REVIEW

Osteoporosis and bone metabolism in patients with Klinefelter syndrome

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Abstract

Low bone mass is common in men with Klinefelter syndrome (KS), with a prevalence of 6–15% of osteoporosis and of 25–48% of osteopenia. Reduced bone mass has been described since adolescence and it might be related to both reduced bone formation and higher bone resorption. Although reduced testosterone levels are clearly involved in the pathogenesis, this relation is not always evident. Importantly, fracture risk is increased independently from bone mineral density (BMD) and testosterone levels. Here we discuss the pathogenesis of osteoporosis in patients with KS, with a particular focus on the role of testosterone and testis function. In fact, other hormonal mechanisms, such as global Leydig cell dysfunction, causing reduced insulin-like factor 3 and 25-OH vitamin D levels, and high follicle-stimulating hormone and estradiol levels, might be involved. Furthermore, genetic aspects related to the supernumerary X chromosome might be involved, as well as androgen receptor expression and function. Notably, body composition, skeletal mass and strength, and age at diagnosis are other important aspects. Although dual-energy x-ray absorptiometry is recommended in the clinical workflow for patients with KS to measure BMD, recent evidence suggests that alterations in the microarchitecture of the bones and vertebral fractures might be present even in subjects with normal BMD. Therefore, analysis of trabecular bone score, high-resolution peripheral quantitative computed tomography and vertebral morphometry seem promising tools to better estimate the fracture risk of patients with KS. This review also summarizes the evidence on the best available treatments for osteoporosis in men with KS, with or without hypogonadism.

Key Words

- osteoporosis
- hypogonadism
- bone
- Klinefelter
- testosterone

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Introduction

Klinefelter syndrome (KS) is the most frequent chromosome disorder in men (1, 2, 3, 4) and the most common genetic cause of male infertility (5) It has an estimated frequency of 1:500 to 1:1000 men, with a median prevalence of 1:600 (6)–1:660 men (7), although it is often under-recognized and, due to that, it has an expected increasing prevalence (8, 9). Moreover, KS is the most frequent cause of hypergonadotropic hypogonadism in men (10).

Most KS patients (80–90% of cases) have a 47,XXY karyotype (2, 8, 10). Higher-grade aneuploidies, such as 48,XXXY or 48,XXYY, structurally abnormal X chromosome or mosaicisms, such as 47,XXY/46,XY represent the remaining 10–20% of cases (2, 8, 11). While KS and higher-grade aneuploidies both involve testicular dysgenesis with hypergonadotropic hypogonadism, they differ in many clinical features so some authors proposed to consider them as two distinct conditions (12, 13).

The prevalence of KS is about 3–4% among infertile males and 10–12% in azoospermic patients (2, 12). Nevertheless, KS remains (2, 12) largely undiagnosed even among infertile men (1, 14, 15) and, in general, about two-thirds of cases remain unrecognized (7, 11, 16). This is due mainly to substantial variation in clinical presentation

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and insufficient professional awareness of the syndrome itself (5). Moreover, the mean age of diagnosis is often late for a congenital disorder, in the mid-30s (7), and the syndrome in the majority of cases is diagnosed during the evaluation of couple infertility (12).

KS is peculiar, as there is not a single, classic phenotype that can describe it (10, 11, 16). The clinical features of KS commonly include hypergonadotropic hypogonadism, small testes, and infertility (17). Moreover, other manifestations include neurocognitive, psychosocial, cardiovascular, metabolic, malignancies, venous thromboembolism, and bone-related conditions (1, 17).

This review deals with osteoporosis, which is frequent in subjects with KS, a condition representing a growing public health problem with a noteworthy impact on the quality and quantity of life (18). It is defined as a silent skeletal disorder characterized by an increased risk of fracture, due to alterations in bone density and bone quality (19).

Osteoporosis in subjects with KS: definition and prevalence

Dual-energy x-ray absorptiometry (DXA) is the standard technique to measure bone mineral density (BMD) and the gold standard technique for the diagnosis and monitoring of osteoporosis. The most analyzed areas are the proximal femur, the lumbar spine, and the distal radius (20). The presence of osteoporosis and/or osteopenia is defined based on the value of T-score, which represents the difference of BMD from the average bone density of healthy young adults, and of Z-score, which uses the average bone density of people of the same age, sex, and size as a comparator. In particular, a T-score of –<2.5 and lower, is defined as osteoporosis, whereas a T-score between –1.0 and –2.4 is defined as osteopenia. Z-score is used for people <50 years and a value lower than –2 is defined as 'BMD below the expected range for age' (21).

