

Diagnosing and treating testosterone deficiency in different parts of the world. Results from global market research

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Abstract

Aim. This study analysed variations between different regions of the world in diagnosing and treating testosterone (T) deficiency.

Methods. Physicians were interviewed in Germany, Spain and the United Kingdom, in Brazil, in Saudi Arabia and South Korea. Items in the survey: 1) reasons/motivation to use or not to use T; 2) what category of patients would not receive T on the basis of these concerns; 3) concerns about prostate pathology in the decision not to provide T treatment; 4) phosphodiesterase type 5 (PDE-5) inhibitors are efficacious, but T treatment makes a comeback.

Results. Between 5% and 10% of consulting patients suffered from T deficiency. The fear to induce prostate cancer appeared very powerful. About 68% of physicians associate the use of T more with risks than benefits, more so in Europe than elsewhere. As a result about 35% of hypogonadal men do not receive treatment. The PDE-5 inhibitors are very prominent in the treatment of erectile dysfunction. Of patients suffering from erectile dysfunction, 18% to 29% have T deficiency which is not always diagnosed and treated.

Conclusion. World-wide physicians require more education on diagnosing T deficiency, on the role of T in erectile dysfunction and the relative safety of testosterone treatment.

Keywords: Testosterone, prostate disease, phosphodiesterase inhibitor 5, geographic difference, treatment decision, physician education

Introduction

This study analysed the potential variations between different countries in different regions of the world in diagnosing and treating testosterone (T) deficiency. It has become clear that T has a far more extensive role to play in biological functions of adult men than hitherto believed. It appears that T not only mediates male reproductive/sexual functions but also has a profound impact on the health of bones and muscles, on metabolic parameters related to the development of diabetes mellitus and cardiovascular disease in the context of metabolic syndrome. T deficiency profoundly impairs male health resulting in increased morbidity and decreased quality of life [1,2]. The decline of T levels with aging has received considerable attention over the last two decades and has raised the interest of several scientific societies dealing with health issues of elderly men [2–4]. Hypogonadism is not uncommon in aging men and especially in those with chronic conditions such as diabetes type 2 and metabolic syndrome. T therapy has been shown to be

efficacious in reversing the symptoms and signs of hypogonadism [2]. Its use in aging men is associated with concerns about safety for prostate cancer. While T continues to be contraindicated in men with prostate cancer and breast cancer, current literature does not provide any evidence of a cause-effect relationship between endogenous T or T treatment and prostate cancer development [5–7]. Scientific data do not find associations between T and future development of prostate cancer, and follow-up studies of men receiving T do not provide evidence that this increases the prevalence of prostate cancer, but members of the medical profession remain wary about prescribing T to elderly men, not least because of potential medico-legal implications if a prostate cancer were to emerge in an elderly patient. The latter is not hypothetical since age is by far the strongest predictor of development of prostate cancer, and age, rather than circulating T, might account for its emergence. It is not unreasonable to assume that physicians in different countries, in different regions of the world take different views on the prescription of

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T to patients, particularly if the patients are elderly. Physicians in different parts of the world may strike the balance of risks and benefits of testosterone treatment differently. Therefore, we undertook research to clarify patterns of prescribing T to men in different countries and in different regions of the world and to identify concerns which physicians have regarding the treatment with T products.

Methods

Items in the survey were:

- 1) reasons/motivation to use or not to use T;
- 2) diagnostic approach in men suspected to be hypogonadal;
- 3) identification of barriers/concerns in prescribing T which might lead to the decision not to prescribe T even if medically prescription would be warranted;
- 4) determine what category of patients would not receive T on the basis of these barriers/concerns;
- 5) establish the percentage of the patient population who do not receive T on these grounds;
- 6) identification of barriers and concerns patients have when the physician recommends T treatment;
- 7) With the advent of highly efficacious phosphodiesterase inhibitors type 5 (sildenafil, Viagra[®], vardenafil, Levitra[®] and tadalafil, Cialis[®], for treatment of erectile dysfunction, T treatment has declined in this associated field but has begun to make a comeback recently [8]. Several questions addressed knowledge and actual usage of T preparations for treatment of erectile dysfunction, as sole treatment or in combination with phosphodiesterase inhibitors type 5.

