Late-onset hypogonadism or ADAM: diagnosis

Hipogonadismo masculino tardio ou DAEM: diagnóstico

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The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize procedures to assist the reasoning and decision-making of doctors.

The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

Description of the evidence collection method

The recommendations were supported by the evidence obtained in the Medline, Embase, Lilacs and Cochrane databases, using the following strategies:

(((((Aged OR aging) AND (androgens/deficiency OR hypogonadism OR testosterone/deficiency))) AND ((health behavior OR hypogonadism/epidemiology OR impotence/diagnosis OR libido OR life style OR penile erection OR quality of life OR reference values OR Risk OR spermatogenesis)))) AND (sensitiv*[title/abstract] OR sensitivity AND specificity[MeSH Terms] OR diagnos*[title/abstract] OR diagnosis[MeSH:noexp] OR diagnostic*[MeSH:noexp] OR diagnosis, differential[MeSH:noexp] OR diagnosis[subheading:noexp]) ((((((aged OR aging) AND (ANDrogens/deficiency OR hypogonadism OR testosterone/deficiency)) AND ((questionnaires OR adam OR smith OR AMS OR mmas OR massachusetts male ageing study OR aging males symptoms scale) OR (health behaviOR OR hypogonadism/epidemiology OR impotence/diagnosis OR libido OR life style OR penile erection OR quality of life OR reference values OR risk OR spermatogenesis)) AND ("last 5 years"[PDat]))) AND (sensitiv*[title/abstract] OR sensitivity AND specificity[MeSH Terms] OR diagnos*[title/abstract] OR diagnosis[MeSH:noexp] OR diagnostic*[MeSH:noexp] OR diagnosis, differential[MeSH:noexp] OR diagnosis[Subheading:noexp]) AND ("last 5 years"[PDat]))) OR ((((((((aged OR aging) AND (ANDrogens/deficiency OR hypogonadism OR testosterone/deficiency)) AND ((questionnaires OR adam OR smith OR AMS OR mmas OR massachusetts male ageing study OR aging males symptoms scale) OR (health behaviOR OR hypogonadism/epidemiology OR impotence/diagnosis OR libido OR life style OR penile erection OR quality of life OR reference values OR risk OR spermatogenesis)) AND ("last 5 years"[PDat]))) AND (sensitiv*[title/abstract] OR sensitivity AND specificity[MeSH Terms] OR diagnos*[title/abstract] OR diagnosis[MeSH:noexp] OR diagnostic*[MeSH:noexp] OR diagnosis, differential[MeSH:noexp] OR diagnosis[Subheading:noexp]) AND ("last 5 years"[PDat]))) NOT ((((((((((aged OR aging) AND (androgens/deficiency OR hypogonadism OR testosterone/deficiency))) AND ((health behavior OR hypogonadism/epidemiology OR impotence/diagnosis OR libido OR life Style OR Penile erection OR quality of life OR reference values OR risk OR spermatogenesis)))) AND (sensitiv*[title/abstract] OR sensitivity AND specificity[MeSH Terms] OR diagnos*[title/abstract] OR diagnosis[MeSH:noexp] OR diagnostic*[MeSH:noexp] OR diagnosis, differential[MeSH:noexp] OR diagnosis[Subheading:noexp]) AND ("last 5 years"[PDat]))) OR ((((((aged OR aging) AND (ANDrogens/deficiency OR hypogonadism OR testosterone/deficiency)) AND ("last 5 years"[PDat]))) AND (((Questionnaires OR ADAM OR Smith OR AMS) AND ("last 5 years"[PDat]))) AND ("last 5 years"[PDat])))))) AND ((((((aged OR aging) AND (ANDrogens/deficiency OR hypogonadism OR testosterone/deficiency)) AND ((questionnaires OR adam OR smith OR AMS OR mmas OR massachusetts male ageing study OR aging males symptoms scale) OR (health behaviOR OR hypogonadism/epidemiology OR impotence/diagnosis OR libido OR life style OR penile erection OR quality of life OR reference values OR risk OR spermatogenesis)) AND ("last 5 years"[PDat]))) AND (sensitiv*[title/abstract] OR sensitivity AND specificity[MeSH Terms] OR diagnos*[title/abstract] OR diagnosis[MeSH:noexp] OR diagnostic*[MeSH:noexp] OR diagnosis, differential[MeSH:noexp] OR diagnosis[Subheading:noexp]) AND ("last 5 years"[PDat]))) AND ("last 5 years"[PDat]))) AND ("last 5 years"[PDat]))).

