Appendix 1 (as supplied by the authors): Full-text guidelines

Multidisciplinary Canadian Clinical Practice Guideline on the Diagnosis and Management of Testosterone Deficiency Syndrome in Adult Males

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INTRODUCTION

Testosterone (T) is a powerful steroid hormone which affects almost all aspects of male physiology—extending even to social, emotional and economic behaviour. Testosterone deficiency (TD) can therefore have serious debilitating effects on the lives of the affected man and his family, friends and colleagues. But the rapid increase in prescriptions over the past decades is being debated globally across many disciplines and is attracting the attention of the general public, journalists, lawyers, advocacy groups, medical licensing and regulatory bodies. Intense debate carries on over cardiovascular (CV) risks and prostate health, while an ever increasing number of men take this powerful androgenic and anabolic drug, often in response to advertising targeting male consumers.

Unfortunately, upwards of 40% of men are receiving or obtaining T without a documented biological deficiency and may be taking unnecessary risks.[1] This is a dangerous situation that can be remedied by evidence-based practice, education and skilled guidance. This important guideline document describes the standards that will help practicing physicians, other health professionals and the general public to understand the physical, emotional and behavioural consequences of TD and all the positive and undesirable effects of available therapies. The Canadian Men's Health Foundation (CMHF) will ensure that this is a "living" document, one that will not become stale, but rather one that is regularly updated as we continue to learn more about this important hormone.

This guideline represents a truly multidisciplinary range of specialists (clinical biochemists, endocrinologists, family physicians and urologists) to ensure that the guideline was representative and would reach a wide audience of health professionals.

The wider scope and target audience of clinicians includes Canadian primary care physicians, general internists and internal medicine sub-specialties (endocrinologists and geriatricians) and urologists. A further group of interest involves clinical biochemists, psychiatrists, nurse practitioners and pharmacists dealing with men at and beyond middle age with manifestations of testosterone deficiency syndrome (TDS).

DEFINITION

TDS, also known as late-onset hypogonadism (LOH), is a clinical and biochemical syndrome occurring in aging men in association with advancing age.[2] TDS is characterized by deficient testicular production of T. It may affect multiple organ systems and can result in substantial health consequences (Table 1).[2-4]

TD results from dysfunction along the hypothalamic-pituitary-gonadal axis (HPGA).[2] Primary TD results from dysfunction predominantly at the testicular level; secondary TD is due to abnormalities mainly at the hypothalamic or pituitary level.[2,5] In older men, hypogonadism often is secondary or mixed, as shown in Table 2.[5] All components of the HPGA are affected by the aging process, albeit to varying extents.[6] TD may also be attributable to co-morbidities, environmental factors or certain medications.[2]

Incidence and prevalence

Due to inconsistencies in published definitions, ages of study subjects and their associated co-morbidities, and heterogeneity in laboratory methods, the incidence and prevalence of TD are difficult to determine.[2,7,8] There is a single Canadian cross-sectional study in a limited, restricted population (316 physicians) that estimated the incidence at 25% based only on a questionnaire and a single bioavailable-T determination.[9]

There are several large, longitudinal and cross-sectional studies done elsewhere that variably estimate the prevalence from as low as 2.1% overall in a 40- to 79-year old population from the European Male Aging Study (EMAS),[7] to a high prevalence of 50% in men over 80 years of age in the Baltimore Area Longitudinal Study on Aging (BALSA).[10] The Massachusetts Male Aging Study (MMAS) reported a crude incidence rate of 12.3 per 1000 person-years and an overall prevalence of symptomatic hypogonadism of 5.6%.[11,12] However, the prevalence was low in men under 70 years of age (3.1% to 7%) but increased to 18.4% for those over 70.[12] A similar large American investigation in men aged 45 years and older found a higher overall crude prevalence of hypogonadism of 38.7%, and this increased to 50% in men over 85 years.[8]

Significant cross-sectional studies carried out in other countries have likewise shown substantial differences in incidence and prevalence. A Japanese investigation showed that, depending on the cut-off values of free T, 27% to 43% of Japanese men aged 40 to 79 years "are candidates for androgen replacement therapy" (although there was no evidence that symptoms were considered).[13] An evaluation of 734 Taiwanese men aged 43 to 87 years reported a biochemical T deficiency of 16.6% (based on both total and free T values) but only 12% demonstrated symptomatic androgen deficiency.[14] A Brazilian report on 1623 healthy military men reported a prevalence of 19.8% using only a single total testosterone (TT) assay.[15] Similar to other investigations, TT levels decreased with increasing age. A smaller Brazilian study of men aged 50 to 84 years used calculated free T (cFT) and diagnosed LOH in 25% of men with osteoporosis and in 12.2% of men in a matched control group.[16]

Taken together, the incidence reported in the small group of Canadian men[9] falls within a realistic range. However, not only can the conclusions of this lone Canadian study be questioned, but likewise those of all other studies due to a variety of methodological issues they share, including: 1. The heterogeneity of the demographics and the clinical assessment; 2. The uncertainty about the most reliable laboratory test for T assessment; 3. Assay variability and lack of validated reference ranges for T assays.[17]

NEEDS ASSESSMENT

A needs assessment of practicing clinicians is an essential element in developing a clinical practice guideline to address improvement in practice performance.[18] The initial step in the development of this guideline was to establish the existence of potential disparities between what was expected to be the status of expertise among Canadian physicians, their

actual familiarity and comfort with the management of TD, and the state of the art. In 2013 an intensive needs assessment was carried out among physicians across Canada regarding TD.[19] A total of 2,200 surveys were sent out in five waves to the target audience who were primarily family physicians. There were 152 responders which was considered a significant sample size for extrapolation to the larger population, with a confidence interval of 95% and an error rate of 10% per 11,000 family physicians (Table 3). There was wide national representation but the majority of responders were from Ontario, British Columbia and Alberta, respectively.

Table 4 shows that 26% of physicians are not comfortable in dealing with the diagnosis of TD. This potentially represents over 5,000 physicians across Canada who are uneasy with the diagnosis and management of TD. It is of considerable interest that 61% of responders (including a portion of those who considered themselves comfortable with the diagnosis of TD) agreed to be a part of a follow up study following the release of the guideline (Table 5). These data from the needs assessment would allow for follow-up related to an objective assessment of the impact of the guideline on the target audience once the document is published.

Another feature of the survey was the inclusion of multiple choice questions aimed at determining the depth of knowledge of the respondents. The multiple choice questions covered topics such as the prevalence of the condition and its clinical manifestations, the causes of male hypogonadism, the selection of diagnostic biochemical tests as well as its differential diagnosis and treatment. The answers were disparate and revealed that there is a great deal of confusion and gaps among practitioners regarding the management of men with suspected TD.

Since the needs assessment survey was conducted, two publications have corroborated the need for an increased effort in educating physicians on the basics of the management of hypogonadism in men. Researchers at the Institute for Clinical and Evaluative Sciences and Toronto's St. Michael's Hospital found that one in every 90 men over age 65 is being treated with testosterone replacement therapy (TRT) but only six per cent have a conclusive diagnosis of hypogonadism.[20] These findings are further validated by a large, long-term study conducted in both the United Kingdom and the United States showing that up to 40% of men obtain T therapy without laboratory documentation TD.[1] These are consistent, reliable and, indeed alarming statistics.

To further compound the problems confronting physicians dealing with men's health there has been intense and unsettled controversy about T use and CV health. In January 2014, the FDA announced its intention to investigate the risk of stroke, heart attack and death in men taking FDA-approved T products.[21] In June 2014, the agency stated that they will require manufacturers to include a general warning about the risk of thrombo-embolism on the labeling of all approved T products.[22]

In July 2014, Health Canada publicized the initiation of a safety review to evaluate the currently available information regarding the possible CV risk associated with the use of T products.[23]

In summary, confusion about diagnosis of TD, inappropriate use of TRT, and recent reports of potentially increased risk of serious side-effects with the use of TRT demonstrate a significant need for guidance of health professionals in this area.

METHODOLOGY

The Canadian Men's Health Foundation (CMHF) sponsored the creation of a multidisciplinary group, the Canadian Men's Health Foundation Multidisciplinary Guidelines Task Force on Testosterone Deficiency, (the Task Force) to develop a clinical practice guideline for the management of TDS in adult males, based on the results of a needs analysis survey sent to Canadian physicians. The chair and co-chair were selected and assembled a panel of experts that met to identify and draft recommendations to address important clinical questions.

The Task Force authors' group met to identify guideline sections and writing responsibilities, in accordance with their clinical or laboratory knowledge, practice and expertise. There were two authors with primary responsibility for writing each section. The authors of each section proposed clinical questions phrased according to the PICO (Patient, Intervention, Comparator and Outcome) format and following the GRADE approach for evaluation of the evidence and development of the recommendations.[24,26] The Task Force worked independently of the CMHF.

A librarian with recognized expertise, affiliated with the DeGroote Institute, McMaster University, Hamilton, Ontario, conducted a systematic search of MEDLINE, EMBASE, CENTRAL and PubMed for clinical trials, observational studies, using key words related to the topic with the aid of a Task Force endocrinologist (PM). The search was conducted in December 2013 and updated in April 2014. Reports from meta-analyses, practice guidelines, clinical conferences and major reviews were also examined, and publications were hand-searched for additional references. Individual authors sent alerts for pertinent papers that might have been published subsequent to these dates and during the writing of the guideline. The systematic review of the available evidence was complemented by an independent pharmacist proficient in literature searches. The search start date was January 2009 as the most recent comprehensive guidelines were published by the Endocrine Society in 2010.[25] From the literature search, 430 articles were used in this review, as shown in Figure 1. Most of the relevant articles were published before 2009, and 60 of the articles used were from the December 2013 and April 2014 literature search. Section authors were sent alerts by the librarian after April 2014 only if high quality data relevant to their sections were published subsequent to the completion of the systematic review. The literature search was updated and reviewed to April 2015 while the document was under editorial assessment by the Journal and in response to reviewers' comments.

Sections of the guideline, the recommendations, and the evidence for the recommendations which were guided by the Task Force authors formulating their own key clinical questions, were presented by the Task Force group at two separate all day authors' meetings for

review and comments. The Task Force adopted consistent language, as recommended by the GRADE Working Group[26]. The strength of the recommendations (weak or strong) is based on the quality of the supporting evidence, the level of uncertainty between desirable and undesirable clinical effects or diagnostic reliability and therapeutic preferences. Strong recommendations are indicated by the phrase "we recommend," while weak recommendations are indicated by the phrase "we suggest." The quality of the evidence relied on the appraisal as to the likelihood that additional research will modify a recommendation. It was rated as very low, low, moderate or high quality. Authors provided the preliminary grading and consensus on the recommendations was obtained using the Delphi process[27]. Revised sections were available to all authors for review, and were merged into a single draft document that was circulated to all authors for initial and final review. We also followed the AGREE II recommendations for guideline development.[28]

All members of the working group complied with the International Committee of Medical Journal Editors policy on conflicts of interest that requires disclosure of any financial or other interests that might be construed as constituting an actual, potential or apparent conflict.[29]

HISTORY AND PHYSICAL EXAMINATION, SCREENING/DIAGNOSTIC QUESTIONNAIRES

Diagnosis
T concentrations decrease with advancing age.[7,10,14,30,31] The manifestations of TD are not specific, they vary in onset and severity and need not all be present to reach a diagnosis.[32-34] Sexual symptoms and fatigue are the earliest and most common presentations.[7,32,35]

Zitzmann and colleagues evaluated psychological and somatic complaints in older men in relation to their T level (grouped by sextiles for statistical power purposes [between "less than 8 nmol/L" to "equal to or greater than 20 nmol/L"]).[36] They found no evidence to support a T threshold for symptom appearance. Loss of libido or vigour appeared in some men at T concentrations of less than 15 nmol/L, and the prevalence increased with decreasing T concentrations. At the other end, hot flushes and erectile dysfunction were observed at T concentrations of less than 8 nmol/L. Other symptoms (depression, sleep alterations, poor concentration) and metabolic disorders (type 2 diabetes mellitus, obesity) were seen at intermediate T concentrations of 9 and 12 nmol/L.

The manifestations of TD are not specific and frequently subtle[7,36] and may be affected by factors such as age, general health, co-morbidities, and medications.[35,37] TD can also occur secondary to systemic illness and environmental factors.[11] Patient history is therefore an important component in the diagnostic process and it can contribute additional information in the presence of symptoms that may appear non-specific. The signs and symptoms associated with TDS are presented in Table 1, and associated patient history features are listed in Table 6. Although not explicitly included in the table, a high index of suspicion is important in men with a decline in sexual activity and desire with or without decrease in the quality of their erections,[38] *unexplained* sarcopenia,[39] and obesity without other components of the metabolic syndrome.[40]

Physical examination

The physical examination bears similar shortcomings much the same as the history, mainly due to lack of specificity. Gonadal atrophy may be present as well as a decrease in pubic and facial hair. A decrease in muscle mass and increase in visceral fat may also be present. The sequela of osteoporosis becomes evident only when the hypogonadism has been present for long periods.[7,32 33] None of these findings, alone or in combination are sufficient to make a diagnosis of TDS. However, the history and results of the examination collectively would make a strong case for the presumptive diagnosis of the syndrome.

Screening

In order to facilitate the diagnosis of TD, a number of screening questionnaires have been developed to identify men with low T. The most widely known are the St Louis University Androgen Deficiency in the Aging Male (ADAM) questionnaire,[41] the Aging Male Survey (AMS)[42], and the screener used in the Massachusetts Male Aging Study (MMAS).[43] In various populations of men aged 23 to 85 years, these tools have demonstrated high sensitivity (60% to 97%) but low specificity (18% to 71%).[44-48] The specificity was consistently lower in multi-questionnaire comparisons (18% to 59%).[45,46]

In an effort to improve the usefulness of questionnaires, several variations have been introduced. A quantitative ADAM questionnaire (qADAM) has been developed,[49] and the ten questions from ADAM have been included in a symptom inventory (PADAM) used in Sweden.[50] In Germany, a new 'Hypogonadism Related Symptom Scale' (HRS) has been developed and recently validated.[51,52] The New England Research Institute developed and validated a 25-item hypogonadism screener (HG Screener) with acceptable psychometrics for clinical or research use,[53] and an Italian group developed and validated a 12-item interview [ANDROTEST] for men with sexual dysfunction.[54]

The AMS, ADAM and MMAS questionnaires have demonstrated low specificity. In addition, they have appeared to be more strongly influenced by patient age than by T levels, as shown by several investigators.[34 48] These issues, plus the lack of broad acceptance of the new questionnaires, limit their usefulness as screening tools for TD. Despite their economy and ease of administration, their availability on the internet and the opportunity they provide patients to self-diagnose, they cannot be relied upon in the absence of confirmatory history, physical findings and laboratory evaluations.

Finally, the clinical diagnosis of TDS can be challenging because the clinician frequently faces a situation where in the presence of symptoms the laboratory results remain inconclusive. Thus it has been suggested that in the presence of a convincing clinical picture but uncertain laboratory results, a therapeutic trial (3 months) is an acceptable diagnostic approach.[55] This concept was later advanced by Morley[56] who proposed that a conclusive diagnosis of TDS requires the triad of symptoms, low T levels and a positive response to treatment.

BIOCHEMICAL INVESTIGATION

Determination of Total Testosterone

Immunoassay

TT is generally measured by automated immunoassay (IA).[57] Comparison studies and results from external quality assurance (EQA) programs demonstrate significant bias and inadequate repeatability for most IAs, to the extent that they do not meet the current clinical performance goals.[58-64] Until such time that T analysis is accurate and repeatable by all commercial methods, replicate analysis of a sample from a given patient may be required to reliably determine their homeostatic set point relative to method-specific reference interval.

Mass spectrometry

IA results may be inconsistent with the patient's clinical presentation. In these cases, determination of TT by liquid chromatography and tandem mass spectrometry (LC-MS/MS), where available, is recommended.[65,66] Analysis by another method involving chromatographic sample preparation could be considered, but these alternate preparation methods are currently not available in Canada.

Several reference laboratories in the US and Canada now offer TT by LC-MS/MS which, when properly validated, produces comparable results to TT reference methods.[67,68] As LC-MS/MS is not yet widely available in Canada, for many sites its use is presently limited to the investigation of problem cases.

Accuracy and measurement uncertainty

The US National Institute of Standards has standardized reference material (NIST SRM 971) to facilitate TT method traceability. Additionally, the US Centre for Disease Control and Prevention (CDC) offers a Hormone Standardization (HoST) program.[69] As of May 2014, one commercial IA and eight LC-MS/MS assays have achieved CDC certification.[70]

We recommend that commercial TT assays should be CDC certified and all methods (commercial or in-house) traceable to an internationally recognized standardized reference material such as NIST SRM 971.

In order to meaningfully apply published diagnostic decision limits, the accuracy of the local laboratory's method must be established. Accredited laboratories are required to provide the analytical measurement uncertainty of results (ie, 95% CI) upon request.

Testosterone Subfraction Analysis

Free testosterone

Measurement of free testosterone (FT; 2% of TT) employing equilibrium dialysis or centrifugal ultrafiltration is theoretically the best measure of tissue exposure to T. Because these methods are labour-intensive and time-consuming, they are available only in a few US-based reference laboratories at this time.[71]

Analog free testosterone
Analog-based "direct" FT methods are inaccurate and are not recommended.[72-75]

Measured bioavailable testosterone
"Bioavailable" testosterone (BAT; 47% of TT; equal to the sum of FT plus albumin-bound T) is performed by measuring T after "selective" precipitation of sex hormone-binding globulin (SHBG) and its bound T using 50% ammonium sulphate. This approach is offered by a small number of laboratories in Canada. It is a manual process and is labour intensive and temperature sensitive. Also, it may be prone to intermethod biases caused by the precipitation reagent.[57,76]

Calculations

Calculated free testosterone and bioavailable testosterone
cFT and calculated BAT (cBAT) use empirically-formulated equations or those derived from the law of mass-action.[77-81] Mass-action calculations use approximate affinity constants and assume that SHBG concentrations are a suitable surrogate for bound T.[81,82] Although between-laboratory comparisons of cFT and cBAT results are poor, these calculations have the advantage of being inexpensive and widely available.[81]

cFT and cBAT require extensive evaluation specific to the methods employed. They require either optimization of empirical constants to yield results matching measured FT or BAT,[80,81] or reference interval (RI) determination that is specific to the TT and SHBG methods.[81] Sartorious et al. have shown that there is significant variability in calculated results using different formulae.[78]

Free androgen index
The correlation of "free androgen index" (FAI = T / SHBG) to FT is poor, except in situations where the molar concentration of SHBG is much higher than that of TT. Therefore, FAI may be a useful tool in women and children, but cannot be recommended for adult men.[81,83]

Future tools
Salivary T is an approach that may gain popularity based on its ease of multiple sample collection and as reliable methods become more readily available.[84-86]

Ancillary diagnostic testing
Elevations in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are used to identify secondary/tertiary forms of hypogondism. It should be remembered that TD may be caused by a combination of primary and secondary causes.[2,87]

Other investigations (and endocrine or other causative disorders) that may be appropriate include: prolactin (prolactinoma); HbA1c (diabetes and the metabolic syndrome); ferritin and transferrin saturation (hereditary hemochromatosis); TSH (hypothyroidism); CBC (anemia); creatinine (chronic kidney disease); ALT and ALP (liver disease); BNP or NT-pro-BNP (congestive heart failure) and urine opiate drug screen(s) (narcotic abuse).[2,87,88]

Patient preparation and population-specific issues

TT results may be affected by: time of collection, fasting, choice of collection tube, obesity, acute and chronic illness (due to alterations in albumin and SHBG), cross-reacting patient-specific metabolites, and drugs.[89-92]

Related Issues

Reference intervals

There are numerous challenges in the validation of reference intervals (RIs), including: the identification of suitable volunteers; the requirement for large cohorts with a wide range of ages; and the constraints of time and cost.[93] Inadvertent inclusion of subfertile men (5% prevalence), or failure to consider confounding issues such as age, diurnal rhythms or body mass index (BMI) can result in inappropriate RIs.[61]

It remains controversial whether the observed age-dependent declines in TT should be considered a normal phenomenon and reflected in RIs.[94-96]

Monitoring

TT results within an individual will vary within ± 18.6% (95% CI) of their homeostatic set point. Thus, a change in TT of approximately 30% is required to be considered statistically significant.[97]

Summary

- The technical challenges of TT determination have been highlighted for more than a decade.
- Accurate determination of a patient's current homeostatic setpoint by measuring TT is the starting point for clinical evaluation of possible TD.
- A change of 30% or more in TT results between two appropriately timed, serial collections in a single patient is required to declare the results significantly different.
- Commercial T assays should be CDC certified and all methods (commercial or in-house) traceable to an internationally recognized standardized reference material such as NIST SRM 971.
- cFT, cBAT, FT and BAT depend on accurate TT determination and are subject to numerous additional sources of analytical error, therefore these approaches should be considered and employed secondarily.

TREATMENT OPTIONS

The goal of TRT is improvement in symptoms and achievement of eugonadal levels of T, approximately in the mid-normal range for healthy young men (14 to 17.5 nmol/L).[98] The Endocrine Society guidelines recommend a similar mid-normal range for TT (400 to 700 ng/dL [14 to 24 nmol/L]).[25] Because there are large inter-individual variations, symptom

improvement should be the primary objective and higher or lower serum T concentrations may be acceptable in patients with a positive response to treatment.[99]

Testosterone products available in Canada
There are a number of T products approved for human use in Canada. These can be identified by searching the *Drug Product Database Online Database Query* section of the Health Canada website (available at: http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp). This Health Canada site also provides official product monographs for many of these products, and these have been included in the reference section.[100-109] Please consult the respective product monograph for complete safety and prescribing information.

The available TRT products in Canada include short-acting injectable T (T enanthate, T cypionate and T propionate), oral T undecanoate, transdermal T patches, transdermal T gel 1% (hydroalcoholic gel, and hydroalcoholic gel with pentadecalactone), axillary transdermal T solution 2%, and compounded T creams. Intramuscular T propionate is used infrequently and will not be mentioned further in this document.[110] Compounded T products are available at many compounding pharmacies in Canada, but there are no published data on the safety and efficacy of compounded T products.

The choice of a product for TRT should be a topic of discussion between the physician, the patient, and possibly also the patient's caregiver. Factors affecting this choice include safety, efficacy, tolerability, availability, preference and cost.[25,111]

A brief description of the benefits and disadvantages of available products is provided in Table 7. Table 8 presents an approximate monthly cost for these products. The following sections provide additional product information.

Oral testosterone capsules
T undecanoate is available in oral form. The recommended product monograph dosage is 120 to 160 mg daily in two divided doses. A 12-month randomized trial of different doses observed a dose response with regards to positive effects on body composition and bone mineral density (BMD), and the highest daily dose in this study was 240 mg (taken with meals three times a day).[112] Oral TRT is convenient, but the bioavailability of this product when taken in the fasted state is minimal. Oral T undecanoate must be taken with food; the bioavailability is 7%.[113,114] Previously, the use of oral methyltestosterone (a 17-alpha alkylated steroid) has been associated with liver damage.[115] Although monitoring liver function has been recommended in men taking oral T undecanoate (a 17-beta androgen), a ten-year study was unable to detect liver abnormalities in 33 men.[116]

Intramuscular injection
T intramuscular injections are effective at restoring T levels. However, earlier investigations administering mixed T esters identified high peaks postinjection and low troughs prior to the next injection.[117-119]
The peaks tend to be at supraphysiologic levels and the troughs can be subphysiologic, and these may adversely affect the patient's mood, energy level, sexual function and sense of wellbeing.[110] Pharmacokinetic studies of biweekly injections have shown T enanthate and

T cypionate produce T levels above normal for several days during the first week following the injection.[120,121] It appears appropriate to measure the T serum level midway between injections.[25]

Transdermal patch

Long-term studies have shown that daily application of the T transdermal delivery system (or 'patch') can restore physiologic levels of T in the majority of patients.[122,123] The recommended starting dose is one 5 mg or two 2.5 mg patches applied nightly, to normalize morning serum T levels.[122] The patch is visible, which may not be desirable to some patients. Each patch needs to be placed on a non-weight bearing area, the location must be changed daily to minimize skin irritation, and there should be an interval of 7 days between applications to the same site.[99] Skin irritation is common, and was observed in 66% of men in one comparative trial, and was responsible for 15% of men in another trial discontinuing treatment.[124] The incidence of skin irritation and the incidence and severity of local skin reactions may be reduced by pretreating the site with a topical corticosteroid cream, or by applying the cream to the site after the patch is removed.[99,125]

Transdermal gel

Two transdermal T 1% hydroalcoholic gel products are available in Canada for TRT. Both products recommend a starting dose of 5 g, applied in the morning to the intact skin of the shoulders and/or upper arms [hydroalcoholic gel with pentadecalactone] or the shoulders and upper arms and/or abdomen [hydroalcoholic gel].

The long-term administration of T hydroalcoholic gel was investigated in 227 hypogonadal men randomized to 50 mg or 100 mg per day or a T patch.[126] After 90 days, the dose was adjusted based on the day 60 T level. The 100 mg dose was reduced for 29% of men, and the 50 mg dose was increased for 30% of men, and no man required a dose higher than 100 mg.

Baseline information in a registry database of hypogonadal men treated with hydroalcoholic gel with pentadecalactone showed the majority of men (over 86%) started treatment with the 5 g dose. After 12 months, one-third of 242 men younger than 65 years old and approximately one-quarter of men age 65 and older were using the higher (10 g) dose, equivalent to 100 mg daily.[127] Although the investigators commented that the product was well tolerated, the unique scent of pentadecalactone has been provided as a reason for discontinuing treatment by a small number of men in clinical trials.[128,129]

An early investigation determined T bioavailability from the 1% hydroalcoholic gel formulation was 9% to 14%.[130] This is reflected in the recommended starting dose of 5 g, which will deliver approximately 50 mg of T to the skin's surface, and approximately 5 mg (10%) systemically.

Pentadecalactone is an emollient that enhances the absorption of T from the hydroalcoholic gel. In a pharmacokinetic investigation of the hydroalcoholic gel and the hydroalcoholic gel with pentadecalactone, it was found that the T maximum concentration (C_{max}) and 24-hour exposure (AUC_{0-24}) were 30% higher with the pentadecalactone product, and the standard

bioequivalence confidence intervals exceeded the range for equivalence.[131] Therefore, these two products are neither bioequivalent nor interchangeable. This difference was confirmed by Grober and associates who observed improved clinical and biochemical responsiveness in men switched to the pentadecalactone product after being nonresponsive to the regular hydroalcoholic gel.[132]

These products are generally well tolerated, but application site reactions have been reported in up to 6% of men.[133-135] For monitoring, most men exhibit steady state levels after the first week of daily application of the product, and midmorning sampling for T determination is appropriate.[99]

Transdermal solution for axillary application
A 2% T topical solution administered with an applicator to the axillae was developed to overcome issues with other TRT products: to reduce the skin irritation associated with T patches; to reduce the large application area for gels; to minimize the likelihood of T gel transfer through skin contact; and to avoid using the hands to apply a topical T product.[136] A phase 3 trial in 155 hypogonadal men showed the product was well tolerated and most skin reactions were mild or occasionally moderate in severity.[137] Efficacy data from the same open-label trial showed 84% of the 138 men completing the study achieved T levels within the eugonadal range.[136] Dose data showed 135 men initially applying the recommended starting dose of 60 mg (2 pump actuations) per day had their dose increased at four months to 90 mg/day (19% of men) and 120 mg/day (7% of men), or reduced to 30 mg/day (2% of men). Serum T levels should be assessed 2 to 8 hours after administration, and after at least two weeks of regular usage.[99] An underarm deodorant or antiperspirant may be used before or after applying the topical solution as these have no significant effect on T absorption. However, if a "stick" or "roll-on" type of product is used, it should be applied prior to using the solution to avoid contamination of the stick or roll-on product.[136]

Safety considerations
Transdermal T gel and axillary T solution can be transferred to others who come into contact with these products following application.[138] It is recommended that after application, a shirt be put on to prevent transfer. Children and pregnant women should avoid direct contact with the gel. With exposure, virilization may occur in children and fetuses.[138,139]

In order to identify adverse effects related to TRT, a systematic review and meta-analysis of T trials was conducted.[140] Data from 51 studies showed T administration was associated with significant increases in hematocrit (Hct) and hemoglobin (Hgb), and a decrease in HDL-cholesterol. Other important findings were that T had no significant effect on CV or prostate outcomes, or on mortality.

The clinical trials leading to the development of these products have identified adverse events in hypogonadal men, and these are listed in the respective monographs for each product. The reader is referred to them for product-specific adverse event information.

ALTERNATIVE AND COMPLIMENTARY TREATMENT FOR TD

With the diagnosis of TD, if deemed appropriate and warranted, treatment would be initiated to correct the hormone deficiency. Most often, treatment would involve T replacement. The specific treatments available are outlined in the section *Treatment Options*.

In men with preserved testicular function, human chorionic gonadotropin (hCG) can be used to stimulate testicular T production. This was demonstrated in a 30-year-old man with delayed puberty and infertility.[141] A Japanese study in 21 men with TD showed significant increases in T following treatment for between 8 and 24 months.[142] However, hCG must be administered intramuscularly, usually three times weekly and on a cyclic basis, and is approved in Canada for men with prepubertal cryptorchidism (not due to anatomical obstruction) or selected cases of hypogonadotrophic hypogonadism.[143]

In men with hypogonadotropic hypogonadism, T administration may produce androgenization, but fertility requires a gonadotropin or gonadotropin-releasing hormone (GnRH).[144] Pulsatile subcutaneous administration of GnRH with an infusion pump can restore T levels in most men, and an intact HPGA is required.[145,146] GnRH is available in Canada, but is not approved for use in men.[147]

Exogenous T suppresses the feedback mechanisms of the HPGA, resulting in impaired spermatogenesis.[148-150] In younger men with TD and desiring fertility, one could administer either HCG, GnRH or clomiphene citrate (CC).[148-150] CC is a selective estrogen receptor modulator that promotes testicular spermatogenesis and increases T levels by blocking estradiol feedback at the hypothalamus, thus increasing pituitary release of LH and FSH.[150] Potentially, CC could be used until conception occurs, then treatment changed to TRT if fertility was no longer an objective. CC is administered orally every second day, and is currently approved in Canada only for ovulation induction.[151]

There has been an increased interest in the serum testosterone:estradiol ratio that might be more important than the respective individual hormone levels in some of the manifestations of TD. The possibility has been raised of increasing T levels in men with TDS, particularly those with secondary hypogonadism, by using aromatase inhibitors. At present there is no convincing literature to recommend their use for this indication. In theory, however, such treatment could circumvent some adverse effects of T administration but also prevent the positive effects of T treatment in the prevention of bone loss.

