Late Onset Hypogonadism (LOH): bone health

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Abstract

Background. Bone health is underdiagnosed and undermanaged in men. Bone loss occurs in men with hypogonadism and in aging men. Thus, patients with a diagnosis of late onset hypogonadism (LOH) are at risk of osteoporosis and osteoporotic fractures.

Objectives. To provide an update on research data and clinical implications regarding bone health in men with LOH by reviewing literature articles on this issue.

Materials and Methods. A thorough search of listed publications in PubMed on bone health in older men with hypogonadism and was performed and other articles derived from the these publications were further identified.

Results. LOH may be associated to reduced bone mineral density (BMD). In a pathophysiological perspective, the detrimental effects of testosterone (T) deficiency on BMD are partly ascribed to relative estrogen deficiency and both serum T and serum estradiol (E2) need to be above 200 ng/dL and 20 pg/mL to prevent bone loss. The effects of exogenous T on BMD are controversial but most of the studies confirm that testosterone replacement therapy (TRT) increases BMD and prevents further bone loss in men with hypogonadism. No data are available on TRT and the prevention of fractures.

Discussion and Conclusion. In men with documented LOH a specific clinical work-up should be addressed to the diagnosis of osteoporosis in order to program subsequent follow-up and consider specific bone active therapy. TRT should be

started according to guidelines of male hypogonadism while keeping in mind that it may also have positive effects also on bone health in men with LOH.

Introduction

Bone health in men is a partially neglected health issue since it is less investigated than in the female counterpart[1-3]. Even the clinical trials investigating the efficacy of bone active drugs involve a smaller number of men than females and not all of these drugs, which are available on the market for the treatment of female osteoporosis, have been approved also for men by regulatory agencies[3,4]. At present, evidence from several studies have unequivocally proved that male osteoporosis i) is often secondary to other clinical conditions[3,5], ii) occurs later in life compared to women in the majority of cases[3], and iii) osteoporotic fractures are associated to higher morbidity and mortality in elderly men compared to women[1,6,7]. Among secondary osteoporosis, male hypogonadism is one of the most important risk factors and accounts for the progressive bone loss in aging men, especially in case of a diagnosis of late onset hypogonadism (LOH)[1,8]. Serum testosterone (T), in fact, decreases with advancing age in elderly men and the amount of serum estradiol (E2) tends to decrease accordingly[9]; the same occurs for bone loss during aging[1-3]. Traditionally, T was considered the main sex steroid acting on male bone, but starting from the Nineties the pivotal role exerted by estrogens started to rise[10-13] thanks to the description of the first cases of men with congenital estrogen deficiency due to estrogen resistance[14] and aromatase deficiency[15,16]. The observation that a condition of severe estrogen deficiency was constantly associated to the arrest of skeletal maturation, and to severe bone loss resulting in osteopenia or osteoporosis in adult

men with these rare diseases[17,18] opened the way to fully understand the role of estrogens on bone as well as on other male physiological processes[12,19-22].

Pathophysiology of T deficiency and its metabolites in bone

Sex steroids, both androgens and estrogens, exert direct and indirect effects on bone tissue and regulate bone homeostasis[23-25]. Estrogens derive from androgens after the aromatization of the A ring of androgens through the activity of the CYP19A1 enzyme, named aromatase, which is expressed in many male tissues[11,12,26].

Effects of T on bone

T exerts direct and indirect effects on bone[27-30]. Direct effects of T involves several cells within the bone; among them human mesenchymal stem cells, osteoblasts and osteocytes express the androgen receptor and are target cells for T[31]; *vice versa* osteoclasts are not target cells for direct action of T and androgens regulate osteoclast proliferation and activity indirectly through the modulation of the receptor activator of nuclear factor κ–B (RANK ligand)[27]. T and its metabolite dihydrotestosterone (DHT) exert anabolic action on osteocytes and osteoblasts by promoting cell proliferation and probably also their differentiation[32], but the latter effect is less clear[27,28]. Furthermore, T inhibits apoptosis of osteoblasts[33]. Locally produced androgens (i.e. DHT) within the bone contribute together with the circulating quote to support the direct effect of androgens on bone and account for different percentages of sex steroids within the tissue compared to blood concentration[29].