DXA also allows measuring the trabecular bone score (TBS), a parameter which is related to the 3D features of the bone and the trabecular characteristics. TBS is a measurement of the variation in gray-level texture between adjacent pixels in two-dimensional projection images. It can be interpreted from the same set of images obtained from DXA, yielding more information on bone quality without additional cost or radiation on the patients. TBS reflects bone microarchitecture, as it correlates with bone volume, connectivity density, trabecular number, and also cortical thickness (22). In particular, an elevation of TBS level is related to fracture-resistant microarchitecture, whereas a low TBS is related to fracture-prone microarchitecture (23).

DXA can also be used to evaluate lateral images of the spine from T4 to L4 to detect fractures of the vertebral bodies. Vertebral fracture assessment (VFA) may improve fracture risk evaluation, since many patients with vertebral fractures may not have a BMD T-score classified as osteoporosis. This procedure involves less radiation and is less expensive than a conventional x-ray examination but performs comparably to traditional radiographs (24).

Other techniques used to evaluate BMD include quantitative ultrasound, quantitative computed tomography, applied both to the appendicular skeleton and to the spine, peripheral DXA, digital x-ray radiogrammetry, radiographic absorptiometry, and other radiographic techniques, as reported in Table 1 (25, 26, 27, 28, 29, 30).

Over the past years, a series of meta-analyses have been undertaken to identify additional clinical risk factors that – apart from BMD – may be used in case-finding strategies, to predict the risk of fractures in patients with osteoporosis. The Fracture Risk Assessment tool (FRAX® tool) analyzes some specific clinical risk factors to predict the 10-year risk of fractures (25).

Studies using DXA to determine BMD and T- or Z-score reported a prevalence of 6–15% of osteoporosis and of 25–48% of osteopenia in KS patients (31) or a presence of both osteopenia/osteoporosis in about 40% of patients with KS (1), mostly because of both reduced bone formation and higher bone reabsorption (32).

More recently, vertebral fractures and impaired TBS have been found in more than 20% of subjects with KS, independently from BMD (33). Similarly, using the FRAX score, no significant differences in the 10-year risk of major fractures and hip fractures were found between fractured and non-fractured patients (34).

Bone mineral status has been evaluated also in adolescents with KS. In 1993, Eulry *et al.* demonstrated that in young patients with non-treated KS the BMD was significantly lower than age, weight- and height-matched control males (35). More recently, Stagi *et al.* reported that 17.5% of KS children and adolescents have a low bone mineral status when compared with controls (36). The aetiopathogenesis of this impaired bone mineral status in KS young patients may be multifactorial, including the specific bone characteristics related to this genetic syndrome and hormonal and environmental factors. Importantly, reduced BMD early in life might compromise the reaching of the BMD peak at the end of puberty, with

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Table 1 Main techniques, besides DXA, used to evaluate BMD.

Technique	Utility	Problematic issues
Calcaneal QUS	Portable, easy to handle, lower in cost, no ionizing radiation	Different cut-off points of T-score in QUS measurement, different ranges according to the population of interest and the device used
QCT	High sensitivity in diagnosing osteoporosis, monitoring the bone density changes, and evaluating the bone trabecular microarchitectural and mechanical property simultaneously; it can obtain important clinical information besides bone quality	High levels of radiation, not always available in I- and II-level medical centers
Peripheral DXA	Portable, uses very low levels of radiation and correlates well with BMD at other sites	Further studied required, not always available in I- and II-level medical centers
Digital x-ray radiogrammetry	Estimation of BMD shown to be associated with fracture risk, a method easy to implement in acute or semiacute settings	Further studies required, indirect method of BMD measurement
Phalanges radiographic absorptiometry	Self-contained system, portable, easy to manage, and associated with a low radiation dose	Further studied required, not always available in I- and II-level medical centers

BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; QCT, quantitative computed tomography; QUS, quantitative ultrasound.

long-term consequences and a higher risk of osteoporosis and fractures later in life.