Physicians in the following countries were interviewed: In Europe, Germany (n = 80), Spain (n = 50) and the United Kingdom (n = 60). These are three countries with large populations in western Europe. In South America, Brazil (n = 50) and in Asia, South Korea (n = 50) were selected because they have large populations and there is a readiness among physicians to prescribe testosterone to hypogonadal patients. The latter is true for Saudi Arabia (n = 63), though this country has a much smaller population than any other country in this research. The selection criteria for approaching physicians for participation in the study were the nature of their clinical practice (sufficient patients to allow a meaningful assessment of the research questions, sufficient numbers of patients with erectile dysfunction and/or prostate pathology to make a balanced decision to treat or not to treat, and being an initiator of T therapy in hypogonadal patients). The following screening criteria were used in order to identify the targeted physicians: they had to see at least 300 patients in an average month (500 in South Korea). Of the physicians' total patient

population per average month, there had to be at least 40 with sign and symptoms of benign prostate hyperplasia for urologists or 15 such patients for general practitioners/endocrinologists respectively. Further, at least 20 patients with erectile dysfunction for urologists and 10 for general practitioners/endocrinologists respectively. Furthermore, only physicians who initialize testosterone therapy in hypogonadal men were interviewed.

Physicians were approached whether they consented to a structured interview using a quantitative questionnaire over the telephone for a duration of 30–40 minutes. In each of the countries a total of 432 to 2878 physicians were contacted, and between 7% to 50% were interested in participation. Eventually, in each country 50–80 physicians were eligible on the basis of the above selection criteria and could be interviewed. A total of 229 urologists, 84 endocrinologists and 40 primary care physicians were interviewed amounting to a total of 353 physicians. Per country there are different rates of interest in the study which could be due to higher frequency of market research activities in specific countries. In order to achieve a representative sample in market research, the ratio between the sample size and the total population is not as relevant as creating a sample that properly reflects the characteristics of the total population. The latter was achieved with the number of 2878 physicians approached.

Of the physicians approached, between 7% and 50% were interested in participation, on average 15%. The latter figure is low but it is a normal result for this type of research. Eventually, in each country 50 to 80 physicians were eligible on the basis of the above selection criteria and could be interviewed. A total of 229 urologists, 84 endocrinologists and 40 primary care physicians were interviewed amounting to a total of 353 physicians. The number of primary care physicians was low in this sample. Actually, only primary care physicians from Germany were interviewed since in the other countries primary care physicians rarely initiate testosterone administration, this rather being the domain of the specialist.

Results

Items surveyed and outcomes

Of the patients seen by the selected physicians, an average of 8% suffered from testosterone deficiency. There were differences between countries: an average of 7% of the patients the physicians seen in Europe, and 9% elsewhere. Notably, Brazil and Saudi-Arabia with 10% scored highest and Spain lowest with 5%, as compared with Germany and the UK with 8% each. Most men diagnosed with testosterone deficiency were >45 years of age (72% in Europe and 69% elsewhere). Of the men diagnosed with testosterone deficiency about 2/3 actually receive testosterone treatment. If this figure is broken down to age

categories, 69% of men <45 years and 64% of men >45 years receive treatment, with somewhat higher figures for Europe than the rest of the world. The reasons stated why patients <45 years do not receive testosterone treatment are patients' concerns (21%), budget reasons (12%), alternative treatment options (8%), and severity of complaints not considered serious enough (7%). The reasons stated why patients >45 years do not receive testosterone treatment are presumed risk of prostate cancer (18%), patients' concerns (15%), enlarged prostate (13%) and budget reasons (9%).

The following questions were posed to physicians:

What laboratory assessment do you employ to verify the diagnosis of testosterone deficiency, regularly, sometimes, never? As expected, total testosterone figured prominently: 74% regularly and 23% sometimes. Measurement of free testosterone was reported to be performed regularly by 42% and sometimes by 35%. Measurement of the main carrier protein of testosterone: sex hormone binding globulin (SHBG) was regularly done by 28% of the respondents and sometimes by 40%. Free testosterone can be calculated by introducing the value of total testosterone and SHBG into a mathematical model and this was regularly done by 26% and sometimes by 35% of the respondents. The Free Androgen Index (FAI) which is calculated by dividing plasma total testosterone by plasma SHBG (a not very accurate index of free testosterone levels) was used by 24% regularly and sometimes by 31% of the respondents. There was not much difference between Europe and the rest of the world in measuring total testosterone, but luteinizing hormone (LH) was (regularly) measured more often in Europe (63%) than elsewhere (45%). Free testosterone was (regularly) measured slightly more in Europe (44%) than elsewhere (39%). SHBG was (regularly) measured more often in Europe (36%) than elsewhere (19%) corresponding with a higher frequency of calculated free testosterone in Europe

(30%) than elsewhere (23%). Also the FAI was calculated (regularly) more often in Europe (30%) than elsewhere (18%).