Indirect effect of androgens on bone cells may be mediated by several cytokines and by the local production of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) that are known to be under the control of T[27]. Other indirect effects on bone are mediated by the mechanical load exerted by the muscle masses surrounding the bone. As muscle mass depends on serum T and hypogonadism leads to sarcopenia this indirect effect is of great relevance for bone homeostasis[1,34,35]. Both hypogonadism[19,36] and aging[37] lead to physiological reduction of body muscle masses and sarcopenia in older men thus promoting bone loss due to mechanical strain[38] and postural instability, thus increasing the risk of fracture due to osteoporosis or increased incidence of falls[38,39] due to altered muscle-bone cross-talk[40].

Effects of E2 on bone

Estrogens in men exert their action through the binding to the ERs. Nuclear ER-alpha and ER-beta and the transmembrane G protein-coupled receptor GPR30 (GPER30) are expressed in human male tissue. The nuclear receptors account for genomic effects of estrogens, while the GPR30 transmembrane receptor accounts for non-genomic, rapid effects of estrogens[11,12,26].

In men locally produced estrogens in bone come from androgens thanks to aromatase that is expressed in fibroblasts and other bone cells (i.e. osteoblasts and osteoclasts)[12,41]; the same occurs in tissues surrounding the bone such as the adipose tissue and the bone marrow[26]. Circulating estrogens as well as locally produced

estrogens exert their effect on bone through the binding to both ER-alpha and -beta that are expressed in the following bone cells: osteoblasts, osteoclasts, and osteocytes[42], all these cell types express also GPER30[43,44]. Furthermore, estrogens increase osteocytes vitality and inhibit their apoptosis[45], induce apoptosis of osteoclasts[46], and inhibit their differentiation through the modulation of RANKL[42]. The final result is the decrease of bone resorption operated by osteoclasts[47]. On the contrary, estrogens promote/maintain bone formation by osteoblasts through an anti-apoptotic effect[48] and by stimulating their differentiation[49]. Apart direct effects, estrogens modulate other hormones and cytokines involved in bone physiology (indirect effects), among them the GH/IGF-1 network being one of the most important[50]. Finally, estrogens positively modulate the bone response to mechanical strain[51,52] similarly to what androgens[38,40] do.

LOH, relative estrogen deficiency and osteoporosis in men

In men, serum T progressively declines with aging[53] according to the decrease of testicular function, a condition which is common in elderly men[54]. On average serum T is below the lower end of the normal range in about 20% of the older men (>60 years)[55] while remains within the normal range in the majority of them[54]. There is, however, a great variability in the decline of both total and free serum T, accounting for interindividual differences and diverse trajectories of T decline over time[56].

The majority of large, prospective studies involving aging men such as the Baltimore Longitudinal Study of Aging (BLSA), the Massachusetts Male Aging Study (MMAS), the Osteoporotic Fractures in Men Study (MrOS), the European Male Aging Study (EMAS), the Rancho Bernardo Study (RBS), the InCHIANTI Study, the Tromsø Study, the Concord Health and Ageing in Men Project (CHAMP), the Health in Men Study (HIMS) found, on average, a decline of total serum T around 3 ng/dl per year[57,58]in aging men[9], which involves also both calculated serum free T and serum free T assayed by equilibrium dialysis[9]. This finding results in an increase of the prevalence of biochemical hypogonadism with advancing age[9,54]. The diagnosis of LOH, however, involves only a minority of cases of older men with low serum T, depending on the severity of serum T deficiency, the presence of symptoms of hypogonadism and concomitant comorbidities that may lead to functional hypogonadism[9,54,59,60].

In men with LOH the reduced amount of T precursor available for aromatization into E2 may result in relative estrogen deficiency[61], which may prompt the acceleration of the physiological process of bone loss occurring in aging[34,62,63]. By an elegant study design, Finkelstein *et al.* proved that the pharmacologically-induced serum T decrease below 200 ng/dL is constantly associated to a corresponding serum E2 fall below 10 pg/mL and to significant changes of both bone turnover markers and BMD[20] (Figure 1). This study proves that relative estrogen deficiency occurs in hypogonadal men and that it is responsible to a great extent for bone loss, whereas T

