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REVIEW ARTICLE

EAA clinical guideline on management of bone health in the andrological outpatient clinic

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SUMMARY

Male osteoporosis is now a well-recognized medical disorder with established clinical guidelines for both diagnosis and management. Prevention as well as management of osteoporosis in men consulting the andrological outpatient clinic because of low testosterone, however, is not well established. This gap of knowledge is—at least partly—explained by the controversy with respect to the threshold of testosterone needed for skeletal maintenance. However, testosterone deficiency may be clearly associated with bone loss as well as frailty in men. If anything, andrologists should therefore be aware of the potential silent presence of osteoporosis in men with confirmed hypogonadism. Therefore, the management of patients with potential hypogonadism should include a complete bone health assessment, besides clinical and biochemical evaluation of gonadal status. Such bone health assessment should include specific items in medical history and physical examination related to fracture risk. Furthermore, dual-energy absorptiometry is indicated to evaluate fracture risk in men with confirmed clinical hypogonadism. Regarding treatment, besides general measures to prevent or manage male osteoporosis testosterone replacement can be initiated (as described in guidelines for hypogonadism), but data on its efficacy in preventing fractures are lacking. Thus, additional anti-osteoporotic may be needed, especially in men with very low testosterone who are at high risk of bone loss and/or in men not able to receive testosterone replacement.

INTRODUCTION

Osteoporosis is an important health problem not only in women but also in men. Hypogonadism is a well-established cause of secondary osteoporosis in men. Both primary hypogonadism and secondary hypogonadism are associated with low bone density (Khosla *et al.*, 1998; Fink *et al.*, 2006; Rochira *et al.*, 2006, 2015). Increase in fracture risk is, however, only well documented in patients following androgen deprivation therapy (ADT: surgical or chemical castration in prostate cancer patients or hypersexuality) (Shahinian *et al.*, 2005). Indeed, ADT is associated with rapid bone loss (Stepan *et al.*, 1989) as well as subsequent bone fragility (Shahinian *et al.*, 2005; Wang *et al.*, 2015; Wu *et al.*, 2015).

Moreover, testosterone prevents bone loss in hypogonadal men (Amory *et al.*, 2004), especially in men with low testosterone concentrations (<200 ng/dL) (Snyder *et al.*, 1999, 2017). In men with borderline low or low normal testosterone levels however, such as in some patients with Klinefelter syndrome, bone density may be preserved also without testosterone replacement (Bonomi *et al.*, 2016).

Although male osteoporosis is now a well-recognized clinical entity, it remains an underdiagnosed and undermanaged condition (Madeo *et al.*, 2007; Willson *et al.*, 2015). Although several general guidelines for the management of osteoporosis contain advice concerning male osteoporosis (Appendix 1), only a few guidelines specific for male osteoporosis have been released. No specific guidelines on hypogonadal osteoporosis are however available.

For this reason, this manuscript presents a more practical approach for the assessment and management of bone health in patients consulting an andrological outpatient clinic, including both prevention and management of osteoporosis in hypogonadal men.

To enhance the value of the clinical advice here provided, we used the GRADE (Grading of Recommendations,

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Assessment, Development, and Evaluation) system for grading the quality of evidence and the strength of recommendations (Swiglo *et al.*, 2008). The GRADE system is a method of developing evidence-based guidelines involving key recommendations and the use of a consistent language and graphical descriptions for standardizing the grading of both the strength of recommendation and the quality of evidence (Swiglo *et al.*, 2008) (17, 20). The number 1 indicates a strong recommendation and is associated with the terminology 'we recommend'; the number 2 denotes a weak recommendation and is associated with the wording 'we suggest'. The grading of the quality of evidence employs the following graphical descriptions: ⊕◯◯◯ denotes very low-quality evidence; ⊕⊕◯◯, low quality; ⊕⊕⊕◯, moderate quality; and ⊕⊕⊕⊕, high quality (Swiglo *et al.*, 2008). In addition, we provide three clinical vignettes that summarize different scenarios common in andrological patient practice (Boxes 1–3).

APPROACHING BONE HEALTH IN THE PATIENT WITH HYPOGONADISM

Low circulating sex steroids (both androgens and estrogens) are associated with reduced bone mineral density (BMD) in men of any age (Khosla *et al.*, 1998; Fink *et al.*, 2006; Rochira *et al.*, 2006, 2015), and this association is supported by clear pathophysiological evidence (Almeida *et al.*, 2017). Bone health assessment is therefore needed in men with confirmed hypogonadism.

Clinical evaluation: the role of patient's medical history and physical examination

Both medical history and appearance at physical examination (Table 1) might prompt further investigation in hypogonadal patients. Further clinical workup should be addressed to (i) diagnose osteopenia/osteoporosis, (ii) assess fracture risk and/or concomitant presence of fractures, and finally (iii) establish therapeutic strategies (Watts *et al.*, 2012; Vescini *et al.*, 2016).

A detailed patient's interview should be considered prior to proceed to a complete bone workup (Lewiecki, 2015). Further examinations are needed if one or more of the aspects listed in Table 1 are present. Furthermore, risk factors for osteoporosis and fractures related to lifestyle, other treatments, and related diseases (Table 2) should be addressed (Kanis *et al.*, 2005a,b; de Kam *et al.*, 2009; Drake *et al.*, 2012; Lewiecki, 2015). In particular, alcohol intake should be evaluated as alcohol abuse is an important cause of male osteoporosis. Smoking and excessive alcohol consumption (daily intake or ≥10 units per week or ≥3 units/day) are major risk factors for osteoporotic fractures in men (Kanis *et al.*, 2005a,b; Drake *et al.*, 2012).

Information on current or past glucocorticoid treatment should be obtained as glucocorticoid treatment is a strong risk factor for both osteoporosis and osteoporotic fractures (Drake *et al.*, 2012).

Physical examination

Statements

- We recommend considering bone health in all andrological patients with documented hypogonadism at first visit. 1|⊕⊕◯◯
- We suggest assessing clinical aspects of bone health as reported in Table 1. 2|⊕⊕◯◯
- We suggest including spine observation and follow-up of patient's height in the clinical workup. 2|⊕⊕◯◯

Evidence

Silent spine fractures may also occur in men similar to women and are an important first sign of osteoporosis (Lewiecki, 2015). Decrease in height, the presence of dorsal kyphosis, a wall-to-occiput distance >0 cm, and a rib-to-pelvis distance <2 fingers might suggest the presence of occult vertebral fractures in men (Table 1) (Green *et al.*, 2004). Wall-to-occiput distance is easily obtained by placing the patient against the wall and measuring the distance between the wall and the occiput (Green *et al.*, 2004).