What do you consider the main symptoms of testosterone deficiency? (Responses were unprompted.) The results are presented in Figure 1. It appears that sexual symptoms are predominant, lack of libido more so (71%) than erectile dysfunction (51%). Fatigue was mentioned by 39% of the respondents. Other symptoms mentioned were loss of power (17%), depression (14%), loss of muscle mass (9%), and loss of hair/reduced body hair (9%). Sexual symptoms scored lower in Europe than in the rest of the world, and this was also the case with loss of power and depression, while fatigue scored higher in Europe.

When asked about the decision to prescribe testosterone, an average of 73% of physicians were prompted rather by symptoms of testosterone deficiency (73%) than by laboratory values of testosterone (27%). This was the case in Europe in 67% of the physicians and in 80% of the physicians elsewhere. It appears that men are capable of sensing signs and symptoms of testosterone deficiency when their own individual plasma levels of testosterone fall below eugonadal levels [9,10]. These publications demonstrate that in individual men there is not a single level of testosterone concentration at which the spectrum of complaints of testosterone deficiency manifest themselves, but for each symptom a different threshold level of testosterone exists. These thresholds vary from man to man. These observations call for a diagnosis of testosterone deficiency that combines clinical symptoms of testosterone deficiency with laboratory diagnosis.

What are your considerations to initiate or not to initiate testosterone treatment even though clinical and laboratory diagnosis warrant testosterone treatment? (Responses were unprompted.) Stating reasons for and against testosterone therapy, physicians could think of as

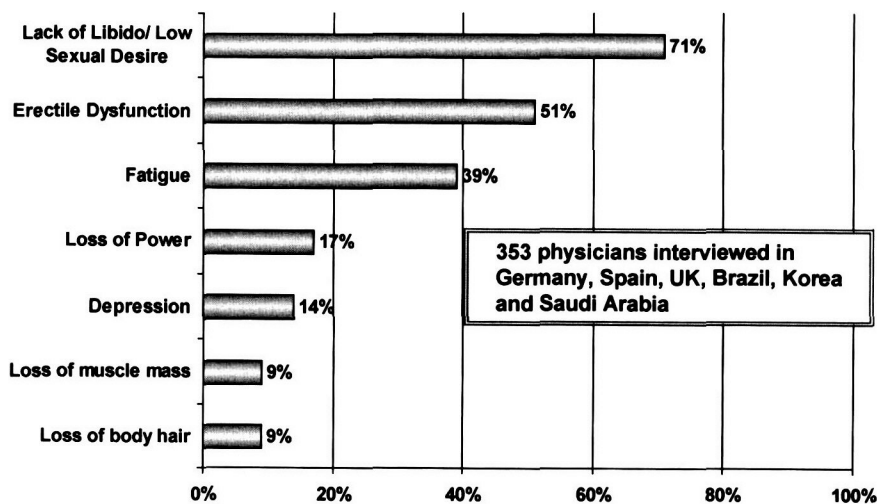


Figure 1. Physicians' perception of main symptoms; testosterone deficiency survey.

many reasons for as against testosterone therapy (1.4 per physician) (Figure 2). Reasons for testosterone therapy are mostly symptom-related, e.g. it improves patient's quality of life (18%), improves patient's symptoms (9%). The main reasons against testosterone therapy are predominantly prostate-related such as indication/risk of prostate cancer (60%).

Physicians were asked whether they associate any risks or side-effects with T therapy in general. The results are presented in Figure 3.