Phosphodiesterase type 5 inhibitors (PDE5-Is) are generally successful in treating men with erectile dysfunction (ED), but 30% to 35% of men are nonresponders, and the nonresponse rate is higher in men with diabetes and in postprostatectomy patients.[152-154] TD reduces the clinical response rate, and this has been confirmed by a study in 162 men aged 60 years or older.[155]

Several investigators have evaluated the addition of T treatment to PDE5-I monotherapy in hypogonadal men with ED failing PDE5-I monotherapy.[152,153,156] Improvements were reported with after 4 and 12 weeks of combination therapy, appeared greater in men with lower baseline T levels, and were not maintained after discontinuing T.

Greenstein and associates used topical T gel to normalize total TT and BAT in 49 hypogonadal men with ED; an oral PDE5-I was added to the T monotherapy for the 17 nonresponders, with good results.[157] Rosenthal and colleagues also used topical T gel to normalize serum T (at 4 weeks) in 24 men with ED and a baseline serum T less than 400 ng/dL who had failed previous PDE5-I monotherapy.[158] None of the men had regained potency at 4 weeks. The addition of a PDE5-I for 16 weeks improved erection quality and potency in 92% of the men.

Two meta-analyses have been published evaluating combination therapy (T plus a PDE5-I) in hypogonadal men failing monotherapy.[154,159] Combination therapy appears effective in treating men with serum T less than 300 ng/dL. In comparative studies of PDE5-Is, efficacy and adverse events were not different between the agents. The available studies have limitations in methodology and reporting, and there is the need for well-designed studies to identify the target population, the T cut-off, the duration of therapy and the optimal doses.

We have not discussed T-like substances or T "boosters" or other over-the-counter substances or supplements for which there is little published literature or scientific evidence. An additional electronic database search identified a small number of clinical trials and reviews addressing sexual dysfunction, but no literature specific to men with TD.

A variety of herbal or plant-derived products have been marketed as T-like substances or T "boosters" for the treatment of sexual dysfunction in both men and women. An early review concluded that "modest empirical support" existed for a small number of products, but there was a lack of well-designed trials of safety and efficacy.[160]

More recent studies have focused primarily on the treatment of men with ED. Investigators have determined benefit by using scales and questionnaires and measuring changes in these tools. The International Index of Erectile Function (IIEF) and shorter versions (eg, IIEF-5), rather than changes in T levels have been used to assess efficacy.[161-166] One investigative group used the Ageing Males' Symptoms (AMS) Rating Scale and serum T to identify patients with LOH and to assess their response to treatment,[167] and another group used changes in AMS, IIEF, and other questionnaires and serum T to assess benefit.[168]

Korean red ginseng was compared against placebo in a 12-week, double-blind study in 60 men with ED.[161] The mean age of participants was 52.6 years. T was initially within the normal range and was unchanged after treatment, and changes in IIEF-5 demonstrated significant ED improvement in the treatment group.

A patented formulation containing extract of pine bark was compared against placebo for the treatment of mild-to-moderate ED in two investigations in men aged 30 to 50 years;

their TT levels were within the normal range before treatment.[163,166] A randomized, placebo-controlled crossover trial in 50 men showed IIEF-based improvement in their ED and a 21% increase in TT after 30 days in the active-treatment group.[166] Results from a 6-month randomized placebo-controlled trial showed a significant difference in IIEF score favouring treatment at 3 and 6 months, and a 19% increase in TT at 6 months in the 54 trial completers in the treatment group.[163]

A water-soluble extract of Tongkat ali (*Eurycoma longifolia* Jack), a herbal remedy found in South-East Asia, is a traditional medicine used to enhance sexuality and fertility.[169] In a 9-month open label trial of Tongkat ali extract 200 mg daily in 350 men with idiopathic male infertility, 3-month semen analysis in 75 subjects showed significant improvement in sperm concentration and in normal sperm morphology. Changes in levels of T were not included in the analyses. Spontaneous pregnancy was reported in the partners of 11 of the 75 men. The investigators suggested further studies of this product for the treatment of male infertility.

In a retrospective analysis using the same dose and conducted with data from men with LOH (based on AMS score and serum T less than 6 nmol/L) and visiting the same clinic in Malaysia, investigators evaluated changes after one month of treatment.[167] Mean serum T concentrations increased from 5.66 nmol/L to 8.31 nmol/L, a 47% increase. The percentage of men with serum T in the normal range increased from 36% to 90%, and changes in the AMS scores also showed significant changes.

Slightly different results were obtained in two company-sponsored, 12-week, double-blind, placebo-controlled studies: in men between 30 and 55 years old with normal serum T;[162] and in men aged 40 to 65 years old with T levels at or below 450 ng/dL.[168] The first study administered placebo or a freeze-dried extract equivalent to 300 mg daily of the herbal extract.[162] Domains within the quality of life assessment (SF-36) and within the sexual well-being (IIEF) questionnaires showed significant differences versus placebo, but the total scores of the questionnaires were not statistically different. Analyses of hormonal profiles from 103 of the 109 randomized subjects showed no changes or differences to placebo in total or FT at week 6 and week 12. The second study administered placebo or 200 mg of the herbal extract combined with 100 mg of *Polygonum minus*, a herbal described as having antioxidant properties.[168] Four of 30 subjects withdrew from the study. Changes in AMS and two of three sexual dysfunction endpoints favoured treatment at 12 weeks; AMS and one other endpoint showed a significant benefit at 6 weeks. Baseline TT was 359.23 ng/dL in the active treatment group, and increased significantly by 10% at week 6 and week 12, with FT showing a significant 4% increase from baseline. In the placebo group, TT showed a smaller but significant increase at week 6 (8%) and week 12 (4%) from the baseline level of 308.47 ng/dL, and FT decreased significantly by 20% at week 6 and by 30% at week 12.

The impact of *Tribulus terrestris*, a herb found in the southern temperate zones of Europe and elsewhere, on ED and serum T levels has been assessed in two prospective, placebo-controlled randomized trials.[164,165] In a 30-day trial in 30 men aged 40 and older, serum T and IIEF-5 score were not different before and after treatment, and serum T was not

different between the treatment groups.[164] A multi-ingredient supplement containing *T. terrestris* was administered to men aged between 25 and 50 in a 12-week trial.[165] The product was well tolerated with a statistically significant improvement in the primary endpoint, IIEF-EF domain, while serum T levels did not change significantly in the 62 subjects for whom data were available. Participants in both trials had serum T within the normal range at study entry.

A multi-ingredient product containing *T. terrestris* with an antioxidant (from *Ecklonia bicyclis*), D-glucosamine and N-acetyl-D-glucosamine was compared with a PGE-5 inhibitor in a 2-month, double-blind randomized controlled trial (RCT) in 70 men over 60 years of age.[170] Changes in IIEF scores showed a significant improvement in libido with the active treatment. Unlike the two *T. terrestris* monotherapy trials, the levels of TT and FT showed substantial and statistically significant increases, and the investigators claimed this effect was due to the androgen-mimetic properties of a steroidal saponin ingredient of *T. terrestris*. The investigators did not suggest a comparative trial using both PGE-5 inhibitor and TRT.

Two systematic reviews have recently assessed *Tribulus terrestris* and *Eurycoma longifolia* Jack.[171,172] The interpretation of available study results are limited by a lack of clarity regarding randomization and blinding, appropriateness of the endpoint, and small study size due in part to dropouts.[171] Other limitations are due to the inclusion of *T. terrestris* as part of a multisupplement combination, poorly defined treatment dose and duration, broad subject eligibility criteria, and the quality of the findings.[172] Additional research is required.

OBESITY AND BARIATRIC SURGERY

The association between obesity and hypogonadism is well recognized.[40, 173] A Canadian study documented an inverse correlation between total T and body, visceral and subcutaneous fat as well as waist circumference.[174] The effect of T administration in body composition (decrease in fat and increase in lean body mass) has been addressed in another section (see Diabetes Mellitus and Obesity).

Weight loss strategies based on a diet, exercise and other lifestyle changes frequently offer only temporary results. Bariatric surgery on the other hand, results in more consistent and long-term weight loss and translates in improvement and resolution of complications of obesity such as hypertension, dyslipidemia and sleep apnea. An increasing number of studies are showing persistent improvement in quality of life and reduction of long-term mortality in patients following gastric bypass surgery.[175] When hormonal evaluations have been carried out after bariatric surgery, studies consistently documented an increase in circulating T levels. These observations range from detailed single case report showing a complete restoration of hormonal profile in an obese man after bariatric surgery,[176] to several small series.[177-179] Rao et al. have published an excellent review on this topic.[180] Evidence is accumulating in support of bariatric surgery as an effective complementary option in obesity-related male hypogonadism. For the interested reader, the European Guidelines are particularly helpful.[181]

CARDIOVASCULAR DISEASE

On July 15, 2014, Health Canada announced a safety review was initiated to evaluate the currently available information regarding the possible CV risk (heart and blood vessel problems) associated with the use of T replacement products.[23] This follows an announcement by the US Food and Drug Administration (FDA) that they were going to investigate the risk of stroke, heart attack and death in men taking FDA-approved T products.[21] In June 2014, the FDA announced they are requiring manufacturers to include a general warning about the risk of blood clots in the veins in the drug labeling of all approved T products.[22]

Association studies in the general population

Hypogonadism as defined by a low T level has been shown to be associated with an increased risk of CV disease (CVD) and CV mortality in observational studies.[182-186] The most compelling data are from a meta-analysis of 70 cross-sectional and prospective studies.[187] In this comprehensive analysis by Corona and colleagues, T levels were inversely associated with CVD and CV mortality, while estradiol levels were positively associated with these outcomes. There were no age-related differences in TT levels between subjects with and without CVD, but subjects with CVD, diabetes and hypertension were shown to have lower levels of T compared with the healthy subjects.

There have also been observational and randomized control trials demonstrating beneficial effects of T therapy on surrogate markers of CV risk such as carotid intima media thickness (CIMT), inflammatory markers, ventricular function, exercise capacity and insulin resistance.[188-192] These are presented in Table 9 and will not be further discussed.

Hypogonadism, erectile dysfunction and cardiovascular disease

Low androgen levels have been shown to be associated with erectile dysfunction (ED), the metabolic syndrome, diabetes, and CVD.[182,193,194] Vascular smooth muscle cells and the endothelium play an important role in the vasculogenic causes of erectile dysfunction and serves to highlight the importance of atherosclerosis in the pathophysiology of erectile dysfunction.[195] CVD and erectile dysfunction have also been shown to share common pathways and risk factors.[196]

There is substantial data supporting the association between ED and a high risk of CAD.[197] Although ED can be considered a warning sign of a future major adverse cardiovascular event, it could also identify men at a higher risk of harboring silent CAD. The incidence of asymptomatic CAD in men with Vasculogenic ED has been found to vary between 19-50%.[198-200]

Based on these data strong consideration should be given to evaluating men with hypogonadism and/or erectile dysfunction for underlying cardiovascular disease. In 2012, the Third Princeton Consensus Conference addressed the role of CVD screening in ED patients according to CVD risk.[201] For organic ED patients with no known CVD, the panel

recommended they be considered at increased risk for CVD until recommended checks suggest otherwise.

Intervention studies of testosterone replacement therapy

Although there has been a wealth of observational data demonstrating an association of lower T levels with poor health outcomes, specifically CV disease and CV mortality, there is a lack of well-conducted high-quality RCTs that would be needed to determine whether a CV benefit can be derived from TRT. The RCTs that have been performed have been conducted in diverse populations with differing baseline states of health and using a variety of formulations of T replacement. Importantly, they have been done in men with varied baseline T levels. Many of these intervention trials have been of short duration, with small numbers of subjects, and lacking statistical power to detect the CV outcomes of clinical importance.

There have been four major meta-analyses of RCTs conducted: Calof and colleagues in 2005; Haddad and associates in 2007; Fernandez-Balsells and colleagues 2010; and Corona and associates in 2014.[140,202-204] These did not demonstrate a significant difference in the occurrence of CV events between the T and placebo arms. The most recent and largest (75 articles; 3016 and 2448 subjects in the TRT and placebo arms, respectively) confirmed the earlier results and showed that CV risk (either composite or single adverse events) was not elevated in men receiving T.[204]

Subsequent to the first 3 meta-analyses, the results of an RCT by Basaria and associates was published showing an increased relative risk of CV-related adverse events in elderly frail men being treated with TRT.[205] The trial was stopped due to a significantly greater incidence of CV adverse events in men randomized to the treatment group (23, versus 5 in the placebo group). Trial participants had a mean age of 74 years and were at high CV risk with various serious chronic illnesses: preexisting diabetes and obesity (nearly one-third of participants), hyperlipidemia (more than one-half), hypertension (more than three-quarters), and preexisting heart disease (nearly one-half). An analysis of risk factors associated with the CV adverse events determined that those men with events had greater increases in FT levels in comparison with men who did not have events.[206] The study was designed to assess TRT-related changes in lower extremity strength and functional status, and was not designed (or powered) to analyze primary or secondary CV outcomes. The reported CV events ranged from serious CV events to symptoms or signs of questionable CV significance such as peripheral edema, tachycardia and hypertension. When only the serious CV outcomes were included, there was no significant difference in the occurrence of events between the two groups. There were several potential sources of bias in this study but because of the effect size, it is weighted heavily in subsequent meta-analyses.

Xu and associates conducted a meta-analysis of placebo-controlled T treatment trials and identified 27 trials including 2994 mainly older men who experienced 180 CV-related events.[207] T therapy increased the risk of a CV-related event (OR 1.54; 95% CI = 1.09 to 2.18). The likelihood varied with the source of funding but not with the baseline T level. In trials not funded by the pharmaceutical industry the risk of a treatment-related CV event

was greater (OR 2.06; 95% CI = 1.34 to 3.17) than in pharmaceutical industry-funded trials (OR 0.89; 95% CI = 0.50 to 1.60). The authors concluded that the effects of T on CV-related events varied with source of funding. Overall, and particularly in trials not funded by the pharmaceutical industry, exogenous T increased the risk of CV-related events. This meta-analysis included studies of varying sizes with differing baseline levels of T, and the primary outcome was a composite system-wide outcome that included events of less certain CV significance. This study was very heavily weighted by the large study reported by Basaria and associates. The authors hypothesized the lower odds ratio for the outcome in industry-sponsored trials may be due to the enrolment of younger men in these trials.

Finkle and colleagues used a large US healthcare database for a cohort study to assess the risk of acute nonfatal myocardial infarction (MI) in the 90-day period following an initial prescription for T.[208] No other CV endpoints were captured. For a cohort, the investigators selected subjects prescribed a PDE5-I from the same database. The authors identified the 90-day post-exposure rate and the 12-month pre-exposure rate in the T prescription group, then in the PDE5-I prescription cohort, then compared the rates between the 55 593 men prescribed T and the 167 279 men prescribed a PDE5-I. The rates of acute nonfatal MI per 1000 persons per year were calculated, the rate ratio (the post/pre-prescription rate) was determined, and subgroup analyses were performed by age and by heart disease (present or absent). By comparing the T prescription group results with those from the PDE5-I prescription group, the ratio of rate ratios was determined.

Compared with the pre-prescription event data, there was an increased risk in the T prescription group (rate ratio 1.36; 95% CI = 1.03 to 1.81) in the first 90-days post-prescription. This risk was higher in men younger than 65 years old with heart disease (rate ratio 2.90; 95% CI = 1.49 to 5.62), in men age 65 years and older without heart disease (rate ratio 2.21; 95% CI = 1.09 to 4.46), and slightly but not significantly higher in men age 65 years and older with heart disease (rate ratio 2.16; 95% CI = 0.92 to 5.10). The ratio of rate ratios was elevated in the T prescription group compared with the PDE5-I prescription group.

The size of the database contributes to the strength of this analysis, but there are several limitations that weaken the authors' conclusion about the magnitude of the increased risk. The diagnostic indications for T were not available and there was no information about the T levels before or after the T was prescribed. Hypogonadism has been linked to an increased risk of CV events, and it isn't possible to determine if the men had achieved the therapeutic range for T. Also, men in the T prescription group tended to have higher comorbidity than those in the PDE5-I cohort, and it is not clear if weighting for this corrected for the differences. Since other outcomes (CV mortality and stroke, for example) were not included, these uncertainties detract from the likelihood that T alone was responsible for the differences in the single CV outcome reported.

In another retrospective cohort study, Baillargeon and colleagues used Medicare beneficiaries' enrolment and claims data to evaluate the risk of MI in 6355 men age 66 years and older treated with intramuscular T.[209] Eligible men were enrolled for 12 months before the first T injection. The average total number of injections was 4.4 in the first year,

and 8.2 over the entire follow-up period. A composite MI prognostic risk score was developed and validated by several statistical methods to identify a matched cohort of 19 065 men (from a pool of 571 136 men) for 99.9% of the T therapy cohort. The investigators used an ICD-9 code to identify hospitalization for MI, the outcome of interest, and used an adjusted Cox regression model to calculate the hazard ratio (HR) for this outcome.

The investigators found that the use of intramuscular TRT was not associated with an increased risk of MI (HR 0.84; 95% CI = 0.69 to 1.02). During the first year of use, there was no increase in hospitalization for MI with increasing cumulative injections (HR 0.98; 95% CI = 0.96 to 1.01). Several sensitivity analyses were conducted, including one that adjusted for all 30 covariates in the composite MI prognostic risk score plus basic demographic characteristics, and the resulting hazard ratio remained in the nonsignificant range (HR 0.65 to 0.87). The investigators concluded that there was no increased risk of MI in older men treated with intramuscular T.

Vigen and colleagues conducted a retrospective cohort study of male veterans with coronary artery disease (CAD) who underwent coronary angiography.[210] Of 8709 hypogonadal men (TT less than 300 ng/dL), 1223 started TRT and at 3 years post-angiography had a statistically significant 5.8% absolute risk increase in the composite endpoint of all-cause mortality, MI and ischemic stroke. The weakness of the study design (a study population limited to male veterans with CAD, retrospective cohort, no randomization, small sample size at the extremes of the follow-up, and lack of chart review to validate outcomes) limits the generalizability of the results. Large RCTs with CV events as the primary outcomes will be required to demonstrate the safety and efficacy of TRT in men with CV disease.

Testosterone replacement therapy in men with cardiovascular disease
A 12-week investigation of TRT was conducted in 87 men (mean age, 74 ± 7 years) with noninsulin-dependent diabetes and stable CAD.[211] The subjects received either oral T undecanoate or placebo. There were significant reductions in the number of angina attacks per week, and in ECG-monitored silent ischemic episodes and total ischemic burden. Lipid profile and insulin resistance were also improved. The investigators recommended studies of longer duration to assess safety and the long-term relevance of the observed clinical benefits.

Caminiti and associates conducted a 12-week double-blind placebo-controlled trial in 70 elderly men with moderate-to-severe congestive heart failure (CHF) to investigate the effect of TRT on functional capacity and ventilatory efficiency.[212] Subjects were clinically stable and had symptomatic heart failure (HF) New York Heart Association (NYHA) class II or III) and a left ventricular ejection fraction (LVEF) of less than 40%. Although the study was limited by its short duration, TRT improved functional capacity and clinical measures of poor prognosis in this population.

In a randomized double-blind placebo-controlled transdermal patch trial conducted in 76 men (mean age, 64 ± 9.9 years) with chronic HF, TRT was associated with a significant

improvement in exercise capacity over a 12-month period, which corresponded to a 15% ± 11% improvement from baseline.[213] In addition, there was an increase in NYHA class by at least one functional class compared with placebo. There was no excess of adverse events. There was a single sudden death reported in the placebo group. In the T arm, 5 subjects required an unplanned hospital admission and one patient suffered a small anterior circulation stroke, one person developed unstable angina, and there were 2 exacerbations of HF in each group (TRT group and placebo patch group). The most common adverse reactions in both groups were skin reactions, reported in 55% of all subjects, and leading to study withdrawal by 19 subjects.

Stout and colleagues conducted a double-blind randomized controlled study of a 12-week program of exercise with and without intramuscular TRT among men with CHF and low T.[214] Of the 41 men randomized (mean age, 67 years; mean T 10.7 nmol/L), only 28 (68%) completed the study, but adherence to exercise and TRT was 100%. The combination of TRT and exercise improved aerobic fitness, leg strength, depression and hypogonadal symptoms, but echocardiographic outcomes, N-terminal pro-brain natriuretic peptide (NT-pro-BNP), and inflammatory markers were mostly unchanged. While TRT in older hypogonadal men with CHF participating in an exercise rehabilitation program is realistic, larger studies are required to address the number of subjects who dropped out of this study.

A recent meta-analysis of TRT in men with HF included 4 trials and 166 subjects with a mean age of 67 years.[215] Compared with placebo, TRT was found to be associated with significant improvements in measures of exercise capacity such as the 6-minute walk test, the incremental shuttle walk test, and peak oxygen consumption. No significant adverse CV events were observed.   The previous study by Stout and colleagues was published in 2012 and is not included in this 2010 meta-analysis.

Testosterone replacement therapy in men without cardiovascular disease
Short-term studies in hypogonadal men with CAD or heart disease have demonstrated that TRT may provide symptomatic improvement. However, there is a lack of high-quality evidence demonstrating a benefit on CV disease incidence, progression or survival.

In order to evaluate the effect of TRT and lifestyle management on CV risk factors, 56 self-referred middle-aged obese men with total FT levels less than 100 pg/mL and clinical signs of TD were selected for a physician-supervised and guided exercise and nutrition program.[216] Subjects were followed for 6 to 18 months. Overall, the participants achieved significant weight loss and a significant reduction in coronary risk factors such as glucose intolerance and hyperlipidemia.

In 2011, Corona and colleagues published a meta-analysis of studies in subjects with and without CV disease.[217] Among cross-sectional studies, they found low T and high estradiol were associated with CV disease. Among longitudinal studies and in comparison with controls, baseline T was lower for subjects with incident overall-mortality and CV-related mortality. There were no differences in baseline T and estradiol levels between cases and controls for incident CV disease. Metabolic components associated with CV risk were

diminished with TRT. However, the analysis was unable to establish causality, or to identity the beneficial and harmful effects of TRT on CV morbidity and mortality.

Testosterone replacement therapy in men with congestive heart failure
Anabolic steroids are determinants of mean exercise capacity. It is known that the administration of anabolic androgenic steroids significantly increases lean muscle mass leading to increased muscle strength. In a study of 205 men with CHF ranging from NYHA class 1 to 4 and a with a mean LVEF of 31%, circulating T levels were independent predictors of exercise tolerance even after adjustment in multivariable models for age, pro-brain natriuretic peptide (pro-BNP), and leg lean tissue.[218]

A prospective study was conducted in 175 consecutive elderly men with systolic CHF and reduced LVEF attending outpatient clinics at 3 centres in China.[88] Total T and SHBG were measured, and cFT (reported as estimated FT [eFT]) was calculated. The age-specific prevalences of low T and low cFT were 21.7% and 27.4%, respectively, and these hormones were inversely associated with LVEF and NT-pro-BNP ($P<0.01$, for both). However, after adjusting for clinical variables, there were no associations of low, medium or high tertiles of either TT or cFT with survival time. The investigators commented that low levels of TT and cFT are present in older men with CHF and are related to disease severity, but the current investigation found they were not independent predictors for mortality.

While low T levels are commonly observed in subjects with HF, a causal association is unproven.[219] Pilot studies have shown TRT to reduce symptom burden in subjects with heart failure, but larger trials are required to demonstrate benefit and safety.[219,220]

Summary
While short-term studies have shown symptomatic improvement in men with coronary artery disease or CHF, evidence regarding a beneficial or harmful effect of TRT on hard endpoints like MI, stroke or sudden CV death is lacking.

In the summary of findings table (Table 10), we review the evidence from the meta-analysis by Fernández-Balsells and colleagues as it includes most of the major RCTs evaluating CV outcomes in patients receiving TRT. We also describe the Basaria paper separately as it has impacted and will continue to impact subsequent meta-analyses. We have described a recent and reasonably well-done observation study using claims data. This latter study is worth discussing given its size and the effort put into matching of the intervention and control groups.

While there have been sporadic reports of TRT increasing CV risk, the published literature over the past 20 years has generally not supported such an association. The results of several large meta-analyses have not supported a causal role between T treatment and CV adverse events. However, the majority of studies included in these meta-analyses have been low-quality studies conducted in heterogenous populations and utilizing different products with different routes of administration. The availability of more conclusive data

from larger and longer duration studies may assist in changing the confidence in current recommendations.

The recommendations have taken into account the positions of both Health Canada and the FDA.

THE METABOLIC SYNDROME

Disorders of glucose metabolism centered on insulin resistance marked by obesity, the metabolic syndrome, or frank type 2 diabetes mellitus (T2DM) have been associated with low T levels.[221] Insulin resistance itself has been linked to decreased T production in men.[222] The prevalence of low T levels in obesity and the metabolic syndrome is increased and can be as high as 33% in men with T2DM.[223-226] The association in type 1 diabetes mellitus, where insulopenia is the hallmark, is not that well defined.[224,225]

Improvements in body composition with TRT and metabolic parameters have been positive, but not universal. Mårin and others have long shown an improvement in visceral fat with TRT in hypogonadal males.[227-229] TRT improves insulin resistance, independent of BMI.[230-232] In hypogonadal men with T2DM, TRT provides better glycemic control and improves lipid parameters in many studies[189,231,233,234] but not in all.[232,235]

DIABETES MELLITUS AND OBESITY

Background
Obesity, the metabolic syndrome (MetS) and T2DM, often co-exist with hypogonadism.[30,33,173] In large observational studies, men with MetS and T2DM have been shown to have significantly lower T levels (approximately 2.5 to 3.0 nmol/L lower) compared with their metabolically healthy counterparts.[236-238] These associations persist even after adjusting for age, BMI and insulin resistance.[238-240] T levels are also lower among men with ED.[238]

There has been considerable debate surrounding the relationship between T and adiposity-related metabolic disorders, specifically regarding the extent to which low T causally contributes to diabetes and its complications, or whether low T is merely a biomarker, coexisting with these disorders because of some common pathophysiology. It is possible that a bidirectional relationship exists between visceral fat and low T levels.[173,241] One explanation is that aromatase in visceral adipose tissue converts androgens to estrogens, which in turn inhibit the HPGA, and promotes the accumulation of fat. Visceral fat is also associated with the release of proinflammatory cytokines which may further disrupt the HPGA.

Weight loss whether by bariatric surgery or a low-calorie diet has been shown to be associated with a significant increase in SHBG, TT and FT levels.[238] The improvement in T levels appears to be greater with higher degrees of weight loss. This is further supported by

the biologic association between adiposity-associated metabolic disease and hypogonadism, but additional research is needed to clarify the mechanisms underlying this as many metabolic parameters improve with weight loss, and T levels may simply be an overall marker of metabolic health.

Body composition
In order to evaluate the effect of T replacement on body composition in hypogonadal men aged 45 years and older, Bhasin and associates performed a meta-analysis of RCTs longer than 90 days in duration and published up to June 2005.[242] T replacement was found to be associated with a 2.7 kg (95% CI = 1.6 to 3.7 kg) increase in lean body mass, right-hand grip strength and a 2 kg (95% CI = −3.1 to 0.8 kg) reduction in whole body fat mass compared with placebo. Body weight change did not differ significantly between the groups. The trials included in this meta-analysis were of variable quality and were heterogeneous in terms of inclusion criteria, T dose, duration of treatment, adequacy of blinding, and outcome measurements.

The mechanisms underlying the effects of androgens on body composition are complex and are thought to involve an increase in muscle protein synthesis, hypertrophy of type I and type II muscle fibres, and an increase in the numbers of myonuclei and satellite cells, but not an increase in muscle fibre number.[242-245] Androgen suppression of preadipocyte differentiation is one possible mechanism of fat mass inhibition that may explain the observed fat mass reduction in men treated with androgens.[246] Clinical trials have evaluated the role of dihydrotestosterone (DHT) in mediating the anabolic effects of T on muscle by using T in combination with either dutasteride, a 5-alpha reductase blocker that inhibits the conversion of T to DHT, or placebo.[247] There were no between-group differences in body composition, muscle strength or sexual function, suggesting that DHT may not be essential for mediating the anabolic effects of T on muscle.

The effect of exercise and weight loss on testosterone levels
The literature supporting the improvement of T levels with weight loss is based on small studies, many of which are prospective and without a control group. The most comprehensive review of this topic to date was conducted by Corona and colleagues who performed a meta-analysis of 24 studies conducted between 1969 and 2012, evaluating the effect of weight loss on sex hormone levels through either a low-calorie diet or bariatric surgery.[248] This meta-analysis included RCTs, as well as controlled cohort before-and-after comparison studies conducted in the same group of patients and between two or more groups of participants receiving different interventions. The authors found weight loss to be associated with an increase in both TT and FT levels, a rise in gonadotropin levels and a decrease in estradiol. After adjustment for the baseline BMI and baseline T level, only the amount of weight lost was the best determinant of the rise in TT. Because of the variable quality of the studies included in this meta-analysis, the quality of the data is rated as being low to moderate at best, with the results being heavily weighted by a few studies. Where possible, lifestyle interventions aimed at treating obesity and its metablic and mechanical complications should be undertaken as this may result in clinically significant improvement in T levels as well as having a positive impact on cardiometabolic parameters.

