gooren <i>et al.</i> , 2012	2006–2010	353	Global ^e	70% of European physicians put more weight on symptoms than lab values for dx, compared to 80% in other countries; 82% of physicians regularly measure TT, and 36% regularly measure FT; decreasing concern about effect of TRT on prostate cancer over study period; increasing concern about side effects of TRT: 54% in 2006, 78% in 2010; 75% of patients with HG received TRT
Gooren <i>et al.</i> , 2015	2006–2015	731	Global ^f	83% of physicians put more weight on symptoms than laboratory values for diagnosis; 77% of Europeans measure TT vs. 86% in other countries; 41% regularly measure FT; most commonly used cut-offs: Europe (9.8 mmol/L), Latin America (8.8 mmol/L); 85–87% of patients with HG received T
Handelsman, 2012	1992–2010	Unknown	Australia	4.5-fold increase in TRT over 20 years—modest when compared to other parts of the world

^a, “Ideal” evaluation in this study consisted of (I) low morning testosterone levels; (II) measurement of luteinizing hormone and or follicle stimulating hormone and (III) no contraindications to testosterone therapy; ^b, European countries included England, Scotland, and Wales; ^c, European country was Sweden; ^d, global study included Germany, Spain, the United Kingdom, Brazil, Saudi Arabia, and South Korea; ^e, global study included Germany, Spain, the United Kingdom, Brazil, and Saudi Arabia; ^f, global study included Germany, the United Kingdom, Spain, Italy, Switzerland, Sweden, Norway, South Africa, Brazil, Mexico, and Colombia. TT, total testosterone; TRT, testosterone replacement therapy; T, testosterone; HG, hypogonadism; dx, diagnosis; lab, laboratory.

initiating TRT appear to be complex.

A study of prescribing patterns in United States military treatment facilities showed a more than 2-fold increase in testosterone prescriptions between 2007 and 2011 (39). Another study examined testosterone prescription pattern in a military population within the Veterans Affairs system between 2009 and 2012 (40). Interestingly, only 3% of men who received TRT met criteria for an “ideal” evaluation, consisting of (I) low morning testosterone levels, (II) measurement of luteinizing hormone and or follicle stimulating hormone, and (III) no contraindications to TRT. In addition, physicians did not routinely obtain follow-up serum TT, prostate specific antigen, or hematocrit, contrary to TRT guidelines.

A controversial topic in the TRT debate is whether or not patients with HG should receive TRT if they also have a history of prostate cancer. A 2015 electronic survey of North American members of the Sexual Medicine Society of North America (SMSNA) revealed that a current or previous diagnosis of prostate cancer did not hinder physicians from prescribing TRT (41). These findings contrasted with a similarly designed 2015 German study which showed that German urologists were far less likely than their American counterparts to prescribe TRT to patients with a history of prostate cancer (42).

In a study comparing TRT in the United States to that of the United Kingdom (UK) between 2000 and 2011 (37), it was observed that while TRT increased in both countries, the increase was pronouncedly higher in the United States. Notably, the United States prescribers tended to initiate TRT at normal TT levels, or even without checking levels, more often than those in the UK. In addition, American men who were tested had more comorbidities (hypertension, diabetes, and cardiovascular disease) than those tested in the UK. One of the main reasons for TT testing in the United States included fatigue, which was a very infrequent practice in the UK. The authors attributed most of these differences to heavy direct-to-consumer marketing of new testosterone formulations in the United States, leading to more treatment in men with non-specific symptoms, as opposed to targeted testing of symptomatic individuals.

In Canada, studies have similarly shown an increase in TRT, although to a lesser extent than in the United States. A study of the Canadian health care system over 12 years (43) found that the annual TRT prescription rate increased only modestly, from 1.6/1,000 in 1976 to 4.6/1,000 in 2000, with substantial variation over time. Contrary to most global studies on TRT prescribing patterns, there

was an annual decrease between 2000 and 2006, thought to be due to the substitution of androgens with newly available oral treatments for erectile dysfunction, namely phosphodiesterase type 5 inhibitors (PDE5-I), which became available in Canada in 1999. A subsequent increase in TRT was noted in 2008. In another Canadian study, nine men who had used TRT, and 13 providers, were interviewed for a qualitative analysis of therapy (44). The factors that were found to influence testosterone prescription for providers included concerns about diagnostic ambiguity of age-related HG (which tests to use, what is the adequate threshold value for HG, etc.) and the appropriateness of TRT. Patient factors included access to information about testosterone therapy. The study concluded that much work is needed to improve diagnostic accuracy, and that both providers and patients need more information about the risks and benefits of TRT.

