# Male osteoporosis and androgenic therapy: from testosterone to SARMs

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**Summary**

**As in the women, male osteoporosis represents an important social problem, amplified by the increasing life expectance. Differently from women, 50% of male osteoporosis is secondary to treatments and/or diseases that make mandatory their search through an accurate clinical investigations in every newly diagnosed osteoporotic men. Male osteoporosis is frequently underdiagnosed and consequently undertreated, and too often it is revealed only after the occurrence of a fragility fracture. Androgens may prevent the loss of cancellous bone and stimulate periosteal cortical bone apposition. The anabolic effect of testosterone on both bone and muscle, is limited by the high incidence of androgenic side effects. Hypogonadism is the only situation where the benefits of the use of testosterone formulations exceed the side effects. Selective androgen receptor modulators can dissociate androgenic and anabolic effect on different tissues with various strategies. Many compounds have been studied with positive results in vivo and in clinical trials.**

*KEY WORDS: male osteoporosis, testosterone, androgen, Sarm, hypogonadism.*

## Introduction

### *Epidemiology of male osteoporosis*

The prevalence of osteoporosis in male, after 50 yr of age, is about 13%, much lower than in women at the same age (40%) (1). Despite of the lower incidence, the mortality in men after hip fracture has been reported to be considerably higher (2-3 fold) (2).
The bone sexual dimorphism (BSD) is an important determinant of the lower incidence of fracture, about 30-50%, in the older men with respect to age-matched women. At the prepubertal stage, the bone of girls and boys doesn't show relevant differences, but after puberty the male bones are larger in size and stronger than females (3).
After the puberty, bone fractures are more commune in male than in woman, and under 45 years of age, the fracture incidence is 3 folds higher in men. This situation, mainly due at higher frequencies of sport injuries, traffic and work accidents, inverts at mid-life (4); in the older men the risk of hip or vertebral fracture is about 30% than in women of the same age. Traumatic fractures are more common in the younger male, whereas regarding the fragility fractures males reach the same incidence of fracture of postmenopausal women only in older age.
In the male wrist fractures indicates an higher risk for subsequent hip or vertebrae fractures (5, 6).
Other fractures occurring in the humerus, clavicula, ribs and pelvis, are often the first and the unique sign of osteoporosis, sometimes associated with increased mortality (7) and must be always carefully investigated.
Dual-energy X-ray absorptiometry (DXA) represents the gold standard for measuring bone mineral density (BMD), according to the WHO's guidelines. However, DXA is a bi-dimensional technique, expressing an areal ($g/cm^2$) and not a volumetric density ($g/cm^3$), that, due to the larger bone size, overestimates the values observed in male (8).
No consensus for the cut-off values associated with an higher risk for fracture is defined in men (9), but the great diffusion of the technique and the wide experience accumulated in the female osteoporosis still makes the DXA-assessed BMD the reference standard for its clinical use also in men (10). Mortality and morbidity per fracture are significantly higher in older men than in age-matched women. As in the women, male osteoporosis represents an important social problem that is amplified by the increasing life expectance.

### *Male osteoporosis causes*

Differently from women, male osteoporosis is frequently secondary, 50% of the cases, to conditions such as glucocorticoid therapies (11), hypogonadism and other endocrinological diseases, and alcohol abuse (12). Unfortunately, male osteoporosis is still frequently underdiagnosed and consequently undertreated, and too often it is revealed only after the occurrence of a fragility fracture.
Causes and incidence may change in populations (13) according also to racial and environmental variables such as different dietary regimens or sun exposition (14).
As above mentioned, approximately 50% of male osteoporosis is secondary to treatments and/or diseases that make mandatory their search through an accurate clinical investigations in every newly diagnosed osteoporotic men (Table I).
Long term glucocorticoid treatment in chronic illness represents the main cause of iatrogenic osteoporosis, however in all the conditions requiring androgen deprivation therapy (ADT) with GNRH agonists bone loss is always present (15). A certain grade of hypogonadism has been reported in 15% of the osteoporotic men, but its incidence greatly varies in the studies, with minimal variation of blood testosterone cut-off values (16).
Other situations such as malabsorption, liver, kidney or lung disease, primary and secondary hyperparathyroidism and hyperthyroidism should be always investigated in osteoporotic

Table I - Main causes of secondary male osteoporosis.