Biochemical evaluation: the role of sex steroid measurements

Statements

- We recommend having serum total testosterone measured twice on a morning blood sample. 1|⊕⊕⊕◯
- We recommend measuring again total testosterone and SHBG if only a single measurement documenting low testosterone is available. LH and prolactin are useful to better characterize hypogonadism. 1|⊕⊕⊕◯
- We do not recommend routine measurement of serum estradiol. 1|⊕⊕◯◯
- We suggest measuring estradiol only when a validated mass spectrometry-based method is available and in rare cases in which severe estrogen deficiency is suspected. 2|⊕⊕◯◯

Evidence

It is well established that circulating sex steroids should be in the male normal range to ensure bone health (Rochira *et al.*, 2006; Almeida *et al.*, 2017). For this reason, all patients with documented low serum testosterone consulting with hypogonadal symptoms should receive a biochemical evaluation of their gonadal status, with measurement of serum total testosterone, SHBG, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin (Wang *et al.*, 2009; Bhasin *et al.*, 2010; Buvat *et al.*, 2013; Huhtaniemi, 2014; Lunenfeld *et al.*, 2015). Gonadotropins are needed to differentiate primary hypogonadism from secondary hypogonadism, whereas normal prolactin levels allow excluding hyperprolactinemia as the cause of hypogonadism (Basaria, 2014).

Serum testosterone

Hypogonadism should be confirmed twice on a morning blood sample (Wang *et al.*, 2009; Bhasin *et al.*, 2010; Buvat *et al.*, 2013; Basaria, 2014; Huhtaniemi, 2014; Lunenfeld *et al.*, 2015). The threshold of serum total testosterone for skeletal maintenance is not well defined (Finkelstein *et al.*, 2016). Some indirect evidence, however, suggests that a threshold below 200 ng/dL may be used (Snyder *et al.*, 1999; Finkelstein *et al.*, 2016).

When serum total testosterone is between 200 and 300 ng/dL, the presence of hypogonadal symptoms may help in confirming the diagnosis and other aspects (e.g., patients' age, obesity) are determinant for clinical relevance of low serum testosterone (e.g., vignette 3; Box 3).

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Box 1

Clinical vignette 1 depicting a standard case of an adult male patient with severe hypogonadism and severe osteoporosis characterized by multiple vertebral fractures at the time of the diagnosis.

Clinical Vignette 1

Patient: 40 year old man
Past history: delayed puberty, one-year treatment with gonadotropins for hypogonadotropic hypogonadism at the age of 18 years, subsequent long-term period without androgen replacement treatment, heavy smoker
Reasons for andrological consultation: signs (eunuchoid habitus, incomplete pubertal development, reduced body hair) and symptoms (anosmia) of hypogonadism (other: low libido, low volume of ejaculate, and erectile dysfunction)
Physical examination: dorsal kyphosis, eunuchoid skeletal proportions
Hormones: Low to suppressed LH and FSH, serum T: 73 ng/dL (normal range: 300–900 ng/dL), normal serum prolactin, and vitamin D
DXA: lumbar T-score: −2.2; femoral T-score: −2.4 (lumbar and femoral osteopenia).
FRAX: 18% risk of major osteoporotic fractures: 13% risk of hip fracture
X-ray of the spine: showed wedge (grade 1) vertebral fractures of T9, T10, and T11 vertebrae.
Diagnosis: severe hypogonadotropic hypogonadism due to Kallmann syndrome associated with severe osteoporosis
Proposed treatment: should receive TRT or gonadotropin treatment if fertility is requested
Summary of relevant aspects
This clinical vignette highlights that:

- *BMD measurement alone may not be sufficient for a complete diagnosis*
- *Osteoporotic, atraumatic fractures may appear early in life in case of severe male hypogonadism, especially if untreated*
- *Physical examination is useful in suggesting further radiological examination that might change the diagnosis of osteoporosis*

Practical tools:

- *Check occult fractures in male patients with hypogonadism, especially in severe hypogonadism*
- *Obtain FRAX score for assessing fracture risk*
- *Young adults with osteoporosis and severe hypogonadism are good candidates for TRT*
- *Occult osteoporotic fractures need also specific antiresorptive treatment*

TRT, testosterone replacement treatment.

Severe hypogonadism and mild hypogonadism have a different impact on bone mass than slightly low serum testosterone (in-between 200 and 300 ng/dL). Severe hypogonadism (serum total testosterone <100 ng/dL) may lead to bone loss and often osteoporosis, independently from the patient's age as illustrated in the clinical vignette 1 (Box 1). In case of severe hypogonadism, concomitant osteoporotic fractures (commonly of the spine) might be present at the diagnosis both in young and older men as in clinical vignette 1 (Box 1) and 2 (Box 2), respectively. Conversely, a clear cause–effect relationship between bone and gonadal status remains weak in case of mild to slight hypogonadism depicted by clinical vignette 3 (Box 3). These different phenotypes of male hypogonadism may therefore have different impact with respect to diagnosis and management of bone health.

Serum estradiol

Serum estradiol is an important determinant of bone mass in men (Rochira *et al.*, 2015; Almeida *et al.*, 2017), and bone loss in hypogonadal men may also be related to estrogen deficiency (Rochira *et al.*, 2006; Finkelstein *et al.*, 2016). Accordingly, hypogonadal men without relative estrogen deficiency have higher BMD than those with both low testosterone and estradiol (Aguirre *et al.*, 2015). Theoretically, serum estradiol may be a good marker to identify hypogonadal men with a worse bone status, but the role of estradiol measurement for the diagnosis and management of hypogonadal osteoporosis is currently not well established, in part due to pitfalls related to the measurement of estradiol in the low male normal range (Rochira *et al.*, 2015, 2016). Estradiol becomes important in hypogonadal osteoporosis only when severe estrogen deficiency is suspected (Rochira & Carani, 2009).

Remarks

Serum total testosterone can be assayed by commercially available kits or using the gold standard represented by liquid chromatography–tandem mass spectrometry (LC-MS/MS), which is becoming more and more available in the clinical setting (Simoni *et al.*, 2012).

We suggest using calculated free testosterone when needed, based on the measurement of total serum testosterone, SHBG, and albumin (Vermeulen *et al.*, 1999). It can easily be obtained using online available calculators (see Appendix 2 for Web links). Commercially available kits for direct measurement of free testosterone should not be used due to their poor accuracy and reliability (Rosner *et al.*, 2007; Bhasin *et al.*, 2010).

Commercially available kits for the measurement of serum estradiol have poor accuracy and are not reliable for the measurement of estradiol within the low male normal range (Rosner *et al.*, 2013; Demers *et al.*, 2015), the finding of elevated or normal to high serum estradiol being useful only to rule out relative estrogen deficiency in men with low testosterone (Finkelstein *et al.*, 2016; Rochira & Carani, 2017). However, even when performed with accurate and precise techniques such as LC-MS/MS, the clinical use of serum estradiol remains not validated (Demers *et al.*, 2015). Thus, at present, the measurement of serum estradiol is not useful in routine clinical practice (Demers *et al.*, 2015).