Type 2 diabetes mellitus and testosterone replacement therapy
There is a high prevalence of hypogonadism and ED among men with T2DM, and up to 40%
of men with T2DM have hypogonadism.[249] TRT is meant to restore physiological levels of T
in men who are hypogonadal, with the intention of improving symptoms. The literature
supporting the improvement in body composition with TRT has been outlined above. TRT
may also have an impact of metabolic parameters such as glycemic control, BP and lipids.
Cai and associates performed a meta-analysis of studies published through to July 2013.[250]
They identified five RCTS of moderate-to-high quality conducted in patients with T2DM
and hypogonadism. The subjects received TRT or placebo, and the effects on glycemic
control, lipids, body composition and blood pressure were assessed. The pooled data
showed a modest improvement in fasting plasma glucose and A1c of −1.1 mmol/L (95% CI
= −1.88 to −0.31 mmol/L) and −0.87% (95% CI = −1.32 to −0.42%) respectively. There was
a modest improvement in TG of −0.35 mmol/L (95% CI = −0.63 to −0.07 mmol/L) but no
improvement in other lipid parameters or BP. The trial duration was variable among the
studies these studies. More recently Hackett and colleagues estimated the improvement in
A1c in hypogonadal men with T2DM treated with TRT to be far more modest with an
estimated mean difference of −0.10% (95% CI = −0.34 to −0.05%) at 18 weeks and −0.11%
(95% CI = −0.34 to 0.13%) at 30 weeks.[251] The total cholesterol was only marginally
improved −0.30 mmol/L (95% CI = −0.46 to −0.13 mmol/L) and there were no
improvements in triglycerides, other lipid parameters or BP. The improvements
demonstrated in these studies are of questionable clinical significance, and are not
consistently demonstrated across trials. No metabolic deterioration was observed in either
of these studies.

Diabetes mellitus, erectile dysfunction and testosterone
Diabetes is a significant risk factor for the development of ED. Results from the
Massachusetts Male Aging Study (a community-based, random sample observational
survey of men aged 40 to 70 years old) found that, in comparison with a 9.6% prevalence in
the general population, the prevalence of ED in diabetic men is 28%.[252] For a man with
diabetes, the lifetime risk of developing ED is 75%, and ED appears at an earlier age in
comparison with nondiabetics.[252,253]

The mechanisms contributing to ED in men with T2DM are multifactorial and include
impaired vasodilatory signaling, non-adrenergic non-cholinergic dysfunction, endothelial
dysfunction, oxidative stress, cavernosal hypercontractility, veno-occlusive dysfunction,
and hypogonadism.[253] Men with T2DM have more severely impaired erectile parameters
than eugonadal men with T2DM. Investigations have found erectile parameters in
hypogonadal diabetic men were more severely impaired than those in eugonadal diabetic
patients.[53,254,255] Furthermore, men with T2DM and ED had worse disease-specific health-
related quality of life, and the severity of the ED was significantly associated with the T
level.[53,254,255]

Among men with T2DM and ED, 20% had TT less than 8 nmol/L, and 31% had TT between
8 and 12 nmol/L. ED was present in 72% of men with TT less than 8 nmol/L, and in 71% of
men with TT between 8 and 12 nmol/L.[256]

Several clinical trials have shown that PDE5-I treatment improves ED in diabetic men, but the results may not be broadly generalizable due to trial selection bias and the exclusion of men with poor glycemic control.[257] In one study in men with ED, only 56% of T2DM patients responded to a PDE5-I compared with 87% of nondiabetic men.[258] Also, although there is an initial response to ED treatment in men with T2DM, the effects may not be sustainable over time.[253,254]

Men with diabetes and ED and not responding to treatment with sildenafil had significantly lower T and more depressed libido at baseline compared with age-matched controls.[259] TRT was shown to improve ED in up to 70% of these previous non-responders. Among patients with ED and T2DM receiving oral antidiabetic agents, low T may be responsible for failure to respond to sildenafil citrate, and combination treatment with TRT and sildenafil may restore sexual function in these patients.[259]

Among men with T2DM, ED was found to be compromised at a TT level of 403.5 ng/dL or less (sensitivity 63.3%, specificity 94%).[252] This threshold identified ED in 33 of 38 men with TT levels below 403.5 ng/dL, while ED was present in 57 of 157 men with TT levels greater than 405.3 ng/dL. The authors proposed a TT cutoff value of 405.3 ng/dL as an indicator for the initiation of TRT in men with T2DM, and recommended further prospective controlled trials.

Summary

Grossmann reviewed the relationship between T and diabetes, and commented that population-based studies have shown low T is common in men with T2DM and the MetS.[241] The metabolic effects of TRT have been reported by several investigators, and their data are reported in Table 11.[231,233-235,260] The management of the aging, overweight diabetic male should incorporate recommendations for weight loss and exercise. Success in these areas will provide health benefits and will raise T levels. Until additional data from adequately powered clinical trials are available to clarify risks and benefits, T therapy cannot be recommended to treat overweight hypogonadal males with T2DM.

CANCER

Breast cancer

Breast cancer in men is rare, representing less than 1% of all breast cancers identified in both men and women.[261] The greatest risk factor for developing male breast cancer is genetic; the lifetime risk is approximately 7% (80- to 100-times greater than that of the general population) in men with an inherited *BRCA2* mutation.[262] Alterations to the estrogen-testosterone ratio also increase the risk, and this is seen in men with Klinefelter syndrome, obesity with a BMI greater than 30, and liver cirrhosis.[262] Although elevated levels of estrogen and decreased levels of T appear to create a higher risk for male breast cancer, these have not been demonstrated in any studies of male breast cancer.

Since low levels of androgens may promote the development and growth of male breast cancer, it is understandable that TRT has not been identified as a risk factor by organizations such as the Canadian Cancer Society.[261]

Published reports of breast cancer in men receiving TRT are uncommon and are limited to case reports.[263-265] Until more data are available, T therapy should be used cautiously in men with a history of breast cancer.[263-265]

Prostate cancer

Prostate cancer (PCa) is the most common non-dermatological malignancy in North American men.[266] Following the demonstration over 65 years ago of a rapid progression of PCa in patients receiving T supplementation and regression of the disease by suppressing androgen levels, the belief was firmly established that T promotes the development and progression of PCa.[267] More recently, evidence has appeared challenging this long-held belief. Additional support has been provided by several other reports and, most convincingly, by an analysis of prospective studies which clearly established a lack of association between the risk of PCa and endogenous serum T concentrations.[268]

Influence of endogenous testosterone levels on prostate-specific antigen and prostate cancer risk

Among 150 men without PCa, Monath and associates demonstrated that physiologic variations of endogenous serum T levels within the normal range do not affect serum prostate-specific antigen (PSA).[269] Moreover, data from the Massachusetts Male Aging Study, a large prospective, population-based random sample, highlighted the lack of an association between endogenous serum levels and PCa risk.[270] In a case-control investigation of 708 Scandinavian men with PCa compared to 2242 men without PCa, no support was found for the hypothesis that high levels of circulating androgens within a physiologic range stimulate development and growth of PCa.[271]

In 2008, Roddam and colleagues performed a collaborative analysis of the world-wide data from 18 prospective studies relating serum concentrations of sex hormones among 3886 men with PCa and 6438 control subjects without PCa.[268] No association was identified between the risk of developing PCa and endogenous serum concentrations of sex hormones including T (total or free) and estradiol.

Among men with PCa, several studies have linked *low* levels of endogenous serum T with PCa,[272] and with adverse prognostic features including advanced cancer stage[273,274] and grade,[275-278] higher rates of positive surgical margins,[279] biochemical progression following treatment,[274] and a decreased overall survival among men with metastatic disease.[280]

However, other early studies have reported higher T levels linked with PCa. In 222 men who developed PCa and 390 matched controls in the Physicians' Health Study, a significant trend was found between the risk of PCa and higher levels of serum T.[281] A similar association was reported for 420 patients undergoing biopsy for suspicion of PCa.[282] These findings were also supported by a meta-analysis showing that men whose T levels were in the highest quartile were more than 2-times more likely to develop PCa.[283]

It should be kept in mind that the levels of serum androgens (both T and DHT) do not necessarily reflect the hormonal intraprostatic micro-environment,[284] and that the intraprostatic androgen concentrations remain significant even in medically castrated men.[285] Taken together, these observations have led to the development of models aimed at explaining the discordance between the evident dependence of the prostate on androgens and the stimulation of PCa following androgen administration in some situations but not in others. The "saturation model" purports that the maximal androgen-stimulated PCa growth is reached at relatively low serum T levels, therefore there is limited influence of T therapy on PSA and prostate cancer risk.[286]

Several investigations have shown that TRT has not been associated with clinically significant increases in PSA or an increased risk of prostate cancer. In a systematic review of published studies of TRT in men with hypogonadism, Bhasin and associates reported that the average increase in serum PSA was between 0.30-0.43 ng/mL following the initiation of TRT.[287] Similarly, in a meta-analysis of 19 RCTs designed to determine the risks of adverse events associated with TRT in older men, Calof and colleagues failed to identify statistically significant differences in the rates of PCa, PSA concentrations greater than 4 ng/mL, and prostate biopsies among men treated with T versus a placebo group.[202]

A Toronto-based group identified no significant correlation between simultaneous PSA and serum T concentrations among eugonadal, untreated hypogonadal and hypogonadal men receiving TRT.[288] Among the 229 hypogonadal men receiving TRT, mean total serum T levels increased significantly with treatment. However, mean PSA levels did not increase in a statistically or clinically significant manner with T therapy; the mean PSA increase from baseline was .05 ng/mL.

Among 81 hypogonadal men on T therapy for 36 months, Coward and associates reported that PSA levels remain stable after normalization of T with treatment, and the incidence of PCa was no greater than that in the general population.[289] A recent report[290] showed no changes in PSA in a group of 322 hypogonadal men participating in a placebo-controlled dose ranging trial of oral T undecanoate. Finally, in a systematic review and meta-analysis of 51 T trials focusing on potential adverse effects of TRT, investigators concluded that T use did not result in an increase in PCa risk.[140]

Monitoring of the prostate on testosterone therapy
Prostate health should be assessed by digital rectal examination (DRE) and PSA prior to the initiation of therapy, after 3-6 months of treatment and annually thereafter in accordance with the evidence-based guidelines for PCa screening, depending on the age and race of the patient.[25,291,292] Significant increases in PSA while on T therapy should not be attributed to the use of T alone, and should be investigated irrespective of the use androgen therapy.

Urological consultation should be sought if any of the following are observed:[287,293-295]
- PSA is elevated for the patient's age and prostate size;

- Among patients with a baseline PSA of >4, an increase in PSA of > 0.75ng/mL is observed within any 18-month period of treatment;
- Among patients with a baseline PSA of <4, a PSA increase of >0.4ng/mL is observed within any 18 month period of treatment;
- A prostate abnormality is identified on DRE.

Absolute and relative contraindications to testosterone replacement therapy related to prostate health

Several studies have recently been published documenting the experience of TRT among men previously diagnosed with PCa – both treated (radical prostatectomy, radiation therapy) and untreated (active surveillance).[286,296-308] Despite consistent reports of no clear increase in rates of biochemical and clinical recurrence or progression, published studies to date for the most part include small numbers of subjects, and lack control groups and long-term follow-up.

For men with untreated PCa, the global experience remains very small and the results are inconsistent. One of the studies showed no evidence of progression of the prostatic malignancy in any of the patients,[296] while another reported some men remained stable while receiving exogenous T but others showed biochemical progression which regressed following discontinuation of therapy.[309]

Based on the current best evidence, professional societies have identified patient characteristics in whom the use of TRT is an absolute contraindication or a relative contraindication.[25,291] This information is reproduced here.

TRT is contraindicated in men with metastatic PCa and in men with treated PCa who are at high risk of recurrence. This is an absolute contraindication.

In men who have been treated for localized PCa (with surgery or radiotherapy), who are currently without evidence of active disease (ie, measurable PSA or PSA progression, abnormal rectal examination, evidence of bone/visceral metastasis), and who show symptomatic and biochemical TD can be cautiously considered for T therapy. This is a relative contraindication.

PROSTATE HEALTH – BENIGN PROSTATIC HYPERPLASIA

T (after conversion by 5α-reductase to DHT) has a fundamental role in the development, normal growth and function of the prostate.[310] This growth-promoting effect on the gland may lead to the development of benign prostatic hyperplasia (BPH). BPH is characterized by an increase in the population of epithelial and stromal cells in the peri-urethral area of the prostate. Despite concerted investigations, the indisputable reason for the development of BPH in association with aging has not been elucidated. Although androgens are clearly necessary, they are not the single causative factor.[311]

There is a scarcity of reliable information on the relationship between endogenous levels of T and the presence of BPH, and reports have been inconsistent. An Austrian cross-sectional study found that T levels did not correlate with prostate volume or voiding parameters.[312] These results were supported by a study of African-American men[313] and, more recently, by a large cross-sectional study of Korean men.[314] But other investigators have reported dissimilar results.[315,316] Comparisons among studies are not particularly helpful because of the heterogeneity of the populations and the criteria for outcome measures.

Better data are available regarding the effect of T treatment on the non-malignant prostate. As early as 1994, in a controlled cross-sectional study it was found that adequate T treatment of hypogonadal men resulted in prostate volume and PSA levels comparable to those of age-matched eugonadal men.[317] Tenover conducted a study with T enanthate injected weekly for 3 months, and her observations did not show any increase in prostate volume or post-voiding residual urine.[318] Similarly, lower urinary tract obstructive symptoms did not worsen, and the changes in PSA were insignificant in a study of men receiving T treatment for 2 years.[319] There are other relatively short-duration studies showing negligible detrimental effects of T treatment on lower urinary tract obstructive symptoms.[320] Only one early study was long term, and it also failed to show adverse prostate events in hypogonadal men treated with T.[116] In addition, there are a number of clinical trials using a variety of T preparations confirming these observations and reporting no cases of urinary retention in carefully selected populations.[321] Although there is consistent evidence across heterogeneous studies, there is no meta-analysis of pooled date to provide a more definitive answer.

Despite the absence of high-quality studies correlating T use with worsening lower urinary tract symptoms (LUTS), clinical experience and case reports suggest caution in treating men with very severe LUTS symptoms. Please refer to the monitoring section of these Guidelines for monitoring recommendations.

SEXUAL FUNCTION

Testosterone and sexual function

T is required for normal sexual development and secondary sex characteristics.[322] In the adult male, sexual alterations are partially related to androgen status. Sexual drive, erection, ejaculatory capacity, and accessory organ function (eg, volume of ejaculatory fluid) require T at variable threshold levels in individual men. In general, younger men retain better sexual function than older men as serum T levels fall.[323]

Aging is not invariably associated with decreased sexual activity, but activity declines from 83.7% among men between 57 and 64 years of age to 38.5% for those over 75 years old. The decline in sexual activity spans the whole spectrum: ED (37%), diminished libido (28%), and anorgasmia (20%).[324]

Sexual dysfunctions have both organic and psychological etiologies, so both components need to be considered in hypogonadal men. In a study that evaluated the association

between T levels and different psychopathological symptoms and traits in men seeking treatment for sexual dysfunction, men with lower T levels showed a positive correlation with depressive and anxiety (somatized and phobic) symptoms, whereas men with higher or elevated T levels were associated with more histrionic/hysterical traits, had better reported sexual functioning and better penile blood flow, and more satisfying sexual relationships.[325]

Sexual symptoms associated with hypogonadism

In a study identifying symptoms of TD, the presence of at least three sexual symptoms (decreased frequency of morning erections, decreased frequency of sexual thoughts and ED) had a syndromic association with decreased T levels (total T levels of less than 11 nmol/L and a free T level of less than 220 pmol/L).[7] Delayed ejaculation (DE) has also been associated with reduced T levels, whereas there are mixed data regarding whether premature ejaculation (PE) is correlated with T levels.[326]

Libido
Low libido, or reduction in sexual drive, is multifactorial and is often affected by various biopsychosocial domains. T is one of the major hormones responsible for sexual motivation and drive for sexual activity. Normal libido requires adequate levels of androgenic hormones. The correlation between libido and T levels is poor as the T levels required to sustain normal sexual interest are somewhat low. Adequate T levels are therefore required, but are not alone sufficient for the maintenance of normal libido.[327]

Libido is self-reported and reduced libido is a hallmark of hypogonadism. Decreased frequency of sexual thoughts and urges is one of the more specific symptoms associated with TD, being apparent with a threshold of TT below 8.0 nmol/L and of cFT below 160 pmol/L.[7] There are several levels of evidence found with large cross-sectional and longitudinal studies showing that lowered T levels affect libido, but the prevalence of TD in isolated hypoactive sexual desire disorders is low.[2]

One study showed that when T levels fall to less than 15 nmol/L, low libido may become evident.[36] On the other hand, the correlation between T and improvement in sexual interest during T supplementation has been confirmed in a meta-analysis of 11 studies, although this beneficial effect was found only in hypogonadal men.[328]

Libido is commonly comorbid and/or consequential of other sexual dysfunctions (such as ED and DE) whose incidence can also be affected by hypogonadism.[329] Men on androgen deprivation therapy (ADT) for PCa consistently report loss of libido as their serum T levels fall and, if on intermittent ADT, experience some recovery of libido and vigor as their T levels rise.[330] In a small study, older men on long-acting GnRH agonist to suppress endogenous T production were randomized to receive one of five doses (25, 50, 125, 300, and 600 mg) of T enanthate weekly for 20 weeks; it was found libido changed by T dose only among men who reported being sexually active at the beginning of the study.[331]

Orgasm
While low libido is multifactorial, the co-existence of ED and delayed orgasm increases the likelihood of hypogonadism. Hypogonadism increases the orgasmic threshold and TRT may decrease this threshold in some men. A recent meta-analysis of controlled randomized studies convincingly demonstrated a positive effect of T administration versus placebo on the orgasmic component in hypogonadal men.[328] However, in a series of 90 men of various ages consulting for anorgasmia or delayed orgasm, only one had TD, stressing the multifactoral nature sexual dysfunctions.[327]

Delayed ejaculation and premature ejaculation
In a large series of subjects (n= 2652) consulting for sexual dysfunction, 674 (25.2%) and 194 (7.3%) reported PE and DE, respectively.[326] The risk of PE was reduced and that of DE (to anejaculation) was increased as T levels declined, independent of selective serotonin reuptake inhibitor (SSRI) use. A similar effect was noted for rising levels of prolactin and TSH. All of these associations were confirmed after adjustment for age, general psychopathology and use of SSRI antidepressants, indicating that the endocrine system is involved in the control of ejaculatory function and also that prolactin, TSH and T play an independent role. However, in the European Male Ageing Study, no relationship was found between PE and TT levels in all age tertiles, whereas low T was a risk for DE (at least in middle-aged men).[332] In contrast, in the younger age group, DE is relatively uncommon.[333,334]

In summary, there is controversy as to the efficacy of T supplementation. Although the preponderance of the evidence supports a positive effect of T on sexual functioning, there are studies that failed to showed efficacy.[335]

INFERTILITY

Testosterone and Male Reproduction/Infertility
T is produced by the Leydig cells of the testis, and T levels in the testis are 100-fold greater than those in the blood.[336] T regulates spermatogenesis by its effect on Sertoli cells, and also regulates the growth factors and cytokines critical to spermatogenesis. The development and maintenance of reproductive tissues (testis, epididymus, vas, seminal vesicles, prostate, penis) is dependent on T, and T also regulates sex drive, erections and orgasmic function.

Although there is considerable inter-individual variation, spermatogenesis can be maintained by relatively low levels of intra-testicular androgens, but full spermatogenesis demands synergistic activities of T and FSH and LH.[337]

T's activity in target tissues depends on activation of the androgen receptor (AR). These receptors are located in both the cytoplasm and the cell nucleus in the target tissues. AR defects may result in abnormal male sexual development. If the defect is less severe, male

infertility is a possible result. In 20% to 30% of infertile men, circulating levels of T are low.[338]

Administration of exogenous T in sufficiently large amounts leads to a suppression of FSH with ensuing oligospermia.[339] This mechanism has been exploited with limited results as a means of male contraception. On the other hand, men with TD may also have reduced sperm production. Given the increased availability and success of *in vitro* techniques for egg fertilization, these men should not receive T while attempting artificial fertilization.

Further supporting the findings of our needs assessement (*vide supra*), a prospective survey in Canada found 1.3% (59/4400) of men attending a male infertility clinic were taking T, prescribed by a variety of physicians.[340] While the majority were being treated for hypogonadism, 12% (7/9) had been prescribed T inappropriately to treat infertility. The majority (88.4%) of men were azoospermic while on treatment. Following discontinuation, spermatogenesis was recovered in 65% without other known causes of azoospermia.

LH has long-term trophic effects on the Leydig cells. Inhibition of LH (eg, by steroid administration) will cause Leydig cell atrophy and loss of cellular volume, and will impair the cell's ability to secrete T in response to LH. Alcohol is toxic to Leydig cells, and it interferes with steroidogenesis. Chronic alcohol abuse and chronic steroid use are less common causes of infertility.[341,342]

In adult men with hypogonadotropic hypogonadism, gonadotropins have been used to stimulate Leydig cells to temporarily restore spermatogenesis.[343] The results, however are variable due to factors such as the cause of the infertility, testicular volume, and a history of cryptorchidism.[344]

Varicocele in infertile males can be linked with Leydig cell dysfunction and is a risk factor for low T levels. Although the mechanism is not known, several theories have been proposed, including venous stasis, increased testicular temperature, oxidative stress, and resulting toxic environment. Recent literature has demonstrated improved T levels following microsurgical varicocelectomy in men with varicocele and low T preoperatively.[345] A review of three adequately powered studies published in 2011 concluded that varicocele repair in hypogonadal men with unilateral or bilateral varicocele was able to restore T to the eugonadal range.[346] However, the surgical repair of varicocele as a mechanism to restore fertility remains a controversial topic.

O'Brien and associates evaluated hypogonadal symptoms and erectile dysfunction in 302 infertile men and a control group of 60 fertile men.[347] Relevant clinical information was collected, and all men were administered the ADAM questionnaire and the Sexual Health Inventory for Men (SHIM) questionnaire. In the infertile group, 38% reported significant symptoms and SHIM scores were abnormal in 28%. In a subgroup with nonobstructive azoospermia, 25% reported symptoms and SHIM scores were abnormal in 27%. Fewer men in the fertile group had symptoms or an abnormal SHIM score (21% and 11%, respectively). Compared with the fertile group, the infertile group had a significantly higher prevalence of erectile dysfunction (P=0.007).

TRT in infertile men can lead to testicular atrophy and may impair spermatogenesis.[149] CC is a selective estrogen receptor modulator that promotes testicular spermatogenesis and increases T levels by blocking estradiol feedback at the hypothalamus, thus increasing pituitary release of LH and FSH.[348] Investigators have shown CC to be safe, and to raise the levels of T and gonadotropins.[148,149] In a recent investigation in hypogonadal men, CC was as effective as T gel in restoring T levels, although both were less effective than parenteral T.[349] Further support to these observations is given by a study demonstrating that 60% of hypogonadal men respond to CC.[350] All three produced similar scores for patient satisfaction on a quantitative ADAM questionnaire.[48,349]

CC can be effective treatment for hypogonadism in appropriate patients. The product is administered orally every second day, and the dose is adjusted to achieve a T target range. In Canada, CC is only approved for use in women for ovulation induction. Enclomiphene citrate is the trans isomer of CC, and a recent phase 2 trial against topical TRT in men with secondary hypogonadism demonstrated its ability to preserve sperm production and to increase levels of T, estradiol and FSH at a daily dose of 12.5 mg or 25 mg.

In peripheral tissues, the aromatase enzyme is responsible for the metabolism of T to estradiol. Excess aromatase activity (identified by an abnormal T/estradiol ratio) can be identified in some men with severely defective sperm production. By blocking T metabolism to estradiol, aromatase inhibitors (testolactone [not available in Canada], anastrazole and letrozole) can increase endogenous T production and increase sperm production. In infertile men with nonobstructive azoospermia, these drugs can return sperm to the ejaculate. The use of these drugs is not approved for this purpose, and more clinical trial data are required.[351]

The correction of metabolic abnormalities associated with TD is a prime consideration not only in men with infertility. Although there is a scarcity of reliable studies assessing the effects of treating the Metabolic Syndrome in cases of infertility, there is increasing evidence showingthat this may be a worthwhile approach.[352] *As mentioned previously, semen parameters improve following bariatric surgery in obesity-related hypogonadism and infertility.[179]*

In situations where maintaining fertility is a priority, patients with hypogonadism should be referred to specialists with expertise in the field.

OSTEOPOROSIS

Researchers in France evaluated sex hormones and bone turnover markers in 65 osteoporotic men and in an age-matched control group of 40 men.[353] They found the mean level of SHBG was 38% higher in middle-aged men with osteoporosis, and it showed a significant negative correlation with BMD. SHBG also correlated strongly with serum

C-telopeptide of type I collagen (sCTX, a marker of bone resorption). TT correlated weakly with BMD.

Polish investigators evaluated BMD and sex steroid hormones in 55 men with CAD and 30 matched controls.[354] They were unable to find a correlation between sex hormones concentrations and BMD; the lowest femoral neck BMD was found in men with the most advanced form of CAD. After adjusting for age and BMI, however, their analyses showed lower serum T in a subgroup of 26 men with lower BMD (T-score less than −1.0 at lumbar or femoral region) compared to the 25 men with CAD and normal BMD.

Twenty-seven older men (age 65 to 85 years) with minimal traumatic hip fracture (MTHF) were recruited into a study between 1 and 3.5 months following the event, thus avoiding the acute and surgical stress that may lower serum T and serum T determinations.[355] There were three control groups: older patients with nonimmobilising stroke (age 65 to 81 years; n=12); healthy younger men (age 20 to 30 years; n=138); and healthy older men (age 60 to 80 years; n=110). Serum T, bioavailable T and free T were significantly lower in MTHF men compared to men after stroke. Approximately 90% of MTHF men had serum T levels 2 standard deviations (SD) below the mean of the healthy young men, and 30% had levels 2 SD below the mean of the healthy older men (less than 11 nmol/L and less than 6 nmol/L, respectively). The mean of trabecular BMD at the spinal level was significantly lower in MTHF men compared with that of men after stroke. The authors suggested low serum T was relevant for bone loss and the development of fragility fractures in men.

Investigators in The Netherlands reported that 8.3% of men with osteoporosis who presented with clinical vertebral or nonvertebral fractures at a hospital emergency department had hypogonadism, defined as a complex of symptoms plus a total T level less than 8 nmol/L.[356]

A Brazilian investigation in men over 50 years of age with osteoporosis also found a 2-fold increase in LOH (cFT less than 6.5 ng/dL), compared with a matched control group with normal BMD (25% versus 12.2%, odds ratio 2.08, 95% CI = 1.14 to 3.79).[16] The prevalence was higher than that observed by Fink and associates in the Osteoporotic Fractures in Men Study (MrOS) of 2447 community-dwelling men aged 65 years and older.[357] BMD and sex steroid measurements were obtained at baseline; osteoporosis was found in 130 men (5.3%), and 73 men (3.0%) had low T (T deficient; TT less than 6.9 nmol/L). The investigators found a 2-fold increase in low T in men who had osteoporosis compared to men with normal BMD (6.9% vs. 3.2%). In T-deficient men, the proportion with osteoporosis was 2-fold increased compared to men with normal T (12.3% versus 6.0%).

Ensrud and colleagues followed 1267 MrOS study participants over an average of 1.8 years and evaluated the 132 men who lost weight.[358] They found an increased rate of bone loss at the hip that was most pronounced in men with a higher baseline SHBG, lower baseline available estradiol, and a greater decline in BAT.

Ten-year data from the Taiji Cohort Study in Japan were available for 153 men in four distinct age cohorts (40 to 49 years, 50 to 59 years, 60 to 69 years, and 70 to 79 years).[359]

The investigators adjusted their analyses for age and BMI, and found the level of FT was significantly related to the rate of BMD change at the femoral neck at three years, but not at 7 or 10 years. They concluded that free T serum levels could be a useful predictor of short-term femoral neck bone loss.

Thus it seems prudent to measure T levels in men with osteoporosis and especially men with fragility fractures. It is also prudent to measure bone density in those men who are found to be hypogonadal.

SARCOPENIA

In older people, loss of muscle mass has been defined as sarcopenia.[360] This loss is associated with a loss of muscle strength and power, although many other causes can produce similar outcomes. Sarcopenia has been defined as a clinical syndrome, and the definition has been recently expanded to include low muscle function.

Investigators at the University of Connecticut Health Center evaluated older community-living men and women and found the prevalence of sarcopenia was 22.6% in 195 women aged 64 to 93 years, and 26.8% in 142 men aged 64 to 92 years.[361] The prevalence was higher in volunteers 80 years and older; 31.0% and 52.9% in women and men, respectively. BMI was a strong predictor of skeletal muscle mass in women and men. In men, strength, power and BAT were also predictive.

van den Beld and colleagues found a relationship with BAT (non-SHBG-bound) and muscle strength in 403 healthy men aged 73 to 94 years.[362] Independent of age, serum T was positively related to isometric grip strength and leg extension strength.

Similar results were obtained by Perry and associates.[363] Age was inversely related to T and bioavailable T in 65 African-American men aged 70 to 102 years, and T was correlated with functional tests and with upper-limb and lower-limb strength.

Men with hypogonadism may present with sarcopenia, either as part of a symptom complex or as their major symptom. If the sarcopenia is part of a symptom complex, then other symptoms and or a complex of symptoms may lead to the measurement of T. In the absence of other identifiable causes of the loss of muscle function and mass, measuring the T level may be appropriate.

ANEMIA

Analyses of data from the Third National Health and Nutrition Examination Survey (NHANES III) identified anemia in 11.0% of noninstitutionalized American men (and 10.2% of women) aged 65 years and older.[364] The cause was indeterminate in one-third of all cases.[364] In older persons, anemia is associated with an accelerated decline in physical functioning and a high risk of disability.[365]

Low T has been identified as a risk factor for anemia in older persons.[365] In an Italian study of 396 men aged 65 years and older, Ferrucci and colleagues found that men in the lowest quartile of total T were 5.4 times as likely to have anemia as men in the highest quartile, with 65% of cases unexplained. The three-year incidence of anemia was 8.3% in 274 men initially without anemia, with a higher likelihood for those men in the lowest total T quartile. The investigators concluded that, in older persons, low T was a risk factor for anemia.

Grossmann and associates studied 464 Australian men with T2DM and found that 24% had anemia (Hgb less than 137 g/L in men aged less than 60, and less than 132 in men aged 60 and older), and 43% had low T (total T less than 10 nmol/L).[366] Low T was found more frequently in men with anemia in comparison to men with Hgb in the normal range (53% versus 41%, $P<0.001$]. While eGFR was lower in patients with anemia (66 mL/min/1.73m^2 versus 79 mL/min/1.73m^2, $P<0.05$), erythropoietin levels were higher (23 IU/L versus 16 IU/L, $P<0.05$), and 83% had erythropoietin levels within the normal range, indicating an inappropriate renal response to anemia in this population.

American investigators evaluated anemia and T in men older than 50 and diagnosed with pituitary adenoma, and found 46.3% of 67 men with low serum T also had anemia (defined as Hct less than 0.4).[367] The investigators also determined that men with low T had a lower average Hct compared to men with normal T (0.399 versus 0.456, $P<0.001$).