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|---|
| Iatrogenic: |
| Glucocorticoids |
| Anticonvulsants |
| Chemotherapy |
| GnRH-analogues |
| Glitazones |
| Immobilization |
| Organ transplantation |
| Gastrectomy |
| Bariatric surgery |
| Intestinal resection |
| Endocrine diseases |
| Hypogonadism |
| Hyperthyroidism |
| Hyperparathyroidism |
| Cushing disease |
| Diabetes mellitus 1 |
| Chronic diseases |
| Coeliac disease and |
| Malabsorption syndromes |
| Chronic inflammatory bowel disease, |
| Primary biliary cirrhosis |
| Pernicious anemia |
| Cystic fibrosis |
| Haemochromatosis |
| Renal insufficiency |
| Idiopathic hypercalciuria renal phosphate wasting |
| Neoplastic and paraneoplastic diseases |
| Rheumatoid Arthritis |
| Other |
| Alcohol abuse |
| Smoking |
| Immobilization |

men; when possible systemic and endocrinological diseases must be treated according to their aetiology; in the idiopathic male osteoporosis no primitive causes (e.g. genetic disease, deficit in reaching peak bone mass) can be identified (17).

*Androgens and bone*

It is well known that androgens may prevent the loss of cancellous bone and stimulate periosteal cortical bone apposition (18). Sex steroids in both sexes play a pivotal role in the development and in the maintenance of bone quality (19). Bone sexual dimorphism (BSD) is partly due to the difference in the age onset of puberty and higher levels of testosterone in pubertal and postpubertal males; testosterone (T) should be regarded to as a prohormone. In fact, in the bone, as in many other tissues, the androgen actions are under a peripheral control: 1) enzymatic conversion of T into dihydrotestosterone (DHT) by 5α reductase I and II isoenzymes amplifying androgenic action; and 2) enzymatic conversion into 17β estradiol ($E_2$) due to the action of CYP-19 aromatase exerting in both sexes as the main hormone for bone maturation and homeostasis (20). Differently from estrogens (Es), that can activate tissue specific estrogen receptors (ERα and ERβ), all the actions of T and DHT are mediated via the same androgen receptor (AR), with a classic genomic mechanism. On the other hand, the non genomic, fast mechanism of androgens uses different intracellular signalling pathways (21) and direct actions of androgens, and their metabolites, require the presence of the sex steroid receptors on the target cell. In fact, AR, ERα and ERβ have been detected on osteoblastes, osteocytes and in condrocytes of the growth plate cartilage. No AR has been detected on human osteoclasts that express only a low expression of ERs (22).
Non genomic faster mechanism seems to be related mainly to the anabolic non androgenic action (23).

*AR and androgenic action modulation*

AR belongs to the family of nuclear receptors, with an high homology with the other receptors for steroids, retinoic acid and thyroid hormones (24); when the receptor bind the ligand (T or DHT) the heat shock proteins (HSPs), that maintain inactive the receptor, dissociate with subsequent conformational modifications that permit the receptor homodimerization and translocation to the nucleus, where interactions with androgen responsive elements (AREs) of the target genes is possible through the recruitment of a family of proteins called co-regulators (25).
Co-regulators modulate the transcription process directly through a physical interaction with transcriptional machinery and indirectly through the modification of histone tails, covalently or through an ATP dependent dynamic remodelling of chromatin. Co-regulators are divided in co-activators and co-repressor on the basis of their final effect on transcription (26). All classes of steroids present non genomic effects with rapid induction of classical second messengers, including calcium, protein kinase A (PKA), protein kinase C (PKC), mitogen activated protein kinase (MAPK), extracellular related kinase (ERK) cascades (27).
However, indirect actions of androgens, as the effect on the pituitary GH secretion (28) or the anabolic effect on muscle mass, and consequently on bone charge, are important in the developing bone sexual dimorphism. T supplementation have no other medical indication except than male hypogonadism treatment, due to the consequences of the androgenic effect (e. g. on the red cells blood count, on the prostate). However, androgens response can be modulated using different pharmacological strategies, like the inhibition of the peripheral conversion into DHT or Es by specific 5α reductase or aromatase inhibitors, respectively.

*Many drugs may modulate androgen action at every level, including bone*

The androgenic power of T is much lower than the 5α derivate, DHT. In fact, it is the local presence of the 5α reductase type I or II, and not of the T in se, that permits a complete androgen action in tissues in which at least one of the two isoenzymes is expressed. In subjects with a congenital deficiency of 5α reductase type II, no benign prostate hyperplasia (BPH), prostate cancer, male patterned baldness or acne is found, despite the normal levels of circulating T (29).
Distribution and expression of the two isoenzymes of the 5α reductase accounts for the tissue specificity of androgenic stimulation. Selective (finasteride) or dual (dutasetride) inhibition of the two isoenzymes is a strategy to cut some androgenic effects (on prostate or on scalp) leaving intact androgenic stimulation where the uninhibited enzyme is present or where T acts directly on the AR or after its aromatization in $E_2$ stimulating ERs.
No negative effects on bone mineralization, metabolism and hip fracture have been observed in patient treated for BPH with type I and type II 5α reductase inhibitors (30, 31).
In the androgen deprivation therapy (ADT), the first line therapy

for metastatic prostate cancer (32), gonadotropins secretion is blocked with GNRH agonists with an arrest of the hypothalamus-pituitary-testis axis. The consequence is a blockage not only of the production of T, but of every sex steroid derivate (DHT and $E_2$ with the exception of the adrenal steroids) with negative consequences on bone mineral density, bone resorption and fractures.
Es may suppress GNRH secretion with a negative feedback mechanism, with an undesirable feminizing effect and a positive effect on bone. Administration of not aromatizable androgens, that may suppress LH secretion, can mimic an estrogen deficit, with increased bone resorption.
Aromatase inhibitors, blocking the aromatization of androgens to estrogens, eliminate the estrogen effect, leaving untouched androgen action.