Biochemical evaluation: other biochemical measurements

Statements

- We suggest measuring serum 25(OH) vitamin D at baseline in all hypogonadal men, independently from their BMD. 2|⊕⊕○○
- We suggest measuring serum calcium (or calcium corrected for albumin when it is applied—see Appendix 2 for Web links), phosphorous, and PTH in all hypogonadal patients with documented low BMD. 2|⊕⊕○○
- We do not recommend the routine use of bone turnover markers in the management of male or hypogonadal osteoporosis. 1|⊕⊕⊕○

Vitamin D, calcium, PTH

Vitamin D deficiency may be more prevalent in hypogonadal men (Lee *et al.*, 2012). Although low testosterone may also contribute to lowering circulating active forms of vitamin D (Ferlin *et al.*, 2013), serum 25(OH) vitamin D should be used as the marker of vitamin D deficiency (Swanson *et al.*, 2014). However, measuring 25(OH) vitamin D levels can be technically challenging and a properly validated assay should be used (Bouillon *et al.*, 2013). For vitamin D, a 25(OH) vitamin D serum level of

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Box 2

Clinical vignette 2 depicting a standard case of an older man with severe hypogonadism and concomitant severe osteoporosis with multiple vertebral fractures.

Clinical Vignette 2

Patient: 70 year old man
Past history: diagnosis of isolated hypogonadotropic hypogonadism treated since the age of 30 years. No TRT treatment during the last 40 years
Reasons for andrological consultation: hospitalization for fatigue, slight degree of sarcopenia, and diffuse bone pain (particularly back pain)
Physical examination: undervirilization, dorsal kyphosis, eunuchoid skeletal proportions, bilateral valgism, and bilateral gynecomastia, 2.5 cm reduction in height during the last 3 years
Hormones: Low to suppressed LH and FSH, serum T: 130 ng/dL (normal range: 300–900 ng/dL), normal serum prolactin, 25(OH) vitamin D: 17.1 ng/mL (normal range: 30–100 ng/mL)
DXA: lumbar T-score: −4.0 (z-score: −3.1); femoral T-score: −3.4
FRAX: 22% risk of major osteoporotic fractures: 11% risk of hip fracture
X-ray of the spine: reduction in height of the vertebral body of D6, D7, D9, D10, D11, and L4 vertebrae together with a fracture of the sixth right rib
Diagnosis: severe hypogonadotropic hypogonadism associated with severe osteoporosis
Proposed treatment: should restart TRT treatment and receive also anti-osteoporotic treatment with proven antifracture efficacy
Summary of relevant aspects
This clinical vignette highlights that:

- *Even when indicated, TRT treatment in older patients might be discontinued due to several reasons: lack of compliance, frailty and poor health conditions, and contraindications that are frequent in the elderly (e.g., increased hematocrit, suspected or diagnosed prostate cancer, severe chronic coronary disease)*
- *The best option is to add antiresorptive or anabolic bone treatment to TRT (combined therapy) as TRT alone is not sufficient to guarantee bone health.*
- *In case of contraindications to TRT administration, antiresorptive or anabolic bone treatment alone should be administered to treat osteoporosis.*
- *Vitamin D deficiency should be corrected*

Practical tools:

- *Focus mainly on prevention of further fracture (specific treatment for osteoporosis) rather than on hypogonadism and prevention of bone loss with TRT*
- *Severe osteoporosis in older patients needs prevention of falls, especially in case of sarcopenia*

TRT, testosterone replacement treatment.

20 ng/mL (50 nmol/L) is generally accepted as sufficient for bone health (Bouillon *et al.*, 2013).

Serum calcium, phosphorous, and parathyroid hormone (PTH) measurement should rule out other prevalent forms of secondary osteoporosis (or osteopenia) such as primary hyperparathyroidism (Marcocci & Cetani, 2011; Bilezikian *et al.*, 2014; Khan *et al.*, 2016) (Table 2).

Bone turnover markers

The role of serum bone turnover markers such as bone-specific alkaline phosphatase, osteocalcin, urinary collagen type 1 cross-linked N-telopeptide (NTX), and collagen type 1 cross-linked C-telopeptide (CTX) in the workup of hypogonadal osteoporosis is not well established. High bone turnover markers in hypogonadal men may however reflect high bone turnover and therefore ongoing bone loss. At present, there is also no evidence about the value of bone turnover markers for either determination of fracture risk or selection of patients who need to be treated (Vasikaran & Chubb, 2016). Antiresorptive treatment may however reduce bone turnover markers in hypogonadal osteoporosis (Vasikaran & Chubb, 2016), but their use in follow-up of treatment is not well validated.

Table 1 Main aspects to be considered during first visit

Aspects to be considered at medical interview
Major aspects
Long-term severe androgen deprivation at any age (not treated congenital hypogonadism, castration, drugs)
Bone pain, especially back pain
Concomitant diseases strictly associated with male osteoporosis: HIV/COPD/thalassemia/viral hepatitis
Medications (e.g., glucocorticoids)
Decrease in stature (height loss), especially in older men
Osteoporosis and/or osteoporotic fractures among relatives
History of prior atraumatic or low trauma fractures
Tendency to fall, especially in older men
Minor aspects
Physical performance changes
Lifestyle (Alcohol and smoking)
Intestinal transit
Aspects to be considered at physical examination
Major aspects
Height measurement
Presence of kyphosis
Wall-to-occiput distance >0 cm
Body composition/muscle masses
Testes volume
Minor aspects
Rib-to-pelvis distance <3 fingers
Eunuchoid body proportions
Humpback
Weight
Tooth loss
Blue sclera, especially in young patients

ADT, androgen deprivation therapy; HIV, human immunodeficiency virus infection; COPD, chronic obstructive pulmonary disease.

Diagnosis: the role of bone imaging

As male hypogonadism may cause osteoporosis, all andrological patients with confirmed hypogonadism should undergo further evaluation of bone density. Bone imaging, by the use of DXA and plain x-ray, aims to (i) ascertain whether osteopenia or osteoporosis is present; (ii) diagnose previous or concomitant osteoporotic fractures (often overlooked or underestimated in men); and (iii) prevent future fractures.