Grade of recommendation and strength of evidence

A: Experimental and observational studies with high consistency.
B: Experimental and observational studies with low consistency.
C: Case reports (non-controlled studies).
D: Opinions without critical evaluation, based on consensus, physiological studies, or animal models.

Conflict of interest

No conflict of interest informed.

Introduction[1](A)

For many years, hormone replacement strategies were mainly based on the treatment of women during the menopause. However, the use of testosterone replacement therapy to prevent and treat aspects of ADAM (Androgen Deficiency of the aging Male) has gained the interest of researchers and physicians. This fact coincides with the trend of demographic data relating to aging, which show an increase in the percentage of older males, including in Latin America[2](**D**).

Male aging is accompanied by signs and symptoms similar to androgen deficiency in young adults, as well as a decrease in muscle mass and strength, and increase in abdominal fat, especially visceral fat with insulin resistance and an atherogenic lipid profile, a decrease in libido and pubic hair, osteopenia, decreased cognitive performance, depression, insomnia, perspiration and a decrease in the general sense of wellbeing.

It is tempting to relate these symptoms to the decrease in androgen associated with aging.

Generally, there is a correlation, albeit weak, between these symptoms and testosterone levels. The decrease in testosterone levels is only one of the factors responsible for the symptoms of aging, which have a multifactorial origin[3](**B**).

For this reason, the diagnosis of androgen deficiency in the aging male should be based on clinical symptoms and testosterone biochemistry below the minimum level in young adults[4](**B**).

Various studies with good evidence indicate that there is a partial reduction in testosterone levels during aging and an increase in SHBG, or sex hormone binding globulin. Based on men aged 40 to 70 years, monitored for 7 to 10 years, there is tendency for a fall of 1.6% per year in total testosterone levels, as well as bioavailable testosterone at 2% to 3% per year, and an increase in sex hormone binding globulin at 1.3% per year[5](**B**). These laboratory observations are correlated with the health of such patients[6](**B**).

The process leading to partial hypogonadism during male aging is known as the andropause, or more appropriately late onset hypogonadism (LOH), or androgen deficiency in the aging male (ADAM), or partial androgen deficiency in the aging male (PADAM)[7](**D**).

What are the main signs and symptoms involved in late-onset hypogonadism?

The main signs and symptoms involved in late-onset hypogonadism are:

- Erectile dysfunction and decreased libido[8,9](**A**);
- Depression: hypogonadism in middle-age appears to be associated with a history of depressive symptoms; research suggests that hypogonadism may be an important factor in male depression[10](**A**);
- Decrease in muscle tissue, increase in muscular fibrous tissue and decrease in some aspects of muscular strength[11](**C**);
- Increase in total adipose tissue and redistribution of fat: various authors report an inverse correlation with testosterone, suggesting that the fall in testosterone levels has a causal role in the accumulation of visceral fat connected to male aging[12,13](**A**);
- Osteopenia and osteoporosis: decrease in bone mineral density[14,15](**B**);
- Decrease in testicular volume[16](**B**).

Recommendation

It is recommendable to carry out a diagnosis of late-onset hypogonadism only in men with some of the main signs and symptoms involved: decrease libido, erectile dysfunction, depression, decrease in muscle tissue, increase in total adipose tissue and redistribution of fat, decrease in bone mineral density, and decrease in testicular volume.

What are the main instruments used in the definition and diagnostic evaluation of male aging?

The main instruments used in the definition and diagnostic assessment of male aging are the clinical aspects of hypogonadism[17](**A**) and demonstration morning serum testosterone level below the minimum reference value of young adults[18](**A**).