It appears that in the decision to treat or not to treat perceived risks of testosterone are balanced against its potential benefits. Remarkably, 68% of physicians associate testosterone administration first and foremost with risks. This sentiment is even

stronger in Europe (73% of physicians) than elsewhere (61%) (Figure 4). Not unexpectedly, when physicians were asked directly, the risk of (inducing) prostate cancer features prominently (63% of physicians), significantly less were concerned about benign prostate hyperplasia (BPH), levels of prostate specific antigen (PSA), polycythemia, liver toxicity and skin problems with topical testosterone preparations.

Some physicians decided not to treat testosterone deficient patients who have serious concerns about testosterone treatment (14%).

There were remarkable country-to-country differences (Figure 5). This was a factor with 24% of German physicians and of 4% in Brazil and 2% in

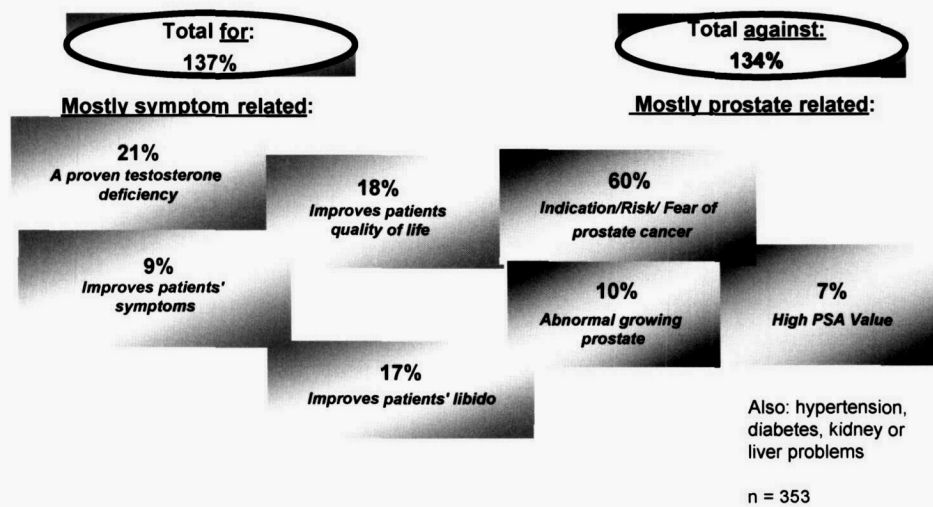
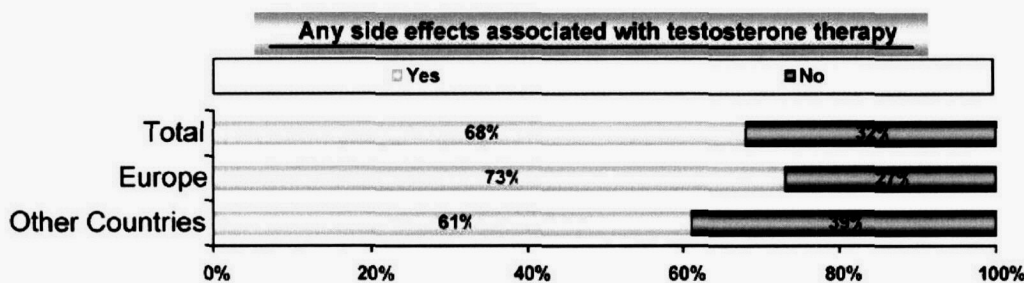


Figure 2. Reasons for and against testosterone therapy - unprompted.



In South Korea, only 32% of the physicians associate side effects with a testosterone therapy, in Spain only 58%.
→ no significant differences between answers by doctor specialties

Particular side effects (Basis: All physicians who answered with 'yes' in Q 18)		
Prostate related side effects		Other side effects
Prostate cancer	(51%)	Hepatic problems (9%)
Abnormal growing prostate	(10%)	Liver toxicity (10%)
PSA Value Problems	(7%)	Skin reactions to application form (6%)

Figure 3. Side effects associated with testosterone therapy - unprompted.