The role of DXA in the evaluation of bone status

Statements

- We recommend BMD measurement by DXA in all hypogonadal patients with documented hypogonadism and/or serum testosterone <200 ng/dL. 1|⊕⊕⊕○
- We suggest BMD measurement by DXA in all hypogonadal patients with slightly decreased serum total testosterone (between 200 and 300 ng/dL), especially in young patients or in patients with hypogonadal symptoms. 2|⊕⊕○○
- We recommend that all patients who need ADT (for prostate cancer or hypersexuality) should also be evaluated by DXA. 1|⊕⊕⊕⊕
- We suggest BMD measurement by DXA in men with a well-documented history of hypogonadism. 2|⊕⊕⊕○

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Box 3

Clinical vignette 3 depicting a standard case of an adult man with borderline serum total testosterone and osteopenia.

Clinical Vignette 3

Patient: 54 year old man
Past medical history: metabolic syndrome since the age of 48, heavy smoker
Reasons for andrological consultation: loss of libido, slight erectile dysfunction
Physical examination: overweight (BMI: 29; normal <25) and visceral obesity (waist circumference: 104 cm; normal <94 cm)
Hormones: Normal LH and FSH, serum T: 270 ng/dL (normal range: 300–900 ng/dL), normal serum prolactin, serum estradiol in the highest quartile of the normal range, 25(OH) vitamin D: 12 ng/mL (normal range: 30–100 ng/mL).
DXA: lumbar T-score: −1.8; femoral T-score: −1.9
FRAX: 5.9% risk of major osteoporotic fractures: 2.2% risk of hip fracture
Diagnosis: slight hypogonadism and osteopenia
Proposed treatment: no need for anti-osteoporotic treatment
Summary of relevant aspects

This clinical vignette highlights that:

- *Slightly reduced borderline serum testosterone has little impact on bone loss*
- *Overweight and obese men with hypogonadism have a reduced risk of osteoporosis thanks to increased aromatization and protective estrogen effect*
- *Borderline serum testosterone usually does not require additional radiological examinations other than DXA*
- *Check vitamin D and replace if deficient*

Practical tools:

- *BMD and fracture risk are not significantly modified by small decrease in serum testosterone*
- *Slight hypogonadism does not necessarily need TRT*
- *Wait-and-see approach preferred*
- *Diet, physical exercise, and other lifestyle changes as first-line therapy*
- *Treat with TRT if both BMD and serum testosterone decline during follow-up*
- *TRT might help preventing further bone loss and the development of overt osteoporosis*

TRT, testosterone replacement treatment.

Table 2 Risk factors for male osteoporosis. Risk factors that are of particular importance in men are reported in bold

Risk factors for osteoporosis
Lifestyle
Alcohol intake/sedentary lifestyle/smoking/undernutrition
Medications
Glucocorticoids/**ADT**/anticonvulsants/chemotherapeutics
Other endocrine diseases
Delayed puberty/hypogonadism/acromegaly/Cushing syndrome/hyperparathyroidism/hyperthyroidism/diabetes mellitus
Other diseases
Gastrointestinal malabsorption (e.g., celiac disease, bariatric surgery)/rheumatoid arthritis/chronic kidney disease/**HIV**[a]/COPD/neoplastic diseases/iron overload (thalassemia, hemochromatosis)/idiopathic hypercalciuria/osteogenesis imperfecta/neuromuscular diseases/multiple myeloma

ADT, androgen deprivation therapy; HIV, human immunodeficiency virus infection; COPD, chronic obstructive pulmonary disease. [a]Osteoporosis is more prevalent in men than in women with HIV.

Evidence

In clinical practice, dual-energy X-ray absorptiometry (DXA) is the best diagnostic tool to assess BMD in hypogonadal men, whereas pQCT and bone ultrasound only have a role in research or screening (Lewiecki, 2013).

All patients with documented or previous history of hypogonadism should undergo DXA analysis at both lumbar and femoral site (Watts *et al.*, 2012). Even patient's documented hypogonadism in the past might have caused bone loss, especially if occurred during puberty or early adult life (Finkelstein *et al.*, 1987; Soyka *et al.*, 2000). In the andrological setting, DXA provides information about baseline bone status as well as on the patient's risk of future osteoporotic fractures. BMD as assessed by DXA, in fact, correlates with fracture risk at all sites in men (Cummings *et al.*, 2006; Lewis *et al.*, 2007) when measured at lumbar and femoral sites (Yang *et al.*, 2012). The association between low BMD and fracture is therefore also valid in hypogonadal patients (Gaffney *et al.*, 2015) and especially patients undergoing androgen deprivation (Wadhwa *et al.*, 2009). In particular, future bone loss is also strongly associated with osteoporotic fractures (Cawthon *et al.*, 2012).

According to the WHO criteria, in men a T-score equal or <−2.5 is used for the clinical diagnosis of osteoporosis, and a T-score between −1.0 and −2.5 indicates low bone mass (osteopenia) (Kanis *et al.*, 1994). The diagnosis of severe osteoporosis occurs also when a fragility fracture is documented (Kanis *et al.*, 1994).

Remarks

The WHO criteria for the diagnosis of osteoporosis in men are still controversial (Binkley *et al.*, 2014). The site of BMD measurement (lumbar vs. femoral), the use of different T-scores coming from different populations (male vs. female), and how to consider a given T-score in relation to a patient's age (young vs. older men) are the main controversial issues (Binkley *et al.*, 2014).

A T-score equal or <−2.5 at the femoral neck is considered as the reference standard in men by the WHO Collaborating Centre, the International Osteoporosis Foundation (IOF) (Kanis *et al.*, 2008, 2011), and the UK National Osteoporosis Guideline Group (NOGG) (Compston *et al.*, 2013).

The recommended site of DXA measurement differs across various guidelines: hip and spine by the US National Osteoporosis Foundation and the Endocrine Society (Watts *et al.*, 2012), and the lowest T-score value for the BMD measured at the lumbar spine, total hip, or femoral neck by the Osteoporosis Canada (Papaioannou *et al.*, 2010).

As far as the population used for the T-score is concerned, the Endocrine Society recommends using male reference data (Watts *et al.*, 2012), the International Society of Clinical Densitometry recommends the female standards for calculating male T-scores (Watts *et al.*, 2013), while the WHO, IOF, and Scientific Advisory Council of Osteoporosis Canada recommend the use of the reference database at the femoral neck of Third National Health and Nutrition Examination Survey (NHANES III) obtained from young women (20–29 years old) (Kanis *et al.*, 2008; Papaioannou *et al.*, 2010).

In guidelines of male osteoporosis, DXA is mostly indicated after age 50 (Watts *et al.*, 2012). However, in young patients with confirmed hypogonadism, it may be important to have a DXA at start of TRT to be able to follow up evolution at later stages (Kanis *et al.*, 2011). For instance, if patients interrupt their TRT,

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DXA may decrease rapidly and give the andrologist an important indication about compliance.