deficiency has a minor direct role[20]. Outside the context of experimental design of pharmacologically-induced hypogonadism, both serum T and E2 decline with advancing age[64-66] as demonstrated by both the MrOS and the EMAS studies. The occurrence of relative estrogen deficiency in aging men with LOH may depend on several factors[61]. First, the severity of hypogonadism obviously influences the amount of circulating serum E2. Second, several associated clinical conditions may modulate aromatase expression and estrogen production[61,67-69]. As an example, obesity may boosts estrogen production even in presence of low serum T in hypogonadal men through an increased rate of aromatization of androgens, thus preventing both relative estrogen deficiency and bone loss[68]. Third, individual genetic differences may predispose to relative estrogen deficiency on equal serum T levels[1]. Both polymorphisms of the ER-alpha gene[70,71] and of the gene encoding for the aromatase enzyme[72,73] are associated to bone loss in men. Individual genetic differences influencing the expression and activity of the aromatase enzyme have been well characterized in recent years[61,68,69,72,73] (Figure 1). By using a genome-wide association study and mendelian randomization analysis on a large number of men, several genetic variants of the aromatase enzyme resulted directly related to the amount of circulating E2 and BMD since the genetically determined increase of 1 pg/mL of serum E2 corresponded to a BMD increase of 0.048 standard deviation at lumbar spine[74]. The same experimental design proved that serum E2, but not T has a causal effect also on bone fractures[75]. The importance of relative estrogen deficiency as

pathophysiological process explaining several changes occurring in hypogonadal men as well as the need of keeping serum T and E2 above a certain threshold were strengthened thanks to these well-designed studies (Figure 1). Estrogen-related bone loss in men occurs especially when serum E2 is very low, similarly to what happens to postmenopausal women[9]. The first evidence came from cases of severe aromatase deficiency where characterized by serum E2 is undetectable leading to bone loss, [76] and exogenous E2 administration results in a dose-dependent increase of BMD[62]. The threshold for serum E2 below which the loss of BMD is relevant and the risk of osteoporosis and osteoporotic fractures increases has been estimated to be comprised between 15 and 20 pg/mL[20,23,34,47,77-83] (Figure 1). In older men with hypogonadism serum E2 remains higher if compared to the quite undetectable levels in postmenopausal older women (below 5 pg/mL),[9], but it may fall below 20 pg/mL[79], thus accounting for the development of osteopenia and osteoporosis. The threshold for serum T ensuring bone mass preservation seems to be 200 ng/dL[20,79](Figure 1).

LOH and Bone Mineral Density (BMD)

It is well-known that mild to severe hypogonadism in young adult men is almost constantly associated to reduced BMD and osteopenia/osteoporosis[4,84,85]. The effects of T on BMD remain, however, conflicting in elderly men who often display only slightly reduction of circulating T, that often is due to functional hypogonadism[60,86]. Several large cohort studies investigating sex steroids in aging

men, such as the BLSA, the MMAS, the inCHIANTI, and the HIMS study did not record data about bone health; in particular, BMD and osteoporotic fractures were not investigated[9,87]. Conversely, other large cohort studies, have investigated the relationships between sex steroids and BMD in aging men[1,2,8,9] showing that low serum T is associated to reduced BMDin older men with overt hypogonadism (total T<230 ng/dL; i.e. 8 nml/L) compared to eugonadal older men (EMAS study)[35,66,88]and that serum bioavailable T is directly correlated to BMD (RBS and the Tromsø Studies)[89-91]. Only few studies such as the CHAMP did not find any association among serum T, E2, SHBG, and bone health[92,93].

Studies on the relationships between circulating sex steroids and osteoporotic fractures in aging men are scanty and provide conflicting results[9] varing from no association (CHAMP and the Tromsø) between circulating sex steroids (total and free serum T, and serum E2) and fracture risk[90,93,94], to the association of an increased risk of nonvertebral osteoporotic fractures with both serum T and serum E2 such as in the MrOS study [95].. Thanks to studies performed in the last 20 years using immunometric assays[1,2,34,96] and those most recent using the gold standard liquid chromatography-tandem mass spectrometry (LC-MS/MS)[97-99] for serum E2 measurement the concept that E2 is the main sex steroid involved in the control of BMD maintenance in adult and older men is now textbook knowledge[21,34,44] (see above the paragraph on pathophysiologyfor more details). Accordingly,. both cross-sectional[70,89,100-103] and longitudinal studies [77,104]have disclosed a direct relationship between serum E2,

especially the bioavailable fraction, and BMD in men pointing out that relative estrogen deficiency rather than serum T decline *per se* is involved in bone loss[1,34,44]. Among them, the most important are the EMAS[88],RBS[89,105], and the MrOS[64]. In addition, the latter study showed also a direct role of serum E2 on fracture risk[95].