Anemia may be diagnosed in conditions associated with a low T level, but is rarely due solely to low T. In the investigation of anemia, if no other etiology is found, then one should consider the measurement of serum T.

CHRONIC ILLNESS

There are many case reports of hypogonadism in association with a variety of chronic medical conditions. This section will present information on the presence of hypogonadism and its response to TRT in two well-studied conditions.

Long-term glucocorticoid use leads to alterations in the hypothalamic-pituitary-testicular axis with a high prevalence of low T[342] and decreases in muscle and bone mass.[368] In a 12-month study in 51 men, Crawford and colleagues observed a significant increase in spine BMD (4.7%), lean body mass (3.5%) and improved quality of life.[369] There was no significant difference in hip BMD. A smaller study in 15 asthmatic men on long-term glucocorticoid therapy found a nearly 4% significant rise in lumbar BMD after 12 months of monthly T injections.[370] There were no changes in hip BMD. Data on fracture rates and long-term data in large groups of patients are lacking.

Long-term opioid use is known to cause hypothalamic-induced hypogonadism affecting up to 5 million people in the US.[371,372] Finch and colleagues reported a prevalence of low T levels in 87% of men receiving intrathecal opioid, with 69% exhibiting low bone mass.[373]

Following TRT for more than 2 years, the rate of low bone mass in these 11 men was reduced to 27%. In a 12-month Italian study, the correction of morphine-induced hypogonadism in 17 chronic noncancer pain patients improved pain rating indexes (QUID, the reconstructed Italian version of the McGill Pain Questionnaire), AMS sexual dimension scores, and SF-36 Mental Index scores.[374] Hallinan and associates found that 54% of 103 men with a mean age of 37.6 years receiving maintenance methadone or buprenorphine had low T levels, and low T levels were found in 65% of the methadone-treated men.[375] Rubinstein and colleagues made the very pertinent observation in a group of 81 men receiving long-term opioids there was a high prevalence of hypogonadism that was associated with the duration of action of the opioid but not with its total daily dose.[376]

HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION

The presence of low levels of T is common in HIV-infected men.[377,378] High rates of hypogonadism were reported prior to the introduction of highly active antiretroviral therapy (HAART) or combined antiviral therapy (cART), mainly in association with low levels of FSH and LH.[379] While hypogonadism still appears more common in HIV-infected men compared to the general population, immunoassay determinations of total and FT can be affected by altered albumin levels and increased levels of SHBG, resulting in variations in the reported prevalence.[379,380]

In AIDS with wasting, there is a correlation between lower androgen levels and loss of both weight and muscle mass, and depressed mood.[381] TRT has shown modest improvements in mood, body composition or muscle strength in many of the early studies in this population, most of which were of short duration.[379]

The TRiUS registry, an observational study of 849 hypogonadal men, identified an improvement in depressive symptoms and sexual function and stabilization in weight and bone mass in the HIV/AIDS cohort of 82 men following 12-months of treatment with topical T gel.[382] In a review of placebo-controlled trials of less than 6-months duration, Bhasin and associates showed a modest improvement in body weight and lean body mass in T-treated men.[242] When compared to resistance exercise, TRT provided similar gains in lean body mass and muscle strength but did not show additive effects in a 16-week randomized, placebo-controlled, double-blind trial.[383]

Hypogonadal men with HIV have shown improvements in fatigue and depression with short courses (typically less than 6 months) of TRT. In a double-blind placebo-controlled trial of 70 men, TRT improved libido, fatigue and depressed mood, and produced gains in muscle mass over the course of 6 weeks, which were maintained to 18 weeks.[384] T was superior to fluoxetine with regards to reducing fatigue in a blinded comparative study in 123 men, and although mood response rates were higher in the T-treated men versus fluoxetine-treated men or men in the placebo group, this did not reach statistical significance.[385] Grinspoon and colleagues conducted a placebo-controlled trial in 52 hypogonadal men with AIDS wasting, and observed that TRT produced a significant improvement in Beck Depression Inventory (BDI) score.[386] They also identified a positive

correlation between weight gain and the depression score in all patients, but weight gain was greater in the T-treated patients.

DEPRESSION

The prevalence of depressive illness is common in hypogonadal males, with prospective follow-up showing an increased incidence.[387-389] Several investigators have also identified an association between low T levels and subthreshold depressive disorders such as dysthymia or minor depression.[390-392] This relationship between low T levels and depressive symptoms is multifactorial and is confounded by numerous factors, including concurrent illness, obesity, smoking, alcohol use, diet and other items.[393]

Trials of TRT have been conducted in men with major depressive disorder and subthreshold depression, and the data generated by the use of psychometric questionnaires have generally favoured the active treatment groups. Less consistent results have been observed in subgroups (eg, men taking an antidepressant, or demonstrating a partial response to a serotonergic antidepressant). In some investigations, the response appears to have been affected by the route of T administration. Overall, these studies suggest TRT has demonstrated short-term tolerability and efficacy in the treatment of depression, but additional research is required.

Early investigations of TRT have shown conflicting results in improving depressive symptoms and cognition.[387,394] A systematic review and meta-analysis published in 2009 identified 7 randomized, placebo-controlled trials of TRT in depressed patients.[395] Using the Hamilton Rating Scale for Depression (HAM-D), the authors showed overall a significant treatment-related improvement in depression ($P<0.0001$). Similar significant improvements were also seen in subpopulations (hypogonadism and HIV/AIDS), and in participants treated with T gel. Nonsignificant improvements were seen in eugonadal participants (in two studies) and in 4 studies of T injection.

Shores and colleagues investigated the blinded use of T or placebo gel for 12 weeks, followed by a 12-week open-label extension phase in 33 men with TT levels less than 280 ng/mL and a DSM-IV diagnosis of subthreshold depression (dysthymia or minor depression).[392] At week 12, T-treated men had a greater increase in HAM-D scores and more TRT-treated men achieved remission that did placebo-treated men (53% versus 19%, $P=0.041$). At 24-weeks the remission rates were comparable in both groups.

Recent RCTs have evaluated different TRT administrations in different populations and have not shown consistent results. A six-week trial of intramuscular T in 23 men with midlife-onset male dysthymic disorder demonstrated a significant improvement in Hamilton Depression Rating Scale (HDRS) score in treated men.[396] More treated men showed an antidepressant response by the Clinical Global Impression (CGI) improvement score (69% [9/13] versus 10% [1/10], $P=0.005$), a greater decline in the mean BDI score ($P=0.017$), and a significant benefit in sexual function domains by IIEF total score ($P<0.001$).

Using the Patient Health Questionnaire-9 (a validated, self-report questionnaire), Khera and associates identified moderately severe to severe depression symptoms in 17% of 762 men prescribed 1% T gel in an American observational cohort registry.[397] Participants were reevaluated quarterly, and significant improvements reached a maximum at 12 months. Clinical improvement was seen in men less than 60 years old and in men taking antidepressants.

The Beck Depression Inventory-IA (BDI-IA), the Aging Males' Symptoms (AMS) scale, and the IIEF-5 scale were used in a randomized trial in 184 hypogonadal men with the MetS.[398] At 30-week assessment, all three measures showed significant improvement in treated men (P=0.003, P<0.001, and P<0.001, respectively), and the effect was greatest in men with a baseline T less than 7.7 nmol/L.

Spitzer and colleagues investigated the relationship between T, well-being and mood in a trial of 140 hypogonadal men with ED.[399] The men were optimized on sildenafil, randomized to T or placebo gel, and evaluated at 14 weeks. The well-being (Psychological General Well-Being Index) and mood (Derogatis Affects Balance Scale) scores were similar to those at baseline, suggesting that TRT in hypogonadal men with ED was not effective in improving well-being or mood.

Twenty-two men with refractory depression and a TT level less than 350 ng/mL were randomized in an 8-week trial of T or placebo gel.[395] Treated patients showed significantly improved scores on the HDRS and CGI severity scale, but not on the BDI. In a 6-week trial in 100 hypogonadal men taking a serotonergic antidepressant for major depressive disorder and randomized to T or placebo gel, Amiaz and associates showed improvement of sexual function irrespective of baseline T levels, but without significant effect on depression scores.[400] The improvement was independent of the baseline T.

SLEEP APNEA

TD is common in men with obstructive sleep apnea (OSA). It involves an interplay of the common feature of obesity and hypoxia to suppress T levels.[401] While low levels of T have been associated with more severe sleep-disordered breathing in older men, much of this association is explained by adiposity.[402] When OAS is treated with continuous positive airway pressure (CPAP) therapy, small studies have shown an improvement in OSA parameters, but the majority of studies have not shown an effect on LH, FSH or T levels.[403,404]

The effect of T replacement in men with OSA has depended on the dose and duration of treatment. In a placebo-controlled crossover study in 17 eugonadal older males, the administration of weekly parenteral high-dose T for 3 weeks reduced sleep and worsened breathing.[405] A follow-up study by the same group in 67 men with severe OSA treated with conventional doses of parenteral T compared to placebo showed worsening OSA

parameters at 7 weeks but not at 18 weeks.[406] The results were not correlated to age or baseline T.

Ventilatory chemoreflex testing was conducted in a subgroup of 21 men participating in previous study to examine the differences between the 7-weeks and 18-weeks results.[407] The investigators observed a positive correlation between changes in T and the hyperoxic ventilatory recruitment threshold, and concluded that time-dependent changes in sleep breathing could be mediated by time-dependent changes in this threshold. They recommended larger and longer studies to confirm their observations.

It is noted that not infrequently, sleep apnea is associated with hypogonadism that may be reversible by treatment with continuous positive airway pressure.[408]

Studies looking at cardiometabolic effects in men with OSA have shown an improvement in some (insulin resistance, muscle mass, arterial stiffness) but not all metabolic parameters.[409] Importantly, adverse CV clinical events in T-treated patients were not increased, but larger long-term studies in severe or untreated disease are lacking.[202,410]

TREATMENT WHEN IN DOUBT

Healthy men show a steady age-associated decline in T levels.[411,412] However, at all ages there are large interindividual variations on the onset, degree and relevance of this decline.[413] There are also, within the same individual, marked circadian and ultradian biological variations.[97] Ethnicity and heredity, fat mass and its distribution, stress, intercurrent illness, medications, diet, life style and environmental factors may also contribute to observed discrepancies.[411,413]

As indicated earlier, the diagnosis of TD should be based on the presence of clinical manifestations and conclusive documentation of subnormal levels of serum T.[411,414] Not infrequently, patients with manifestations compatible with the clinical diagnosis of TD may have serum levels of T at the lower end of acceptable normal values.[36,413] After ruling out other conditions that mimic TD and conducting a comprehensive hormonal evaluation, the levels of T may persist at the lower end of the "normal" range of values reported by the local laboratory. The question arises as to what to do in these situations.

Experts disagree on the levels of total T that should trigger therapy. Although there is a general consensus that to initiate treatment there must be clinical manifestations of TD, the levels of total T are a matter of significant disagreement.[7,415] This still leaves a population of men with symptoms of hypogonadism but total T levels as "persistently borderline" (usually with values between 8 and 12 nmol/L).[2,414]

There are 2 strategies of TRT: a) substitution to alleviate symptoms and prevent complications of TD in men with documented low serum T; and b) pharmacological treatment in older men who are not biochemically androgen deficient, but where the aim is to prevent osteoporosis, anemia, frailty or sexual dysfunction.[36,98,140,416,417]

There are numerous valid, controlled, randomized studies and meta-analyses supporting the benefits of substitution T therapy.[98,124,140,205,321,416-419] However, an electronic database search of published literature was unable to identify clinical trials supporting the use of androgen treatment to prevent potential pharmacological adverse outcomes.

Due to the absence of reliable long-term data supporting the risk-benefit ratio of T therapy, T administration should be only in symptomatic men with convincingly low serum T.[98,140,413,417] In the presence of a man with clinical manifestations of TD in whom other causes have been excluded but in whom a thorough laboratory assessment fails to convincingly confirm the diagnosis, a three-month therapeutic trial of T administration has been suggested.[55,417] Also, it has been suggested that the response to T treatment be considered part of the diagnosis, but there are no clinical data to support this position.[56]

MONITORING RESPONSE

There are no randomized placebo-controlled studies of TRT looking for adverse events as primary outcomes. Adverse events are gleaned from reports from within randomized placebo-controlled studies and case reports. Monitoring guidelines are therefore based on low-quality evidence but are nonetheless of high priority to ensure that any potential adverse events will be detected promptly and rectified.[420,421]

Protocols for monitoring have also been derived from knowledge of the physiology of T and reviews of the expected timeline for the potential onset of the event or side effect.[422] In addition to monitoring to identify if the patient has reached endocrinologic targets, monitoring also identifies hematologic and prostate changes, as described below.

Hematologic monitoring

Hypogonadal men have lower Hct levels as part of the TD, and it is accepted that TRT will increase Hgb and Hct levels. Increases in Hct of 5% to 10% are not uncommon, and depend in large part on the pretreatment T level and the T formulation used. Intramuscular (IM) administration of T is most likely to increase the Hct. Polycythemia was reported in 24% of men in two IM placebo-controlled studies.[423,424] Hct is a major determinant of blood viscosity. It is recommended to follow Hct because it is more predictive of the risk of thrombosis than is Hgb.[25,425] However, there is no hard endpoint above which thrombosis risk becomes significant, nor below which the risk of thrombosis is zero.

The Endocrine Society Guidelines have chosen an Hct of 54% as the upper limit of safety for T therapy.[25] There is no randomized study that validates this cutoff. Since the Endocrine Society Guidelines were published in 2010, many practitioners have adopted this protocol, which pragmatically has worked well. Thrombosis with TRT in the absence of overt polycythemia or structural venous disease is an exquisitely rare event. The authors of these guidelines believe that in the absence of definitive data, an Hct cut off of 54% is reasonable. However, a lower Hct of 52% would, in theory, provide for a lower risk of thrombosis.

Three months after the initiation of TRT coincides with one cycle of red blood cell turnover. This has historically been chosen as a time to verify polycythemia has not developed. We agree that a three-month check is appropriate, but note that the peak effect of red cell mass may occur after 3 months and before 12 months.[422]

Prostate monitoring
TRT will increase PSA and prostate volume over the first year of treatment.[422] Current society guidelines contain evidence-based recommendations for monitoring men receiving TRT for prostate changes.[25,291] Guidelines recommend both DRE and PSA testing, and the combination has been found more effective in detecting PCa than either alone.[426,427] General monitoring recommendations are provided in Table 12 and more specific prostate-related information is contained in the *Prostate Cancer* section of this Guideline.

RECOMMENDATIONS

Diagnosis

1. Strong recommendation for. In patients with strong clinical evidence (Table 1) of TDS and low T levels, we recommend making the diagnosis of TDS and conducting a trial of TRT rather than not making such a diagnosis and beginning treatment, except in circumstances shown in recommendations 23 and 24. **(Strong recommendation, moderate quality evidence).**

2. Strong recommendation against. In patients who do not have both clinical (Table 1) and at least equivocal biochemical evidence of TD, we recommend against making a diagnosis of TDS and a consequent trial of TRT, except in circumstances shown in recommendations 3 to 6. **(Strong recommendation, low quality evidence).**

3. Weak recommendation for. We suggest assessing T levels and treating with T those men with documented low T presenting with symptoms of depression who are refractory to standard therapy, rather than no further evaluation for hypogonadism.[389] **(Weak recommendation, very low quality evidence).**

4. Strong recommendation for. We recommend assessing T levels and treating with T those men with documented low T and sarcopenia and/or anemia in the absence of other identifiable causes, even if they have no other signs and symptoms of hypogonadism, rather than no evaluation or treatment for hypogonadism.[361,365,428] **(Strong recommendation, moderate quality evidence).**

5. Weak recommendation for. We suggest assessing T levels and treating with T those men with documented low T receiving chronic glucocorticoid or chronic opioid therapy even in the absence of symptoms or signs of hypogonadism, rather than no evaluation for hypogonadism.[375] **(Weak recommendation, low quality evidence).**

6. Weak recommendation for. We suggest assessing T levels and treating with T those men with documented low T and with HIV who have had weight loss even in the absence

of other symptoms and signs of hypogonadism rather than no evaluation for hypogonadism.[429] **(Weak recommendation, low quality evidence).**

7. Weak recommendation against. We suggest against biochemical testing for hypogonadism in men with ED who are otherwise asymptomatic, in favour of testing only when they have failed a trial of PDE-5 inhibitors.[329] **(Weak recommendation, low quality evidence).**

8. Weak recommendation against. We suggest against the exclusive use of questionnaires to identify symptomatic patients appropriate for biochemical testing, in favour of a thorough history and physical examination. **(Weak recommendation, low quality evidence).**

9. Strong recommendation for. We recommend that all men with TDS be evaluated for secondary or reversible causes of hypogonadism, rather than no further investigation (Table 2). **(Strong recommendation, moderate quality evidence).**

10. Strong recommendation for. We recommend that T levels be measured using T assays traceable to internationally recognized standardized reference material and that all commercial T assays be certified by the Centres for Disease Control Testosterone Standardization Program.[430] **(Strong recommendation, high quality evidence).**

11. Strong recommendation for. We recommend determination of TT as the first-line biochemical test among men with signs and symptoms of hypogonadism, rather than BAT or FT.[60] **(Strong recommendation, high quality evidence).**

12. Strong recommendation for. We recommend that laboratory testing for SHBG, cFT, cBAT or BAT be restricted to men with symptoms of TDS and equivocally low T levels, rather than being performed routinely in all patients being investigated for hypogonadism. **(Strong recommendation, moderate quality evidence).**

13. Strong recommendation for. We recommend that sample collection for T, occurs between 7 am and 11 am, or within 3 hours of waking in the case of shift-workers, rather than sampling later in the day.[90] **(Strong recommendation, moderate quality evidence).**

14. Strong recommendation against. We recommend against routine measurement of bone mineral density (BMD) in men with TDS before age 50.[45,356] **(Strong recommendation, very low quality evidence).**

15. Weak recommendation for. We suggest that men with TDS over the age of 50 undergo a fracture risk assessment with subsequent management based on the osteoporosis guidelines.[356] **(Weak recommendation, very low quality evidence).**

Treatment

16. Strong recommendation for. We recommend that men with TDS and no contraindications receive a therapeutic trial of TRT.[98] **(Strong recommendation, high quality evidence).**

17. Weak recommendation for. We suggest that men with symptomatic TDS and stable cardiovascular disease receive an adequate therapeutic trial of TRT rather than no treatment.[194,204,210,215,431,432] **(Weak recommendation, low quality evidence).**

18. Weak recommendation for. We suggest that men with symptomatic TDS and localized prostate cancer who have no evidence of active disease receive a therapeutic trial of TRT.[292,433] **(Weak recommendation, low quality evidence).**

19. Weak recommendation for. We suggest that men with indications for treatment of TDS who have mild-to-moderate lower urinary tract symptoms due to BPH receive TRT.[319] **(Weak recommendation, very low quality evidence).**

20. Strong recommendation against. We recommend against TRT among men who place a higher value on maintaining fertility over symptomatic improvement.[339] **(Strong recommendation, high quality evidence).**

21. Strong recommendation for. We recommend treatment with a PDE-5 inhibitor in men with persistent ED, who have TDS that is adequately treated with TRT, rather than no further treatment.[159] **(Strong recommendation, high quality evidence).**

22. Weak recommendation against. We suggest against the use of T "boosters" and herbal or plant-derived products to improve libido or erectile function among men with TDS in favour of no treatment or treatment with TRT where appropriate. **(Weak recommendation, very low quality evidence).**

23. Weak recommendation against: We suggest against TRT in men with a history of breast cancer, in favour of no treatment.[264] **(Weak recommendation, very low quality evidence).**

24. Strong recommendation against: We recommend against the use of TRT among men with metastatic prostate cancer and in men at high risk for recurrent prostate cancer, in favour of no treatment.[286] **(Strong recommendation, moderate quality evidence).**

Treatment When in Doubt

25. Weak recommendation for. We suggest that men with a clinical picture strongly suggestive of TDS (Box 1) but with T levels in the low-normal range, receive a therapeutic trial of T rather than no further evaluation or treatment. **(Weak recommendation, very low quality evidence).**

Recommendations on Discontinuing Testosterone Replacement Therapy

26. Strong recommendation for. We recommend discontinuing TRT in men with TDS if contraindications to therapy arise or if there is no improvement in symptoms after an adequate therapeutic trial, rather than continuing therapy. **(Strong recommendation, high quality evidence).**

Recommendations on Monitoring

27. Strong recommendation for. We recommend assessing symptom improvement, lack of response or occurrence of adverse events at 3 and 6 months after initiating therapy, rather than no monitoring. **(Strong recommendation, high quality evidence).**

28. Weak recommendation for. We suggest assessing T levels at 3 and 6 months following initiation of therapy, and then annually thereafter if stable, rather than less frequent or no monitoring of T levels. **(Weak recommendation, low quality evidence).**

29. Strong recommendation for. We recommend assessing hematocrit at baseline, 3 and 6 months after initiation of therapy and then annually thereafter if the hematocrit remains stable, rather than no monitoring of hematocrit. **(Strong recommendation, high quality evidence).**

30. Weak recommendation for. We suggest that men being treated with TRT have determinations of PSA at baseline, 3 and 6 months after initiation of therapy and then annually thereafter, rather than no monitoring.[25,98] **(Weak recommendation, low quality evidence).**

31. Weak recommendation for. We recommend that men with TDS being treated with TRT have a DRE performed at baseline, 6 months, and then annually, following initiation of TRT, rather than no monitoring.[287] **(Weak recommendation, very low quality evidence).**

CONCLUSION

Despite the contentious nature of many issues involved in the management of TDS, the Task Force reached consensus in a series of recommendations of practical value for health care professionals. These range from the need for an in-depth evaluation of the patient including an appropriate laboratory assessment to reach a diagnosis and the options available for treatment. The controversial concerns related to cardiovascular and prostate health in men receiving TRT have been clarified in the light of the best current available evidence. A sensible plan for follow-up of men treated with T has been delineated. The role of TRT in body composition and metabolic issues as well as other chronic illnesses (HIV, depression) has been addressed. Regardless of the comprehensive nature of the guideline, clinicians must consider the unique characteristics of each patient and make the necessary adjustments in the management of TD in order to provide the safest and most beneficial results.

GUIDELINES WRITING GROUP

All of the task force members participated in writing and contributed their respective sections to the initial manuscripts and presented their sections of the guideline at two separate task force meetings. Final manuscript edits were carried out by Alvaro Morales, and Priya Majoo.

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ABBREVIATIONS

ADAM	Androgen Deficiency in the Aging Male questionnaire
AMS	Aging Males' Symptoms scale
AR	Androgen receptor
BAT	Bioavailable testosterone
BDI	Beck Depression Index
BMD	Bone mineral density
BMI	Body mass index
BP	Blood pressure
BPH	Benign prostatic hyperplasia
CAD	Coronary artery disease
cBAT	Calculated bioavailable testosterone
CBC	Complete blood count
CC	Clomiphene citrate
CDC	Centers for Disease Control and Prevention
cFT	Calculated free testosterone
CGI	Clinical Global Impression
CHF	Congestive heart failure
CMHF	Canadian Men's Health Foundation
CV	Cardiovascular
CVD	Cardiovascular disease
DE	Delayed ejaculation
DHT	Dihydrotestosterone
DRE	Digital rectal examination
ED	Erectile dysfunction
FAI	Free androgen index
FDA	US Food and Drug Administration

FSH	Follicle-stimulating hormone
FT	Free testosterone
GnRH	Gonadotropin-releasing hormone
HAM-D	Hamilton Rating Scale for Depression
hCG	human chorionic gonadotropin
Hct	Hematocrit
HDRS	Hamilton Depression Rating Scale
HF	Heart failure
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HPGA	Hypothalamic-pituitary-gonadal axis
IIEF	International Index of Erectile Function
IM	Intramuscular
LH	Luteinizing hormone
LOH	Late-onset hypogonadism
LUTS	Lower urinary tract symptoms
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MetS	Metabolic syndrome
MI	Myocardial infarction
MTHF	Minimal traumatic hip fracture
NT-pro-BNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OSA	Obstructive sleep apnea
PCa	Prostate cancer
PE	Premature ejaculation
PDE5-Is	Phosphodiesterase type 5 inhibitors
pro-BNP	pro-brain natriuretic peptide
PSA	Prostate-specific antigen
RCT	Randomized controlled trial
RIs	Reference intervals
SF-36	Short Form (36) Health Survey
SHBG	Sex hormone-binding globulin
SHIM	Sexual Health Inventory for Men
SD	Standard deviation
T	Testosterone
TD	Testosterone deficiency
TDS	Testosterone deficiency syndrome
TRT	Testosterone replacement therapy
TT	Total testosterone
TSH	Thyroid-stimulating hormone
T2DM	Type 2 diabetes mellitus

TABLES AND FIGURES

DEFINITION

Table 1. Signs and Symptoms Associated with TDS

Domain	Signs and symptoms
Sexual	Decreased libido; erectile dysfunction; decreased frequency of morning erections; decreased performance
Somatic	Increased visceral body fat/obesity; decreased lean muscle mass; decreased strength; fatigue/loss of energy; decreased physical activity/vitality; low bone mineral density; anemia; flushes; loss of facial, axillary and pubic hair/slow beard growth; decline in general feeling of well-being
Psychological	Depression/depressed mood; mood changes; irritability; inability to concentrate; insomnia/sleep disturbances

Table 2. Primary, Secondary and Mixed Hypogonadism[5,25,30,33,87]

	Primary	Secondary	Mixed
Etiology	Testicular failure (primarily affected by aging)	HPGA impairment (impaired by obesity)	Combined, although one may predominate
T level	Low	Low	Low
Gonadotropin (LH and FSH) levels	Elevated	Normal or low-normal	LH normal (may be low in obese men)
Spermatogenesis	Impaired	Impaired	Impaired

Note: T = testosterone; HPGA = hypothalamic-pituitary-gonadal axis; LH = luteinizing hormone; FSH = follicle-stimulating hormone.

NEEDS ASSESSMENT

Table 3. Needs Assessment: Distribution of the target audience by specialty

Response	Chart	Percentage	Count
A. Family Physician		76%	115
B. Urologist		9%	14
C. Endocrinologist		7%	10
D. Other		9%	13
	Total Responses		**152**

Table 4. Needs Assessment: How comfortable are you with the diagnosis of TD?

Response	Chart	Percentage	Count
A. Not comfortable		26%	40
B. Somewhat comfortable		46%	71
C. Very comfortable		27%	42
	Total Responses		**153**

Table 5. Needs Assessment: As part of our ongoing educational needs assessment, would you agree to being contacted by the Canadian Men's Health Foundation in the future about this topic?