*T therapy of male hypogonadism (MH)*

The correction of MH is the only indication for testosterone therapy. The anabolic effect of T on both bone and muscle, or the positive effect on the mood and libido are limited by the high incidence of side effects, especially on the red cells blood count (polycythemia) and prostate when supraphysiologic levels are maintained for long periods. However, MH is the only situation were the benefits of the use of testosterone exceed the side effects.
MH is a clinical condition featured by low level of T associated with signs and symptoms such as loss of libido, muscle mass and bone, but its diagnosis should be posed not only on the basis of the T circulating levels, but according to the clinical examination. Effects of MH on bone, as for other tissues and organs, change with the age of its onset (pre- o post- pubertal) and with the severity of androgenic (and consequently estrogenic) deficit.
In primary hypogonadism (hypergonadotropic), the T deficit is caused by a decreased production of testicular T, with raised serum levels of gonadotropins (LH and FSH).
On the contrary, in secondary hypogonadism (hypogonadotropic) a low pituitary gonadotropins production is observed with a consequent low T production, from the inadequately and ineffectively stimulated testis.
Many causes of primitive hypogonadism causing testicular defects are known, such as Klinefelter's syndrome, post mumps orchitis, orchiepididymitis. Less commune are the causes of secondary hypogonadism and the best known are hypopituitarism, Kallmann syndrome, idiopathic hypogonadotropic hypogonadism; in secondary hypogonadism, with the exception of substitutive gonadotropin therapy for the induction and maintaining of fertility, T, in different formulations and delivery systems, is the only used therapy .
T replacement therapy (TRT) is necessary for inducing and maintaining secondary sex characteristics with anabolic effects on many tissues like muscles mass, bone, blood; moreover, as above mentioned, T modulates metabolism, mood, and sex activity.
The use of non aromatizable or not 5$\alpha$ reducible steroids should be avoided in MH for the uncompleted substitutive effects. During TRT the control of hematocrit for the risk of polycythemia, PSA and prostate examination for the risk of prostate cancer are mandatory.
Many pharmaceutical formulations of T are available for TRT (Table II).

Intramuscular Injection

T esters like enanthate or cypionate were used since many years in MH treatment, with 2 or 3 weeks intervals between injections and doses ranging from 100 to 250 mg.
However, most of patients are perfectly corrected with these regimens, without exhibiting side effects. Sometimes the high peak of T reached after injection in the first days of treatment may determine an overstimulation of erythropoiesis, while the low level of T during the last days, before the next administration, may cause oscillations of mood and sex behaviour (33).
T undecanoate, previously used only as an oral preparation, permits intervals of up 12-14 weeks between the injections, avoiding alternate periods of supraphysiological T levels and hypogonadism (34). A control of side effects is necessary, and for its long-term effects this formulation should be avoided in people at risk for the reported complications.

Oral agents

T undecanoate is the only oral formulation with a safe profile. This formulation partly bypasses the hepatic filter, due to the dimension of the ester tail, and is directly adsorbed from intestine as a medium-chain fatty acid. However, high doses are necessary to reach normal to low level of blood T. Other oral agents, like the 17$\alpha$ alkylated derivate, present severe liver toxicity and metabolic issues (35).

Transdemal T

Skin patches and T gel, with daily application, restore T circulating levels into the physiologic range without periodical oscillations (36, 37). Sexual skin surfaces and other areas with high expression of 5$\alpha$ reductase should be avoided for the local metabolization to DHT.
Transdermal formulations permit, when necessary, a rapid cessation of therapy, and represents the therapy of choice for people at risk for TRT side effects. The use of gel and skin patches permits to rapidly asset the effects on mood and sex behaviour of men with borderline hypogonadism. Sometimes treated pa-

Table II - Testosterone preparations in clinical use.

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|---|---|---|---|
| T enanthate | intramuscular | 100-250 mg | every 2-3 weeks |
| T cypionate | intramuscular | 200 mg | every 2 weeks |
| T undecanoate | intramuscular | 1000 mg | every 10-12 weeks |
| T implants | subdermal Implants | 4 pellets 200 | every 5-6 months |
| T undecanoate | oral | 40 mg capsules 2-4 per day | |
| T mucoadhesive tablets | buccal mucosal | 30 mg tablets twice per day | |
| Transdermal T patch | scrotal skin | 1 patch per day | |
| Transdermal T patch | non genital skin | 1-2 patch per day | |
| Transdermal T gel | non genital skin | 5-10 g of gel (50-100 mg of T) per day | |

tients lament discomfort for the daily application of gel and are concerned about the possible virilizing effects on the female partners.