In clinical practice, serum T, E2, and SHBG should be considered, however, weak predictors of vertebral fractures in older men[106]. It should be considered, in fact, that most of these large cohort studies were not specifically addressed to investigate the relationships between sex steroids and bone as their primary endpoint, thus often failed to find an association[9]. Almost all the studies that had as primary endpoint the investigation of the role of sex steroids on bone in men have clearly demonstrated that low circulating T is associated to low BMD[77,102,107,108].

Bone health: clinical approach in men with LOH

Andrological consultation is a good opportunity to check general health status in men, including bone[4].

In presence of a diagnosis of LOH the investigation of bone health becomes mandatory[4,5]. The first step is represented by the clinical interview, which should keep information on past medical history with particular concern to general health and physical changes, endocrinological issues, lifestyle, ongoing or previous medications, and additional risk factors for osteoporosis (i.e. comorbidities) other than hypogonadism[4] (Figure 2). Physical examination should check the presence of skeletal

features associated to hypogonadism, such as eunuchoid skeletal proportions and the body composition paying particular attention to the presence of reduced muscle mass (sarcopenia), which is common in hypogonadal men[19,40,109]. Furthermore, specific features related to severe osteoporosis should be ruled out. Among them height changes, kyphosis, wall-to-occiput distance (>0 cm), rib-to-pelvis distance (<3 fingers), and tooth loss[110] are simple signs that may suggest osteoporosis and possible occult vertebral fractures[4,111].

Clinical examinations

In order to investigate bone health status in men with LOH further biochemical, hormonal and imaging examination may be performed.

Sex Steroids Measurements

Biochemical examinations should be addressed to gonadotropins, T and SHBG for the diagnosis of LOH, according to available guidelines[60,112].

As previously outlined, relative estrogen deficiency is clinically relevant for the development of osteopenia/osteoporosis in older men with LOH[1,20,61,68] but the measurement of serum E2 is not recommended in clinical practice since the commercially available assays are not accurate for measuring low values typical of men (20-40 pg/mL)[4,13,61,113], thus leaving the diagnosis of relative estrogen deficiency in men with hypogonadism still challenging[61]. Having serum E2 measured at baseline

may help, theoretically, to better stratify the risk of fracture and the effectiveness of TRT in normalizing not only serum T but also serum E2 (Figure 1), higher BMD being associated to higher serum E2 within the normal range for men[68]. Hopefully, the widespread diffusion of LC-MS/MS, which is the only accurate and reliablemethodology[114,115], among clinical laboratories[116,117] together with the standardization of LC-MS/MS reference ranges for serum sex steroids[117] will probably lead to the validation of this technique for the measurement of serum E2 in men also for clinical purposes in the next future.

At present, the measurement of serum E2 is not recommended in men in the diagnostic work-up of osteoporosis[4,112], hypogonadism[60,112,118,119] and in general in the routine, clinical assessment of the male patient[61] remaining confined to research or clinical settings for which the LC-MS/MS measurement is available or in rare cases in which one of the most accurate immunometric assay is available[120]. Only in this setting serum E2 may be useful to rule out/rule in relative estrogen deficiency in a man with LOH and as a reliable target of TRT[1,34,61].

Biochemical evaluation of bone metabolism

In men with LOH and documented low BMD (osteopenia or osteoporosis) serum calcium, phosphorous, vitamin D, and parathyroid hormone (PTH) should be checked in order to rule out other disorders of calcium/phosphorous metabolism [4,121,122].

Measuring markers of bone turnover are not mandatory, and their use should be confined to the monitoring of the effects of bone active therapy even though no clear evidence about their usefulness in the clinic is available[4,123].

Imaging

The gold standard for obtaining information on bone health in men is dual-energy X-ray absorptiometry (DXA)[4,111]. This simple, safe and rapid tool measures BMD at different skeletal sites (lumbar spine and femoral neck) and allows the diagnosis of osteopenia or osteoporosis when the t-score is between -1.0 and 2.5 or below -2.5, respectively[124,125]. A DXA examination at both lumbar and femoral site is mandatory for men with a long history of hypogonadism [1] and for older men with LOH and a serum T below 200 ng/dL since in these cases an impairment of BMD is highly probable[4,5,20,79](Figure 1). In men with LOH and serum T between 200 and 300 ng/dL DXA at both lumbar and femoral site is indicated in presence of symptoms of hypogonadism or if other risk factors for osteoporosis are present (Figure 2). Pitfalls of DXA measurement should be taken into account in order to minimize errors in the diagnostic interpretation of DXA report. Among them the most common are the coexistence of osteomalacia, previous fractures resulting in compacted bone tissue, severe scoliosis, vertebral deformities (e.g. osteophytes,), and inadequate operating procedures (e.g. machine calibration, patient's position)[126].