Response	Chart	Percentage	Count
A. Yes, please contact me 6 months from now.		61%	94
B. No, I prefer not to be contacted by the Canadian Men's Health Foundation.		39%	59
	Total Responses		**153**

HISTORY AND PHYSICAL EXAMINATION, SCREENING/DIAGNOSTIC QUESTIONNAIRES

Table 6. Patient History Features Associated with TDS

Patient history feature
Type 2 diabetes mellitus
Insulin resistance
Metabolic syndrome
Obstructive sleep apnea
Chronic obstructive pulmonary disease
Osteoporosis or low trauma fracture
Chronic kidney disease and maintenance hemodialysis
Liver disease
Hemochromatosis
Infertility
Frailty
Peyronie disease and penile fibrosis
HIV-1 infection or HIV-associated weight loss
Chronic heroin use
Alcohol abuse
Sellar mass, disease, radiation or trauma
Hyperprolactinemia
Drug therapy (opioids, systemic glucocorticoids, ketoconazole, alkylating agent chemotherapy, GnRH analogs, antiandrogens, cannabinoids, spironolactone, carbamazepine, valproate)
Testicular cancer treatment (high-dose chemotherapy, adjuvant radiotherapy, unilateral or bilateral orchiectomy)

TREATMENT OPTIONS

Table 7. Testosterone Products for the Treatment of TDS[5,98,434,435]

Compound	Starting or standard dose	Advantages	Disadvantages
Oral agents			
Testosterone undecanoate	120-240 mg TID	Oral convenience Modifiable dosage	Serum T levels and clinical responses vary Must be taken with fatty food
Intramuscular agents			
Testosterone enanthate	250 mg q2-3 weeks	Low cost Self injection for some men	Wide fluctuations in circulating T levels, occasionally symptomatic Multiple injections Pain and redness at injection site Relative higher risk of polycythemia
Testosterone cypionate	200 mg q2-3 weeks	Low cost Self injection for some men	Wide fluctuations in circulating T levels, occasionally symptomatic Multiple injections Pain and redness at injection site Relative higher risk of polycythemia
Testosterone propionate	100 mg q2 days	Low cost Self injection for some men	Wide fluctuations in circulating T levels, occasionally symptomatic Multiple injections Pain and redness at injection site Relative higher risk of polycythemia
Transdermal agents			
Testosterone patch	5 to 10 mg/day	Mimics T circadian rhythm Simple administration	Skin irritation, occasional allergic contact dermatitis Daily administration
Testosterone gel 1%	40 to 80 mg/day	T levels within normal range Flexible dose modifications Easy to apply Readily absorbed Skin irritation less common	Possible transfer during intimate contact Skin irritation at application site in a small number of men Daily administration
Testosterone solution 2% (for underarm application)	60 to 120 mg/day	T levels within normal range Skin irritation less common	Possible transfer during intimate contact Daily administration

The following products are not marketed in Canada:
Testosterone undecanoate injection in castor oil (long-acting IM injection)
Testosterone buccal system (mucoadhesive)
Testosterone pellets for subcutaneous administration (implantation)
Testosterone gel 1.62%, 2%

Table 8. Testosterone Preparations: Approximate Cost Per Month

Compound	Availability and cost	Cost of usual or maximum recommended dose: 30 days' supply (not including pharmacy markup and professional [dispensing] fee)
Oral agents		
Testosterone undecanoate	$0.564 per 40 mg capsule[a]	6 capsules (240 mg)/day; 180 capsules = $101.52
Intramuscular agents		
Testosterone enanthate	$50.65 per 5 mL vial; 200 mg/mL[a]	200 mg (1 mL) q2weeks; 2 mL/month; $20.26
Testosterone cypionate	$28.59 per 10 mL vial; 100 mg/mL[a]	200 mg (2 mL) q2weeks; 4 mL/month; $11.436
Transdermal agents		
Testosterone patch	$2.0929 per 12.2 mg patch[a] $4.1858 per 24.3 mg patch[a]	One 24.3 mg patch (equivalent to 5 mg testosterone) per day; 30 patches; $125.574
Testosterone gel 1%	$2.23 per 2.5 g tube[a] $3.9533 per 5 g tube[a]	One 5 g tube daily; 30 tubes; $118.299
Testosterone gel 1%	$133.98 per 2 x 90 mL pump[b] (1.25 g per actuation, 60 actuations per pump)	5 g (4 actuations)/day; 2 x 90 mL (120 actuations); $133.98
Testosterone gel 1% with pentadecalactone	$3.6030 per 5 g tube[a]	One 5 g tube daily; 30 tubes; $108.09
Testosterone solution 2% (for underarm application)	$138.86 per 90 mL pump[b]; (30 mg per actuation, 60 actuations per pump)	120 mg (4 actuations)/day; 2 x 60 mL; $277.72

Cost information (June 2014):

a. Ontario Drug Benefit Formulary/Comparative Drug Index lists the "Drug Benefit Price" for nine generic and brand testosterone products (available: https://www.healthinfo.moh.gov.on.ca/formulary/ accessed 2014 June 14). Not all available products are reimbursed by this program and product cost and/or coverage in other provinces may be different.

b. Price obtained from manufacturer's or pharmaceutical wholesaler's price list

CARDIOVASCULAR DISEASE

Table 9. Investigations of Cardiovascular Surrogate Measures

Ref	Population and study design	Surrogate measure or outcome(s) of interest	Results
188	26 hypogonadal men, treated with IM T for 1 year	Markers of blood coagulation (plasma free tissue factor pathway inhibitor antigen [TFPI Ag] and TF-induced thrombin generation *ex vivo*	Markers were unchanged
190	Retrospective chart review, Veterans Affairs database, total T checked in 2008; n=1479	Framingham risk scores for developing hard coronary heart disease	Framingham score was negatively associated with total T ($P<0.0001$) and FT ($P=0.03$)
436	12-week double-blind RCT in men with stable angina; T patch (n=22) or placebo patch (n=24)	Time to 1-mm ST-segment depression during the Bruce treadmill exercise test	T patch group increased at 4 and 12 weeks ($P=0.02$); greater magnitude of change with lower baseline levels of BAT ($P=0.024$)
437	Men aged 19-72 y, community based, single-sample survey; n=1891	N-terminal pro-B-type natriuretic peptide (NT-proBNP)	Increasing NT-proBNP levels related to decreasing cFT and increasing SHBG
438	9-week open-label study in men with MetS + TD (n=30), men with MetS (n=25), and healthy controls (n=25); IM T q3 weeks to men with MetS + TD	NT-proBNP	TRT had no significant effect on NT-proBNP
439	6-month trial in hypogonadal men age 50-64 with isolated arterial erectile dysfunction; T gel 2% (n=30), not treated due to contraindications to TRT (n=20)	Markers of endothelial dysfunction (blood endothelial progenitor cells [EPCs] and endothelial microparticles [EMPs])	EPCs and EMPs were significantly higher in men in the T group
440	12-month single-arm study in symptomatic men between 40 and 70 years old; 29 hypogonadal men received open-label T gel 1%, 17 eugonadal were not treated	Circulating EPC levels	No difference at baseline; treated men showed significant increase at 3, 6, and 12 months
191	12-month RCT in hypogonadal men with stable angina pectoris; long-acting T IM (n=7) or placebo IM (n=6)	Exercise-induced ischemia, lipid profiles, carotid intima media thickness (CIMT), and body composition	TRT: significant improvements in exercise-induced ischemia, BMI and triglycerides; nonsignificant reduction in CIMT; no change in total cholesterol and HDL-cholesterol
189	24-month double-blind double-dummy RCT in hypogonadal men, 1000 mg T IM q12 weeks (n=40) or placebo gel (n=10)	HOMA-IR, CIMT, high-sensitivity C-reactive protein (hsCRP)	T group: HOMA-IR, CIMT and hsCRP significantly reduced at 12 but not at 24 months

441	Survey of 195 community-living men ≥70 years old, to measure endogenous sex hormones and CIMT in 1996 and in 2000	Progression of CIMT	FT inversely related to mean progression of age-adjusted CIMT; total T not related to progression
442	A single survey in 403 community-living men aged 73 to 94 years	CIMT	Age-adjusted serum T, estrone, and free IGF-1 were inversely related to CIMT
192	9-week open-label study in men with MetS + TD (n=30), men with MetS (n=25), and healthy controls (n=25); IM T q3 weeks was given to men with MetS + TD	Heart-rate variability (HRV) by 24-hour Holter monitor	At baseline, all time-domain and most frequency-domain HRV parameters were significantly lower in MetS + TD versus controls; TRT improved HRV parameters; they did not reach control values
443	3 trials (106 men) comparing T vs placebo in men with intermittent claudication or critical leg ischemia; meta-analysis		TRT produced no significant improvements
444	Double-blind, cross-over RCT; 12 men received 60 mg T or placebo via the buccal route	Central hemodynamics monitored over 6 hours, using a pulmonary flotation catheter	Acute increase in cardiac output, apparently via reduction of left ventricular afterload
445	Measure of T in men 30 to 85 years old with recent (within 6 to 12 hours) myocardial infarction (MI, confirmed by troponin I level) (n=60), versus matched controls (n=60)	The relationship of total T in men with a recent MI versus matched controls	Strong inverse relationship between T in men with recent MI compared with controls
446	18 hypogonadal males and 12 matched controls; transdermal T gel 1%, 90-day trial	Arterial stiffness, as assessed by pulse wave velocity	Normalizing T improved arterial stiffness

Table 10. Testosterone Replacement Compared to Placebo for Adult Men with Testosterone Deficiency Syndrome

Patient or population: Adult men with TDS
Settings:
Intervention: TRT
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Ref
	Assumed risk	Corresponding risk				
	Placebo	Testosterone Replacement				
MedDRA classified cardiac events Examination by physician, review of medical records, physician notification and self-report Follow-up: <12 to 24 weeks	Study population		**OR 5.4** (2 to 14.9)	209 (1 study)	**Low**[1,2,3,4,5,6]	205,206
	49 per 1000	**216 per 1000** (93 to 432)				
	Moderate					
Risk of hospitalization for MI Claims data Medicaid Services beneficiaries. Follow-up: mean 1495 days[7]	**13 per 1000**	**11 per 1000** (9 to 13)	**HR 0.84** (0.69 to 1.02)	25431 (1 study)	**Very low**	209
All cause mortality Follow-up: 6 – 36 months	Study population		**RR 1.21** (0.7 to 1.81)	476 (5 studies)	**Low**[4,8,9,10]	140,447-451
	107 per 1000	**129 per 1000** (75 to 194)				
	Moderate					
	50 per 1000	**61 per 1000** (35 to 90)				
	High					
	200 per 1000	**242 per 1000** (140 to 362)				
Coronary bypass surgery Follow-up: 3 – 36 months	Study population		**RR 1.35** (0.26 to 6.96)	158 (2 studies)	**Very low**[4,11,12]	436,449,450
	25 per 1000	**34 per 1000** (7 to 176)				
	Moderate					
Myocardial infarction Follow-up: 3 – 36 months	Study population		**RR 0.91** (0.29 to 2.82)	1054 (7 studies)	**Very low**[8,13,14]	124,140,436,448-453
	10 per 1000	**9 per 1000** (3 to 28)				
	Moderate					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Note: CI = confidence interval; RR = risk ratio; OR = odds ratio; HR = hazard ratio

[1] Cardiovascular-related events included serious cardiovascular adverse events and events of uncertain cardiovascular significance such as elevated blood pressure, tachycardia with fatigue, peripheral edema, LV strain pattern during exercise testing, ectopy on ECG. When only the life-threatening and serious cardiovascular events were included, there was not a significant difference between the intervention and treatment groups. Furthermore, based on the adverse events, the trial was stopped early. Finally, most of the patients were recruited from one site, which may also have influenced the results.

[2] The results of this trial are not in keeping other meta-analyses and systematic reviews such as those conducted by Carson et al. 2012,[454] Fernández-Balsells et al. 2010[140] and Haddad et al. 2007.[203] Additionally, systematic review and meta-analyses evaluating the use of T in high-risk patients such as those with congestive heart failure did not demonstrate significant adverse cardiovascular events.

[3] Although the confidence intervals are wide, the imprecision of the estimate is less relevant as the lower limit of the confidence intervals are 2.0.

[4] No explanation was provided.

[5] Sensitivity analyses were conducted for potential sources of confounding and did not change the results significantly.

[6] Secondary analyses were done of the sera of men who had had cardiovascular events in the intervention and placebo arm. Logistic regression performed in these 25 subjects showed a potential association between free T levels and the odds of a cardiovascular event as defined in this study. The estimate for the OR (95% CI) for this association was 1.07 (1.00 to 1.15). This inference is limited by the small numbers and the limits of the confidence interval.

[7] 1495 days in the intervention arm and 1193 days in the control arm.

[8] Allocation of concealment, blinding and loss to follow-up not consistently reported between studies. Most of the study numbers were small, varying from 40 to 221.

[9] The RR was 1.12, with a confidence interval varying from 0.70 to 1.81. The results of the pooled data are therefore inconclusive with the true effect ranging from a 30% reduction or an 81% increase in the risk of mortality with T replacement therapy.

[10] Given the small size some of these studies it is quite possible that the groups would not be well balanced in regards to potential confounders despite randomization. It is however, difficult to determine the direction of influence on the RR.

[11] Trial numbers are small and event rates were low, resulting in very wide confidence intervals.

[12] English et al. 2000.[436]The placebo group potentially had a higher incidence of risk factors for CAD, This may therefore have contributed to a lower than expected RR.

[13] Individual RR of T therapy in the included studies varied from 0.27 to 1.96.

[14] Wide confidence intervals around the pooled estimate of 0.91, varying from 0.29 to 2.82

DIABETES MELLITUS and OBESITY

Table 11. Evidence Profile of Studies Evaluating the Metabolic Effects of TRT in Patients with Type 2 Diabetes

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Study details	Quality	Ref
Glycemic Control (follow-up 3 to 52 weeks; measured with: Laboratory tests; Better indicated by lower values)									
5	Randomised trials	No serious risk of bias[1]	Serious[1]	No serious indirectness	No serious imprecision	None	N=323. A1c was lower in T treated groups compared with placebo. Pooled mean difference for 4 studies was -0.87 (-1.31, -0.42) %, and mean difference for the 5th study was -0.20 (-0.34, -0.05) % at 18 weeks and -0.11 (-0.34, 0.13) at 30 weeks.	MODERATE	234,235,250,251,260
Blood Pressure (follow-up mean 3-12 weeks; assessed with: Clinical Examination)									
4	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	N=277. No significant difference in BP in T treated group versus placebo.	HIGH	IMPORTANT 231,233,234,250,260

Lipids (follow-up mean 3-30 weeks; assessed with: Laboratory Measurement)								
5	Randomised trials	No serious risk of bias	Serious[3]	No serious indirectness	No serious imprecision	None	N=427 Total cholesterol was improved in the T treated group in one study by -0.21(-0.44-0.01) mmol/L at 30 weeks, with no significant change in the other lipid fractions. In the pooled results for the remaining four studies, the triglyceride level was improved in the T treated group by -0.35 (-0.62, -0.07) mmol/L, however there was no difference for the other lipid fractions.	MODERATE	IMPORTANT [233-235,250,251]

[1] The effect size was small and not consistent for the duration of the longer trials suggesting that the improvent may be transient.

[2] Variable changes in anthropometric parameters according to the baseline testosterone level.

[3] Results not consistent across trials. Very small changes noted in lipid parameters of questionable clinical significance.

MONITORING RESPONSE

Table 12. Recommendations for Monitoring

Parameter	Baseline	3 months	6 months	Annually for the duration of TRT	Intermittently
CBC	X	X	X	X	
Testosterone	X	X (see note)	X	X	
PSA	X	X	X	X	
DRE	X		X	X	

Note: Or sooner, to ensure physiological replacement and to allow dose titration (depending on the formulation of testosterone used).
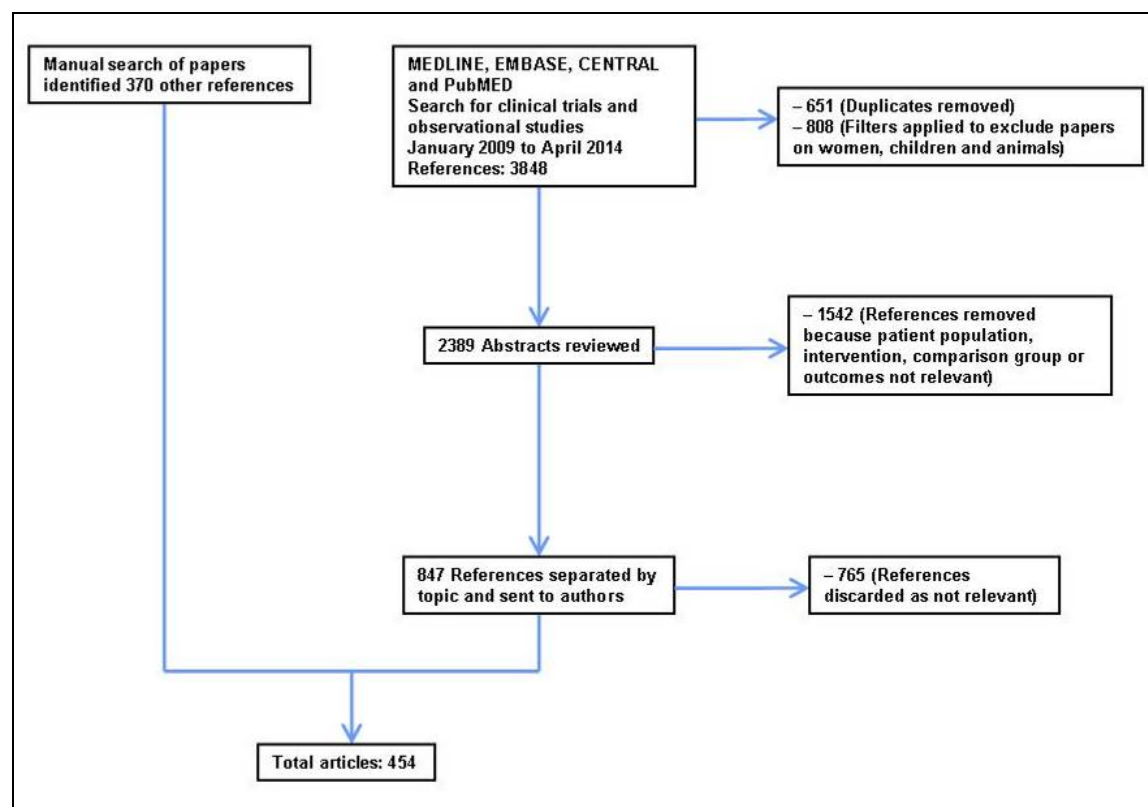
METHODOLOGY

Figure 1. Study Selection Flow Diagram

DIAGNOSTIC ALGORITHM

Diagnostic Algorithm

Clinical Suspicion of TDS

- Type II diabetes
- Insulin resistance
- Metabolic syndrome
- HIV-associated weight loss
- Treatment with opioids,
  glucocorticoids or ketoconazole
- Chronic alcohol abuse or heroin use
- Liver disease
- Hemochromatosis

- Osteoporosis
- End-stage renal disease
- COPD
- Obstructive sleep apnea
- Infertility
- Frailty
- Hyperprolactinemia
- Sellar region mass, disease,
  radiation or trauma
- Testicular cancer treatment

Measure T in AM (between 7 am and 11 am, or within 3 hours of waking)

Normal → **No TDS**

Low T

Borderline low or low normal T (repeat for confirmation)

Comprehensive laboratory evaluation
- FSH
- LH
- Prolactin
- SHBG
- cFT or cBAT
- TSH
- Ferritin
  (or percent iron saturation)
- CBC
- PSA

Consider referral to TDS expert if strong clinical manifestations and low normal T

1° Hypogonadism (Testicular) Low T + High LH/FSH

2° Hypogonadism (Pituitary/hypothalamic) Low T + Normal LH/FSH

Consider treatment or referral to TDS expert

Note: cBAT = calculated bioavailable testosterone, CBC = complete blood count, cFT = calculated free testosterone, COPD = chronic obstructive pulmonary disease, FSH = Follicle-stimulating hormone, HIV = human immunodeficiency virus, LH = luteinizing hormone, PSA = prostate-specific antigen, SHBG = sex hormone-binding globulin, T = testosterone, TDS = testosterone deficiency syndrome, TSH = thyroid-stimulating hormone.
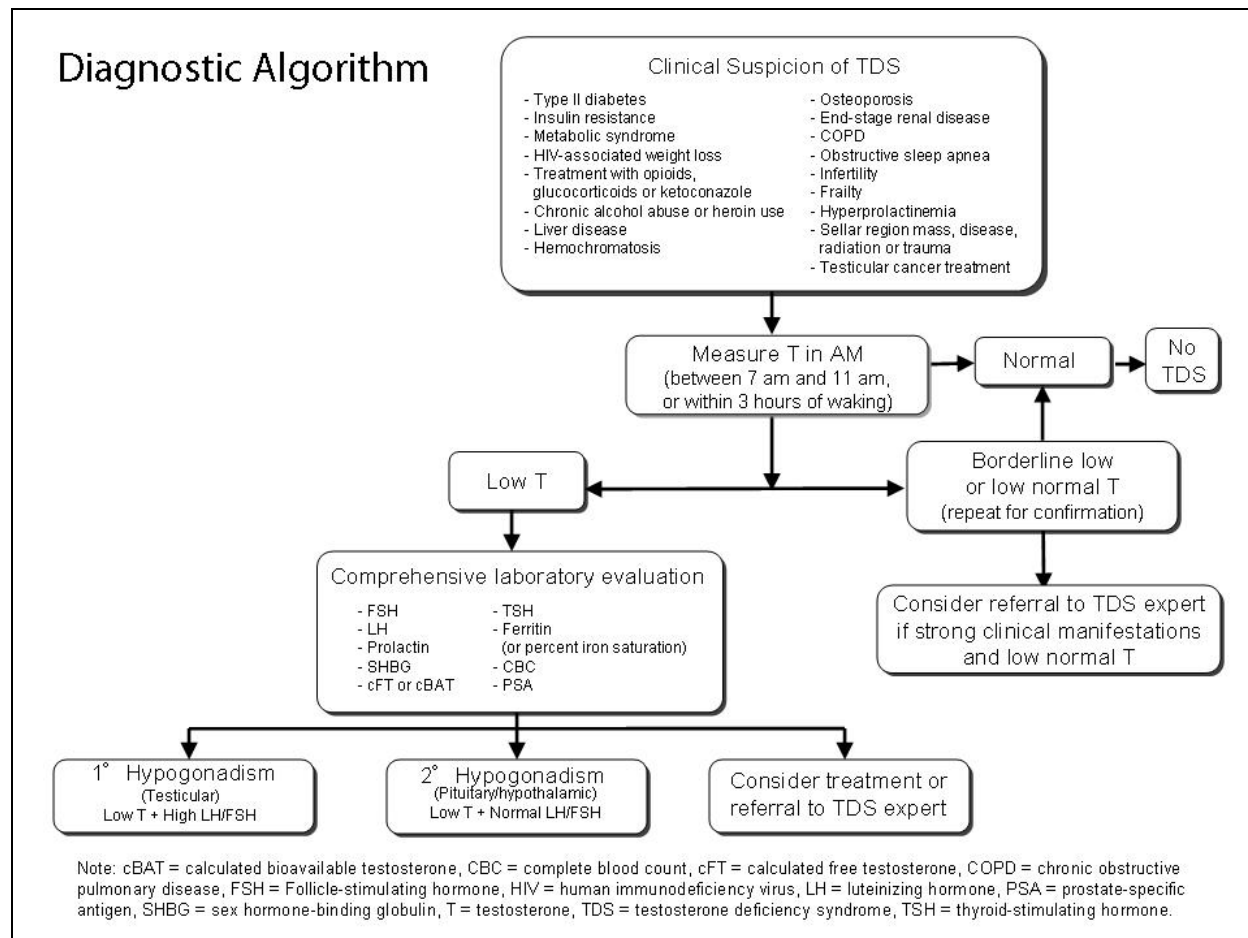
Figure 2. Clinical Decision Making Algorithm for the Diagnosis of Testosterone Deficiency Syndrome.
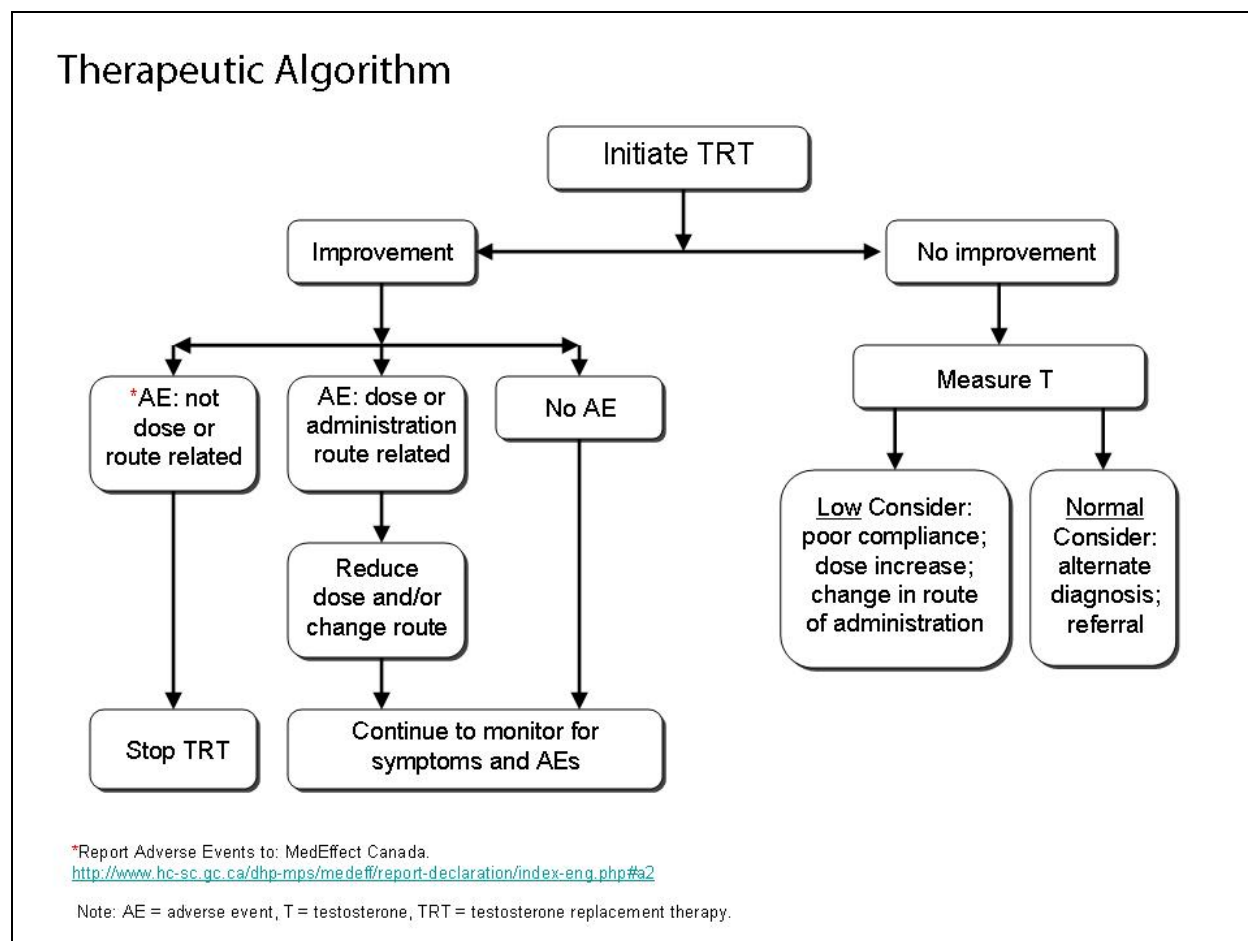
THERAPEUTIC ALGORITHM

Figure 3. Clinical Decision Making Algorithm for the Treatment of Testosterone Deficiency Syndrome.

REFERENCES

1.   Layton JB, Li D, Meier CR, et al. Testosterone lab testing and initiation in the United Kingdom and the United States, 2000 to 2011. *Journal of Clinical Endocrinology and Metabolism.* March 2014;99(3):835-842.
2.   Buvat J, Maggi M, Guay A, Torres LO. Testosterone Deficiency in Men: Systematic Review and Standard Operating Procedures for Diagnosis and Treatment. *Journal of sexual medicine.* 2013;10:245-284.
3.   Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. *The Journal of clinical endocrinology and metabolism.* Jan 2008;93(1):68-75.
4.   Shi Z, Araujo AB, Martin S, O'Loughlin P, Wittert GA. Longitudinal changes in testosterone over five years in community-dwelling men. *The Journal of clinical endocrinology and metabolism.* Aug 2013;98(8):3289-3297.
5.   Surampudi PN, Wang C, Swerdloff R. Hypogonadism in the aging male diagnosis, potential benefits, and risks of testosterone replacement therapy. *International journal of endocrinology print.* 2012;2012:625434.
6.   Veldhuis JD, Urban RJ, Lizarralde G, Johnson ML, Iranmanesh A. Attenuation of luteinizing hormone secretory burst amplitude as a proximate basis for the hypoandrogenism of healthy aging in men. *The Journal of clinical endocrinology and metabolism.* Sep 1992;75(3):707-713.
7.   Wu FC, Tajar A, Beynon JM, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. *The New England journal of medicine.* Jul 8 2010;363(2):123-135.
8.   Mulligan T, Frick MF, Zuraw QC, Stemhagen A, McWhirter C. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. *Int J Clin Pract.* Jul 2006;60(7):762-769.
9.   Morley JE, Charlton E, Patrick P, et al. Validation of a screening questionnaire for androgen deficiency in aging males. *Metabolism.* Sep 2000;49(9):1239-1242.
10.   Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR, Baltimore Longitudinal Study of A. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *The Journal of clinical endocrinology and metabolism.* Feb 2001;86(2):724-731.
11.   Araujo AB, O'Donnell AB, Brambilla DJ, et al. Prevalence and incidence of androgen deficiency in middle-aged and older men: estimates from the Massachusetts Male Aging Study. *The Journal of clinical endocrinology and metabolism.* Dec 2004;89(12):5920-5926.
12.   Araujo AB, Esche GR, Kupelian V, et al. Prevalence of symptomatic androgen deficiency in men. *The Journal of clinical endocrinology and metabolism.* Nov 2007;92(11):4241-4247.
13.   Okamura K, Ando F, Shimokata H. Serum total and free testosterone level of Japanese men: a population-based study. *International journal of urology : official journal of the Japanese Urological Association.* Sep 2005;12(9):810-814.
14.   Liu CC, Wu WJ, Lee YC, et al. The prevalence of and risk factors for androgen deficiency in aging Taiwanese men. *The journal of sexual medicine.* Apr 2009;6(4):936-946.
15.   Nardozza Junior A, Szelbracikowski Sdos S, Nardi AC, Almeida JC. Age-related testosterone decline in a Brazilian cohort of healthy military men. *International braz j urol : official journal of the Brazilian Society of Urology.* Sep-Oct 2011;37(5):591-597.
16.   Clapauch R, Braga DJ, Marinheiro LP, Buksman S, Schrank Y. Risk of late-onset hypogonadism (andropause) in Brazilian men over 50 years of age with osteoporosis: usefulness of screening questionnaires. *Arq Bras Endocrinol Metabol.* Dec 2008;52(9):1439-1447.
17.   McLachlan RI, Allan CA. Defining the prevalence and incidence of androgen deficiency in aging men: where are the goal posts? *The Journal of clinical endocrinology and metabolism.* Dec 2004;89(12):5916-5919.

18.   Davis DA, Thomson MA, Oxman AD, Haynes RB. Changing physician performance. A systematic review of the effect of continuing medical education strategies. *JAMA.* Sep 6 1995;274(9):700-705.

19.   Canadian Men's Health Foundation Multidisciplinary Guidelines Task Force on TDS. Data on file. 2013.

20.   Piszczek J, Mamdani M, Antoniou T, Juurlink DN, Gomes T. The impact of drug reimbursement policy on rates of testosterone replacement therapy among older men. *PLoS One.* 2014;9(7):e98003.

21.   U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA evaluating risk of stroke, heart attack and death with FDA-approved testosterone products. Available at: http://www.fda.gov/drugs/drugsafety/ucm383904.htm. (Accessed July 22, 2014). 2014.

22.   Administration USFaD. Testosterone products and venous thromboembolic events label change. June 2014. Available at: http://www.fda.gov/safety/medwatch/safetyinformation/ucm402877.htm. (Accessed July 22, 2014). 2014.

23.   Canada H. Health Canada. Summary safety review – testosterone replacement products – cardiovascular risk. July 15, 2014. Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/review-examen/testosterone-eng.php. (Accessed July 22, 2014).

24.   GRADE Working Group. GRADE approach to guideline development. Available: www.gradeworkinggroup.org (Accessed 2014 Sept. 6).

25.   Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *The Journal of clinical endocrinology and metabolism.* Jun 2010;95(6):2536-2559.

26.   Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. *BMJ (Clinical research ed.).* May 10 2008;336(7652):1049-1051.

27.   de Meyrick J. The Delphi method and health research. *Health Educ* 2003;103:7-16.

28.   Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* Dec 14 2010;182(18):E839-842.

29.   International Committee of Medical Journal Editors. ICMJE Form for Disclosure of Potential Conflicts of Interest. Available: http://www.icmje.org/conflicts-of-interest (Accessed 2014 Sept. 6).

30.   Wu FC, Tajar A, Pye SR, et al. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. *The Journal of clinical endocrinology and metabolism.* Jul 2008;93(7):2737-2745.

31.   Travison TG, Araujo AB, Kupelian V, O'Donnell AB, McKinlay JB. The relative contributions of aging, health, and lifestyle factors to serum testosterone decline in men. *The Journal of clinical endocrinology and metabolism.* Feb 2007;92(2):549-555.

32.   Travison TG, Shackelton R, Araujo AB, et al. The natural history of symptomatic androgen deficiency in men: onset, progression, and spontaneous remission. *J Am Geriatr Soc.* May 2008;56(5):831-839.