The role of X-ray in the detection of vertebral fractures

Statements

- We recommend X-ray of the dorsolumbar spine when osteoporotic fractures are suspected on the basis of patient's medical history, physical examination, and/or the presence of localized bone pain. 1|⊕⊕⊕◯
- We recommend using X-ray to confirm the diagnosis of severe osteoporosis. 1|⊕⊕◯◯
- We however do not recommend the use of X-ray for the diagnosis of osteoporosis or osteopenia. 1|⊕⊕⊕⊕

Evidence

X-ray is the best diagnostic tool to identify vertebral fractures as first-line examination. Spine fractures in men as well as in women occur at the distal thoracic and upper lumbar spine. CT scan and MRI may confirm the diagnosis but are rarely needed (Lewiecki, 2013). X-rays are easy to perform, not expensive, available worldwide also in basic clinical setting, and are very sensitive for the detection of fractures (especially vertebral fractures) (see Appendix 2 for Web links to the Genant classification).

The role of other imaging techniques

Statements

- We do not recommend the use of other different techniques than DXA and X-ray for the diagnosis of osteoporosis or osteopenia and osteoporotic fractures. 1|⊕⊕⊕◯

Evidence

Although QCT shows a disturbed microarchitecture and bone density assessed by ultrasound is also lower in hypogonadal men (Tajar *et al.*, 2012; Finkelstein *et al.*, 2016), these techniques are less well-established markers of fracture risk (Lewiecki, 2013).

Fracture risk assessment

Statements

- We suggest calculating the FRAX score in all men with confirmed hypogonadism. 2|⊕⊕⊕◯

Evidence

BMD measurement represents a surrogate marker of fracture risk as low BMD is associated with an increased risk of fractures at all sites in men (Pasco *et al.*, 2014).

The Fracture Risk Assessment Tool (FRAX)® (see Appendix 2 for Web links) is also of value in predicting fracture risk in men (Harvey *et al.*, 2016) with or without BMD value (Ettinger *et al.*, 2013). It is not time-consuming and therefore could be easily used in hypogonadal patients. The score obtained allows an estimation of future osteoporotic fractures and hereby might help to decide whether or not additional anti-osteoporotic treatment is needed (Cosman *et al.*, 2014).

Remarks

It has been suggested that a 10-year risk of hip fracture greater than or equal to 3% (obtained by FRAX) in men older than 50 years with low bone mass (osteopenia or osteoporosis) at femoral neck, total hip, or lumbar spine by DXA should be considered as a possible threshold for starting a treatment for osteoporosis (Cosman *et al.*, 2014).

It has been suggested that a 10-year risk of major osteoporotic fractures greater than or equal to 20% (obtained by FRAX) in men older than 50 years with low bone mass (osteopenia or osteoporosis) at femoral neck, total hip, or lumbar spine by DXA should be considered as a possible threshold for starting a treatment for osteoporosis (Cosman *et al.*, 2014).

No evidence exists to propose treatment thresholds based on FRAX score in men younger than 50 years.

Treatment

The main goal of treating hypogonadal men with osteoporosis is to decrease the risk of osteoporotic fractures. However, most studies in men have addressed only surrogate endpoints such as BMD, but not fracture endpoints. Furthermore, the data available from the trials investigating the efficacy of anti-osteoporotic drugs for the treatment of osteoporosis represent an additional limitation as the number of men enrolled in those studies is much smaller compared to the female participants.

Lifestyle factors

Statements

- In general, smoking cessation, a reduction in alcohol intake, and weight-bearing exercises are recommended. 1|⊕⊕◯◯
- We suggest introducing lifestyle interventions when hypogonadism is diagnosed or when ADT is started and should be continued throughout life. 2|⊕⊕◯◯

Evidence

Lifestyle interventions are recommended in all men at risk of osteoporosis and therefore also in all hypogonadal men (Pye *et al.*, 2010). Smoking cessation and alcohol abstention are needed for heavy smokers or alcoholics, and in general, reduction in smoking and in alcohol intake is advisable (Vescini *et al.*, 2016). Furthermore, increasing physical activity can have a positive effect on BMD and may reduce the risk of falls and fall-related fractures (de Kam *et al.*, 2009). In addition, weight loss in obese subjects might, in part, increase serum testosterone (Corona *et al.*, 2013).

Calcium and vitamin D supplementation

Statements

- We suggest increasing dietary intake of calcium if the dietary calcium intake is insufficient. 2|⊕⊕◯◯
- If dietary calcium intake remains inadequate and/or vitamin D serum levels are low, we suggest initiating pharmacological supplementation with both calcium and vitamin D. 2|⊕◯◯◯
- We do not recommend monotherapy with either one of them. 1|⊕⊕◯◯

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- We do not recommend the use of calcium/vitamin D supplementation as the only treatment for hypogonadal osteoporosis or androgen deprivation therapy-associated bone loss. 1|⊕⊕⊕○
- We recommend starting antiresorptive therapy only in combination with calcium and vitamin D supplementation. 1|⊕⊕○○

Evidence

Both calcium and vitamin D are important for bone health. An average daily intake of 1000–1200 mg of calcium and 800 units of vitamin D is generally recommended, ideally via dietary intake (Bouillon *et al.*, 2013). Daily dietary calcium intake can be estimated via a dietary history (see Appendix 2 for Web links).

Remarks

Men with malabsorption (for instance, after bariatric surgery) or low sunlight exposure (institutionalized patients) are at increased risk of vitamin D deficiency.

Monotherapy with either calcium or vitamin D, however, has not proven to increase BMD or decrease fracture risk (Bouillon *et al.*, 2013; Avenell *et al.*, 2014; Reid *et al.*, 2014).

Compliance and continuation of treatment with calcium/vitamin D are important. BMD increases are lost when supplementation is stopped.

Antiresorptive therapy in hypogonadal men

Statements

- We recommend antiresorptive treatment in hypogonadal men at high fracture risk (see also our practical proposal in our clinical vignettes). 1|⊕⊕⊕○

Evidence

Antiresorptive therapy (bisphosphonates as well as denosumab) has not been evaluated in a selected population of hypogonadal patients as randomized controlled trials were performed in osteoporotic men, including both eugonadal and hypogonadal men. Most of the hypogonadal men in these trials had low or borderline serum testosterone levels without clear documentation of their gonadal status. An overview of the drugs available for treating osteoporosis in men is given in Table 3.

Antiresorptive treatment increases bone density in osteoporotic men, but data on fracture risk are limited (Vescini *et al.*, 2016). To date, evidence for fracture risk reduction in men with low bone density is only available for zoledronate IV. Importantly, in this study hypogonadal subgroup was included, new osteoporotic fractures were a primary endpoint, and X-ray assessment of spinal fractures was used (Boonen *et al.*, 2012).