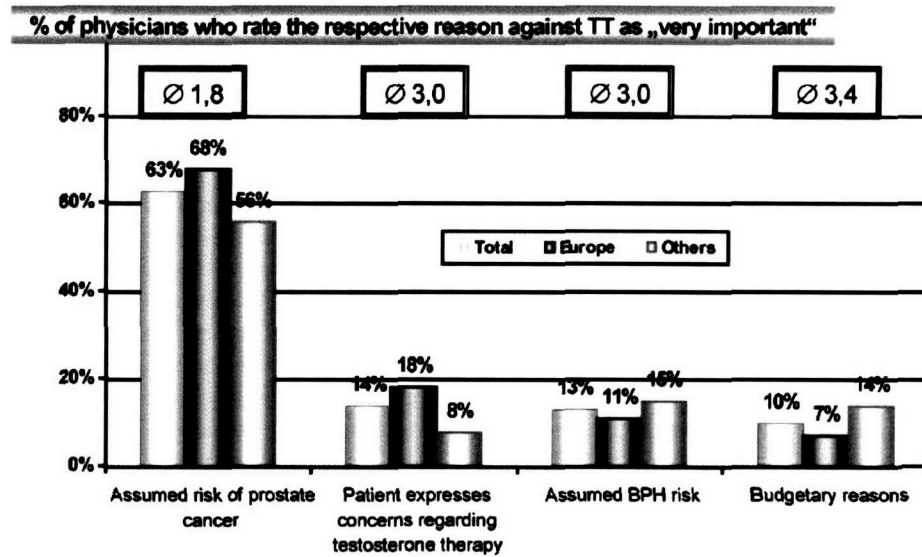


Figure 4. Importance of reasons against testosterone therapy – prompted – Europe versus others.

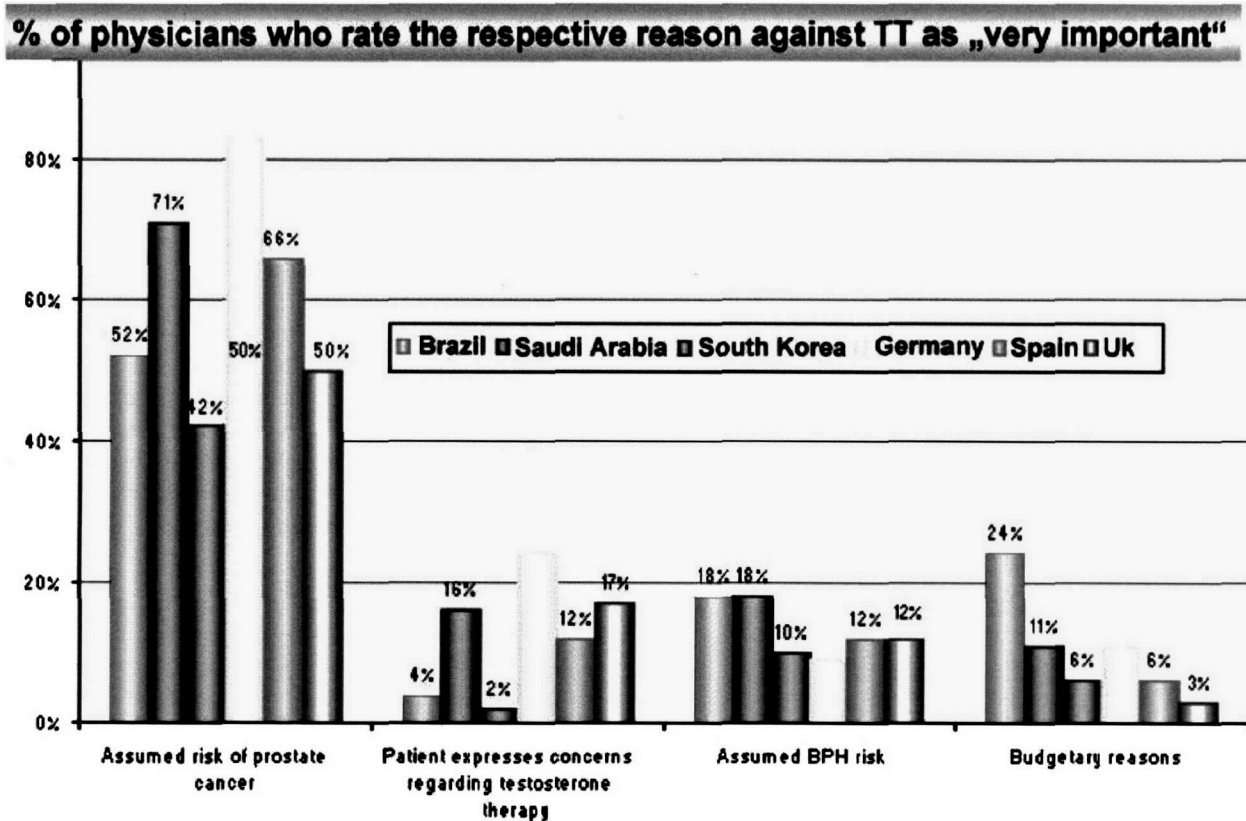


Figure 5. Importance of risks of testosterone therapy – prompted – by country.