Europe

While not as prevalent as in the United States, testosterone use in Europe has been studied extensively. Prescriptions for TRT increased by nearly 90% over a 10-year period (2001 to 2010) in a study in England, Scotland, and Wales (30). The authors noted that while the prevalence of diagnosed primary HG, cancer-survivorship, and opioid use were on the rise and may have contributed to the increase in TRT, it was unlikely that these were the only reasons. A local survey performed by the same group revealed that the absolute number of men with unequivocal HG has remained relatively constant, suggesting that many eugonadal men may be receiving unnecessary treatment (45).

Similar trends have been observed in other European countries (46). The rate of TRT prescription almost doubled, according to a Swedish study, from 2006–2014. This increase was particularly notable among men in the highest income quintile when compared to those in the lowest. The highest rate of TRT was in divorced men and those aged 65–69 years. Interestingly, an overwhelming majority of men who received TRT did not have a diagnosis of HG, which the authors attributed to an increased interest in using testosterone as a means to retain virility in cases of age-related reduction in testosterone production.

Overall, it appears that there was a dramatic rise in the rates of TT testing and TRT in the United States when compared to Canada and other European countries during the same time period.

The differences between countries in Europe and

those in Africa, Asia, and South America have also been examined in several studies. In a global survey of physicians conducted in 2007, researchers inquired about the reasons for and against the use of TRT (47). The fear of inducing prostate cancer was a very powerful motivator against TRT, but more so in Europe than elsewhere. Most physicians associated TRT with a greater risk than benefit, leading to over one-third of patients not receiving treatment. Most physicians were motivated by symptoms, rather than by laboratory results (but less so than physicians in the other countries analyzed in the study). There was not much difference between Europe and the rest of the world in measuring TT, but luteinizing hormone was more regularly measured in Europe (63%) than elsewhere. The inconsistent use of biochemical means for the diagnosis of HG, along with differing emphasis on clinical symptoms, invoked a high amount of variability in prescribing patterns.

A global study conducted by the same group between 2006 to 2010 attempted to identify the most influential factors for initiating TRT (29). Similar to the previous study, European physicians were much more likely than their counterparts to consider the severity of HG-related complaints rather than measured serum TT levels in their decision to provide TRT. Those who placed more emphasis on symptoms of androgen deficiency ranged from 7–96%, highlighting practice variability. Over time, physicians were more likely to provide TRT and less likely to express concerns about prostate cancer in 2010 when compared to 2006, but more likely to be concerned about other side effects. The main reasons for not giving therapy to older patients (>45 years old) were clinicians' concerns about prostate cancer and patients' own concerns about treatment. For younger patients, it was attributed to alternative treatments (sports and diet), which were recommended more often in 2010 than in 2006.

To further evaluate these trends from 2006 to 2015, the same authors interviewed 731 physicians worldwide (48). When compared to their previous studies, more emphasis was placed on clinical symptoms of HG than laboratory values of TT. European physicians were less inclined to measure TT than their Latin American counterparts. Interestingly, ~10% of participating physicians did not know the cut-off level for TT in the diagnosis of HG, and less than half used a certain value of TT for diagnosis, again demonstrating the inconsistency in diagnosing HG. European practices had the least stringent cut-off for the diagnosis of HG, but all thresholds used were lower than the cut-off of 300 ng/dL cited the most in the literature (49).

Once diagnosed with HG, the majority of patients received testosterone prescriptions, but treatment compliance was problematic with 36% of patients deciding not to start or continue treatment.

South America

Although less literature is available on TRT in South America, trends from the region could be garnered from global studies. After interviewing 50 Brazilian physicians, it was noted that Brazil had a higher incidence of diagnosed TD (10%) when compared to Europe (5–8%) (47). Brazilian physicians were more inclined to continue treating patients who had serious concerns about treatment, and were more receptive to evidence demonstrating that TRT is safe in the setting of a diagnosis of prostate cancer.