Other techniques for the measurement of BMD such as ultrasound and quantitative computed tomography (QCT) are not validated in clinical practice and are only useful in research settings[4,5,111,125,127].

X-ray of the spine is a simple and inexpensive examination, which is mandatory for patients with back pain or with documented signs or symptoms of reduction in height of the spine, such as height or abnormal wall-to-occiput distance[4,110] (Figure 2). X-ray of the spine allows confirming the diagnosis of severe osteoporosis while it is not useful for the diagnosis of osteopenia or osteoporosis[4]. Furthermore, X-ray of the spine allows better characterizing the type and severity of fracture according to the Genant classification of vertebral fractures[128] (https://www.iofbonehealth.org/radiological-assessment-and-bone-turnover-markers).

Fracture risk in men with LOH

Fracture risk assessment needs a careful collection of information from the male patient with a diagnosis of LOH in order to rule in/rule out additional risk factors that may modify the risk stratification (Figure 2).

All available data may be pooled all together in order to calculate the cumulative risk of fracture by using the Fracture Risk Assessment Tool (FRAX)® (https://www.sheffield.ac.uk/FRAX/)[129]. At the condition that the patient's interview is well-conducted and all information are available (Figure 2), FRAX is a simple and effective tool able to predict fracture risk in men both when BMD values are

included[130] or not[131] allowing to identify patients at high risk to develop fractures[132] and to choose adequate therapeutic options[125].

BMD measurement by DXA is also useful to establish the risk of fractures in men since low BMD is associated to an increased prevalence of future osteoporotic fractures at all sites in men[125,133,134]. Besides, change from baseline over time are able to predict future fractures in older men[135]. Accordingly, a 10-year risk of hip and major osteoporotic fractures obtained by FRAX > 3% >20%, respectively are a good threshold useful to decide starting bone active therapy in men older than 50 years[125].

Effects of T treatment on bone in LOH patients

During adulthood bone mass remains the same in men after the achievement of the peak of bone mass and begins to decline only after the age of 50, with a significant bone loss starting around the age of 70[1,44,61,136]. In young hypogonadal men T replacement therapy (TRT) prevents further bone loss and ensures the achievement of a physiological peak of bone mass[137]. The role of TRT in older men is, however, more controversial. In uncontrolled studies long-term TRT is able to improve BMD both at lumbar and femoral site[138-141] or at the femoral site only in other research settings[142] and to decrease markers of bone turnover[140]. In older men with osteopenia or osteoporosis and concomitant documented hypogonadism TRT leads to a greater increase of spine BMD in the treated group compared to controls[143]. The effects of TRT seem to be dose-dependent[140] and there is evidence that even T administration to eugonadal men is able to increase BMD by bringing serum T to levels near the upper end of the normal range[144]. Conversely, several studies did not find any significant effect of TRT on BMD[145-147] and on bone turnover markers[148].

Randomized controlled studies provided conflicting results. TRT is able to significantly decrease bone turnover markers compared to placebo[147], but no difference[147] or only a small improvement[149] was found in BMD in some studies. On the contrary, other randomized, controlled studies found a significant increase of vertebral and femoral BMD in the TRT group compared to placebo[150,151] coupled with changes in bone markers[150].

Meta-analyses of clinical studies/trials confirm that TRT is effective in increasing BMD at the lumbar spine[152,153] and in improving markers of bone turnover[152]. The effect of TRT at the femoral site remains doubtful even though a not significant positive trend has been shown[153]. The effect of TRT on BMD remains at least doubtful since the patients enrolled in various studies were heterogeneous regarding the presence/absence and the severity of T deficiency. Some studies enrolled patients with low-normal serum T above the lower end of the normal range (300 ng/dL)[145,146,148] or patients with various degree of T deficiency ranging from severe (<100 ng/dL)[138,154,155] to mild hypogonadism (between 200 and 300 ng/dL)[139-142,146,147,149,150,156]. However, the heterogeneity of serum T at baseline among studies and among subjects enrolled in each study together with different study designs (duration, end points, methodologies) do not help to reach robust evidence on the effects of TRT on bone and further studies are needed. T trail performed on men older than 65 and documented serum T below 275 ng/dL have found a significant effect of T on spine BMD and hip BMD[151]. The efficacy of TRT on BMD increase probably is proportional to the severity of hypogonadism and serum T at baseline and a greater effect on bone should be expected in men with very low serum T at baseline.