Table 3 Overview of the available drugs for osteoporosis treatment in men

Drug	Dose	Men with low or borderline T included in RCTs	Data on fractures in men	Side effects	Contraindications	Refs
Bisphosphonates						
Alendronate	10 mg once daily or 70 mg once weekly Oral	Yes	No	- Osteonecrosis of the jaw - Atypical femoral fracture - Gastrointestinal disorders: reflux, ulcer, diarrhea - Muscle and joint pain	- Renal insufficiency (eGFR < 30 mL/min) - Hypocalcemia - Gastrointestinal ulcer	Orwoll *et al.* (2000)
Risedronate	5 mg once daily or 35 mg once weekly Oral	Yes	No	- Osteonecrosis of the jaw - Atypical femoral fracture - Gastrointestinal disorders: reflux, ulcer, diarrhea - Muscle and joint pain	- Renal insufficiency (eGFR < 30 mL/min) - Hypocalcemia - Gastrointestinal ulcer	Boonen *et al.* (2009), Ringe *et al.* (2009)
Zoledronic acid	5 mg once yearly IV	Yes	Yes	- Osteonecrosis of the jaw - Atypical femoral fracture - Fever after infusion - Muscle and joint pain - Hypocalcemia if calcium/vitamin D substitution is insufficient	- Renal insufficiency (eGFR < 35 mL/min) - Dehydration - Hypocalcemia	Boonen *et al.* (2011, 2012), Lyles *et al.* (2007)
Human monoclonal antibody RANKL						
Denosumab	60 mg every 6 months SC	Yes	No	- Hypocalcemia if calcium/vitamin D substitution is insufficient - Hypersensitivity reactions - Atypical femoral fracture - Osteonecrosis of the jaw	Hypocalcemia	Langdahl *et al.* (2015), Orwoll *et al.* (2012)
PTH analog						
Teriparatide	20 μg daily SC	Yes	No	- Nausea, headache, dizziness, muscle pain - Hypercalcemia - Nephrolithiasis	- Hyperparathyroidism - Osteosarcoma - Skeletal metastases - Paget disease - Open epiphyses	Kaufman *et al.* (2005), Orwoll *et al.* (2003)

IV, intravenous; SC, subcutaneous administration; eGFR, estimated glomerular filtration rate.

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Remarks

Bisphosphonates increase BMD and improve bone mass in men with osteoporosis (Orwoll *et al.*, 2000; Boonen *et al.*, 2009; Ringe *et al.*, 2009).

In addition, there is also evidence that zoledronate reduces fracture risk as well as mortality in mixed male–female population irrespective of bone density (Lyles *et al.*, 2007).

Calcium and vitamin D supplements should always be started when starting antiresorptive therapy as supplements were used in all clinical trials.

Hypocalcemia and/or vitamin D deficiency should be corrected before an antiresorptive drug is started.

Impact of testosterone replacement therapy (TRT) on bone

Statements

- We recommend TRT in young adult hypogonadal patients in order to prevent bone loss and to help acquire peak bone mass. 1|⊕⊕◯◯
- For the indication of TRT in other patient groups, we suggest referring to guidelines on male hypogonadism. The potential benefit of TRT on BMD and fracture risk will probably depend on the etiology of hypogonadism, age of onset, duration, and severity of testosterone deficiency but is not well documented. 2|⊕⊕◯◯
- We do not recommend using TRT alone to treat osteoporosis in hypogonadal men with high fracture risk (in the absence of documented effect on fracture risks), and we recommend to add specific antiresorptive drugs to the therapy, even if these men are receiving adequate TRT. 1|⊕⊕◯◯

Evidence

In young hypogonadal men (<25 years old), testosterone replacement therapy may prevent bone loss, reduce markers of bone resorption, and help to acquire peak bone acquisition (Laitinen *et al.*, 2012). Furthermore, in young hypogonadal patients with open epiphyses the effect of testosterone replacement on bone density may be more pronounced.

Besides, in elderly men, the effect of TRT on bone density seems to depend on the severity of testosterone deficiency. This was evaluated in a meta-analysis. The effect of TRT was considered significant at the lumbar spine and when using parenteral testosterone (Tracz *et al.*, 2006). Furthermore, in a recent randomized controlled trial, testosterone treatment increased BMD in hypogonadal men. Also in this study, the effect was more pronounced in the spine than in the hip (Snyder *et al.*, 2017). Importantly, there is no evidence that TRT reduces fracture risk in older men with normal or borderline low testosterone levels (Vescini *et al.*, 2016). Additionally, the role of testosterone replacement on top of antiresorptive treatment in hypogonadal patients at high risk of fractures is not established.

Antiresorptive therapy in patients receiving ADT

Statements

- We recommend starting antiresorptive treatment in ADT-treated prostate cancer patients with moderate to high fracture risk (see section on FRAX score). 1|⊕⊕⊕⊕
- We suggest close follow-up of ADT-treated patients with a low fracture risk. 2|⊕⊕◯◯

Evidence

Despite their high fracture risk, prostate cancer patients and hypersexuality patients on ADT remain undertreated for osteoporosis. A decrease in BMD is already observed following 6 months of ADT therapy. The longer the duration of ADT, the higher the fracture risk (Bienz & Saad, 2015).

Benefits of antiresorptive therapy on fracture risk are well established, and several antiresorptive drugs have been evaluated in these patients. Both bisphosphonates and denosumab have positive effects on BMD as well as on fracture risk. In most RCTs, antiresorptive therapy is initiated when ADT is started, to prevent ADT-related bone loss, also in men without osteoporosis. For some drugs, higher doses were used than in men with idiopathic osteoporosis. An overview is given in Table 4.

Remarks

Calcium/vitamin D supplementation alone, without an antiresorptive agent, is inadequate to prevent ADT-associated bone loss.

The risk of osteonecrosis of the jaw following antiresorptive treatment is overall considered very low but may be higher in the population of oncological patients. Therefore, dental evaluation before initiating therapy is recommended at the start of treatment.

In men with hormone-sensitive bone metastatic prostate cancer, bisphosphonates have not shown to decrease the rate of skeletal-related events (complications from bone metastases: pain, functional impairment, pathologic fractures). Denosumab has not been tested for this indication (Smith *et al.*, 2014).

Monotherapy with the anti-androgen bicalutamide results in a stable or increased BMD (Smith, 2002; Wadhwa *et al.*, 2009). These patients are not at risk of developing osteoporosis.

Follow-up

DXA is useful to follow up the efficacy as well as compliance of antiresorptive treatment. The frequency of DXA follow-up is however not well defined or established. In patients considered at low risk at baseline, a 5-year follow-up of bone status should probably be sufficient. In patients at higher risks, shorter intervals may be needed. In men treated with antiresorptive therapy, regular measurement of calcium, vitamin D, and kidney function is recommended.