Three questionnaires, the ADAM (Androgen Deficiency in aging Male), AMS (aging Male's Symptoms Scale), and the scale used by Smith et al. in the MMAS (Massachusetts Male Ageing Study) have been developed as potential instruments for the triage of hypogonadism in

older men. These may be useful, but are nonspecific although being sensitive[1,20](**A**).

Recommendation

It is recommendable to carry out a diagnosis of late-onset hypogonadism only in men with some of the main signs and symptoms of hypogonadism and morning serum testosterone level below the minimum reference values for young adults. The three ADAM, AMS and Smith Scale questionnaires may be used as LOH (late-onset hypogonadism) triage instruments.

What is the role of the ADAM questionnaire?

Ten symptoms commonly observed in men with bioavailable testosterone (BAT) were used to develop the ADAM questionnaire[20](**B**). Various studies with good evidence have shown that the ADAM questionnaire has high sensitivity for identifying ADAM, yet low specificity. Thus, it cannot be used as a substitute for serum testosterone dose in the diagnosis[21-23](**A**). Studies have shown that the diagnosis of late-onset hypogonadism or ADAM may be clinically suspected when the symptoms of sexual dysfunction are present[24](**A**).

Recommendation

When analyzing the responses to the ADAM questionnaire, clinically suspected cases of LOH are those in which the symptoms of sexual dysfunction are present.

What is the role of the Smith scale?

The Smith scale is based on men between 40 and 79 years that participated in the Massachusetts Male Ageing Study (MMAS). A questionnaire with eight items was developed based on age, BMI, diabetes, asthma, headache, sleep patterns, dominance preferences, and smoking status. The questionnaire performed significantly better than chance in identifying men with low levels of testosterone and encourages men at risk of low testosterone to seek professional evaluation of their testosterone levels. It is a self-administered questionnaire for triage of the risk of testosterone deficiency[25](**B**).

One study suggests that the ADAM and AMS questionnaires are superior to the MMAS questionnaire as a triage instrument for late-onset hypogonadism, as they have higher sensitivity. The Smith questionnaire is more related to risk rather than being a questionnaire of symptoms[20](**A**).

Recommendation

The Smith questionnaire is considered a questionnaire to assess the risk of LOH.

What is the role of the AMS scale?

This measurement instrument was designed as a scale of quality of life (QoL) connected to health and standardized to be self-administered, firstly to assess symptoms of aging (regardless of being connected to the disease) among groups of men under different conditions, secondly, to assess the severity of symptoms/QoL over time, and thirdly, to measure changes before and after androgen replacement therapy. The scale has been translated into 21 languages and is widely used.

The AMS scale measures similar phenomena to those measured by the ADAM and Smith questionnaires, despite not being designed as a triage instrument[26](**B**). Comparing the three questionnaires in relation to sensitivity for diagnosing hypogonadism in men, the result was 97% for the ADAM, 83% for the AMS and 60% for the Smith scale. In relation to specificity, the result was 30% for the ADAM, 59% for Smith scale and 39% for the AMS. In conclusion, the ADAM and AMS can be useful instruments for triage of male hypogonadism but are relatively unspecific, therefore the diagnosis of hypogonadism should depend on functional criteria and biochemistry[20](**A**). A promising triage instrument related to the AMS has been described for the diagnosis of androgen deficiency. This "AMS screener" is composed of the AMS scale + age + BMI. It would be acceptable for triage of a large number of people and for pre-selection of individuals for a fuller diagnostic assessment[27,28](**A**).

Recommendation

It is recommendable for the AMS scale and ADAM questionnaire to be used as triage instruments, and the diagnosis of LOH should also depend on functional criteria and biochemistry.

What is the role of the serum and free testosterone levels in the diagnosis of late-onset hypogonadism?