33.   Tajar A, Forti G, O'Neill TW, et al. Characteristics of secondary, primary, and compensated hypogonadism in aging men: evidence from the European Male Ageing Study. *The Journal of clinical endocrinology and metabolism.* Apr 2010;95(4):1810-1818.

34.   Emmelot-Vonk MH, Verhaar HJJ, Nakhai-Pour HR, Grobbee DE, Van Der Schouw YT. Low testosterone concentrations and the symptoms of testosterone deficiency according to the Androgen Deficiency in Ageing Males (ADAM) and Ageing Males' Symptoms rating scale (AMS) questionnaires. *Clinical endocrinology.* 2011;74:488-494.

35.   Gruenewald DA, Matsumoto AM. Testosterone supplementation therapy for older men: potential benefits and risks. *J Am Geriatr Soc.* Jan 2003;51(1):101-115; discussion 115.

36.   Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. *The Journal of clinical endocrinology and metabolism.* Nov 2006;91(11):4335-4343.

37.   Hall SA, Esche GR, Araujo AB, et al. Correlates of low testosterone and symptomatic androgen deficiency in a population-based sample. *The Journal of clinical endocrinology and metabolism.* Oct 2008;93(10):3870-3877.

38.   Cunningham GR, Stephens-Shields AJ, Rosen RC, et al. Association of sex hormones with sexual function, vitality, and physical function of symptomatic older men with low testosterone levels at baseline in the testosterone trials. *The Journal of clinical endocrinology and metabolism.* Mar 2015;100(3):1146-1155.

39.   Gielen E, O'Neill TW, Pye SR, et al. Endocrine determinants of incident sarcopenia in middle-aged and elderly European men. *Journal of cachexia, sarcopenia and muscle.* 2015:n/a-n/a.

40.   Khaw KT, Barrett-Connor E. Lower endogenous androgens predict central adiposity in men. *Annals of epidemiology.* Sep 1992;2(5):675-682.

41.   Heinemann LA ZT, Vermeulen A, Thiel C, Hummel W. A new aging males' symptoms (AMS) rating scale. *J Aging Male.* 1999(2):105-114.

42.   Smith KW, Feldman HA, McKinlay JB. Construction and field validation of a self-administered screener for testosterone deficiency (hypogonadism) in ageing men. *Clin Endocrinol (Oxf).* Dec 2000;53(6):703-711.

43.   Morley JE, Perry HM, 3rd, Kevorkian RT, Patrick P. Comparison of screening questionnaires for the diagnosis of hypogonadism. *Maturitas.* Mar 20 2006;53(4):424-429.

44.   Mah PM, Wittert GA. Obesity and testicular function. *Molecular and cellular endocrinology.* Mar 25 2010;316(2):180-186.

45.   Drake MT, Murad MH, Mauck KF, et al. Clinical review. Risk factors for low bone mass-related fractures in men: a systematic review and meta-analysis. *The Journal of clinical endocrinology and metabolism.* Jun 2012;97(6):1861-1870.

46.   Tancredi A, Reginster JY, Schleich F, et al. Interest of the androgen deficiency in aging males (ADAM) questionnaire for the identification of hypogonadism in elderly community-dwelling male volunteers. *Eur J Endocrinol.* Sep 2004;151(3):355-360.

47.   Zengerling F, Schrader AJ, Cronauer MV, Stemann H, Schrader M, Rinnab L. The "Aging Males' Symptoms" Scale (AMS): predictive value for lowered circulating androgens. *Aging Male.* Dec 2012;15(4):253-257.

48.   Mohamed O, Freundlich RE, Dakik HK, et al. The quantitative ADAM questionnaire: a new tool in quantifying the severity of hypogonadism. *Int J Impot Res.* Jan-Feb 2010;22(1):20-24.

49.   Spetz AC, Palmefors L, Skobe RS, et al. Testosterone correlated to symptoms of partial androgen deficiency in aging men (PADAM) in an elderly Swedish population. *Menopause.* Nov-Dec 2007;14(6):999-1005.

50.   Wiltink J, Beutel ME, Brahler E, Weidner W. Hypogonadism-related symptoms: development and evaluation of an empirically derived self-rating instrument (HRS 'Hypogonadism Related Symptom Scale'). *Andrologia.* Oct 2009;41(5):297-304.

51.   Alidjanov J, Wolf J, Schuppe HC, et al. Validation of the German version of the 'Hypogonadism Related Symptom Scale' (HRS) in andrological patients with infertility, HIV infection and metabolic syndrome. *Andrologia.* Jan 6 2014.

52.   Rosen RC, Araujo AB, Connor MK, et al. The NERI Hypogonadism Screener: psychometric validation in male patients and controls. *Clin Endocrinol (Oxf).* Feb 2011;74(2):248-256.

53. Corona G, Mannucci E, Petrone L, et al. ANDROTEST: a structured interview for the screening of hypogonadism in patients with sexual dysfunction. *The journal of sexual medicine.* Jul 2006;3(4):706-715.

54. Sun K, Liang GQ, Chen XF, et al. Survey for late-onset hypogonadism among old and middle-aged males in Shanghai communities. *Asian J Androl.* Mar 2012;14(2):338-340.

55. Black AM, Day AG, Morales A. The reliability of clinical and biochemical assessment in symptomatic late-onset hypogonadism: can a case be made for a 3-month therapeutic trial? *BJU Int.* Nov 2004;94(7):1066-1070.

56. Morley JE. The diagnosis of late life hypogonadism. *Aging Male.* Dec 2007;10(4):217-220.

57. Lepage R. Measurement of testosterone and its sub-fractions in Canada. *Clinical biochemistry.* Feb 2006;39(2):97-108.

58. Rosner W, Auchus RJ, Azziz R, Sluss PM, Raff H. Position statement: Utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement. *The Journal of clinical endocrinology and metabolism.* Feb 2007;92(2):405-413.

59. Taieb J, Mathian B, Millot F, et al. Testosterone measured by 10 immunoassays and by isotope-dilution gas chromatography-mass spectrometry in sera from 116 men, women, and children. *Clinical chemistry.* Aug 2003;49(8):1381-1395.

60. Wang C, Catlin DH, Demers LM, Starcevic B, Swerdloff RS. Measurement of total serum testosterone in adult men: comparison of current laboratory methods versus liquid chromatography-tandem mass spectrometry. *The Journal of clinical endocrinology and metabolism.* Feb 2004;89(2):534-543.

61. Sikaris K, McLachlan RI, Kazlauskas R, de Kretser D, Holden CA, Handelsman DJ. Reproductive hormone reference intervals for healthy fertile young men: evaluation of automated platform assays. *The Journal of clinical endocrinology and metabolism.* Nov 2005;90(11):5928-5936.

62. Vesper HW, Botelho JC, Shacklady C, Smith A, Myers GL. CDC project on standardizing steroid hormone measurements. *Steroids.* Dec 12 2008;73(13):1286-1292.

63. Yun YM, Botelho JC, Chandler DW, et al. Performance criteria for testosterone measurements based on biological variation in adult males: recommendations from the Partnership for the Accurate Testing of Hormones. *Clinical chemistry.* Dec 2012;58(12):1703-1710.

64. Vesper HW, Botelho JC, Wang Y. Challenges and improvements in testosterone and estradiol testing. *Asian J Androl.* Mar-Apr 2014;16(2):178-184.

65. Stanczyk FZ. Extraction/chromatographic testosterone RIA can be used as the "gold standard" for determining the reliability of direct testosterone immunoassay measurements. *Clinical chemistry.* Nov 2004;50(11):2219-2220; author reply 2220-2211.

66. Groenestege WM, Bui HN, ten Kate J, et al. Accuracy of first and second generation testosterone assays and improvement through sample extraction. *Clinical chemistry.* Jul 2012;58(7):1154-1156.

67. Thienpont LM, Van Uytfanghe K, Blincko S, et al. State-of-the-art of serum testosterone measurement by isotope dilution-liquid chromatography-tandem mass spectrometry. *Clinical chemistry.* Aug 2008;54(8):1290-1297.

68. Botelho JC, Shacklady C, Cooper HC, et al. Isotope-dilution liquid chromatography-tandem mass spectrometry candidate reference method for total testosterone in human serum. *Clinical chemistry.* Feb 2013;59(2):372-380.

69. Vesper HW, Botelho JC. Standardization of testosterone measurements in humans. *The Journal of steroid biochemistry and molecular biology.* Aug 2010;121(3-5):513-519.

70. CDC HoST-Testosterone Certified Procedures (Updated 05/2014). Atlanta (GA): US Centers for Disease Control and Prevention; 2014. Available:

http://www.cdc.gov/labstandards/pdf/hs/CDC_Certified_Testosterone_Procedures.pdf (Accessed 2014 Aug. 31). 2014.

71.   Van Uytfanghe K, Stockl D, Kaufman JM, Fiers T, De Leenheer A, Thienpont LM. Validation of 5 routine assays for serum free testosterone with a candidate reference measurement procedure based on ultrafiltration and isotope dilution-gas chromatography-mass spectrometry. *Clinical biochemistry.* Mar 2005;38(3):253-261.

72.   Winters SJ, Kelley DE, Goodpaster B. The analog free testosterone assay: are the results in men clinically useful? *Clinical chemistry.* Oct 1998;44(10):2178-2182.

73.   Rosner W. An extraordinarily inaccurate assay for free testosterone is still with us. *The Journal of clinical endocrinology and metabolism.* Jun 2001;86(6):2903.

74.   Fritz KS, McKean AJ, Nelson JC, Wilcox RB. Analog-based free testosterone test results linked to total testosterone concentrations, not free testosterone concentrations. *Clinical chemistry.* Mar 2008;54(3):512-516.

75.   Swerdloff RS, Wang C. Free testosterone measurement by the analog displacement direct assay: old concerns and new evidence. *Clinical chemistry.* Mar 2008;54(3):458-460.

76.   Gheorghiu I, Moshyk A, Lepage R, Ahnadi CE, Grant AM. When is bioavailable testosterone a redundant test in the diagnosis of hypogonadism in men? *Clinical biochemistry.* Sep 2005;38(9):813-818.

77.   Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. *The Journal of clinical endocrinology and metabolism.* Oct 1999;84(10):3666-3672.

78.   de Ronde W, van der Schouw YT, Pols HA, et al. Calculation of bioavailable and free testosterone in men: a comparison of 5 published algorithms. *Clinical chemistry.* Sep 2006;52(9):1777-1784.

79.   Ho CK, Stoddart M, Walton M, Anderson RA, Beckett GJ. Calculated free testosterone in men: comparison of four equations and with free androgen index. *Annals of clinical biochemistry.* Sep 2006;43(Pt 5):389-397.

80.   Emadi-Konjin P, Bain J, Bromberg IL. Evaluation of an algorithm for calculation of serum "bioavailable" testosterone (BAT). *Clinical biochemistry.* Nov 2003;36(8):591-596.

81.   Sartorius G, Ly LP, Sikaris K, McLachlan R, Handelsman DJ. Predictive accuracy and sources of variability in calculated free testosterone estimates. *Annals of clinical biochemistry.* Mar 2009;46(Pt 2):137-143.

82.   Giton F, Fiet J, Guechot J, et al. Serum bioavailable testosterone: assayed or calculated? *Clinical chemistry.* Mar 2006;52(3):474-481.

83.   Kapoor P, Luttrell BM, Williams D. The free androgen index is not valid for adult males. *The Journal of steroid biochemistry and molecular biology.* Apr 1993;45(4):325-326.

84.   Morley JE, Perry HM, 3rd, Patrick P, Dollbaum CM, Kells JM. Validation of salivary testosterone as a screening test for male hypogonadism. *Aging Male.* Sep 2006;9(3):165-169.

85.   Macdonald PR, Owen LJ, Wu FC, Macdowall W, Keevil BG, team N. A liquid chromatography-tandem mass spectrometry method for salivary testosterone with adult male reference interval determination. *Clinical chemistry.* May 2011;57(5):774-775.

86.   Keevil BG, MacDonald P, Macdowall W, Lee DM, Wu FC, Team N. Salivary testosterone measurement by liquid chromatography tandem mass spectrometry in adult males and females. *Annals of clinical biochemistry.* May 2014;51(Pt 3):368-378.

87.   Morales A, Bella AJ, Chun S, et al. A practical guide to diagnosis, management and treatment of testosterone deficiency for Canadian physicians. *Canadian Urological Association journal = Journal de l'Association des urologues du Canada.* Aug 2010;4(4):269-275.

88.   Wu HY, Wang XF, Wang JH, Li JY. Testosterone level and mortality in elderly men with systolic chronic heart failure. *Asian J Androl.* Sep 2011;13(5):759-763.

89.   Plumelle D, Lombard E, Nicolay A, Portugal H. Influence of diet and sample collection time on 77 laboratory tests on healthy adults. *Clinical biochemistry.* Jan 2014;47(1-2):31-37.

90.   Diver MJ, Clinical Scince Reviews Committee of the Association for Clinical B. Analytical and physiological factors affecting the interpretation of serum testosterone concentration in men. *Annals of clinical biochemistry.* Jan 2006;43(Pt 1):3-12.

91.   Raff H, Sluss PM. Pre-analytical issues for testosterone and estradiol assays. *Steroids.* Dec 12 2008;73(13):1297-1304.

92.   Shi RZ, van Rossum HH, Bowen RA. Serum testosterone quantitation by liquid chromatography-tandem mass spectrometry: interference from blood collection tubes. *Clinical biochemistry.* Dec 2012;45(18):1706-1709.

93.   Andrew CE, Hanning I, McBain AM, Moody D, Price A. A model for a multicentre approach to the derivation of reference intervals for thyroid hormones and testosterone for laboratories using identical analysers. *Clinical chemistry and laboratory medicine : CCLM / FESCC.* Oct 2000;38(10):1013-1019.

94.   Nahoul K, Roger M. Age-related decline of plasma bioavailable testosterone in adult men. *Journal of steroid biochemistry.* Feb 1990;35(2):293-299.

95.   Mohr BA, Guay AT, O'Donnell AB, McKinlay JB. Normal, bound and nonbound testosterone levels in normally ageing men: results from the Massachusetts Male Ageing Study. *Clin Endocrinol (Oxf).* Jan 2005;62(1):64-73.

96.   Zimmerman AC, Buhr KA, Lear SA, Holmes DT. Age-dependent reference intervals for measured bioavailable testosterone on the Siemens Advia Centaur: ethnicity-specific values not necessary for South Asians. *Clinical biochemistry.* Jun 2009;42(9):922-925.

97.   Collier CP, Morales A, Clark A, Lam M, Wynne-Edwards K, Black A. The significance of biological variation in the diagnosis of testosterone deficiency, and consideration of the relevance of total, free and bioavailable testosterone determinations. *The Journal of urology.* Jun 2010;183(6):2294-2299.

98.   Corona G, Rastrelli G, Maggi M. Diagnosis and treatment of late-onset hypogonadism: systematic review and meta-analysis of TRT outcomes. *Best practice & research.Clinical endocrinology & metabolism.* 2013;27:557-579.

99.   Ullah MI, Riche DM, Koch CA. Transdermal testosterone replacement therapy in men. *Drug design, development and therapy.* 2014;8:101-112.

100.   Health Canada. Drug and Health Products. Notice of Compliance. Available: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/index-eng.php. (Accessed 2014 June 18). 2014.

101.   Andriol (testosterone undecanoate capsules) product monograph. Kirkland, QC: Merck Canada Inc.; November 15, 2011.

102.   Androderm Testosterone Transdermal Delivery System product monograph. Mississauga, ON; Actavis Specialty Pharmaceuticals Co.; June 10, 2013.

103.   Androgel Testosterone gel 1% product monograph. Saint-Laurent, QC: Abbott Laboratories, Limited; February 21, 2014.

104.   Axiron (testosterone topical solution 2%) product monograph. Toronto, ON: Eli Lilly Canada Inc.; March 30, 2012.

105.   Delatestryl testosterone enanthate product monograph. Montreal, QC. Valeant Canada LP; September 26, 2011. .

106.   Depo-Testosterone (testosterone cypionate injection USP) product monograph. Kirkland, QC.; Pfizer Canada Inc.; July 3, 2007.

107.   pms-Testosterone (testosterone undecanoate) product monograph. Montreal, QC. Pharmascience Inc.; February 6, 2013.

108.   Testim 1% (testosterone gel) product monograph. Montreal, QC: Paladin Labs Inc. October 1, 2009.

109.   Testosterone cypionate injection, USP product monograph. Halifax, NS: Cytex Pharmaceuticals Inc.; December 21, 2007.

110.   Seftel A. Testosterone replacement therapy for male hypogonadism: part III. Pharmacologic and clinical profiles, monitoring, safety issues, and potential future agents. *Int J Impot Res.* Jan-Feb 2007;19(1):2-24.

111.   Szeinbach SL, Seoane-Vazquez E, Summers KH. Development of a men's Preference for Testosterone Replacement Therapy (P-TRT) instrument. *Patient preference and adherence.* 2012;6:631-641.

112.   Bouloux PM, Legros JJ, Elbers JM, et al. Effects of oral testosterone undecanoate therapy on bone mineral density and body composition in 322 aging men with symptomatic testosterone deficiency: A 1-year, randomized, placebo-controlled, dose-ranging study. *Aging male.* 2013;16:38-47.

113.   Franchimont P, Kicovic PM, Mattei A, Roulier R. Effects of oral testosterone undecanoate in hypogonadal male patients. *Clin Endocrinol (Oxf).* Oct 1978;9(4):313-320.

114.   Bagchus WM, Hust R, Maris F, Schnabel PG, Houwing NS. Important effect of food on the bioavailability of oral testosterone undecanoate. *Pharmacotherapy.* Mar 2003;23(3):319-325.

115.   Westaby D, Ogle SJ, Paradinas FJ, Randell JB, Murray-Lyon IM. Liver damage from long-term methyltestosterone. *Lancet.* Aug 6 1977;2(8032):262-263.

116.   Gooren LJ. A ten-year safety study of the oral androgen testosterone undecanoate. *J Androl.* May-Jun 1994;15(3):212-215.

117.   Conway AJ, Boylan LM, Howe C, Ross G, Handelsman DJ. Randomized clinical trial of testosterone replacement therapy in hypogonadal men. *Int J Androl.* Aug 1988;11(4):247-264.

118.   Cantrill JA, Dewis P, Large DM, Newman M, Anderson DC. Which testosterone replacement therapy? *Clin Endocrinol (Oxf).* Aug 1984;21(2):97-107.

119.   Behre HM WC, Handelsman DJ, Nieschlag E. . Pharmacology of testosterone preparations. In: Nieschlag E, Behre HM, eds. Testosterone: Action-Deficiency-Substitution. . 2014.

120.   Ferrando AA, Sheffield-Moore M, Yeckel CW, et al. Testosterone administration to older men improves muscle function: molecular and physiological mechanisms. *American journal of physiology. Endocrinology and metabolism.* Mar 2002;282(3):E601-607.

121.   Nankin HR. Hormone kinetics after intramuscular testosterone cypionate. *Fertil Steril.* Jun 1987;47(6):1004-1009.

122.   Arver S, Dobs AS, Meikle AW, et al. Long-term efficacy and safety of a permeation-enhanced testosterone transdermal system in hypogonadal men. *Clin Endocrinol (Oxf).* Dec 1997;47(6):727-737.

123.   Dobs AS, Bachorik PS, Arver S, et al. Interrelationships among lipoprotein levels, sex hormones, anthropometric parameters, and age in hypogonadal men treated for 1 year with a permeation-enhanced testosterone transdermal system. *The Journal of clinical endocrinology and metabolism.* Mar 2001;86(3):1026-1033.

124.   Steidle C, Schwartz S, Jacoby K, Sebree T, Smith T, Bachand R. AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. *The Journal of clinical endocrinology and metabolism.* Jun 2003;88(6):2673-2681.

125.   Wilson DE, Kaidbey K, Boike SC, Jorkasky DK. Use of topical corticosteroid pretreatment to reduce the incidence and severity of skin reactions associated with testosterone transdermal therapy. *Clinical therapeutics.* Mar-Apr 1998;20(2):299-306.

126.   Swerdloff RS, Wang C, Cunningham G, et al. Long-term pharmacokinetics of transdermal testosterone gel in hypogonadal men. *The Journal of clinical endocrinology and metabolism.* Dec 2000;85(12):4500-4510.

127.   Bhattacharya RK, Khera M, Blick G, Kushner H, Miner MM. Testosterone replacement therapy among elderly males: the Testim Registry in the US (TRiUS). *Clinical Interventions In Aging.* 2012;7:321-330.

128.   Frederiksen L, Hojlund K, Hougaard DM, Brixen K, Andersen M. Testosterone therapy increased muscle mass and lipid oxidation in aging men. *Age (Dordrecht, Netherlands).* 2012;34:145-156.

129.   Spitzer M, Basaria S, Travison TG, et al. Effect of testosterone replacement on response to sildenafil citrate in men with erectile dysfunction: a parallel, randomized trial.[Summary for patients in Ann Intern Med. 2012 Nov 20;157(10):I-18; PMID: 23165675]. *Annals of internal medicine.* 2012;157:681-691.

130.   Wang C, Berman N, Longstreth JA, et al. Pharmacokinetics of transdermal testosterone gel in hypogonadal men: application of gel at one site versus four sites: a General Clinical Research Center Study. *The Journal of clinical endocrinology and metabolism.* Mar 2000;85(3):964-969.

131.   Marbury T, Hamill E, Bachand R, Sebree T, Smith T. Evaluation of the pharmacokinetic profiles of the new testosterone topical gel formulation, Testim, compared to AndroGel. *Biopharmaceutics & drug disposition.* Apr 2003;24(3):115-120.

132.   Grober ED, Khera M, Soni SD, Espinoza MG, Lipshultz LI. Efficacy of changing testosterone gel preparations (Androgel or Testim) among suboptimally responsive hypogonadal men. *Int J Impot Res.* Mar-Apr 2008;20(2):213-217.

133.   Dean JD, Carnegie C, Rodzvilla J, Smith T. Long-term effects of testim(r) 1% testosterone gel in hypogonadal men. *Reviews in urology.* Spring 2005;7(2):87-94.

134.   Wang C, Swerdloff RS, Iranmanesh A, et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. *The Journal of clinical endocrinology and metabolism.* Aug 2000;85(8):2839-2853.

135.   Wang C, Cunningham G, Dobs A, et al. Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. *The Journal of clinical endocrinology and metabolism.* May 2004;89(5):2085-2098.

136.   Wang C, Ilani N, Arver S, McLachlan RI, Soulis T, Watkinson A. Efficacy and safety of the 2% formulation of testosterone topical solution applied to the axillae in androgen-deficient men. *Clinical endocrinology.* 2011;75:836-843.

137.   Muram D, Melby T, Alles Kingshill E. Skin reactions in a phase 3 study of a testosterone topical solution applied to the axilla in hypogonadal men. *Current medical research and opinion.* 2012;28:761-766.

138.   de Ronde W. Hyperandrogenism after transfer of topical testosterone gel: case report and review of published and unpublished studies. [Review] [12 refs]. *Human reproduction (Oxford, England).* 2009;24:425-428.

139.   Nelson D, Ho J, Pacaud D, Stephure D. Virilization in two pre-pubertal children exposed to topical androgen. *Journal of pediatric endocrinology & metabolism : JPEM.* 2013;26(9-10):981-985.

140.   Fernandez-Balsells MM, Murad MH, Lane M, et al. Clinical review 1: Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. [Review] [72 refs]. *Journal of clinical endocrinology and metabolism.* 2010;95:2560-2575.

141.   Beckers A. [Hypogonadism due to LH deficiency]. *Bulletin et memoires de l'Academie royale de medecine de Belgique.* 2007;162(5-6):291-297; discussion 298.

142.   Tsujimura A, Matsumiya K, Takao T, et al. Treatment with human chorionic gonadotropin for PADAM: a preliminary report. *Aging Male.* Sep-Dec 2005;8(3-4):175-179.

143.   Pregnyl (chorionic gonadotropin for injection, USP) product monograph. Kirkland, QC: Merck Canada Inc.; February 3, 2011.

144.   Buchter D, Behre HM, Kliesch S, Nieschlag E. Pulsatile GnRH or human chorionic gonadotropin/human menopausal gonadotropin as effective treatment for men with hypogonadotropic hypogonadism: a review of 42 cases. *Eur J Endocrinol.* Sep 1998;139(3):298-303.

145.   Sykiotis GP, Hoang XH, Avbelj M, et al. Congenital idiopathic hypogonadotropic hypogonadism: evidence of defects in the hypothalamus, pituitary, and testes. *Journal of Clinical Endocrinology & Metabolism.* 2010;95(6):3019-3027.

146.   Pitteloud N, Hayes FJ, Dwyer A, Boepple PA, Lee H, Crowley WF, Jr. Predictors of outcome of long-term GnRH therapy in men with idiopathic hypogonadotropic hypogonadism. *The Journal of clinical endocrinology and metabolism.* Sep 2002;87(9):4128-4136.

147.   Lutrepulse (gonadorelin acetate for injection) product monograph. North York, ON:Ferring Inc.; December 13, 2012.

148.   Katz DJ, Nabulsi O, Tal R, Mulhall JP. Outcomes of clomiphene citrate treatment in young hypogonadal men. *BJU International.* 2012;110(4):573-578.

149.   Moskovic DJ, Katz DJ, Akhavan A, Park K, Mulhall JP. Clomiphene citrate is safe and effective for long-term management of hypogonadism. *BJU Int.* Nov 2012;110(10):1524-1528.

150.   Taylor F, Levine L. Clomiphene citrate and testosterone gel replacement therapy for male hypogonadism: efficacy and treatment cost. *The journal of sexual medicine.* Jan 2010;7(1 Pt 1):269-276.

151.   Clomid (clomiphene citrate USP) product monograph. Laval, QC: sanofi-aventis Canada Inc,; August 9, 2013.

152.   Buvat J, Montorsi F, Maggi M, et al. Hypogonadal Men Nonresponders to the PDE5 Inhibitor Tadalafil Benefit from Normalization of Testosterone Levels with a 1% Hydroalcoholic Testosterone Gel in the Treatment of Erectile Dysfunction (TADTEST Study). *Journal of sexual medicine.* 2011;8:284-293.

153.   Kim JW, Oh MM, Park MG, et al. Combination therapy of testosterone enanthate and tadalafil on PDE5 inhibitor non-reponders with severe and intermediate testosterone deficiency. *International journal of impotence research.* 2013;25:29-33.

154.   Tsertsvadze A, Fink HA, Yazdi F, et al. Oral phosphodiesterase-5 inhibitors and hormonal treatments for erectile dysfunction: a systematic review and meta-analysis. [Review] [226 refs]. *Annals of internal medicine.* 2009;151:650-661.

155.   Park K, Ku JH, Kim SW, Paick JS. Risk factors in predicting a poor response to sildenafil citrate in elderly men with erectile dysfunction. *BJU Int.* Feb 2005;95(3):366-370.

156.   Shabsigh R, Kaufman JM, Steidle C, Padma-Nathan H. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. *The Journal of urology.* Aug 2004;172(2):658-663.

157.   Greenstein A, Mabjeesh NJ, Sofer M, Kaver I, Matzkin H, Chen J. Does sildenafil combined with testosterone gel improve erectile dysfunction in hypogonadal men in whom testosterone supplement therapy alone failed? *The Journal of urology.* Feb 2005;173(2):530-532.

158.   Rosenthal BD, May NR, Metro MJ, Harkaway RC, Ginsberg PC. Adjunctive use of AndroGel (testosterone gel) with sildenafil to treat erectile dysfunction in men with acquired androgen deficiency syndrome after failure using sildenafil alone. *Urology.* Mar 2006;67(3):571-574.

159.   Alhathal N, Elshal AM, Carrier S. Synergetic effect of testosterone and phophodiesterase-5 inhibitors in hypogonadal men with erectile dysfunction: A systematic review. *Canadian*

Urological Association journal = Journal de l'Association des urologues du Canada. Aug 2012;6(4):269-274.

160.   Rowland D, Tai W. A review of plant-derived and herbal approaches to the treatment of sexual dysfunctions. *J Sex Marital Ther.* May-Jun 2003;29(3):185-205.

161.   de Andrade E, de Mesquita AA, Claro Jde A, et al. Study of the efficacy of Korean Red Ginseng in the treatment of erectile dysfunction. *Asian J Androl.* Mar 2007;9(2):241-244.

162.   Ismail SB, Wan Mohammad WM, George A, Nik Hussain NH, Musthapa Kamal ZM, Liske E. Randomized Clinical Trial on the Use of PHYSTA Freeze-Dried Water Extract of Eurycoma longifolia for the Improvement of Quality of Life and Sexual Well-Being in Men. *Evidence-based complementary and alternative medicine : eCAM.* 2012;2012:429268.

163.   Ledda A, Belcaro G, Cesarone MR, Dugall M, Schonlau F. Investigation of a complex plant extract for mild to moderate erectile dysfunction in a randomized, double-blind, placebo-controlled, parallel-arm study. *BJU Int.* Oct 2010;106(7):1030-1033.

164.   Santos CA, Jr., Reis LO, Destro-Saade R, Luiza-Reis A, Fregonesi A. Tribulus terrestris versus placebo in the treatment of erectile dysfunction: A prospective, randomized, double blind study. *Actas Urol Esp.* May 2014;38(4):244-248.

165.   Shah GR, Chaudhari MV, Patankar SB, Pensalwar SV, Sabale VP, Sonawane NA. Evaluation of a multi-herb supplement for erectile dysfunction: a randomized double-blind, placebo-controlled study. *BMC complementary and alternative medicine.* 2012;12:155.

166.   Stanislavov R, Nikolova V, Rohdewald P. Improvement of erectile function with Prelox: a randomized, double-blind, placebo-controlled, crossover trial. *Int J Impot Res.* Mar-Apr 2008;20(2):173-180.

167.   Tambi MI, Imran MK, Henkel RR. Standardised water-soluble extract of Eurycoma longifolia, Tongkat ali, as testosterone booster for managing men with late-onset hypogonadism? *Andrologia.* 2012;44 Suppl 1:226-230.

168.   Udani JK, George AA, Musthapa M, Pakdaman MN, Abas A. Effects of a Proprietary Freeze-Dried Water Extract of Eurycoma longifolia (Physta) and Polygonum minus on Sexual Performance and Well-Being in Men: A Randomized, Double-Blind, Placebo-Controlled Study. *Evidence-based complementary and alternative medicine : eCAM.* 2014;2014:179529.