CONCLUSIONS (SEE KEY MESSAGES)

Within the context of the andrological setting, bone health should receive full consideration in patients with hypogonadism and osteoporosis should be ruled out or treated based on specific partial or complete workup (Box 4 & Fig. 1).

List of all recommendations

- We recommend considering bone health in all andrological patients with documented hypogonadism at first visit. 1|⊕⊕◯◯
- We suggest assessing clinical aspects of bone health as reported in Table 1. 2|⊕⊕◯◯

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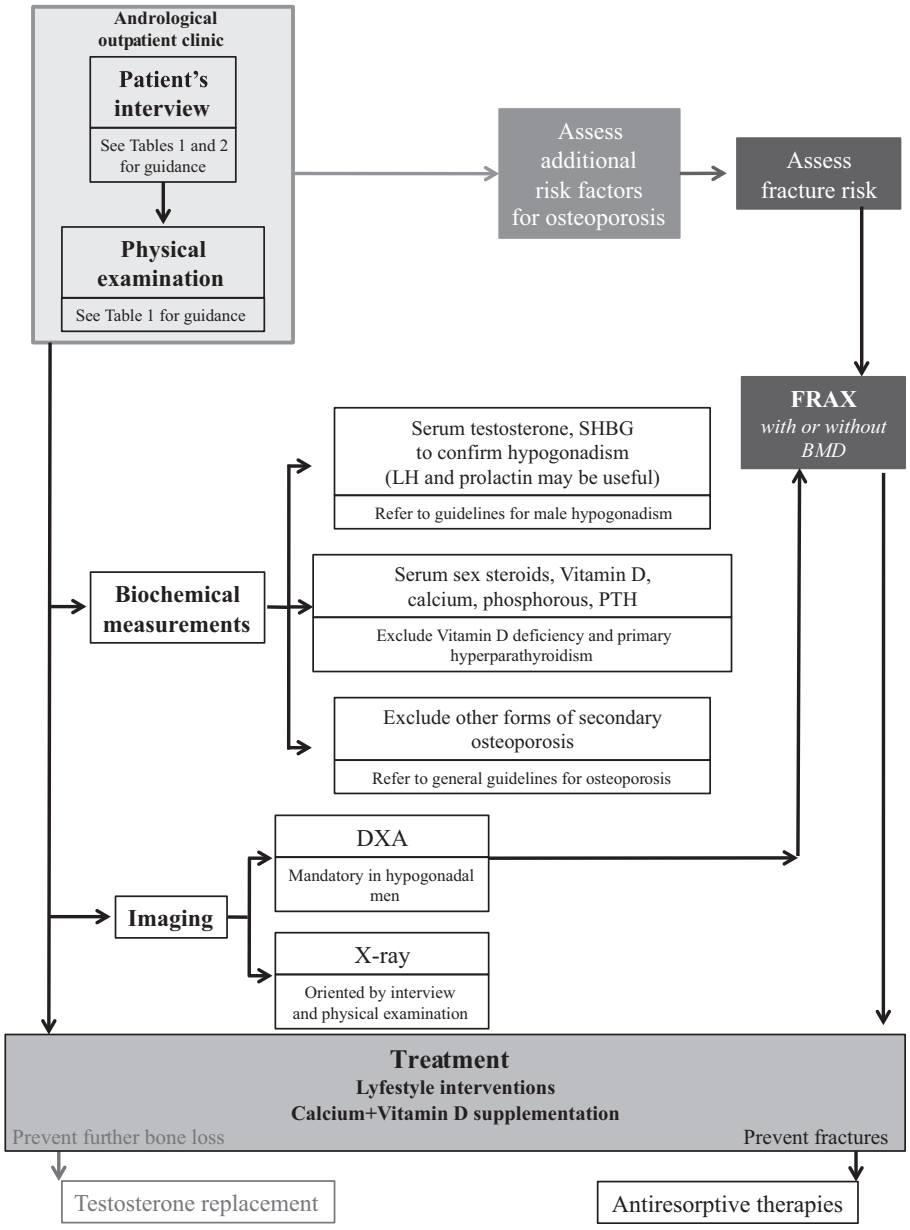

Figure 1 Workup for the assessment of bone health in the andrological outpatient clinic.

- We suggest including spine observation and follow-up of patient's height in the clinical workup. 2|⊕⊕◯◯
- We recommend having serum total testosterone measured twice on a morning blood sample. 1|⊕⊕⊕◯
- We recommend measuring again total testosterone and SHBG if only a single measurement documenting low testosterone is available. LH and prolactin are useful to better characterize hypogonadism. 1|⊕⊕⊕◯
- We do not recommend routine measurement of serum estradiol. 1|⊕⊕◯◯
- We suggest measuring estradiol only when a validated mass spectrometry-based method is available and in rare cases in which severe estrogen deficiency is suspected. 2|⊕⊕◯◯
- We suggest measuring serum 25(OH) vitamin D at baseline in all hypogonadal men, independently from their BMD. 2|⊕⊕◯◯
- We suggest measuring serum calcium (or calcium corrected for albumin when it is applied—see Appendix 2 for Web links), phosphorous, and PTH in all hypogonadal patients with documented low BMD. 2|⊕⊕◯◯
- We do not recommend the routine use of bone turnover markers in the management of male or hypogonadal osteoporosis. 1|⊕⊕⊕◯

Table 4 Overview of antiresorptive drugs in ADT patients

Drug	Dose	Refs
Zoledronic acid	4 mg IV every 3 months	Smith *et al.* (2003)
Risedronate	35 mg oral weekly	Choo *et al.* (2013)
Pamidronate	60 mg IV every 12 weeks	Smith *et al.* (2001)
Alendronate	70 mg oral weekly	Greenspan *et al.* (2007), Klotz *et al.* (2013)
Denosumab	60 mg SC every 6 months	Smith *et al.* (2009)

IV, intravenous; SC, subcutaneous administration.

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Box 4

Key message.

- **Every patient with confirmed or clinical suspicion of hypogonadism in andrological practice should have initial fracture assessment** on basis of history and clinical examination on top of gonadal status/testosterone measurement.
- **If fracture risk is considered low** (e.g., young age, no personal, or familial fracture history): a) follow clinical guidelines of hypogonadism; and b) if testosterone needed still, consider DXA (as marker of improvement in bone health).
- **If fracture risk is considered high** (e.g., old age, personal and/or familial history of fracture, very low serum testosterone, and/or indication for androgen deprivation): (a) plan DXA and consider spine X-ray; and (b) manage male osteoporosis independently of indication needed for testosterone replacement.