The diagnosis of late-onset hypogonadism is based both on plasma levels of testosterone and clinical symptoms. Almost all testosterone circulates in the blood (98%) bound to serum proteins, mainly SHBG (sex hormone binding globulin) and albumin, with only 1% to 2% of serum testosterone free from protein binding. SHBG binds to T

(testosterone) with high affinity. SHBG-bound T would not be available for dissociation in target tissues via the classical androgen receptor mechanism. Contrarily, albumin binds to testosterone with low affinity, and the dissociation of albumin-bound T is quick. Therefore, both albumin-bound T and free T are referred to as bioavailable T (BAT). Based on these physiological facts, this small free fraction is the most biologically active T circulating, owing to its accessibility to tissues. For clinical purposes, this simplified paradigm of fractions of circulating testosterone and its actions is reasonable[29](**A**).

Thus, TT (total testosterone) would not be the ideal scale for measuring late-onset hypogonadism, as the increase of SHBG associated with aging results in an increase in testosterone binding. The FT or BAT, fraction of T available, during male aging would be a more precise marker of hypogonadism. It has been demonstrated that there is a fall in testosterone and BAT levels at 1.1%/year and 2.3%/year[27](**A**).

As free testosterone levels, whether verified through equilibrium dialysis, calculation of bioavailable testosterone or calculation of the total testosterone coefficient and SHBG, are dependent on the exact level of total testosterone, the result of the TT level has implications on the determination of free testosterone[18](**A**).

Recommendation

Free testosterone, the fraction of testosterone that is bioavailable, is a more precise marker of hypogonadism. As the levels of free testosterone are dependent on the exact level of total testosterone, the result of the total testosterone level has implications on the determination of free testosterone.

What are the reference values for the serum levels of total and free testosterone used in the diagnosis of late-onset hypogonadism?

For the level of TT (total testosterone), clinical laboratories use commercial RIA kits and competitive-type immunoassays that use chemiluminescence technology. These TT tests use standard and reference levels provided by the manufacturer[18](**A**). For example, in São Paulo, the laboratory studied uses electrochemiluminescence testing and liquid chromatography coupled with mass spectrometry in tandem. At this laboratory, the reference values for total testosterone in males for both methods are 240 to 816 ng/dL. Another laboratory, whose data were used in a Brazilian study with good evidence, established the following reference data for total testosterone: total testosterone values above 320 ng/dL (11.1 nM) are considered normal, while TT below 200 ng/dL (6.9 nM) is diagnosed as hypogonadism, though there is controversy in the TT range between 320 and 200 ng/dL (6.9 -11.1 nM). These ranges established by the laboratory cover all adult men while not taking into account the variation of age groups. The standard for laboratory diagnosis of late-onset hypogonadism, in this study, was defined as a patient having two free testosterone values calculated as less than 6.5 ng/dL obtained using the Vermeulen formula, with a minimum interval of one month between measurements[28](**A**). The laboratory definition of late-onset hypogonadism has not yet been established. Thus, the diagnosis of late-onset hypogonadism is usually based on the clinical features of hypogonadism and a demonstration of morning serum testosterone level below the minimum reference value for young adults[18](**A**).

A major problem occurs when the reference texts for physicians describe a reference value for adult men that does not correspond to the values cited by many laboratories. The reference values supplied by the manufacturer are significantly lower than the reference values to which many publications refer, based on traditional RIA methods[18](**A**).

According to the recommendations of many scientific societies, there is no lower limit for TT universally accepted for the diagnosis of male hypogonadism. There is a general consensus that total TT levels above 12 nmol/L (350 ng/dL) do not require testosterone replacement.

Similarly, based on data from young men, there is a consensus that patients with total serum testosterone below 8 nmol/L (230 ng/nL) would be hypogonadic. There is controversy in the range between 8 and 12 nmol/L[30](**B**).

Free testosterone levels, whether verified through equilibrium dialysis, calculation of bioavailable testosterone or calculation of the total testosterone coefficient and SHBG, are dependent on the exact level of total testosterone, and the result of the study has implications on the determination of free testosterone[18](**A**).

There are various assays available to measure free and bioavailable testosterone in blood serum. There is the gold standard dosing method for these values, but as they take time and are technically more complicated, they are only used by reference laboratories. FT can be measured through direct method with RIA using a commercial kit, which is the method used in many laboratories in the country, with the values obtained being lower than those in the reference methods.