South Korea. Further, there were budgetary reasons not to treat (10%). This wary attitude of physicians regarding risks of prostate disease resulted in non-treatment with testosterone for patients eligible for treatment: in Europe 14% for fear of prostate cancer and 7% for other prostate diseases and elsewhere 10% for fear of prostate cancer and 8% for other

prostate diseases. Also, patients themselves were opinionated about the risks of testosterone treatment; risk of cancer (41%), fear of hormones in general (15%), opinion of the spouse (5%), and financial aspects (10%). Physicians were asked whether their readiness to prescribe testosterone to elderly men would increase if authoritative scientific studies



would dismiss the fear that testosterone treatment would increase the risk of prostate cancer and BPH. The response was overwhelmingly: yes, 67% of physicians (in European countries (62%), and even more so elsewhere (74%). Twenty-one per cent of the physicians stated their prescriptions for testosterone would increase considerably if this could be proven. This sentiment was more pronounced in Brazil, South Korea and Saudi-Arabia (32%) than in the European countries (12%). Not unexpectedly, prostate cancer carried greater weight in the responses than BPH.

So, while concerns about potential side-effects of T administration were pervasive, physicians thought that T administration would have a beneficial effect on a patient's quality of life (18%), improvement of libido (17%) and that proven T deficiency would constitute a good reason to start T treatment.

Which of the available testosterone preparations do you prescribe? Naturally, the response will be influenced by the commercial availability in the countries researched. The results are presented in Figure 6.

In Europe the traditional (three-weekly) and the new long-acting parenteral testosterone undecanoate and the testosterone gels are dominant. In the other countries oral testosterone (not further specified but probably referring to oral testosterone undecanoate) and the traditional (three-weekly) parenteral testosterone esters are most prominent. Overall, 36% of patients are treated with the three-weekly parenteral testosterone esters. It is chosen because it is cheaper (25%), and effective (18%), the only formulation available (10%) and easy to apply (9%). This was the dominant mode of treatment in Brazil (73%) and very prominent in Saudi-Arabia (50%), still widely used in Germany (31%), the UK (27%), and South Korea (25%) but little in Spain (11%). Oral treatment figured around 8–9% in most countries, but was considerably higher in Saudi-Arabia (46%)

and South Korea (33%). Motivations for oral treatment were its convenience of administration, and the patient's choice. The testosterone gel is mainly used in Europe (Germany: 28%, Spain 40%, and the UK 26%, but also South Korea had a large number of users (37%). Its convenience was a reason to use it for doctor and patients. The use of the long-acting parenteral testosterone injection was high in Europe (Germany 30%; Spain 34%, and less in the UK, 12%). Its use elsewhere was low as it had not yet been launched in Brazil and Saudi Arabia at time of interviews. Its merits were not always known, which are the stable physiological plasma T levels and the duration of the injection interval of 12 weeks which means significant convenience.

In conclusion, there are important regional differences in the use of testosterone preparations. Europe is the continent where several testosterone manufacturers are based and, consequently, patients may have earlier access to innovative treatment. At the same time, patients in Europe usually benefit from health insurance schemes which cover (approved) prescription drugs, so financial considerations are significantly less decisive in the choice of a testosterone preparation in Europe than elsewhere.

What duration of testosterone administration was used? Overall, testosterone was prescribed as short-term or medium-term treatment in 49% of the cases and 51% as long-term or lifelong treatment. The nature of the short- to medium-term treatment was a period of 6–12 weeks, often initiated to observe whether patients would respond favorably, but was also prompted by the diagnosis. For this purpose the short-term injection or the testosterone gel were used. Usually, there was a laboratory analysis after the first cycle of testosterone administration. The short- to medium-term treatment was practised less often in Europe (43%) than elsewhere (56%) in relation to long-term/lifelong treatment.