Testosterone and bone health in subjects with KS

Testosterone is clearly the major testicular factor influencing bone metabolism (1), having a direct effect on osteoclasts, osteoblasts, and osteocytes and promoting periosteal bone formation during puberty and reducing bone resorption during adult life (31, 37). Those effects lead both to higher bone size and bone strength in men with respect to women and are mediated directly through the androgen receptor (AR) and indirectly through the estrogen receptor (ER) after the transformation of testosterone to estradiol by the aromatase enzyme (32, 37).

In detail, testosterone modulates bone metabolism throughout life in males (38). The increase in the production of sex steroids at puberty induces and increases bone mineral acquisition and contributes to the establishment of sex differences in bone growth. From mid-puberty onward, boys develop a larger periosteal perimeter than girls, whilst girls have more endocortical apposition (39). Moreover, men gain more bone mass during growth and lose less of it during aging than women. The traditional hypothesis is that in males androgens stimulate periosteal bone formation, whereas estrogens in females inhibit periosteal bone formation (40). Androgens, in fact, through the AR pathway, preserve or increase trabecular bone via suppression of trabecular reabsorption, thus reducing trabecular spaces and, therefore, increasing trabecular number (41). Previous studies in rats and in mice with *AR* gene mutations confirmed this evidence. Insensitivity to testosterone, or genetic manipulation of the *AR* gene to reduce expression of the receptor, in fact, induced a reduction in periosteal bone apposition and an increase in trabecular bone reabsorption (42). The role of testosterone is, therefore, fundamental in bone maturation at the end of puberty for bones to reach their peak mass, and during adult life to maintain it. Other than through a direct effect on the bone, testosterone exerts its beneficial effect on skeletal growth and homeostasis by increasing mechanical loading (42). Testosterone increases muscle mass and strength, which are fundamental for bone health.

As a consequence of the effects of testosterone on bone metabolism, hypogonadism is the main cause of secondary osteoporosis in males, being found in about 15% of men with osteoporosis (31) and men with hypogonadism have a significantly lower BMD than age-matched men without hypogonadism (43).

Therefore, osteoporosis in subjects with KS is easily attributed to the hypogonadism that these subjects often manifest. Indeed, there are much data on the role of testosterone in the determination of BMD and osteoporosis. For example, long-term testosterone replacement therapy (TRT) reduces the incidence of vertebral and femoral fractures and improves BMD (44, 45). Moreover, TRT has been shown to increase the spinal and femoral BMD, with a more evident effect in patients with lower serum testosterone levels (46). Moreover, TRT is associated with a meaningful reduction of bone resorption markers (46). Piot *et al.*, in a recent study (45), showed how,

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after 30 months of TRT, KS patients presented higher spine BMD and higher relative appendicular lean mass index, with a noteworthy increase of both cortical and trabecular bone parameters evaluated.

Early T treatment, in patients with KS, is associated with a higher proportion of normal values BMD, whilst late T treatment might indeed be associated with lower BMD values (47), further suggesting low T levels before or during puberty might cause inadequate bone development and low BMD and that only early T substitution might prevent bone mineral deficiency.

However, the relation between testosterone and bone health in patients with KS is indeed not so clear. As a matter of fact, low BMD and fragility fractures have a similar prevalence in hypogonadal and eugonadal subjects with KS, suggesting that bone loss in KS might be, at least in part, independent of the presence of hypogonadism. Furthermore, even prolonged TRT does not completely reverse the decreased bone mass in hypogonadal men with KS (48, 49).

A meta-analysis of TRT in patients with KS (50) confirmed the limited role of testosterone treatment on bone health in KS patients. In fact, testosterone treatment causes a significant increase in lumbar, but not in femoral neck BMD. Similar results have been observed in a recent meta-analysis that reported the effect of testosterone supplementation on bone parameters in hypogonadal non-KS patients (46). The study demonstrated that TRT increases BMD, particularly at the lumbar spine level when the duration of the treatment is long enough to allow the anabolic effect of testosterone and estrogens on bone metabolism to take place.

Importantly, no studies have been published about the effect of TRT on fractures in hypogonadal men, so the real contribution of testosterone treatment in these patients on preventing osteoporotic fracture is still debated. Other factors beyond testosterone reduction should be therefore considered in the pathogenesis of osteoporosis in KS patients. These factors might be important in determining bone health in subjects with KS and normal testosterone levels, as well as they can contribute to cases of low testosterone concentrations.