Both free and bioavailable testosterone can be calculated based on the level of SHBG and total testosterone, using the formula published by Vermeulen. The values obtained correlate significantly with the values obtained

in levels considered as the gold standard for free testosterone level. The normal value of this method in men is 131 to 640 pmol/L[31](**D**).

As weekly variations can occur in testosterone, especially in older men whose levels of testosterone fluctuate between lower and normal limits, at least two testosterone measurements should be made to confirm the diagnosis of hypogonadism[18](**A**).

Recommendation

The diagnosis of LOH is based on clinical aspects of hypogonadism and demonstration of morning serum levels of total and free testosterone below the minimum reference value for healthy young adults. The laboratory definition of LOH has not yet been established.

What is the role of salivary testosterone levels?

The measurement of hormones using saliva is easy and noninvasive.

It is believed that for various hormones the concentrations in saliva represent the concentration of forms unbound to protein in the blood. Landman et al. demonstrated the presence of testosterone in saliva in 1976, and this fact was confirmed by various other studies. One recent study conducted with 144 men between 20 and 89 years old demonstrated that salivary testosterone (ST) correlates with TT (total testosterone), FTc (calculated free testosterone) and BAT (bioavailable testosterone). This fact adds to the previous literature demonstrating that ST is correlated with free testosterone using dialysis. A circadian rhythm was observed in ST similar to that observed in serum testosterone levels. The data from the study confirmed the validity of the determination of ST as a measurement that evaluates bioavailable testosterone. The, study was the largest to confirm the decrease of ST with male aging. It demonstrated a good correlation with the symptoms of late-onset hypogonadism evaluated using the ADAM test[32](**B**).

It was demonstrated that the level of ST is a reliable option for the measurement of free testosterone, but as yet cannot be recommended for generalized use because the methodology has not been standardized, and the ranges for adult men are not available at the majority of hospitals and reference laboratories[30](**B**).

Recommendation

It was demonstrated that the level of ST is a reliable substitute for the measurement of free testosterone, but as yet it cannot be recommended for generalized use because the methodology has not been standardized, and the ranges for adult men are not available at the majority of hospitals and reference laboratories.

What are the main advancements in the standardization of testosterone levels?

Recent work with good evidence expressed concern about the need for standardization of a biochemical test for diagnosing late-onset hypogonadism. In the opinion of the authors, the best fraction for diagnosis is FT, but there is a global variation in the literature among authors with regard to the fraction of testosterone considered valid as a parameter for male hypogonadism diagnosis[21](**A**).

Efforts to create a standardization of testosterone levels, consensuses about testosterone measurement standards and reliable reference ranges are being developed[30](**B**).

According to a study with major evidence, various types of commercial tests from various non-validated manufacturers were compared with the gold standard TT level (LC-MS/MS - liquid chromatography–mass spectrometry in tandem). The authors concluded that the majority of manual and automated immunoassays were capable of distinguishing hypogonadic men from eugonadic men, if the reference value for adult males had been established individually at each laboratory, as there are important variations using the same or different type of test[18](**A**).

There are various assays available to measure free and bioavailable testosterone in blood serum. There is the gold standard dosing method for these values, but as they take time and are technically complicated, they are only used by reference laboratories. For example, equilibrium dialysis is the gold standard for assessment of free testosterone. Free testosterone can be measured using the direct method with RIA using a commercial kit, which is the method used in many laboratories in the country, with the values obtained being lower than those in the reference methods[18](**A**).

The gold standard for measurement of total testosterone is LC-TM/MS, and reliable reference ranges for TT measurements using this method are being developed[30](**B**). Improvements in terms of easiness to read LM-MS/MS will make more laboratories develop new measurement procedures. These new levels should be validated for an international reference developed by a competent reference laboratory. Standardization is crucial to improve patient care, otherwise the proliferation of procedures using the method could impair the LC-MS/MS, which is a method with good precision. This conclusion is true for all methods used for the measurement of testosterone[33](**B**).