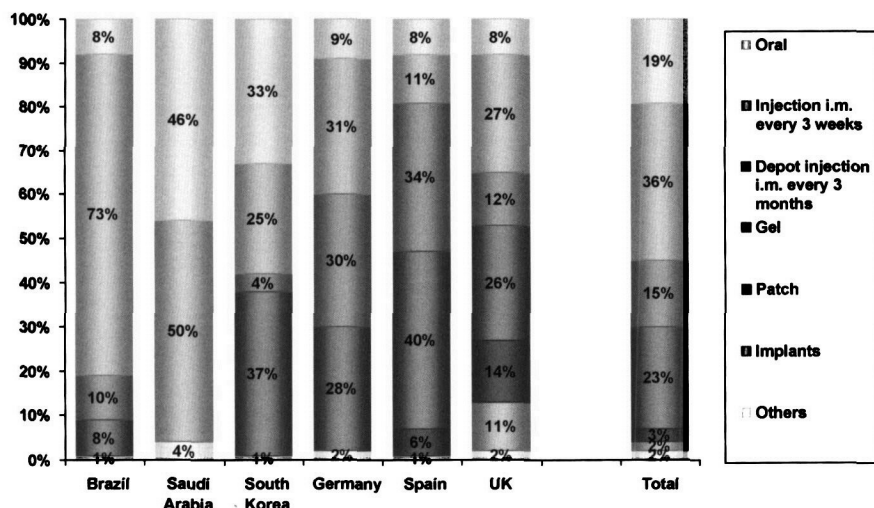


Figure 6. Distribution of testosterone therapy options by country.



Do you routinely measure testosterone levels in patients with sexual complaints, namely erectile dysfunction? About 63% of physicians reported that they measured regularly plasma testosterone levels in patients complaining of erectile dysfunction (ranging from 26% in South Korea up to 84% in Saudi Arabia). Of the patients whose testosterone levels were actually measured, 18–29% turned out to be, indeed, testosterone deficient. This figure was very similar in Europe and in non-European countries. Reasons not to measure testosterone were financial (15%), unnecessary (9%), not related to erectile dysfunction (6%), no specific reasons (15%). When a low value of plasma testosterone had been encountered, testosterone was often part of the treatment of erectile dysfunction. Overall, in 31% as monotherapy in patients with erectile dysfunction (13% of all patients), and in 29% combined with a phosphodiesterase inhibitor type 5 (PDE-5 inhibitor) (12% of all patients). The latter remains the predominant mode of treatment, also when testosterone deficiency has been diagnosed, more so in Europe (40%) than elsewhere (31%). There were variations per country: testosterone monotherapy was used only in 15% of patients with low testosterone in South Korea and between 26%–44% in other countries. Asked about the response rate to treatment modalities, monotherapy with a PDE-5 inhibitor had the highest success rate (56%), and the testosterone monotherapy the lowest (45%). European doctors (61%) favoured PDE-5 inhibitor monotherapy more often than doctors elsewhere (50%).

Discussion

This study analysed the attitudes of physicians, and to a lesser degree of patients, towards diagnosing and treating testosterone deficiency, particularly in the light of benefits and risks. It examined the potential variations which might exist between different countries in different regions of the world.

There are identifiable differences between countries, and even more so between regions of the world, but overall views on testosterone are largely shared. The following issues emerge from this survey.

Fear of prostate complications

What became overwhelmingly clear is the fear that testosterone treatment of elderly men is associated with an increased risk of prostate cancer. This sentiment appeared stronger in Europe than elsewhere. In line with this, the readiness to prescribe testosterone more often, if it could be proven that this was safe, was greater in Europe than elsewhere. With the latest insight into the relationship between testosterone and prostate cancer [5–7], or prostate disease in general [4], and the guidelines now in existence for prescribing testosterone to elderly men [4,11], these trepidations are no longer appropriate.

Admittedly, the authoritative study to prove or disprove the relationship between testosterone treatment and the development of prostate cancer has not been carried out [4] but epidemiological studies fail to produce a relationship between testosterone levels and the development of prostate cancer [5,7]. Several professional bodies have provided guidelines for responsible testosterone treatment of elderly men [4,11]. So authorities in the field agree that properly diagnosed testosterone deficiency of elderly men need no longer be a barrier for testosterone treatment [2,4,11]. The conclusion must be that in Europe and elsewhere physicians are not abreast with the latest insights into the relationship of testosterone and prostate cancer.