Endocrine modulation of bone mass in subjects with KS beyond testosterone

Vitamin D

When considering the hormonal milieu in patients with KS, we must underline that KS is not only associated with testosterone deficiency, but – in a wider perspective – it is a cause of global impairment of the testicular function. Leydig cells, in fact, under the control of LH/hCG, also produce the peptide hormone insulin-like factor 3 (INSL3) and express CYP2R1, a 25-hydroxylase enzyme that converts the inactive cholecalciferol to 25-OH-D3 (calcifediol), which can be further hydroxylated to the active form $1,25(OH)_2$-D3 by renal 1-hydroxylase. Therefore, part of the 25-OH-D3 derives from correct testis function other than classical 25 OH-activation from the liver (37).

The physiological importance of CYP2R1 expression in the testis clearly indicates a pathophysiological link between testiculopathy, reduced levels of 25-OH-D3, and alteration of the bone status (51). Initial studies analyzing the expression of CYP2R1 in the testis and on male patients who underwent bilateral and unilateral orchiectomy and infertile patients suggested that the testis contributes to about 60% of the 25-hydroxylation of cholecalciferol and that men with testicular damage are at high risk of hypovitaminosis D, low BMD, and osteoporosis (52).

These studies have been confirmed later also in the general population and the general consensus nowadays is that 25-OH-D3 levels might represent a marker of Leydig cell function, being reduced not only in men with low testosterone (both primary and secondary hypogonadism) but also in men with subclinical hypogonadism.

Vitamin D is essential for bone health and calcium metabolism, as it increases the absorption of calcium and phosphate in the intestine, calcium reabsorption in the renal distal tubules and has a crucial role in the growth and development of bones and teeth.

Previous studies reported that 25-OH-D3 is often reduced and PTH is increased in subjects with KS (36). Furthermore, subjects with KS, for the same testosterone levels, have lower BMD in the presence of a reduction in vitamin D levels. Moreover, treatment with testosterone and calcifediol induced an increase in lumbar BMD and lumbar T- and Z-score significantly higher with respect to patients treated with testosterone alone (49).

Insulin-like factor 3

Together with vitamin D, insulin-like factor 3 (INSL3) has an anabolic role on the bone acting on osteoblasts and osteocytes, acting through the G-protein coupled receptor RXFP2 (37).

INSL3 is not acutely regulated by the HPG axis but it is constitutively secreted by mature and differentiated Leydig cells, and so its levels directly depend on the number and

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state of these cells (53). Therefore, INSL3 could serve as an ideal marker of Leydig cell differentiation and function.

INSL3 declines gradually with aging, reflecting a slow progressive loss of adult Leydig cells (54). Moreover, there are some testicular endocrine disorders and pathophysiological conditions in which the INSL3 levels are reduced in adult men. Among these, one is a history of cryptorchidism since it can be associated with Leydig cell dysfunction (55). INSL3 is low also in many diseases with undifferentiated or altered Leydig cell status, such as testicular neoplasia (56), hypogonadotropic hypogonadism (due to lack of LH stimulation on Leydig cells) (53), and primary hypogonadism with testicular Leydig cell impairment (e.g. anorchid men or KS) (53, 57), Moreover, low INSL3 values can be observed in several patients with subclinical hypogonadism (elevated LH with normal testosterone), suggesting the presence of testicular endocrine impairment (58).

Serum INSL3 reflects chronic hypogonadal status and is associated with reduced sexual function, BMD, and physical activity, as well as increased occurrence of hypertension, cardiovascular disease, cancer, and diabetes

In bone tissue, INSL3 induces osteoblast proliferation, differentiation, and production of osteoblastic bone formation markers, such as osteonectin, osteocalcin, and alkaline phosphatase (59). Furthermore, INSL3 reduces the release of sclerostin from osteocytes, further inducing the proliferation of osteoblasts (60). Thus, INSL3 appears to be noteworthy for the balance between deposition and resorption of the skeletal matrix, stimulating bone mineralization and maintenance of bone mass (60).

Importantly, INSL3 has an anabolic effect also on the skeletal muscle (60) and lack of INSL3 activity resulted also in reduced contractile force. According to this evidence, the complex INSL3/RXFP2 has a role in protein turnover, thus contributing to muscle wasting in male hypogonadism (61).

Therefore, low INSL3 level might be a determinant of low BMD in subjects with KS. Moreover, low levels of INSL3 may explain the limited efficacy of TRT alone on bone status in KS (33).