Equilibrium Dialysis is the gold standard for the measurement of free testosterone, but it takes time and is technically complicated, being thus used only in reference laboratories[18](**A**). International reference standards, characterization of methodology and reference ranges based on populations for measurement of FT using equilibrium dialysis are required[30](**B**).

On the other hand, measuring SHBG in the serum together with a reliable determination of TT provides sufficient data to calculate FT levels. Calculated FT correlates well with FT using equilibrium dialysis[31](**D**). Consensus in relation to the equilibrium constants for testosterone binding to SHBG and albumin will allow advancements in the calculations of FT. For example, a study comparing five algorithms published for the calculation of FT concluded that these should be reevaluated at each location, otherwise values much higher or lower than the reference values could occur[34,35](**B**).

In the United States, representatives of various professional societies, the government and industry met in February of 2010 with the objective of ensuring that testosterone levels are measured with precision and reliability, identifying the targets objectives and actions required for standardization of testosterone measurements.

Results: a series of recommendations were made to ensure very precise testosterone measurements that will result in more adequate diagnoses, treatments and prevention through the use of standardized testosterone tests. The recommendations included technical improvements in the standardization of tests; education of health workers, patients and others involved in testosterone measurement; plans to encourage publications; government agencies and health insurers involved to support this effort; and encouragement for manufacturers to develop better and more economically viable measurements. Some of these actions are already underway[36](**D**).

Recommendation

The gold standard for total testosterone measurement is LC-TM/MS (liquid chromatography–mass spectrometry in tandem), and reliable reference ranges for total serum testosterone using this method are being developed. These should be validated for an international reference. Standardization is crucial for the improvement of patient care. Equilibrium dialysis is the gold standard for measurement of free testosterone, though it is time consuming and technically complicated. International reference standards, characterization of methodology and reference ranges based on populations for measurement of free testosterone using equilibrium dialysis are required. Consensus in relation to the equilibrium constants for testosterone binding to SHBG and albumin will allow advancements in the calculations of free testosterone.

Which examinations should be requested before the start of ART?

Baseline testosterone measurement: the reference ranges and measurements methods have already been covered in previous questions.

Lipid evaluation: in a recent meta-analysis with good evidence of 11 studies on the adverse effects of ART, 4 studies showed a reduction in HDL, while 7 showed no significant change[37](**A**).

Prostate assessment: baseline PSA measurement and rectal exam should be conducted on all patients aged 40 or over. Prostate biopsy should be indicated in cases of suspected prostate cancer suggested by alterations to the touch and/or PSA levels.

Only patients with light or moderate urinary tract symptoms or negative biopsy for prostate carcinoma should be treated[38](**B**).

Baseline measurement of hematocrit: the administration of testosterone in hypogonadic men is associated with a dose-dependent increase in hemoglobin. The increase in hemoglobin is higher in older men. Men with baseline hematocrit over 50% should be submitted to an accurate clinical assessment before considering ART[38](**B**).

Disregard history of sleep apnea: the frequency of men with a new diagnosis of sleep apnea during ART is not statistically significant[37](**A**). Cases of obstructive sleep apnea should be treated before starting ART[39](**B**).

Recommendation

The following procedures are recommended: lipid evaluation, baseline PSA level, baseline hematocrit level, disregard history of sleep apnea.

How should the patient undergoing ART be monitored with regard to the frequency of consultations?

Consultations should be held every three or six months after starting treatment, and then annually to evaluate if the symptoms have responded to treatment or if the patient is having any adverse effects.

The patient should be questioned about urinary tract symptoms and sleep apnea. During the physical exami-

nation, include rectal prostate examination and blood samples for measurement of testosterone, PSA, hematocrit and hemoglobin levels[39](**B**).

Recommendation

Consultations should be held every three or six months after starting treatment, and then annually to evaluate if the symptoms have responded to treatment or if the patient had any adverse effects.

What level should the testosterone dose be kept at for patients undergoing ART?

The current data is insufficient to determine the optimum level of testosterone for efficacy and safety. Currently, average-to-low levels for healthy young adults appear to be appropriate as therapeutic target.