169.   Tambi MI, Imran MK. Eurycoma longifolia Jack in managing idiopathic male infertility. *Asian J Androl.* May 2010;12(3):376-380.

170.   Iacono F, Prezioso D, Illiano E, Romeo G, Ruffo A, Amato B. Sexual asthenia: Tradamixina versus Tadalafil 5 mg daily. *BMC surgery.* 2012;12 Suppl 1:S23.

171.   Ulbricht C, Conquer J, Flanagan K, Isaac R, Rusie E, Windsor RC. An evidence-based systematic review of tongkat ali (Eurycoma longifolia) by the Natural Standard Research Collaboration. *Journal of dietary supplements.* Mar 2013;10(1):54-83.

172.   Qureshi A, Naughton DP, Petroczi A. A systematic review on the herbal extract tribulus terrestris and the roots of its putative aphrodisiac and performance enhancing effect. *Journal of dietary supplements.* Mar 2014;11(1):64-79.

173.   Allan CA, McLachlan RI. Androgens and obesity. *Curr Opin Endocrinol Diabetes Obes.* Jun 2010;17(3):224-232.

174.   Blouin K, Boivin A, Tchernof A. Androgens and body fat distribution. *The Journal of steroid biochemistry and molecular biology.* Feb 2008;108(3-5):272-280.

175.   Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. *The New England journal of medicine.* Aug 23 2007;357(8):753-761.

176.   Mollar Puchades MA, Gomez RC, del Olmo Garcia MI, et al. Hypogonadotropic hypogonadism in a patient with morbid obesity. *Obesity surgery.* Aug 2007;17(8):1127-1131.

177. Botella-Carretero JI, Balsa JA, Gomez-Martin JM, et al. Circulating free testosterone in obese men after bariatric surgery increases in parallel with insulin sensitivity. *J Endocrinol Invest.* Apr 2013;36(4):227-232.

178. Hammoud A, Gibson M, Hunt SC, et al. Effect of Roux-en-Y gastric bypass surgery on the sex steroids and quality of life in obese men. *The Journal of clinical endocrinology and metabolism.* Apr 2009;94(4):1329-1332.

179. Legro RS, Kunselman AR, Meadows JW, et al. Time-related increase in urinary testosterone levels and stable semen analysis parameters after bariatric surgery in men. *Reproductive biomedicine online.* Feb 2015;30(2):150-156.

180. Rao SR, Kini S, Tamler R. Sex hormones and bariatric surgery in men. *Gend Med.* Oct 2011;8(5):300-311.

181. Fried M, Yumuk V, Oppert JM, et al. Interdisciplinary European Guidelines on metabolic and bariatric surgery. *Obes Facts.* 2013;6(5):449-468.

182. Khaw KT, Dowsett M, Folkerd E, et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. *Circulation.* Dec 4 2007;116(23):2694-2701.

183. Maggio M, Lauretani F, Ceda GP, et al. Relationship between low levels of anabolic hormones and 6-year mortality in older men: the aging in the Chianti Area (InCHIANTI) study. *Arch Intern Med.* Nov 12 2007;167(20):2249-2254.

184. Araujo AB, Dixon JM, Suarez EA, Murad MH, Guey LT, Wittert GA. Clinical review: Endogenous testosterone and mortality in men: a systematic review and meta-analysis. *The Journal of clinical endocrinology and metabolism.* Oct 2011;96(10):3007-3019.

185. Yeap BB, Alfonso H, Chubb SA, et al. In older men an optimal plasma testosterone is associated with reduced all-cause mortality and higher dihydrotestosterone with reduced ischemic heart disease mortality, while estradiol levels do not predict mortality. *The Journal of clinical endocrinology and metabolism.* Jan 2014;99(1):E9-18.

186. Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR. Low serum testosterone and mortality in male veterans. *Arch Intern Med.* Aug 14-28 2006;166(15):1660-1665.

187. Corona G, Rastrelli G, Monami M, et al. Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. [Review]. *European journal of endocrinology.* 2011;165:687-701.

188. Agledahl I, Brodin E, Svartberg J, Hansen JB. Impact of long-term testosterone treatment on plasma levels of free TFPI and TF-induced thrombin generation ex vivo in elderly men with low testosterone levels. *Thrombosis and haemostasis.* 2009;102:945-950.

189. Aversa A, Bruzziches R, Francomano D, et al. Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: Results from a 24-month, randomized, double-blind, placebo-controlled study. *Journal of sexual medicine.* 2010;7:3495-3503.

190. Chock B, Lin TC, Li CS, Swislocki A. Plasma testosterone is associated with Framingham risk score. *Aging Male.* Sep 2012;15(3):134-139.

191. Mathur A, Malkin C, Saeed B, Muthusamy R, Jones TH, Channer K. Long-term benefits of testosterone replacement therapy on angina threshold and atheroma in men.[Erratum appears in Eur J Endocrinol. 2009 Oct;161(4):653]. *European journal of endocrinology / European Federation of Endocrine Societies.* 2009;161:443-449.

192. Poliwczak AR, Tylinska M, Broncel M. Effect of shortterm testosterone replacement therapy on heart rate variability in men with hypoandrogenmetabolic syndrome. *Pol Arch Med Wewn.* Sep 30 2013;123(9):467-473.

193. Mirone V, Imbimbo C, Fusco F, Verze P, Creta M, Tajana G. Androgens and morphologic remodeling at penile and cardiovascular levels: a common piece in complicated puzzles? *Eur Urol.* Aug 2009;56(2):309-316.

194. Traish AM, Guay AT, Morgentaler A. Death by testosterone? We think not! *The journal of sexual medicine.* Mar 2014;11(3):624-629.

195. Gratzke C, Angulo J, Chitaley K, et al. Anatomy, physiology, and pathophysiology of erectile dysfunction. *The journal of sexual medicine.* Jan 2010;7(1 Pt 2):445-475.

196. Kostis JB, Jackson G, Rosen R, et al. Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). *The American journal of cardiology.* Dec 26 2005;96(12B):85M-93M.

197. Gandaglia G, Briganti A, Jackson G, et al. A systematic review of the association between erectile dysfunction and cardiovascular disease. *Eur Urol.* May 2014;65(5):968-978.

198. Vlachopoulos C, Rokkas K, Ioakeimidis N, et al. Prevalence of asymptomatic coronary artery disease in men with vasculogenic erectile dysfunction: a prospective angiographic study. *Eur Urol.* Dec 2005;48(6):996-1002; discussion 1002-1003.

199. Mulhall J, Teloken P, Barnas J. Vasculogenic erectile dysfunction is a predictor of abnormal stress echocardiography. *The journal of sexual medicine.* Mar 2009;6(3):820-825.

200. Jackson G, Padley S. Erectile dysfunction and silent coronary artery disease: abnormal computed tomography coronary angiogram in the presence of normal exercise ECGs. *Int J Clin Pract.* Jun 2008;62(6):973-976.

201. Nehra A, Jackson G, Miner M, et al. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. *Mayo Clinic proceedings.* Aug 2012;87(8):766-778.

202. Calof OM, Singh AB, Lee ML, et al. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. *The journals of gerontology. Series A, Biological sciences and medical sciences.* Nov 2005;60(11):1451-1457.

203. Haddad RM, Kennedy CC, Caples SM, et al. Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clinic proceedings.* Jan 2007;82(1):29-39.

204. Corona G, Maseroli E, Rastrelli G, et al. Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. *Expert Opin Drug Saf.* Oct 2014;13(10):1327-1351.

205. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. *New England journal of medicine.* 2010;363:109-122.

206. Basaria S, Davda MN, Travison TG, Ulloor J, Singh R, Bhasin S. Risk factors associated with cardiovascular events during testosterone administration in older men with mobility limitation. *Journals of gerontology.Series A, Biological sciences and medical sciences.* 2013;68:153-160.

207. Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. *BMC medicine.* 2013;11:108.

208. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS One.* 2014;9(1):e85805.

209. Baillargeon J, Urban RJ, Kuo YF, et al. Risk of Myocardial Infarction in Older Men Receiving Testosterone Therapy. *The Annals of pharmacotherapy.* Jul 2 2014;48(9):1138-1144.

210. Vigen R, O'Donnell CI, Baron AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA.* 2013;310:1829-1836.

211. Cornoldi A, Caminiti G, Marazzi G, et al. Effects of chronic testosterone administration on myocardial ischemia, lipid metabolism and insulin resistance in elderly male diabetic patients with coronary artery disease. *International journal of cardiology.* 2010;142:50-55.

212. Caminiti G, Volterrani M, Iellamo F, et al. Effect of Long-Acting Testosterone Treatment on Functional Exercise Capacity, Skeletal Muscle Performance, Insulin Resistance, and Baroreflex Sensitivity in Elderly Patients With Chronic Heart Failure. A Double-Blind, Placebo-Controlled, Randomized Study. *Journal of the American College of Cardiology.* 2009;54:919-927.

213. Malkin CJ, Pugh PJ, West JN, van Beek EJ, Jones TH, Channer KS. Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo controlled trial. *European heart journal.* Jan 2006;27(1):57-64.

214. Stout M, Tew GA, Doll H, et al. Testosterone therapy during exercise rehabilitation in male patients with chronic heart failure who have low testosterone status: a double-blind randomized controlled feasibility study. *American heart journal.* 2012;164:893-901.

215. Toma M, McAlister FA, Coglianese EE, et al. Testosterone supplementation in heart failure: a meta-analysis. [Review]. *Circulation.Heart failure.* 2012;5:315-321.

216. Schwarz ER, Willix Jr RD. Impact of a physician-supervised exercise-nutrition program with testosterone substitution in partial androgen-deficient middle-aged obese men. *Journal of geriatric cardiology.* 2011;8:201-206.

217. Corona G, Monami M, Rastrelli G, et al. Testosterone and metabolic syndrome: a meta-analysis study. [Review]. *Journal of sexual medicine.* 2011;8:272-283.

218. Jankowska EA, Filippatos G, Ponikowska B, et al. Reduction in circulating testosterone relates to exercise capacity in men with chronic heart failure. *Journal of Cardiac Failure.* 2009;15(5):442-450.

219. Guder G, Allolio B, Angermann CE, Stork S. Androgen deficiency in heart failure. [Review]. *Current heart failure reports.* 2011;8:131-139.

220. Chahla EJ, Hayek ME, Morley JE. Testosterone replacement therapy and cardiovascular risk factors modification. *Aging male.* 2011;14:83-90.

221. Corona G, Mannucci E, Petrone L, et al. NCEP-ATPIII-defined metabolic syndrome, type 2 diabetes mellitus, and prevalence of hypogonadism in male patients with sexual dysfunction. *The journal of sexual medicine.* Jul 2007;4(4 Pt 1):1038-1045.

222. Pitteloud N, Hardin M, Dwyer AA, et al. Increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men. *The Journal of clinical endocrinology and metabolism.* May 2005;90(5):2636-2641.

223. Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A, Dandona P. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. *The Journal of clinical endocrinology and metabolism.* Nov 2004;89(11):5462-5468.

224. Dandona P, Dhindsa S, Chaudhuri A, Bhatia V, Topiwala S, Mohanty P. Hypogonadotrophic hypogonadism in type 2 diabetes, obesity and the metabolic syndrome. *Current molecular medicine.* Dec 2008;8(8):816-828.

225. Dandona P, Dhindsa S, Chandel A, Chaudhuri A. Hypogonadotropic hypogonadism in men with type 2 diabetes. [Review] [68 refs]. *Postgraduate medicine.* 2009;121:45-51.

226. Dandona P, Dhindsa S. Update: Hypogonadotropic hypogonadism in type 2 diabetes and obesity. *The Journal of clinical endocrinology and metabolism.* Sep 2011;96(9):2643-2651.

227. Marin P, Krotkiewski M, Bjorntorp P. Androgen treatment of middle-aged, obese men: effects on metabolism, muscle and adipose tissues. *The European journal of medicine.* Oct 1992;1(6):329-336.

228. Marin P, Holmang S, Jonsson L, et al. The effects of testosterone treatment on body composition and metabolism in middle-aged obese men. *International journal of obesity and related*

metabolic disorders : journal of the International Association for the Study of Obesity. Dec 1992;16(12):991-997.

229. Rebuffe-Scrive M, Marin P, Bjorntorp P. Effect of testosterone on abdominal adipose tissue in men. *Int J Obes.* Nov 1991;15(11):791-795.

230. Aversa A, Bruzziches R, Francomano D, Spera G, Lenzi A. Efficacy and safety of two different testosterone undecanoate formulations in hypogonadal men with metabolic syndrome. *Journal of endocrinological investigation.* 2010;33:776-783.

231. Jones TH, Arver S, Behre HM, et al. Testosterone replacement in hypogonadal men with Type 2 diabetes and/or metabolic syndrome (the TIMES2 study). *Diabetes care.* 2011;34:828-837.

232. Kalinchenko SY, Tishova YA, Mskhalaya GJ, Gooren LJG, Giltay EJ, Saad F. Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study.[Erratum appears in Clin Endocrinol (Oxf). 2011 Aug;75(2):275]. *Clinical endocrinology.* 2010;73:602-612.

233. Kapoor D, Goodwin E, Channer KS, Jones TH. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. *Eur J Endocrinol.* Jun 2006;154(6):899-906.

234. Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. *Aging Male.* Mar 2003;6(1):1-7.

235. Gopal RA, Bothra N, Acharya SV, et al. Treatment of hypogonadism with testosterone in patients with type 2 diabetes mellitus. *Endocrine practice.* 2010;16:570-576.

236. Brand JS, van der Tweel I, Grobbee DE, Emmelot-Vonk MH, van der Schouw YT. Testosterone, sex hormone-binding globulin and the metabolic syndrome: a systematic review and meta-analysis of observational studies. *International journal of epidemiology.* Feb 2011;40(1):189-207.

237. Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA.* Mar 15 2006;295(11):1288-1299.

238. Corona G, Monami M, Rastrelli G, et al. Type 2 diabetes mellitus and testosterone: a meta-analysis study. *International journal of andrology.* 2011;34:528-540.

239. Li C, Ford ES, Li B, Giles WH, Liu S. Association of testosterone and sex hormone-binding globulin with metabolic syndrome and insulin resistance in men. *Diabetes Care.* Jul 2010;33(7):1618-1624.

240. Zhang J, Huang X, Liao M, et al. Both total testosterone and sex hormone-binding globulin are independent risk factors for metabolic syndrome: results from Fangchenggang Area Male Health and Examination Survey in China. *Diabetes/metabolism research and reviews.* 2013;29:391-397.

241. Grossmann M. Low testosterone in men with type 2 diabetes: significance and treatment. [Review]. *Journal of clinical endocrinology and metabolism.* 2011;96:2341-2353.

242. Bhasin S, Calof OM, Storer TW, et al. Drug insight: Testosterone and selective androgen receptor modulators as anabolic therapies for chronic illness and aging. *Nature clinical practice. Endocrinology & metabolism.* Mar 2006;2(3):146-159.

243. Brodsky IG, Balagopal P, Nair KS. Effects of testosterone replacement on muscle mass and muscle protein synthesis in hypogonadal men--a clinical research center study. *The Journal of clinical endocrinology and metabolism.* Oct 1996;81(10):3469-3475.

244. Bhasin S, Taylor WE, Singh R, et al. The mechanisms of androgen effects on body composition: mesenchymal pluripotent cell as the target of androgen action. *The journals of gerontology. Series A, Biological sciences and medical sciences.* Dec 2003;58(12):M1103-1110.

245. Sinha-Hikim I, Artaza J, Woodhouse L, et al. Testosterone-induced increase in muscle size in healthy young men is associated with muscle fiber hypertrophy. *American journal of physiology. Endocrinology and metabolism.* Jul 2002;283(1):E154-164.

246. Singh R, Artaza JN, Taylor WE, et al. Testosterone inhibits adipogenic differentiation in 3T3-L1 cells: nuclear translocation of androgen receptor complex with beta-catenin and T-cell factor 4 may bypass canonical Wnt signaling to down-regulate adipogenic transcription factors. *Endocrinology.* Jan 2006;147(1):141-154.

247. Bhasin S, Travison TG, Storer TW, et al. Effect of testosterone supplementation with and without a dual 5alpha-reductase inhibitor on fat-free mass in men with suppressed testosterone production: a randomized controlled trial. *JAMA - journal of the american medical association.* 2012;307:931-939.

248. Corona G, Rastrelli G, Monami M, et al. Body weight loss reverts obesity-associated hypogonadotropic hypogonadism: a systematic review and meta-analysis. *Eur J Endocrinol.* Jun 2013;168(6):829-843.

249. Corrales JJ, Burgo RM, Garca-Berrocal B, et al. Partial androgen deficiency in aging type 2 diabetic men and its relationship to glycemic control. *Metabolism.* May 2004;53(5):666-672.

250. Cai X, Tian Y, Wu T, Cao CX, Li H, Wang KJ. Metabolic effects of testosterone replacement therapy on hypogonadal men with type 2 diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials. *Asian Journal of Andrology.* 01 Jan 2014;16(1):146-152.

251. Hackett G, Bhartia M, Kennedy D, et al. Testosterone Replacement Therapy Improves Metabolic Parameters in Hypogonadal Men with Type 2 Diabetes but Not in Men with Coexisting Depression: The BLAST Study. *Journal of Sexual Medicine.* 2014;11(3):840-856.

252. Ghazi S, Zohdy W, Elkhiat Y, Shamloul R. Serum testosterone levels in diabetic men with and without erectile dysfunction. *Andrologia.* 2012;44(6):373-380.

253. Hidalgo-Tamola J, Chitaley K. Review type 2 diabetes mellitus and erectile dysfunction. *The journal of sexual medicine.* Apr 2009;6(4):916-926.

254. Penson DF, Latini DM, Lubeck DP, et al. Do impotent men with diabetes have more severe erectile dysfunction and worse quality of life than the general population of impotent patients? Results from the Exploratory Comprehensive Evaluation of Erectile Dysfunction (ExCEED) database. *Diabetes Care.* Apr 2003;26(4):1093-1099.

255. Kapoor D, Clarke S, Channer KS, Jones TH. Erectile dysfunction is associated with low bioactive testosterone levels and visceral adiposity in men with type 2 diabetes. *Int J Androl.* Dec 2007;30(6):500-507.

256. Kapoor D, Aldred H, Clark S, Channer KS, Jones TH. Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes: correlations with bioavailable testosterone and visceral adiposity. *Diabetes Care.* Apr 2007;30(4):911-917.

257. Chitaley K, Kupelian V, Subak L, Wessells H. Diabetes, obesity and erectile dysfunction: field overview and research priorities. *The Journal of urology.* Dec 2009;182(6 Suppl):S45-50.

258. Rendell MS, Rajfer J, Wicker PA, Smith MD. Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. Sildenafil Diabetes Study Group. *JAMA.* Feb 3 1999;281(5):421-426.

259. Kalinchenko SY, Kozlov GI, Gontcharov NP, Katsiya GV. Oral testosterone undecanoate reverses erectile dysfunction associated with diabetes mellitus in patients failing on sildenafil citrate therapy alone. *Aging Male.* Jun 2003;6(2):94-99.

260. Heufelder AE, Saad F, Bunck MC, Gooren L. Fifty-two-week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. *Journal of andrology.* 2009;30:726-733.

261. Canadian Cancer Society. Breast cancer in men. http://www.cancer.ca/en/cancer-information/cancer-type/breast/breast-cancer/breast-cancer-in-men/?region=on (Accessed 2014 Aug. 21).

262.   Johansen Taber KA, Morisy LR, Osbahr AJ, 3rd, Dickinson BD. Male breast cancer: risk factors, diagnosis, and management (Review). *Oncology reports.* Nov 2010;24(5):1115-1120.

263.   Medras M, Filus A, Jozkow P, Winowski J, Sicinska-Werner T. Breast cancer and long-term hormonal treatment of male hypogonadism. *Breast cancer research and treatment.* Apr 2006;96(3):263-265.

264.   Thomas SR, Evans PJ, Holland PA, Biswas M. Invasive breast cancer after initiation of testosterone replacement therapy in a man--a warning to endocrinologists. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists.* Mar 2008;14(2):201-203.

265.   Sorscher S, Krause W. 54-year-old man with breast cancer after prolonged testosterone therapy. *Clinical advances in hematology & oncology : H&O.* Jun 2005;3(6):475; discussion 476.

266.   Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA: a cancer journal for clinicians.* Jan-Feb 2014;64(1):9-29.

267.   Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. 1941. *The Journal of urology.* Feb 2002;167(2 Pt 2):948-951; discussion 952.

268.   Group; EHaPCC, Roddam AW, Allen NE, Appleby P, Key TJ. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. *Journal of the National Cancer Institute.* Feb 6 2008;100(3):170-183.

269.   Monath JR, McCullough DL, Hart LJ, Jarow JP. Physiologic variations of serum testosterone within the normal range do not affect serum prostate-specific antigen. *Urology.* Jul 1995;46(1):58-61.

270.   Mohr BA, Feldman HA, Kalish LA, Longcope C, McKinlay JB. Are serum hormones associated with the risk of prostate cancer? Prospective results from the Massachusetts Male Aging Study. *Urology.* May 2001;57(5):930-935.

271.   Stattin P, Lumme S, Tenkanen L, et al. High levels of circulating testosterone are not associated with increased prostate cancer risk: a pooled prospective study. *International journal of cancer. Journal international du cancer.* Jan 20 2004;108(3):418-424.

272.   Lane BR, Stephenson AJ, Magi-Galluzzi C, Lakin MM, Klein EA. Low testosterone and risk of biochemical recurrence and poorly differentiated prostate cancer at radical prostatectomy. *Urology.* Dec 2008;72(6):1240-1245.

273.   Massengill JC, Sun L, Moul JW, et al. Pretreatment total testosterone level predicts pathological stage in patients with localized prostate cancer treated with radical prostatectomy. *The Journal of urology.* May 2003;169(5):1670-1675.

274.   Isom-Batz G, Bianco FJ, Jr., Kattan MW, Mulhall JP, Lilja H, Eastham JA. Testosterone as a predictor of pathological stage in clinically localized prostate cancer. *The Journal of urology.* Jun 2005;173(6):1935-1937.

275.   Hoffman MA, DeWolf WC, Morgentaler A. Is low serum free testosterone a marker for high grade prostate cancer? *The Journal of urology.* Mar 2000;163(3):824-827.

276.   Botto H, Neuzillet Y, Lebret T, Camparo P, Molinie V, Raynaud JP. High incidence of predominant Gleason pattern 4 localized prostate cancer is associated with low serum testosterone. *The Journal of urology.* Oct 2011;186(4):1400-1405.

277.   Dai B, Qu Y, Kong Y, et al. Low pretreatment serum total testosterone is associated with a high incidence of Gleason score 8-10 disease in prostatectomy specimens: data from ethnic Chinese patients with localized prostate cancer. *BJU Int.* Dec 2012;110(11 Pt B):E667-672.

278.   Mearini L, Zucchi A, Nunzi E, Villirillo T, Bini V, Porena M. Low serum testosterone levels are predictive of prostate cancer. *World J Urol.* Apr 2013;31(2):247-252.

279. Teloken C, Da Ros CT, Caraver F, Weber FA, Cavalheiro AP, Graziottin TM. Low serum testosterone levels are associated with positive surgical margins in radical retropubic prostatectomy: hypogonadism represents bad prognosis in prostate cancer. *The Journal of urology.* Dec 2005;174(6):2178-2180.

280. Chodak GW, Vogelzang NJ, Caplan RJ, Soloway M, Smith JA. Independent prognostic factors in patients with metastatic (stage D2) prostate cancer. The Zoladex Study Group. *JAMA.* Feb 6 1991;265(5):618-621.

281. Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. *Journal of the National Cancer Institute.* Aug 21 1996;88(16):1118-1126.

282. Yano M, Imamoto T, Suzuki H, et al. The clinical potential of pretreatment serum testosterone level to improve the efficiency of prostate cancer screening. *Eur Urol.* Feb 2007;51(2):375-380.

283. Shaneyfelt T, Husein R, Bubley G, Mantzoros CS. Hormonal predictors of prostate cancer: a meta-analysis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Feb 2000;18(4):847-853.

284. Mohler JL, Gregory CW, Ford OH, 3rd, et al. The androgen axis in recurrent prostate cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research.* Jan 15 2004;10(2):440-448.

285. Page ST, Lin DW, Mostaghel EA, et al. Persistent intraprostatic androgen concentrations after medical castration in healthy men. *The Journal of clinical endocrinology and metabolism.* Oct 2006;91(10):3850-3856.

286. Khera M, Crawford D, Morales A, Salonia A, Morgentaler A. A new era of testosterone and prostate cancer: from physiology to clinical implications. *Eur Urol.* Jan 2014;65(1):115-123.

287. Bhasin S, Singh AB, Mac RP, Carter B, Lee MI, Cunningham GR. Managing the risks of prostate disease during testosterone replacement therapy in older men: recommendations for a standardized monitoring plan. *J Androl.* May-Jun 2003;24(3):299-311.

288. Grober ED, Lamb DJ, Khera M, Murthy L, Lipshultz LI. Correlation between simultaneous PSA and serum testosterone concentrations among eugonadal, untreated hypogonadal and hypogonadal men receiving testosterone replacement therapy. *Int J Impot Res.* Nov-Dec 2008;20(6):561-565.

289. Coward RM, Simhan J, Carson I. Prostate-specific antigen changes and prostate cancer in hypogonadal men treated with testosterone replacement therapy. *BJU international.* 2009;103:1179-1183.

290. Meuleman EJ, Legros JJ, Bouloux PM, et al. Effects of long-term oral testosterone undecanoate therapy on urinary symptoms: data from a 1-year, placebo-controlled, dose-ranging trial in aging men with symptomatic hypogonadism. *Aging Male.* Jun 1 2015:1-7.

291. Dohle GR AS, Bettocchi C, Kliesch S, Punab M, deRonde W. . Guidelines on male hypogonadism. . *Arnhem (The Netherlands): European Association of Urology.* 2012.

292. Izawa JI, Klotz L, Siemens DR, et al. Prostate cancer screening: Canadian guidelines 2011. *Canadian Urological Association journal = Journal de l'Association des urologues du Canada.* Aug 2011;5(4):235-240.

293. Carter HB, Pearson JD, Metter EJ, et al. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. *JAMA.* Apr 22-29 1992;267(16):2215-2220.

294. Carter HB, Ferrucci L, Kettermann A, et al. Detection of life-threatening prostate cancer with prostate-specific antigen velocity during a window of curability. *Journal of the National Cancer Institute.* Nov 1 2006;98(21):1521-1527.

295. Loeb S, Roehl KA, Helfand BT, Kan D, Catalona WJ. Can prostate specific antigen velocity thresholds decrease insignificant prostate cancer detection? *The Journal of urology.* Jan 2010;183(1):112-116.

296.   Morgentaler A, Morales A. Should hypogonadal men with prostate cancer receive testosterone? *The Journal of urology.* Oct 2010;184(4):1257-1260.
297.   Morgentaler A. Testosterone Therapy in Men With Prostate Cancer: Scientific and Ethical Considerations. *Journal of urology.* 2009;181:972-979.
298.   Rhoden EL, Morgentaler A. Testosterone replacement therapy in hypogonadal men at high risk for prostate cancer: results of 1 year of treatment in men with prostatic intraepithelial neoplasia. *The Journal of urology.* Dec 2003;170(6 Pt 1):2348-2351.
299.   Kaufman JM, Graydon RJ. Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal men. *The Journal of urology.* Sep 2004;172(3):920-922.
300.   Agarwal PK, Oefelein MG. Testosterone replacement therapy after primary treatment for prostate cancer. *The Journal of urology.* Feb 2005;173(2):533-536.
301.   Khera M, Grober ED, Najari B, et al. Testosterone replacement therapy following radical prostatectomy. *Journal of sexual medicine.* 2009;6:1165-1170.
302.   Pastuszak AW, Pearlman AM, Lai WS, et al. Testosterone replacement therapy in patients with prostate cancer after radical prostatectomy. *The Journal of urology.* Aug 2013;190(2):639-644.
303.   Sarosdy MF. Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachytherapy. *Cancer.* Feb 1 2007;109(3):536-541.
304.   Pastuszak AW, Pearlman AM, Godoy G, Miles BJ, Lipshultz LI, Khera M. Testosterone replacement therapy in the setting of prostate cancer treated with radiation. *International Journal of Impotence Research.* 2013;25(1):24-28.
305.   Morgentaler A, Lipshultz LI, Bennett R, Sweeney M, Avila D, Jr., Khera M. Testosterone therapy in men with untreated prostate cancer. *Journal of Urology.* 2011;185(4):1256-1260.
306.   Szmulewitz R, Mohile S, Posadas E, et al. A randomized phase 1 study of testosterone replacement for patients with low-risk castration-resistant prostate cancer. *European urology.* 2009;56:97-103.
307.   Leibowitz RL, Dorff TB, Tucker S, Symanowski J, Vogelzang NJ. Testosterone replacement in prostate cancer survivors with hypogonadal symptoms. *BJU international.* 2010;105:1397-1401.
308.   Morales A, Black AM, Emerson LE. Testosterone administration to men with testosterone deficiency syndrome after external beam radiotherapy for localized prostate cancer: preliminary observations. *BJU International.* 2009;103(1):62-64.
309.   Morales A. Effect of testosterone administration to men with prostate cancer is unpredictable: a word of caution and suggestions for a registry. *BJU Int.* May 2011;107(9):1369-1373.
310.   Andriole G, Bruchovsky N, Chung LW, et al. Dihydrotestosterone and the prostate: the scientific rationale for 5alpha-reductase inhibitors in the treatment of benign prostatic hyperplasia. *The Journal of urology.* Oct 2004;172(4 Pt 1):1399-1403.
311.   Wang W, Bergh A, Damber JE. Chronic inflammation in benign prostate hyperplasia is associated with focal upregulation of cyclooxygenase-2, Bcl-2, and cell proliferation in the glandular epithelium. *Prostate.* Sep 15 2004;61(1):60-72.
312.   Schatzl G, Brossner C, Schmid S, et al. Endocrine status in elderly men with lower urinary tract symptoms: correlation of age, hormonal status, and lower urinary tract function. The Prostate Study Group of the Austrian Society of Urology. *Urology.* Mar 2000;55(3):397-402.
313.   Joseph MA, Wei JT, Harlow SD, et al. Relationship of serum sex-steroid hormones and prostate volume in African American men. *Prostate.* Dec 1 2002;53(4):322-329.
314.   Lee JH, Kim Y, Park YW, Lee DG. Relationship between benign prostatic hyperplasia/lower urinary tract symptoms and total serum testosterone level in healthy middle-aged eugonadal men. *The journal of sexual medicine.* May 2014;11(5):1309-1315.
315.   Roberts RO, Jacobson DJ, Rhodes T, Klee GG, Leiber MM, Jacobsen SJ. Serum sex hormones and measures of benign prostatic hyperplasia. *Prostate.* Oct 1 2004;61(2):124-131.