Antiestrogens (i.e. aromatase inhibitors and estrogen receptors blockers) have been suggested as a possible therapeutic alternative to TRT in men with LOH but their efficacy has not been proved to be equal to that of TRT, especially in long-term

treatment[157]. Furthermore, the number of studies with antiestrogens is limited as well as safety data. For these reasons antiestrogens remains off-label and are not recommended for the treatment of hypogonadism, including LOH[60,157]. In men with LOH and concomitant osteopenia or osteoporosis the use of antiestrogens may unbalance the E/T ratio and cause relative estrogen deficiency and are not considered safe for preventing bone loss and ensure bone health[34,61]. Accordingly, TRT increases BMD but the aromatase inhibitor anastrozole did not in a study involving older men with low serum T[158] and there is evidence that aromatase inhibitors can cause bone loss[157-159].

For all these reasons, TRT alone must not be considered as a treatment for osteoporosis in older men with low serum T[4,60,160]. In clinical practice, TRT should be offered to older men with a documented diagnosis of LOH according to available advice from clinical guidelines[60,112]. TRT should be started after having informed and discussed with the patients about possible risk and benefits and expected outcomes of TRT[59,60,112,119,161]. In the clinical context of LOH, TRT may have beneficial effects on bone health too but an impaired bone status should not lead the decision to start TRT since the latter must be based on the complex of both signs and symptoms (not solely the impaired BMD) of hypogonadism together with the evaluation of potential risks and benefits[4,60,84,112]. TRT in men with LOH and osteoporosis may help preventing further bone loss and may increase BMD but to a lesser extent than bone active drugs[162]. Of note, TRT has no documented effect on the prevention of fractures

and for this reason cannot be considered a therapy for the treatment of osteoporosis. All formulations of exogenous T such as transdermal[138,156], oral[154], and intramuscular are able to act on bone[60,148]. Men with LOH treated with TRT should expect that TRT may help in preventing further bone loss and increase BMD especially in men with very low serum T at baseline[146]. In order to have beneficial effects on bone TRT should ensure serum T levels at least above 200 ng/dL[20,79] and, if accurate assays for estradiol are available, a serum E2 above 20 pg/mL[1,34,61,68,69] in order to exert a protective role on bone (Figure 1). In this perpective serum T and E2 may be considered reliable targets of TRT for bone health[34,61,68].

Follow-up

Follow-up of men with LOH should also be addressed to bone health in men with no osteopenia or osteoporosis at first or previous visits and interview focusing on bone health should be repeated at each visit (Figure 2). Furthermore, DXA remains the gold standard to monitor BMD over time and may be repeated every two to three years, depending on patient's health status and risk factors for osteoporosis.

In patients on treatment with active bone drugs it is important to check about patient's compliance to therapy. Clinical investigation should include regular measurement of calcium, vitamin D, and kidney function. Bone turnover markers may be useful for checking efficacy of bone active therapy even if they are not mandatory.

Physical activity and prevention of further bone loss

Among lifestyle changes that may be beneficial for bone health (Figure 2), physical activity merits to be considered in a comprehensive way in men with LOH for its beneficial effects on muscle mass, skeletal trophism (see above the paragraph on pathophysiology for details) as well as its direct effects on T secretion. Accordingly, physical activity acts in a synergic fashion together with T by increasing and ensuring muscle mass and both the muscle contraction during physical activity and the muscle mass itself exert an anabolic action on bone through enhanced mechanical load[163-165]. Besides, physical exercise is able to increase serum T after short time[166,167], thus supporting the concept that physical activity and serum T take part to a virtuous circle able to prevent bone loss[165]. In addition, physical activity is effective in preventing falls in older patients[165]. For all these reasons, the prescription of physical activity and exercise should be part of the therapeutic approach to the older man with LOH in order to ensure bone health and prevent fractures[4,165,168].

Treatment of osteopenia/osteoporosis in men with LOH

After the diagnosis of osteoporosis, a man with concomitant LOH requires a specific therapeutic approach which needs to be tailored according to patient's clinical data. In men with LOH and a diagnosis of osteoporosis a specific treatment with a bone active drug is indicated, according to guidelines and expert advices for the treatment of male osteoporosis[3-5,160]. Among them bisphosphonates (zoledronic

acid, alendronate, risedronate, and pamidronate), teriparatide or PTH analogues, and denosumab are all approved by regulatory agencies for the treatment of osteoporosis in men[4,160]. These drugs should be prescribed in association to calcium plus vitamin D supplementation. In men, the treatment with calcium and vitamin D is indicated also in case of osteopenia when active bone therapy is not yet necessary[4,160,169]. Lifestyle changes and behavioral advice aiming to prevent falls are also indicated in men with osteoporosis[3-5].