Supraphysiological levels should be avoided. Pharmacogenetics linked to AR (Androgen Receptor) may be a future option to individualize the optimal level of testosterone[40](**B**).

Monitor testosterone levels 3 and 6 months after starting ART. For patients that receive intramuscular replacement, the levels of testosterone should be interpreted in midway between one injection and another[38](**B**).

Recommendation

Currently, average or low levels for healthy young adults appear to be appropriate as a therapeutic target.

What level should hematocrit be kept at for patients undergoing ART?

In patients underg oing ART, hematocrit should be measured 3, 6 and 12 months after the start of treatment, and then yearly. An increase in hematocrit over 50% was the most common adverse effect found in ART according to a major review of evidence. This review showed that there was a significantly higher number of participants with hematocrit above 50% in the group undergoing testosterone replacement than the placebo group[37](**A**). The critical threshold for hematocrit is not yet clear. Dose adjustments may be required to keep hematocrit below 52% to 55%[39](**B**). According to another recommendation, if the hematocrit is above 54% ART should be discontinued until the hematocrit returns to safe levels[38](**B**).

Recommendation

Maintain the level of hematocrit at up to 54%.

What about liver funcion tests?

The use of oral testosterone preparations could lead to hepatotoxic effects. testosterone undecanoate is an oral preparation that seems to have no significant hepatotoxicity.

A study with good evidence conducted with 237 men aged between 60 and 80 for 6 months showed no changes in liver function with ART using oral testosterone undecanoate. The study suggests that long term research is needed to establish safety[41](**A**).

Intramuscular injections and transdermal preparations do not appear to be associated with liver dysfunction.

Therefore, the measurement of liver function is required only in patients with orally administered ART[42](**D**).

Only 17a-alkylated oral preparations such as fluoxymesterone and methyltestosterone display hepatotoxicity.

Recommendation

Liver function monitoring is not recommended in patients on ART with any pharmaceutical form other than 17a-alkylated oral preparations.

Is it important to monitor bone mass?

A systematic review of randomized clinical trials lasting 6 months to 3 years that evaluated the effects of ART on bone mineral density remained inconsistent and inaccurate, though bone mineral density appears to increase with ART[43-45](**A**).

It is recommended to assess bone mass of the lumbar spine and femur neck after one to two years of ART in hypogonadic men with osteopenia or osteoporosis[38](**B**).

Recommendation

It is recommended to assess bone mass of the lumbar spine and femur neck after one to two years of ART in hypogonadic men with osteopenia or osteoporosis.

How should prostate cancer be monitored?

After starting ART, patients should be monitored for prostate disease, with rectal examination and PSA measurements 3, 6 and 12 months after treatment, and then annually, if there are no abnormalities.

The patient should undergo prostatic investigation if:

1. PSA is higher than 4 ng/mL or 3 ng/mL in men with a high risk of prostate cancer;

2. An increase in PSA levels higher than 1.4 ng/mL in any 12 month period during treatment;
3. The speed of any increase in PSA is higher than 0.4 ng/mL/year, using the PSA level after 6 months of testosterone administration as a baseline (only valid if the PSA levels are known for a period of more than two years);
4. Detection of prostatic abnormality during rectal examination[38](**B**).

If the patient's risk of prostate cancer is sufficiently high as stated above (suspected findings during rectal examination, increase PSA and other risk factors such as age, family history, race, etc.) an ultrasound-guided prostate biopsy is recommended[38](**B**)[46,47](**A**).

Recommendation

After starting ART, patients should be monitored for prostate disease, with rectal examination and PSA measurements 3, 6 and 12 months after treatment, and then annually, if there are no abnormalities. The patient should undergo prostatic investigation if: PSA is higher than 4 ng/mL or 3 ng/mL in high-risk patients, an increase in PSA higher than 1.4 ng/mL in any 12 month period during treatment, the speed of increase in PSA is higher than 0.4 ng/mL/year, using the PSA level after 6 months of testosterone administration as baseline, and detection of prostatic abnormality during rectal examination.

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