Other formulations

Normal levels of T are reached with muchoadesive formulations (twice a day applied at the gum of the lateral incisors) (38), but not every patient is able to maintain the patch well positioned.
Subdermal implants of T pellets permit a long duration with restoring and maintaining physiological T levels for over 6 months, with some risk of infection in the site of inoculation and extrusion of the pellet (39).
The androgen-dependent quality of male bone suggest a possible therapeutic use of androgens that could be potentially useful in early future also for female osteoporosis treatment. After several unsuccessful attempts with different anabolic androgenic steroids (always exhibiting androgenic effects, and sometimes relevant liver toxicity in the long term therapy) (40), new non steroidal compounds, able to modulate the androgenic action, have been now developed: the selective androgen receptor modulators (SARMs).

*SARMs*

Antiandrogens antagonize the effect of both T and DHT on the AR. They can be classified as steroidal, like spironolactone, cyproterone acetate, or non steroidal, like the anilide derivatives flutamide, nilutamide and bicalutamide.
Bicalutamide is the first member of a generation of non steroidal ligand (propionamides), with a great improve in terms of liver toxicity, half life and bind affinity to the AR. Slight modifications of bicalutamide and hydroxyflutamide lead to compounds with androgenic activity.
Antiandrogenic effect of Bicalutamide can be seen as the extreme aspect of the spectrum of AR modulation. Other compounds of the family of propionamides are currently under study as SARMs, with selective myoanabolic and osteoanabolic effects.
Different classes of putative SARMs are under development with huge variety of chemical structures like quinolinones, tetrahydroquinolines, hydantoins, azasteroids and many others (41).
In a "historical" commentary of Negro-Vilar ideal characteristics for an anabolic SARM were defined as the follow: drug orally active, with once a day administration, anabolic effects on bone and muscle and no, or lesser action, on prostate (42). Another desirable effect of an ideal SARM is to leave intact the hypothalamus-pituitary-testis axis, thus preserving FSH and LH secretion necessary for a normal sperm production and maintenance of appropriate testicular volume.
As already above described, androgen action is quite complex and exerted in many different tissues. Mechanisms by which SARMs can dissociate androgenic and anabolic effect on different tissues have been studying and proposing (43).
Some of these mechanisms have been borrowed from the selective estrogen receptors modulators (SERMs), hypothesizing a specific recruitment of co-regulators. Different conformational modifications of the AR-SARM complex, selective recruitment, activation or inactivation of co-activators or co-repressor can be specific target of the selective action of SARMs (44).
Non genomic effects of the androgens appear to be another possible target for SARMs like the observed preferential activation of ERK pathway with a proliferative effect on bone cells (anabolic tissue) and of the anti proliferative p38-MAPK pathway effecting on the intranuclear-cytoplasmatic AR handling on the prostate (androgenic tissue) (45). Of course, non steroidal SARMs cannot be a substrate of 5$\alpha$ reductase or aromatase, exhibiting an another related tissue specificity with respect to the 5$\alpha$ reducible or aromatizable androgens.
Many SARMs are under development but not yet available for clinical use.
Among the currently studied SARMs, Ostarine (mk 2866) recently showed, in a successful completed phase II clinical trial, to significantly increase the lean body mass (LBM) and physical performance compared to baseline in patient of both sexes affected by cancer cachexia, with a reduction in serum lipids and LDL/HDL in the low cardiovascular risk class (46); the results can be extended to the bone in elderly men and postmenopausal women, with evident implications for a wide clinical use.

## Conclusions

Male osteoporosis is an underdiagnosed and undertreated condition with serious consequences; often is secondary to severe disease and need a causal treatment. Despite the positive effect of androgen therapy on the bone only hypogonadism can be treated with testosterone replacement therapy, because the associated androgenic effects limit, especially in the older patient the benefits. Dissociating anabolic effects from androgenic activities is the strategy to obtain osteoanabolic and an associated and positive myoanabolic effect without side effects on prostate in the male or virilization in the woman. Steroidal compounds failed to obtain suitable result, but many new non steroidal compounds under development, showed in vivo and in clinical trials positive results. SARMs well dissociating anabolic and androgenic activities following the AR activation, represent the androgenic counterpart of the SERMs, in terms of tissue and action specificity. An anabolic drug, with no significant or antagonist androgenic action would posses the ideal features to become a first line therapy in the field of osteoporosis and in the diseases where an anabolic effect is required.

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