Estrogens

Human and rodent studies have shown that estrogen is involved in the regulation of bone development and maintenance also in males (62, 63, 64). Furthermore, serum E2 levels are strongly associated with both BMD and fracture risk in men (65, 66). Estrogen deficiency, which leads to decreased bone mass after menopause in women, is even proposed to be a causal effect of male age-related bone loss (67). In addition, a causal effect of serum E2 levels on both BMD and fracture risk in men has been demonstrated (68, 69).

Finally, studies in AR and ER-knockout mice showed that periosteal and cortical bone mass acquisition is regulated by both receptors (70). These findings suggest at least a role of aromatization into estrogens in the process of the androgen action on periosteal growth and cortical bone.

Even if estradiol levels are generally normal or high in KS, low estrogen levels have been related to decreased bone mass also in these patients (35) and estradiol levels are inversely related to the rate of bone loss (71). However, these data have not been replicated, and firm conclusions on this possible pathogenetic mechanism cannot be made.

Follicle-stimulating hormone

Follicle-stimulating hormone (FSH) has been suggested to have a role in stimulating bone resorption (72, 73, 74, 75), by binding to its receptor FSHR on osteoclasts. Furthermore, FSH may negatively regulate osteoblast differentiation from mesenchymal stem cells (76).

FSH plasma concentrations are increased in men with primary hypogonadism and in menopausal women with osteoporosis; however, a direct effect of FSH on the bone is not easily discernible, as osteoporosis in these cases is easily attributed to low sex hormone levels. Indeed, clinical studies about this hypothetical role of FSH on the bone in humans reported conflicting results. In fact, studies involving osteoporotic men (77) and patients on androgen deprivation therapy for prostate cancer (78) suggested that high FSH levels might have a detrimental effect on the male bone. On the other hand, no significant changes have been observed in bone mass in patients with infertility and high FSH but normal testosterone levels (79). More recently, Giovannelli *et al.* (80) analyzed the bone mass in patients with KS, hypogonadotropic hypogonadism, or hypergonadotropic hypogonadism. After adjusting for potential confounders (age at diagnosis, BMI, smoking habits, degree of hypogonadism, and 25 OH vitamin D levels), the authors reported that non-KS patients with hypergonadotropic hypogonadism showed significantly lower lumbar spine BMD and tended to show lower femoral neck BMD values, as compared to those with hypogonadotropic hypogonadism. According to these data, a potential negative effect of FSH excess on the male bone mass may be considered, especially at the spine.

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In men with KS, lumbar spine BMD was significantly lower than in those with non-KS hypergonadotropic hypogonadism, which might reflect both the effect of long-lasting FSH excess (starting from puberty) on trabecular bone and the simultaneous presence of other pathogenetic factors of osteoporosis in KS, as mentioned earlier. Indeed, more data are needed to clarify the possible contribution to low bone mass and fracture risk of elevated FSH in subjects with KS, considering that increased levels of FSH are a hallmark of this syndrome and such increased levels start in mid-puberty and are observed also in subjects with normal testosterone concentrations.

The androgen receptor

A specific pathogenetic role for osteoporosis in KS has been postulated for genetic factors and the possible role of the AR has been widely highlighted in this perspective. The AR function and sensitivity might in fact modulate the effects of testosterone on the bone (31).

The *AR* gene is located on the X chromosome. As a consequence, it is present in double copy in 47,XXY KS. Moreover, a nonrandom X inactivation in men with more than one X chromosome has been reported (81). Furthermore, the *AR* gene contains the highly polymorphic CAG repeat, the length of which is inversely correlated with the sensitivity to androgens (82). Therefore, in KS patients, the CAG repeat length depends on the inactivation rate of the two X-chromosomes, and the effective CAG repeat value in heterozygous KS men is calculated as an X-weighted biallelic mean (83). Starting from these premises, different clinical outcomes and the response to testosterone therapy (BMD, gynecomastia, testes and prostate volume, hemoglobin concentration) have been associated with *AR* CAG length in KS, and a negative correlation between BMD (phalangeal ultrasound) and the X-weighted biallelic mean of CAG repeats has been documented (83). However, conflicting results have been reported. By analyzing 112 men with KS, we found that the mean CAG repeat length calculated after X-chromosome inactivation analysis was not different between patients with normal and low bone mass, suggesting that the CAG polymorphism of the *AR* gene seems not to contribute to the decreased bone mass in KS (84).