Unresolved Issues

The interpretation of DXA measurement in men suffers from the absence of normative values obtained from male populations. Most of the data used for obtaining reference ranges and for the calculation of t-scores comes from female populations, thus there is no consensus on BMD-based definition of osteoprosis[1,170]. Future studies are needed in order to consider the risk of fracture based on BMD values by considering also sexual dimorphism of the skeleton[23,44] and avoiding to transpose to men what we have learnt from women without considering differences between the two sexes in terms of bone pathophysiology[171]. To do this more stringent criteria based on validated male reference ranges for BMD are required in order to appropriately diagnose and manage osteoporosis in older men.

Concerning the role of TRT on the prevention of fractures there are no available data. However, TRT is effective in ensuring bone anabolism, in preventing

sarcopenia, and in improving physical performance and all these effects defend against both frailty and falls, that are known factors involved in the occurrence of fractures, especially the femoral one[40].

There is a lack of data concerning both the possible use of estrogen treatment in men and in particular in men with hypogonadism[61]. At present, we have indirect information on estrogen effects on bone from rare cases of men with aromatase deficiency showing that physiological doses of exogenous E2 are able to increase BMD in a dose-dependent way[62,76]. Little is known about the efficacy of selective ERs modulators (SERMs) in men and suggest that raloxifene is no so effective as E2 in men with aromatase deficiency[172].

Conclusions

The assessment of bone health should be included in the clinical work-up of men with LOH bearing in mind that osteoporosis is undermanaged and underdiagnosed in older men and remains less investigated by researchers than in the female counterpart. Bone health, in fact, may be considered a rare case of gender health inequality favoring women rather than men[2,3]. Normative data obtained by studies on male population are urgently need for both DXA reference values and FRAX risk calculation in order to better tailor the diagnosis and the follow-up of men with osteoporosis. Andrological consultation performed in men with LOH represents an opportunity for male health[173] including bone[4].

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Legends

Figure 1. Circulating sex steroids and bone pathophysiology in men: relationship between serum T, E2, individual factors involved in the conversion of T into E2, putative thresholds for serum T[20,79] and E2[20,34,47,80-82], and bone health.

Figure 2. Information and issues to be covered during medical interview and at each visit.