Another world study on trends of testosterone use between 2006 and 2010 included Brazil (29). Similar to the previous study, TD was highest in Brazil, but even more notably so, reaching 24% during this time period, which starkly contrasted with rates seen in the UK and Germany (8–9%). Brazilian physicians placed more weight on the symptoms of TD, rather than on serum TT values. Improvement in sexuality was the predominant reason to initiate treatment in Brazil, while improvement of libido was the leading cause in Europe and S-Arabia.

Global testosterone prescribing trends between 2007 and 2015 were recently examined (48). Latin American physicians obtained testosterone laboratory values more often than Europeans (86% vs. 77%) and 87% indicated that the severity of HG symptoms carried greater weight than the laboratory values when deciding to treat, in keeping with previous reports (29). Once a diagnosis of HG was obtained, Latin American physicians initiated treatment in 85–87% of patients, which was higher than rates recorded from 2006–2010 (63–74%).

Australia

Testosterone treatment patterns have been studied in Australia since the early 1990's. In a study looking at the expenditure on TRT in Australia between 1991 and 2001, there were two significant upsurges (1993–1994 and 1998–1999), followed by declines, in national prescribing of testosterone (50). The increase in TRT prescription revenue during the 1990s in Australia was modest, which sharply contrasted with a 20-fold increase in revenue from TRT sales in the US during the same time period.

In another study evaluating almost 20 years of prescribing TRT in Australia [1992–2010], a 4.5 increase in total annual expenditures on TRT products were described (51). The researchers postulated that the overall increase in testosterone usage could not be explained solely by an increased diagnosis of HG, and attributed it to robust marketing and advertising for indications such as “andropause” and sexual dysfunction.

Asia, Africa, and the Middle East

The data on testosterone-prescribing patterns in Asia is scarce. Fifty South Korean physicians were surveyed in a 2007 global study (47). When compared to physicians elsewhere, South Korean physicians were the least concerned about prostate cancer when prescribing TRT, with only 2% reporting it was a factor in their decision to avoid treatment. Oral TRT was more frequently used in South Korea (33%) when compared to most other countries (8–9%). Lastly, it was noted that South Korean physicians were the least likely to measure testosterone levels in patients with sexual complaints, with only 26% of physicians doing so (compared to 84% in S-Arabia). More studies are needed to better elucidate testosterone-prescribing patterns in Asia.

A lack of literature on TRT patterns in Africa necessitates the extrapolation from global studies. In an international study of testosterone use between 2006 and 2015, surveys from 262 testosterone prescribers in South Africa were analyzed (48). It was found that the greatest limiting factor in patient compliance in South Africa was the financial burden of long-term treatment, commented by up to 79% of physicians, significantly higher than elsewhere. Problems with reimbursement were also especially prominent in South Africa. Like Asia, more studies are needed to elucidate testosterone-prescribing patterns in Africa.

The literature on TRT in the Middle East is similarly limited. In the 2007 global study, 63 physicians from S-Arabia were surveyed (47) and found most likely to increase testosterone prescription if it could be proven that this medication was not dangerous in patients with prostate cancer. Oral treatment for testosterone was much more commonly used in S-Arabia (46%) when compared to Europe (8–9%). Lastly, 84% of Saudi Arabian physicians measured testosterone levels when patients presented with ED, significantly higher than the 63% proportion observed in the rest of the world. In the second global study [2006–2010] (29), Saudi physicians reported less influence of clinical symptoms as a reason

to start TRT when compared to physicians from other countries (36% *vs.* 70%). Popular reasons to start therapy in S-Arabia include low testosterone levels and hope for improvement in erectile function.

Conclusions

Most of the available data on TRT are derived from North America and Europe, but an estimate of the trends in other continents can be made from global studies. A significant limitation of the published data is the inconsistent methodology used to identify HG, namely differing emphasis placed on biochemical HG *vs.* symptomatic androgen deficiency. While there are significant differences in factors used to prescribe testosterone, most countries appear to follow the same strategy. More investigation is needed to better describe these various patterns, especially in Asia, Africa, and the Middle East.

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Footnote

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