Other than CAG repeat length, AR expression could play a role in KS. In fact, a reduced AR expression in patients with KS has been reported in peripheral blood (85), testis (86) and testicular smooth muscle cells. (87) Thus, low BMD could be attributable to lower AR expression in the bone but, unfortunately, data on bone AR expression in KS are lacking. Indeed, a potential decrease in AR expression in the bone could also explain the frequent ineffectiveness of TRT in increasing BMD in KS. Besides, as differences in androgen signaling and AR expression in vertebral (trabecular) and femoral (cortical) bone are well known, a reduced AR expression in bone generally results in a further decrease in BMD of trabecular rather than cortical bone, a finding which is consistent with previously published data (84).

Role of skeletal muscle and body composition

We have previously discussed the role of testosterone, INSL3, and vitamin D on bone mass. Nevertheless, one has to consider that the bone function is strictly connected to that of the skeletal muscles and both testosterone and INSL3 increase muscle mass and strength (37).

It is well known that hypogonadal patients frequently report a reduction in muscle bulk and strength (88). Testosterone plays an important role in muscle metabolism and strength. AR is widely expressed in myonuclei and satellite cells (89, 90). Testosterone has an effect on myogenesis and muscle hypertrophy by increasing protein synthesis and inhibiting protein degradation in muscle cells (91) and promoting mitotic activity and differentiation of satellite cells (92). Numerous *in vitro* studies have demonstrated the anabolic actions of testosterone by increasing the expression of insulin-like growth factor-1 expression (93), beta-catenin and T-cell factor-4 pathway signaling (94), regulation of peroxisome proliferator-activated receptor-gamma coactivator 1 alpha, and p38 mitogen-activated protein kinases (95). The molecular machinery by which male hypogonadism might cause muscle atrophy has been therefore studied and clarified (96).

Indeed, INSL3 has an anabolic effect, acting on RXFP2 on myofibers, in which it mediates the increase of cell size (but not of myotubes number) and promotes myotubular protein synthesis through Akt/mTOR/S6 phosphorylation signaling pathway (61). INSL3 does not affect myoblast differentiation while it increases myotubes size, with an hypertrophic effect similar to testosterone, and the myotubular expression of proteins as myosin-heavy chain (61). INSL3 moreover downregulates protein degradation by the ubiquitin-proteasome system (61). As a consequence, INSL3 has a protective role in skeletal muscle physiology, protecting subjects against atrophy

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and weakness. In knockout mice with impairment of INSL3/RXFP2 system, an increase in proteasome activity and a reduction in the anabolic Akt pathway has been reported, thus suggesting that low INSL3 levels might play a role in sarcopenia in hypogonadal patients.

Furthermore, the identification of VDR in skeletal muscle cells provided evidence of the role of vitamin D in skeletal muscle (97, 98). A severe reduction in vitamin D levels has been associated with skeletal muscle fiber atrophy, muscle pain, weakness, and elevated risk of sarcopenia and falls, in both active and non-active individuals (99). Several molecular mechanisms have been reported to explain the effect of vitamin D on muscle strength, performance, and metabolism, including alterations in protein synthesis, myogenesis, mitochondrial activity, muscle regeneration, and glucose metabolism.(100, 101, 102).

Because of this complex endocrine machinery, KS adult patients may have significant reductions in muscle mass (103) and decreased muscle strength and maximal oxygen consumption (104).

A reduction in lean mass has been previously reported as a risk factor for osteoporosis both in postmenopausal (105) and in women with premature ovarian failure (106). The association between reduced lean mass and a reduction in BMD has been demonstrated also in elderly males (107).

More recently, Vena *et al*. (33) demonstrated that vertebral fractures in patients with KS were significantly associated with truncal/leg fat ratio, whereas impaired TBS was associated with older age, BMI, waist circumference, fat mass index (FMI), and the FMI/lean mass index ratio. These data underline that body composition, namely a reduction in lean mass and an increase in fat mass, might influence bone quality and risk of vertebral fractures in subjects with KS.

Clinical management

Although current guidelines do not agree on screening programs for osteoporosis in men, they all agree that DXA is recommended in male patients with hypogonadism, including patients with KS.