- We recommend BMD measurement by DXA in all hypogonadal patients with documented hypogonadism and/or serum testosterone <200 ng/dL. 1|⊕⊕⊕◯
- We suggest BMD measurement by DXA in all hypogonadal patients with slightly decreased serum total testosterone (between 200 and 300 ng/dL), especially in young patients or in patients with hypogonadal symptoms. 2|⊕⊕◯◯
- We recommend that all patients who need ADT (for prostate cancer or hypersexuality) should also be evaluated by DXA. 1|⊕⊕⊕⊕
- We suggest BMD measurement by DXA in men with a well-documented history of hypogonadism. 2|⊕⊕⊕◯
- We recommend X-ray of the dorsolumbar spine when osteoporotic fractures are suspected on the basis of patient's medical history, physical examination, and/or the presence of localized bone pain. 1|⊕⊕⊕◯
- We recommend using X-ray to confirm the diagnosis of severe osteoporosis. 1|⊕⊕◯◯
- We however do not recommend the use of X-ray for the diagnosis of osteoporosis or osteopenia. 1|⊕⊕⊕⊕
- We do not recommend the use of other techniques different than DXA and X-ray for the diagnosis of osteoporosis or osteopenia and osteoporotic fractures. 1|⊕⊕⊕◯
- We suggest calculating the FRAX score in all men with confirmed hypogonadism. 2|⊕⊕⊕◯
- In general, smoking cessation, a reduction in alcohol intake, and weight-bearing exercises are recommended. 1|⊕⊕◯◯
- We suggest introducing lifestyle interventions when hypogonadism is diagnosed or when ADT is started and should be continued throughout life. 2|⊕⊕◯◯
- We suggest increasing dietary intake of calcium if the dietary calcium intake is insufficient. 2|⊕⊕◯◯
- If dietary calcium intake remains inadequate and/or vitamin D serum levels are low, we suggest to initiate pharmacological supplementation with both calcium and vitamin D. 2|⊕◯◯◯
- We do not recommend monotherapy with either one of them. 1|⊕⊕◯◯
- We do not recommend the use of calcium/vitamin D supplementation as the only treatment for hypogonadal osteoporosis or androgen deprivation therapy-associated bone loss. 1|⊕⊕⊕◯
- We recommend starting antiresorptive therapy only in combination with calcium and vitamin D supplementation. 1|⊕⊕◯◯
- We recommend antiresorptive treatment in hypogonadal men at high fracture risk (see also our practical proposal in our clinical vignettes). 1|⊕⊕⊕◯
- We recommend TRT in young adult hypogonadal patients in order to prevent bone loss and to help acquire peak bone mass. 1|⊕⊕◯◯
- For the indication of TRT in other patient groups, we suggest to refer guidelines on male hypogonadism. The potential benefit of TRT on BMD and fracture risk will probably depend on the etiology of hypogonadism, age of onset, duration, and severity of testosterone deficiency but is not well documented. 2|⊕⊕◯◯
- We do not recommend using TRT alone to treat osteoporosis in hypogonadal men with high fracture risk (in the absence of documented effect on fracture risks), and we recommend to add specific antiresorptive drugs to the therapy, even if these men are receiving adequate TRT. 1|⊕⊕◯◯
- We recommend starting antiresorptive treatment in ADT-treated prostate cancer patients with moderate to high fracture risk (see section on FRAX score). 1|⊕⊕⊕⊕
- We suggest close follow-up of ADT-treated patients with a low fracture risk. 2|⊕⊕◯◯

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APPENDIX 1

List of available guidelines on the management of bone loss in men published in the last 10 years

Male Osteoporosis Guidelines	Year	Refs
Specific for male osteoporosis		
The Endocrine Society Guidelines	2012	Watts *et al.* (2012)
Toward a diagnostic and therapeutic consensus in male osteoporosis	2011	Kanis *et al.* (2011)
Advice in Generic (mainly female) Guidelines of Osteoporosis		
Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update from the American College of Physicians	2017	Qaseem *et al.* (2017)
Italian Society of Osteoporosis, Mineral Metabolism, and Bone Diseases	2016	Rossini *et al.* (2016)
(UK guidelines for postmenopausal osteoporosis and older men)	2013	Compston *et al.* (2013)
Japanese Society for Bone and Mineral Research	2013	Soen *et al.* (2013)
Polish guidelines for the diagnosis and management of osteoporosis: a review of 2013 update	2013	Gluszko *et al.* (2014)
2011 Guidelines for the Diagnosis and Treatment of Osteoporosis in Greece	2011	Makras *et al.* (2012)
Canadian Guidelines for Osteoporosis	2010	Papaioannou *et al.* (2010)
Australian guidelines for postmenopausal osteoporosis and older men	2010	https://www.anzbms.org.au/downloads/racgp_osteo_guideline.pdf
Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK (on behalf of the National Osteoporosis Guideline Group)	2009	Compston *et al.* (2009)
Advice in Generic (mainly female) Position Statements		
Italian association of clinical endocrinologists (AME) position statement: drug therapy of osteoporosis.	2016	Vescini *et al.* (2016)
The clinical diagnosis of osteoporosis: a position statement from the National Bone Health Alliance Working Group	2014	Siris *et al.* (2014)
Clinician's Guide to Prevention and Treatment of Osteoporosis (provided by expert committee of the National Osteoporosis Foundation)	2014	Cosman *et al.* (2014)
Vitamin D and Calcium Supplementation to Prevent Fractures in Adults: U.S. Preventive Services Task Force Recommendation Statement	2013	Moyer (2013)
Screening for Osteoporosis: U.S. Preventive Services Task Force Recommendation Statement (provided by the U.S. Preventive Services Task Force)	2011	U.S.-Preventive-Services-Task-Force, (2011)
Screening for Osteoporosis in the Adult U.S. Population ACPM Position Statement on Preventive Practice	2009	Lim *et al.* (2009)

APPENDIX 2

Useful online resources for the management of bone loss and osteoporosis in men

Resource name	Utility	Website (URL)
Free testosterone calculator	Calculation of free serum testosterone	http://www.issam.ch/freetesto.htm
Serum corrected calcium	Calcium correction for albumin	https://www.mdcalc.com/calcium-correction-hypoalbuminemia
Genant classification	Vertebral fractures classification	https://www.iofbonehealth.org/radiological-assessment-and-bone-turnover-markers
The Fracture Risk Assessment Tool (FRAX)	Fracture risk measurement	https://www.shef.ac.uk/FRAX/tool.jsp?lang=en
Dietary calcium	Esteem of dietary calcium intake	http://www.osteoporosis.ca/osteoporosis-canada-calcium-calculator/
eGFR calculator	Esteem of glomerular filtration rate	http://egfrcalc.renal.org

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