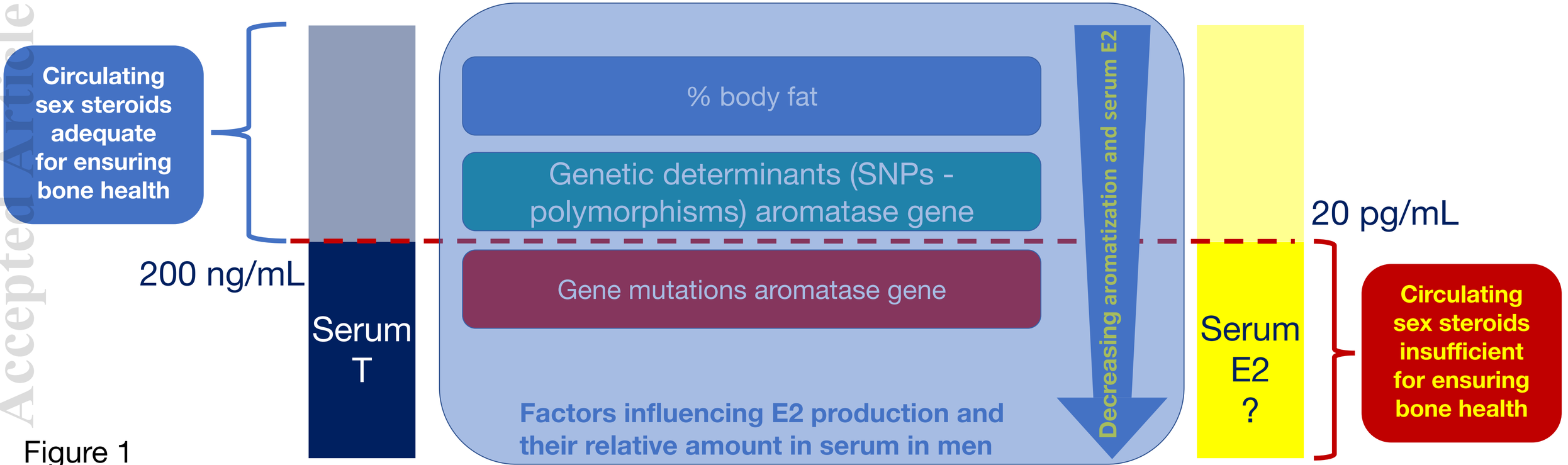

Figure 1

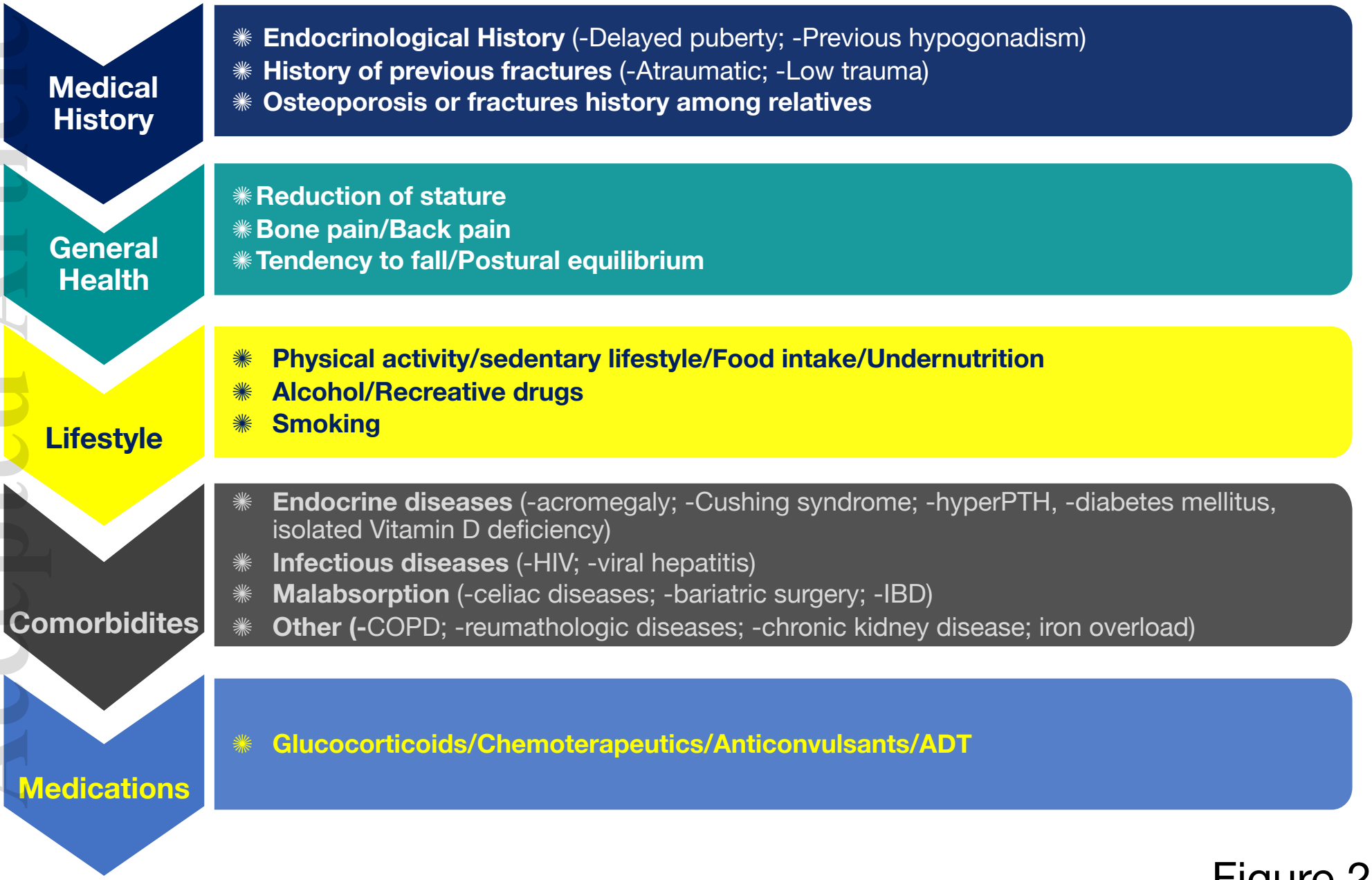

Figure 2