However, although the mandatory role of BMD, evaluated by DXA, in the screening and diagnosis of osteoporosis in patients with KS, BMD only accounts for 60–70% of bone strength and many fragility fractures are found in patients with osteopenia or even normal BMD (108). Hence, the micro-architecture also plays a crucial role in determining bone strength and fracture risk. In this perspective, a role for TBS evaluation in KS patients, as an adjunctive tool to provide information about bone quality and risk of vertebral fractures, has been demonstrated (33). All these parameters should be considered, together with clinical data, to predict the risk of fractures in KS patients.

Moreover, recent data suggest an analysis of vertebral fractures in subjects with KS independently from the results of DXA. The guidelines recommend VFA using DXA equipment or, if DXA is not available or is technically limited, by lateral spine radiographs (109). Interestingly, total body DXA, where available, could also give important information on body composition, which are strong determinants of bone and skeletal muscle health.

In this light, we also suggest a more detailed analysis of bone mass and strength in subjects with KS, with the established methods recommended for the diagnosis of sarcopenia (110). In particular, this consensus defined low muscle strength as a key characteristic of sarcopenia and suggests using the detection of low muscle quantity and quality to confirm the sarcopenia diagnosis. Those include the SARC-F questionnaire, the evaluation of grip strength and the chair stand test, the appendicular skeletal muscle mass by DXA and the bioelectrical impedance analysis, the use of computed tomography or magnetic resonance imaging, the evaluation of gait speed, the short physical performance battery, the timed-up-and-go test, and the 400-m walk (110). Regarding the diagnosis of sarcopenia and osteoporosis, as suggested by few studies (such as (111)), the commonly used method, which can be used for the diagnosis of both conditions, is DXA.

In general, the treatment of osteoporosis in patients with KS does not differ from the treatment of osteoporosis secondary to other forms of hypogonadism. In fact, patients with KS should receive TRT when hypogonadal (33, 102), albeit the first therapeutical approach regards general measures and lifestyle (physical exercise, balanced diet, and sun exposure) (1, 31, 112). However, the exact effect of hypogonadism and TRT on the skeletal health of KS patients remains not completely clarified and TRT does not allow to completely restore BMD and lower fracture risk (113).

Furthermore, TRT, by reducing LH production, further reduces INSL3 production and 25-hydroxylation of vitamin D from the testis, and this might be important for bone and skeletal muscle health. In this regard, supplementation with vitamin D, when indicated, should consider calcifediol rather than cholecalciferol (49). In fact, patients with KS, even if with normal testosterone levels, have a reduction in testicular 25-hydroxylase activity, and integration of vitamin D levels is preferable using 25-hydroxy vitamin D.

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Furthermore, as said earlier, general measures are recommended, including the reduction of alcohol intake, smoking cessation, and a calcium intake of 1000–1200 mg per day (1200–1500 mg per day if osteoporosis is present) (1, 31, 112). On the other hand, there are currently no indications of TRT in men affected by KS with low BMD and normal testosterone levels (31, 33). In this specific case, of a patient with KS and still normal T and free T levels and without symptoms of male hypogonadism, bisphosphonates might represent a valuable option for primary therapy, although bisphosphonates only have reliable efficacy/safety data for 5–10 years (114). Therefore, it is mandatory to evaluate testosterone treatment as early T deficiency and the presence of symptoms appear (31). Similarly, in hypogonadal men with osteoporosis, bisphosphonates may be used when TRT alone is not able to restore BMD.

Conclusion

KS is a major cause of male osteoporosis, with different and peculiar mechanisms of bone alterations. Male hypogonadism represents the major causal pathway to induce osteoporosis in patients with KS, albeit other mechanisms, such as Leydig cells dysfunction associated with the alterations of INSL3 and vitamin D levels, are involved. Moreover, it is important to underline that KS affects not only bone density but involves the biological processes regulating bone quality, thus causing a reduction in bone density and an increase in bone fragility.

According to these premises, DXA appears to be mandatory in the clinical workflow for patients with KS but probably is not sufficient to clearly define the bone features in these subjects. TRT represents the main target therapy in hypogonadal KS patients, whereas bisphosphonates represent the primary therapy in patients with KS with normal testosterone values. TRT should be associated with antiosteoporotic drugs in hypogonadal patients with high fracture risk and in those in which TRT is not sufficient to restore BMD.

Declaration of interest

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