Diagnosing testosterone deficiency

Physicians experience some problems with diagnosing testosterone deficiency. The survey shows that economical considerations may play a role in carrying out laboratory tests. In general, the determination of LH is helpful in the differentiation between primary and secondary hypogonadism, but the survey shows that the majority of men suspected of testosterone deficiency are elderly men with so-called late-onset hypogonadism [2]. In this category measurement of LH is not very helpful. In this category, measurement (or usually calculation) of bio-available or free testosterone is more expedient, requiring the measurement of total testosterone and SHBG. Many physicians made claims of actually measuring free testosterone levels, which are not very plausible. Others indicated that they calculated free testosterone with available tools to calculate free testosterone from total testosterone and sex hormone binding globulin, but this is probably an overstatement. More information on how to accurately diagnose testosterone deficiency to physicians seems necessary.

Short- to medium-term testosterone treatment

The practice of prescribing testosterone for a short to medium term was common among physicians (40–50%) in this survey. This finds, indeed, more and more support in professional circles [12]. The diagnosis of testosterone deficiency (based on clinical symptoms and laboratory testing) is often ambiguous. This state of affairs has been explained by a number of recent literature reports finding within one individual different thresholds of plasma testosterone for different testosterone-dependent biological functions, and also that these thresholds vary between individual men [9,10,13]. So it seems justified if the clinical symptomatology of testosterone deficiency is convincing and the laboratory diagnosis is ambiguous, to give treatment with testosterone as a trial for 3 to 6 months to see whether the supposed symptoms of testosterone clear up [12].

Testosterone treatment of erectile dysfunction

With the advent of the PDE-5 inhibitors, testosterone treatment of erectile dysfunction had largely fallen into disregard, but testosterone treatment is making a comeback [8]. Studies show that the anatomical and physiochemical mechanisms underlying erectile function require largely normal testosterone values [8,14]. Further, not a small proportion, up to 50%, of patients treated with monotherapy with PDE-5 inhibitors fail to respond, and many of them respond favourably to a combination of PDE-5 inhibitors and testosterone [15,16], or even to testosterone monotherapy [14]. Most guidelines for diagnosing erectile dysfunction now recommend measurement of testosterone in the primary diagnostic process [17,18]. The findings of this survey warrant the updating of physicians on the newly established role of testosterone in diagnosing and treating erectile dysfunction.

The role of testosterone in other than sexual functions

While testosterone undoubtedly plays a key role in sexual functioning, the last two decades have convincingly shown that its biological role is much wider. It has potent effects on muscle and bone; on bone the effects may be androgenic in nature or come about via its aromatization product estradiol [2]. Testosterone deficiency is associated with the emergence of the so-called metabolic syndrome and its sequelae diabetes mellitus type 2 and cardiovascular disease [19–21]. This new information will carry weight in the future in the decision to actually treat elderly men with testosterone deficiency. It is of note that metabolic syndrome and its associated diseases diabetes and cardiovascular disease also are factors in the development of erectile failure [22,23]. So in the not too distant future adequate testosterone levels will be a consideration in the assessment of health of elderly men.

Conclusion

This study found regional differences in diagnosing and treating testosterone deficiency. But, strikingly, the issues in different countries in different parts of the world show a large degree of overlap. Similarities are larger than differences. A substantial proportion of men (1/3) who are diagnosed with testosterone deficiency are not treated because of fears that their physicians or the patients themselves have about potentially carcinogenic effects of testosterone on the prostate. With the presently available information this attitude is no longer warranted. How dominant this fear is became clear when the readiness to prescribe testosterone was probed into assuming it could be established that testosterone administration to elderly men carried no prostate risks. Physicians would indeed treat many more patients with testosterone.

Also, physicians need to be updated on the role of testosterone in erectile dysfunction as well as on properly diagnosing testosterone deficiency. Further, they must acquire new insights in the ramifications of testosterone deficiency on general health in elderly men.

Disclosures

Farid Saad, Annika Frank, Sebastian Schwerdt are employees of Bayer Schering Pharma AG.

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