316. Favilla V, Cimino S, Castelli T, Madonia M, Barbagallo I, Morgia G. Relationship between lower urinary tract symptoms and serum levels of sex hormones in men with symptomatic benign prostatic hyperplasia. *BJU Int.* Dec 2010;106(11):1700-1703.

317. Behre HM, Bohmeyer J, Nieschlag E. Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age-matched normal controls. *Clin Endocrinol (Oxf).* Mar 1994;40(3):341-349.

318. Tenover JS. Effects of testosterone supplementation in the aging male. *The Journal of clinical endocrinology and metabolism.* Oct 1992;75(4):1092-1098.

319. Pearl JA, Berhanu D, Francois N, et al. Testosterone supplementation does not worsen lower urinary tract symptoms. *The Journal of urology.* Nov 2013;190(5):1828-1833.

320. Karazindiyanoglu S, Cayan S. The effect of testosterone therapy on lower urinary tract symptoms/bladder and sexual functions in men with symptomatic late-onset hypogonadism. *Aging Male.* Sep 2008;11(3):146-149.

321. Kaufman JM, Miller MG, Garwin JL, Fitzpatrick S, McWhirter C, Brennan JJ. Efficacy and Safety Study of 1.62% Testosterone Gel for the Treatment of Hypogonadal Men. *Journal of sexual medicine.* 2011;8:2079-2089.

322. Boas M, Boisen KA, Virtanen HE, et al. Postnatal penile length and growth rate correlate to serum testosterone levels: a longitudinal study of 1962 normal boys. *Eur J Endocrinol.* Jan 2006;154(1):125-129.

323. Travison TG, Morley JE, Araujo AB, O'Donnell AB, McKinlay JB. The relationship between libido and testosterone levels in aging men. *The Journal of clinical endocrinology and metabolism.* Jul 2006;91(7):2509-2513.

324. Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. *The New England journal of medicine.* Aug 23 2007;357(8):762-774.

325. Bandini E, Corona G, Ricca V, et al. Hysterical traits are not from the uterus but from the testis: a study in men with sexual dysfunction. *The journal of sexual medicine.* Aug 2009;6(8):2321-2331.

326. Corona G, Jannini EA, Lotti F, et al. Premature and delayed ejaculation: two ends of a single continuum influenced by hormonal milieu. *Int J Androl.* Feb 2011;34(1):41-48.

327. Buena F, Swerdloff RS, Steiner BS, et al. Sexual function does not change when serum testosterone levels are pharmacologically varied within the normal male range. *Fertil Steril.* May 1993;59(5):1118-1123.

328. Corona G, Isidori AM, Buvat J, et al. Testosterone supplementation and sexual function: a meta-analysis study. *The journal of sexual medicine.* Jun 2014;11(6):1577-1592.

329. Corona G, Rastrelli G, Ricca V, et al. Risk factors associated with primary and secondary reduced libido in male patients with sexual dysfunction. *The journal of sexual medicine.* Apr 2013;10(4):1074-1089.

330. Trost LW, Serefoglu E, Gokce A, Linder BJ, Sartor AO, Hellstrom WJ. Androgen deprivation therapy impact on quality of life and cardiovascular health, monitoring therapeutic replacement. [Review]. *Journal of sexual medicine.* 2013;10 Suppl 1:84-101.

331. Gray PB, Singh AB, Woodhouse LJ, et al. Dose-dependent effects of testosterone on sexual function, mood, and visuospatial cognition in older men. *The Journal of clinical endocrinology and metabolism.* Jul 2005;90(7):3838-3846.

332. Corona G, Jannini EA, Vignozzi L, Rastrelli G, Maggi M. The hormonal control of ejaculation. *Nature reviews. Urology.* Sep 2012;9(9):508-519.

333. Corona G, Rastrelli G, Vignozzi L, Mannucci E, Maggi M. How to recognize late-onset hypogonadism in men with sexual dysfunction. *Asian J Androl.* Mar 2012;14(2):251-259.

334.   Corona G, Jannini EA, Mannucci E, et al. Different testosterone levels are associated with ejaculatory dysfunction. *The journal of sexual medicine.* Aug 2008;5(8):1991-1998.

335.   Emmelot-Vonk MH, Verhaar HJJ, Nakhai-Pour HR, Grobbee DE, Van Der Schouw YT. Effect of testosterone supplementation on sexual functioning in aging men: A 6-month randomized controlled trial. *International journal of impotence research.* 2009;21:129-138.

336.   Roth MY, Lin K, Amory JK, et al. Serum LH correlates highly with intratesticular steroid levels in normal men. *J Androl.* Mar-Apr 2010;31(2):138-145.

337.   O'Donnell L, Nicholls PK, O'Bryan MK, McLachlan RI, Stanton PG. Spermiation: The process of sperm release. *Spermatogenesis.* Jan 2011;1(1):14-35.

338.   Lombardo F, Sgro P, Salacone P, et al. Androgens and fertility. *J Endocrinol Invest.* 2005;28(3 Suppl):51-55.

339.   Nieschlag E, Vorona E, Wenk M, Hemker AK, Kamischke A, Zitzmann M. Hormonal male contraception in men with normal and subnormal semen parameters. *Int J Androl.* Dec 2011;34(6 Pt 1):556-567.

340.   Samplaski MK, Loai Y, Wong K, Lo KC, Grober ED, Jarvi KA. Testosterone use in the male infertility population: prescribing patterns and effects on semen and hormonal parameters. *Fertil Steril.* Jan 2014;101(1):64-69.

341.   Emanuele MA, Emanuele NV. Alcohol's effects on male reproduction. *Alcohol health and research world.* 1998;22(3):195-201.

342.   Reid IR. Serum testosterone levels during chronic glucocorticoid therapy. *Ann Intern Med.* Apr 1987;106(4):639-640.

343.   Pitteloud N, Dwyer AA, DeCruz S, et al. The relative role of gonadal sex steroids and gonadotropin-releasing hormone pulse frequency in the regulation of follicle-stimulating hormone secretion in men. *The Journal of clinical endocrinology and metabolism.* Jul 2008;93(7):2686-2692.

344.   Liu PY, Baker HW, Jayadev V, Zacharin M, Conway AJ, Handelsman DJ. Induction of spermatogenesis and fertility during gonadotropin treatment of gonadotropin-deficient infertile men: predictors of fertility outcome. *The Journal of clinical endocrinology and metabolism.* Mar 2009;94(3):801-808.

345.   Dabaja A, Wosnitzer M, Goldstein M. Varicocele and hypogonadism. *Curr Urol Rep.* Aug 2013;14(4):309-314.

346.   Fisch H, Hyun G. Varicocele repair for low testosterone. *Current opinion in urology.* Nov 2012;22(6):495-498.

347.   O'Brien JH, Lazarou S, Deane L, Jarvi K, Zini A. Erectile dysfunction and andropause symptoms in infertile men. *The Journal of urology.* Nov 2005;174(5):1932-1934; discussion 1934.

348.   Taylor F, Levine L. Clomiphene citrate and testosterone gel replacement therapy for male hypogonadism: efficacy and treatment cost. *Journal of Sexual Medicine.* 2010;7(1 Pt 1):269-276.

349.   Ramasamy R, Scovell JM, Kovac JR, Lipshultz LI. Testosterone supplementation versus clomiphene citrate for hypogonadism: an age matched comparison of satisfaction and efficacy. *The Journal of urology.* Sep 2014;192(3):875-879.

350.   Mazzola CR, Katz DJ, Loghmanieh N, Nelson CJ, Mulhall JP. Predicting biochemical response to clomiphene citrate in men with hypogonadism. *The journal of sexual medicine.* Sep 2014;11(9):2302-2307.

351.   Schlegel PN. Aromatase inhibitors for male infertility. *Fertil Steril.* Dec 2012;98(6):1359-1362.

352.   Morrison CD, Brannigan RE. Metabolic syndrome and infertility in men. *Best practice & research. Clinical obstetrics & gynaecology.* May 2015;29(4):507-515.

353.   Lormeau C, Soudan B, d'Herbomez M, Pigny P, Duquesnoy B, Cortet B. Sex hormone-binding globulin, estradiol, and bone turnover markers in male osteoporosis. *Bone.* Jun 2004;34(6):933-939.

354.   Dunajska K, Milewicz A, Jozkow P, Jedrzejuk D, Kuliczkowski W, Lwow F. Sex steroids concentrations in relation to bone mineral density in men with coronary atherosclerosis. *Maturitas.* Sep 20 2006;55(2):142-149.

355.   Leifke E, Wichers C, Gorenoi V, Lucke P, von zur Muhlen A, Brabant G. Low serum levels of testosterone in men with minimal traumatic hip fractures. *Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association.* Apr 2005;113(4):208-213.

356.   Bours SP, van Geel TA, Geusens PP, et al. Contributors to secondary osteoporosis and metabolic bone diseases in patients presenting with a clinical fracture. *The Journal of clinical endocrinology and metabolism.* May 2011;96(5):1360-1367.

357.   Fink HA, Ewing SK, Ensrud KE, et al. Association of testosterone and estradiol deficiency with osteoporosis and rapid bone loss in older men. *The Journal of clinical endocrinology and metabolism.* Oct 2006;91(10):3908-3915.

358.   Ensrud KE, Lewis CE, Lambert LC, et al. Endogenous sex steroids, weight change and rates of hip bone loss in older men: the MrOS study. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* 2006;17(9):1329-1336.

359.   Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T. Capacity of endogenous sex steroids to predict bone loss in Japanese men: 10-year follow-up of the Taiji Cohort Study. *Journal of bone and mineral metabolism.* Jan 2011;29(1):96-102.

360.   Morley JE. Sarcopenia in the elderly. *Family practice.* Apr 2012;29 Suppl 1:i44-i48.

361.   Iannuzzi-Sucich M, Prestwood KM, Kenny AM. Prevalence of sarcopenia and predictors of skeletal muscle mass in healthy, older men and women. *The journals of gerontology. Series A, Biological sciences and medical sciences.* Dec 2002;57(12):M772-777.

362.   van den Beld AW, de Jong FH, Grobbee DE, Pols HA, Lamberts SW. Measures of bioavailable serum testosterone and estradiol and their relationships with muscle strength, bone density, and body composition in elderly men. *The Journal of clinical endocrinology and metabolism.* Sep 2000;85(9):3276-3282.

363.   Perry HM, 3rd, Miller DK, Patrick P, Morley JE. Testosterone and leptin in older African-American men: relationship to age, strength, function, and season. *Metabolism.* Aug 2000;49(8):1085-1091.

364.   Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. *Blood.* Oct 15 2004;104(8):2263-2268.

365.   Ferrucci L, Maggio M, Bandinelli S, et al. Low testosterone levels and the risk of anemia in older men and women. *Arch Intern Med.* Jul 10 2006;166(13):1380-1388.

366.   Grossmann M, Panagiotopolous S, Sharpe K, et al. Low testosterone and anaemia in men with type 2 diabetes. *Clin Endocrinol (Oxf).* Apr 2009;70(4):547-553.

367.   Ellegala DB, Alden TD, Couture DE, Vance ML, Maartens NF, Laws ER, Jr. Anemia, testosterone, and pituitary adenoma in men. *Journal of neurosurgery.* May 2003;98(5):974-977.

368.   van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* Oct 2002;13(10):777-787.

369. Crawford BA, Liu PY, Kean MT, Bleasel JF, Handelsman DJ. Randomized placebo-controlled trial of androgen effects on muscle and bone in men requiring long-term systemic glucocorticoid treatment. *The Journal of clinical endocrinology and metabolism.* Jul 2003;88(7):3167-3176.

370. Reid IR, Wattie DJ, Evans MC, Stapleton JP. Testosterone therapy in glucocorticoid-treated men. *Arch Intern Med.* Jun 10 1996;156(11):1173-1177.

371. Smith HS, Elliott JA. Opioid-induced androgen deficiency (OPIAD). *Pain physician.* 2012;15:ES145-ES156.

372. Katz N, Mazer NA. The impact of opioids on the endocrine system. *The Clinical journal of pain.* Feb 2009;25(2):170-175.

373. Finch PM, Price LM, Pullan PT, Drummond PD. Effects of Testosterone Treatment on Bone Mineral Density in Hypogonadal Men Receiving Intrathecal Opioids. *Pain practice : the official journal of World Institute of Pain.* Apr 1 2014.

374. Aloisi AM, Ceccarelli I, Carlucci M, et al. Hormone replacement therapy in morphine-induced hypogonadic male chronic pain patients. *Reproductive biology and endocrinology : RB&E.* 2011;9:26.

375. Hallinan R, Byrne A, Agho K, McMahon CG, Tynan P, Attia J. Hypogonadism in men receiving methadone and buprenorphine maintenance treatment. *International Journal of Andrology.* 2009;32(2):131-139.

376. Rubinstein AL, Carpenter DM, Minkoff JR. Hypogonadism in men with chronic pain linked to the use of long-acting rather than short-acting opioids. *The Clinical journal of pain.* Oct 2013;29(10):840-845.

377. Rochira V, Zirilli L, Orlando G, et al. Premature decline of serum total testosterone in HIV-infected men in the HAART-era. *PLoS One.* 2011;6(12):e28512.

378. Cohan GR. HIV-associated hypogonadism. *The AIDS reader.* Jul 2006;16(7):341-345, 348, 352-344.

379. Ashby J, Goldmeier D, Sadeghi-Nejad H. Hypogonadism in human immunodeficiency virus-positive men. *Korean Journal of Urology.* January 2014;55(1):9-16.

380. Moreno-Perez O, Escoin C, Serna-Candel C, et al. The determination of total testosterone and free testosterone (RIA) are not applicable to the evaluation of gonadal function in HIV-infected males. *The journal of sexual medicine.* Aug 2010;7(8):2873-2883.

381. Grinspoon S, Corcoran C, Lee K, et al. Loss of lean body and muscle mass correlates with androgen levels in hypogonadal men with acquired immunodeficiency syndrome and wasting. *The Journal of clinical endocrinology and metabolism.* Nov 1996;81(11):4051-4058.

382. Blick G, Khera M, Bhattacharya RK, Kushner H, Miner MM. Testosterone replacement therapy in men with hypogonadism and HIV/AIDS: results from the TRiUS registry. *Postgraduate medicine.* 2013;125:19-29.

383. Bhasin S, Storer TW, Javanbakht M, et al. Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. *JAMA.* Feb 9 2000;283(6):763-770.

384. Rabkin JG, Wagner GJ, Rabkin R. A double-blind, placebo-controlled trial of testosterone therapy for HIV-positive men with hypogonadal symptoms. *Archives of general psychiatry.* Feb 2000;57(2):141-147; discussion 155-146.

385. Rabkin JG, Wagner GJ, McElhiney MC, Rabkin R, Lin SH. Testosterone versus fluoxetine for depression and fatigue in HIV/AIDS: a placebo-controlled trial. *J Clin Psychopharmacol.* Aug 2004;24(4):379-385.

386. Grinspoon S, Corcoran C, Stanley T, Baaj A, Basgoz N, Klibanski A. Effects of hypogonadism and testosterone administration on depression indices in HIV-infected men. *The Journal of clinical endocrinology and metabolism.* Jan 2000;85(1):60-65.

387. Amore M, Scarlatti F, Quarta AL, Tagariello P. Partial androgen deficiency, depression and testosterone treatment in aging men. [Review] [120 refs]. *Aging clinical and experimental research.* 2009;21:1-8.

388. Amore M, Innamorati M, Costi S, Sher L, Girardi P, Pompili M. Partial androgen deficiency, depression, and testosterone supplementation in aging men. *International journal of endocrinology.* 2012;2012:280724.

389. Shores MM, Sloan KL, Matsumoto AM, Moceri VM, Felker B, Kivlahan DR. Increased incidence of diagnosed depressive illness in hypogonadal older men. *Archives of general psychiatry.* Feb 2004;61(2):162-167.

390. Seidman SN, Orr G, Raviv G, et al. Effects of testosterone replacement in middle-aged men with dysthymia: A randomized, placebo-controlled clinical trial. *Journal of clinical psychopharmacology.* 2009;29:216-221.

391. Delhez M, Hansenne M, Legros JJ. Andropause and psychopathology: minor symptoms rather than pathological ones. *Psychoneuroendocrinology.* Oct 2003;28(7):863-874.

392. Shores MM, Kivlahan DR, Sadak TI, Li EJ, Matsumoto AM. A randomized, double-blind, placebo-controlled study of testosterone treatment in hypogonadal older men with subthreshold depression (dysthymia or minor depression). *Journal of clinical psychiatry.* 2009;70:1009-1016.

393. Carnahan RM, Perry PJ. Depression in aging men: the role of testosterone. *Drugs & aging.* 2004;21(6):361-376.

394. Amore M. Partial androgen deficiency and neuropsychiatric symptoms in aging men. *J Endocrinol Invest.* 2005;28(11 Suppl Proceedings):49-54.

395. Pope HG, Jr., Cohane GH, Kanayama G, Siegel AJ, Hudson JI. Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. *The American journal of psychiatry.* Jan 2003;160(1):105-111.

396. Seidman SN, Araujo AB, Roose SP, et al. Low testosterone levels in elderly men with dysthymic disorder. *The American journal of psychiatry.* Mar 2002;159(3):456-459.

397. Khera M, Bhattacharya RK, Blick G, Kushner H, Nguyen D, Miner MM. The effect of testosterone supplementation on depression symptoms in hypogonadal men from the Testim Registry in the US (TRiUS). *Aging male.* 2012;15:14-21.

398. Giltay EJ, Tishova YA, Mskhalaya GJ, Gooren LJ, Saad F, Kalinchenko SY. Effects of Testosterone Supplementation on Depressive Symptoms and Sexual Dysfunction in Hypogonadal Men with the Metabolic Syndrome. *Journal of sexual medicine.* 2010;7:2572-2582.

399. Spitzer M, Basaria S, Travison TG, Davda MN, DeRogatis L, Bhasin S. The effect of testosterone on mood and well-being in men with erectile dysfunction in a randomized, placebo-controlled trial. *Andrology.* 2013;1:475-482.

400. Amiaz R, Pope Jr HG, Mahne T, et al. Testosterone gel replacement improves sexual function in depressed men taking serotonergic antidepressants: a randomized, placebo-controlled clinical trial. *Journal of sex & marital therapy.* 2011;37:243-254.

401. Gambineri A, Pelusi C, Pasquali R. Testosterone levels in obese male patients with obstructive sleep apnea syndrome: relation to oxygen desaturation, body weight, fat distribution and the metabolic parameters. *J Endocrinol Invest.* Jun 2003;26(6):493-498.

402. Barrett-Connor E, Dam TT, Stone K, et al. The association of testosterone levels with overall sleep quality, sleep architecture, and sleep-disordered breathing. *The Journal of clinical endocrinology and metabolism.* Jul 2008;93(7):2602-2609.

403. Wittert G. The relationship between sleep disorders and testosterone in men. *Asian J Androl.* Mar-Apr 2014;16(2):262-265.

404.   Meston N, Davies RJ, Mullins R, Jenkinson C, Wass JA, Stradling JR. Endocrine effects of nasal continuous positive airway pressure in male patients with obstructive sleep apnoea. *Journal of internal medicine.* Nov 2003;254(5):447-454.

405.   Liu PY, Yee B, Wishart SM, et al. The short-term effects of high-dose testosterone on sleep, breathing, and function in older men. *The Journal of clinical endocrinology and metabolism.* Aug 2003;88(8):3605-3613.

406.   Hoyos CM, Killick R, Yee BJ, Grunstein RR, Liu PY. Effects of testosterone therapy on sleep and breathing in obese men with severe obstructive sleep apnoea: A randomized placebo-controlled trial. *Clinical endocrinology.* 2012;77:599-607.

407.   Killick R, Wang D, Hoyos CM, Yee BJ, Grunstein RR, Liu PY. The effects of testosterone on ventilatory responses in men with obstructive sleep apnea: A randomised, placebo-controlled trial. *Journal of sleep research.* 2013;22:331-336.

408.   Luboshitzky R, Aviv A, Hefetz A, et al. Decreased pituitary-gonadal secretion in men with obstructive sleep apnea. *The Journal of clinical endocrinology and metabolism.* Jul 2002;87(7):3394-3398.

409.   Hoyos CM, Yee BJ, Phillips CL, Machan EA, Grunstein RR, Liu PY. Body compositional and cardiometabolic effects of testosterone therapy in obese men with severe obstructive sleep apnoea: A randomised placebo-controlled trial. *European journal of endocrinology.* 2012;167:531-541.

410.   Hanafy HM. Testosterone therapy and obstructive sleep apnea: is there a real connection? *The journal of sexual medicine.* Sep 2007;4(5):1241-1246.

411.   Tajar A, Huhtaniemi IT, O'Neill TW, et al. Characteristics of androgen deficiency in late-onset hypogonadism: results from the European Male Aging Study (EMAS). *The Journal of clinical endocrinology and metabolism.* May 2012;97(5):1508-1516.

412.   Rohrmann S, Platz EA, Selvin E, et al. The prevalence of low sex steroid hormone concentrations in men in the Third National Health and Nutrition Examination Survey (NHANES III). *Clin Endocrinol (Oxf).* Aug 2011;75(2):232-239.

413.   Kaufman JM, Vermeulen A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. *Endocr Rev.* Oct 2005;26(6):833-876.

414.   Wang C, Nieschlag E, Swerdloff R, et al. Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. *Eur J Endocrinol.* Nov 2008;159(5):507-514.

415.   Bhasin S, Pencina M, Jasuja GK, et al. Reference ranges for testosterone in men generated using liquid chromatography tandem mass spectrometry in a community-based sample of healthy nonobese young men in the Framingham Heart Study and applied to three geographically distinct cohorts. *The Journal of clinical endocrinology and metabolism.* Aug 2011;96(8):2430-2439.

416.   Kenny AM, Kleppinger A, Annis K, et al. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels, low bone mass, and physical frailty. *Journal of the American Geriatrics Society.* 2010;58:1134-1143.

417.   Wang C, Swerdloff RS, Iranmanesh A, et al. Effects of transdermal testosterone gel on bone turnover markers and bone mineral density in hypogonadal men. *Clin Endocrinol (Oxf).* Jun 2001;54(6):739-750.

418.   Legros JJ, Meuleman EJ, Elbers JM, et al. Oral testosterone replacement in symptomatic late-onset hypogonadism: effects on rating scales and general safety in a randomized, placebo-controlled study. *European journal of endocrinology / European Federation of Endocrine Societies.* 2009;160:821-831.

419. Tan WS, Low WY, Ng CJ, et al. Efficacy and safety of long-acting intramuscular testosterone undecanoate in aging men: A randomised controlled study. *BJU international.* 2013;111:1130-1140.
420. Ruige JB, Ouwens DM, Kaufman JM. Beneficial and adverse effects of testosterone on the cardiovascular system in men. *Journal of Clinical Endocrinology & Metabolism.* 2013;98(11):4300-4310.
421. Cunningham GR, Toma SM. Clinical review: Why is androgen replacement in males controversial?. [Review]. *Journal of clinical endocrinology and metabolism.* 2011;96:38-52.
422. Saad F, Aversa A, Isidori AM, Zafalon L, Zitzmann M, Gooren L. Onset of effects of testosterone treatment and time span until maximum effects are achieved. *Eur J Endocrinol.* Nov 2011;165(5):675-685.
423. Hajjar RR, Kaiser FE, Morley JE. Outcomes of long-term testosterone replacement in older hypogonadal males: a retrospective analysis. *The Journal of clinical endocrinology and metabolism.* Nov 1997;82(11):3793-3796.
424. Sih R, Morley JE, Kaiser FE, Perry HM, 3rd, Patrick P, Ross C. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. *The Journal of clinical endocrinology and metabolism.* Jun 1997;82(6):1661-1667.
425. Braekkan SK, Mathiesen EB, Njolstad I, Wilsgaard T, Hansen JB. Hematocrit and risk of venous thromboembolism in a general population. The Tromso study. *Haematologica.* Feb 2010;95(2):270-275.
426. Richie JP, Catalona WJ, Ahmann FR, et al. Effect of patient age on early detection of prostate cancer with serum prostate-specific antigen and digital rectal examination. *Urology.* Oct 1993;42(4):365-374.
427. Bretton PR. Prostate-specific antigen and digital rectal examination in screening for prostate cancer: a community-based study. *South Med J.* Jul 1994;87(7):720-723.
428. Carrero JJ, Barany P, Yilmaz MI, et al. Testosterone deficiency is a cause of anaemia and reduced responsiveness to erythropoiesis-stimulating agents in men with chronic kidney disease. *Nephrology Dialysis Transplantation.* 2012;27(2):709-715.
429. Rietschel P, Corcoran C, Stanley T, Basgoz N, Klibanski A, Grinspoon S. Prevalence of hypogonadism among men with weight loss related to human immunodeficiency virus infection who were receiving highly active antiretroviral therapy. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Nov 2000;31(5):1240-1244.
430. CDC HoST-Testosterone Certified Procedures (Updated 05/2014). Atlanta (GA): US Centers for Disease Control and Prevention; 2014.
431. Correction: incorrect number of excluded patients reported in the text and figure. *JAMA.* 2014;311:967.
432. Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM. Testosterone treatment and mortality in men with low testosterone levels. *Journal of clinical endocrinology and metabolism.* 2012;97:2050-2058.
433. Pastuszak AW, Pearlman AM, Lai WS, et al. Testosterone replacement therapy in patients with prostate cancer after radical prostatectomy. *Journal of Urology.* 2013;190(2):639-644.
434. Harle L, Basaria S, Dobs AS. Nebido: a long-acting injectable testosterone for the treatment of male hypogonadism. *Expert Opin Pharmacother.* Aug 2005;6(10):1751-1759.
435. Matsumoto AM. Testosterone administration in older men. *Endocrinol Metab Clin North Am.* Jun 2013;42(2):271-286.
436. English KM, Steeds RP, Jones TH, Diver MJ, Channer KS. Low-Dose Transdermal Testosterone Therapy Improves Angina Threshold in Men With Chronic Stable Angina: A Randomized, Double-Blind, Placebo-Controlled Study. *Circulation.* October 17, 2000 2000;102(16):1906-1911.

437. Lam CS, Cheng S, Choong K, et al. Influence of sex and hormone status on circulating natriuretic peptides. *J Am Coll Cardiol.* Aug 2 2011;58(6):618-626.

438. Poliwczak AR, Tylinska M, Broncel M. Testosterone therapy improves the heart rate turbulence without effect on NT-proBNP level in men with metabolic syndrome. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme.* Feb 2014;46(2):116-119.

439. La Vignera S, Condorelli R, Vicari E, D'Agata R, Calogero A. Original immunophenotype of blood endothelial progenitor cells and microparticles in patients with isolated arterial erectile dysfunction and late onset hypogonadism: Effects of androgen replacement therapy. *Aging male.* 2011;14:183-189.

440. Liao CH, Wu YN, Lin FY, Tsai WK, Liu SP, Chiang HS. Testosterone replacement therapy can increase circulating endothelial progenitor cell number in men with late onset hypogonadism. *Andrology.* 2013;1:563-569.

441. Muller M, van den Beld AW, Bots ML, Grobbee DE, Lamberts SW, van der Schouw YT. Endogenous sex hormones and progression of carotid atherosclerosis in elderly men. *Circulation.* May 4 2004;109(17):2074-2079.

442. van den Beld AW, Bots ML, Janssen JA, Pols HA, Lamberts SW, Grobbee DE. Endogenous hormones and carotid atherosclerosis in elderly men. *American journal of epidemiology.* Jan 1 2003;157(1):25-31.

443. Price J, Leng GC. Steroid sex hormones for lower limb atherosclerosis. *The Cochrane database of systematic reviews.* 2012;10:CD000188.

444. Pugh PJ, Jones TH, Channer KS. Acute haemodynamic effects of testosterone in men with chronic heart failure. *European heart journal.* May 2003;24(10):909-915.

445. Seth M, Sachdeva A, Saharoy P, Seth S, Madaan H. Relationship of testosterone levels in males with coronary heart disease. *International journal of pharma and bio sciences.* 2011;2:566-570.

446. Yaron M, Greenman Y, Rosenfeld JB, et al. Effect of testosterone replacement therapy on arterial stiffness in older hypogonadal men. *European journal of endocrinology / European Federation of Endocrine Societies.* 2009;160:839-846.

447. Brockenbrough AT, Dittrich MO, Page ST, Smith T, Stivelman JC, Bremner WJ. Transdermal Androgen Therapy to Augment EPO in the Treatment of Anemia of Chronic Renal Disease. *American Journal of Kidney Diseases.*47(2):251-262.

448. Testosterone treatment of men with alcoholic cirrhosis: a double-blind study. The Copenhagen Study Group for Liver Diseases. *Hepatology.* Sep-Oct 1986;6(5):807-813.

449. Snyder PJ, Peachey H, Hannoush P, et al. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. *The Journal of clinical endocrinology and metabolism.* Aug 1999;84(8):2647-2653.

450. Snyder PJ, Peachey H, Berlin JA, et al. Effect of transdermal testosterone treatment on serum lipid and apolipoprotein levels in men more than 65 years of age. *The American journal of medicine.* Sep 2001;111(4):255-260.

451. Svartberg J, Aasebo U, Hjalmarsen A, Sundsfjord J, Jorde R. Testosterone treatment improves body composition and sexual function in men with COPD, in a 6-month randomized controlled trial. *Respir Med.* Sep 2004;98(9):906-913.

452. Emmelot-Vonk MH, Verhaar HJ, Nakhai Pour HR, et al. Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: a randomized controlled trial. *Jama.* Jan 2 2008;299(1):39-52.

453. Morley JE, Perry HM, 3rd, Kaiser FE, et al. Effects of testosterone replacement therapy in old hypogonadal males: a preliminary study. *J Am Geriatr Soc.* Feb 1993;41(2):149-152.

454.   Carson CC, 3rd, Rosano G. Exogenous testosterone, cardiovascular events, and cardiovascular risk factors in elderly men: a review of trial data. *The journal of sexual medicine.* Jan 2012;9(1):54-67.