An Elsevier Indexed Journal ISSN-2230-7346

Journal of Global Trends in Pharmaceutical Sciences

GENETICS OF OSTEOPOROSIS AND CLINICAL MANAGEMENT

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ARTICLE INFO

Key Words
Osteoporosis, Pathogenesis, Bone mineral density, Genetic architecture, Genome wide association studies

Access this article online
Website: https://www.jgtps.com/
Quick Response Code:

ABSTRACT

Osteoporosis is a frequent disorder having robust familial factor which is distinguished through decreased bone mass, bone tissue defects and a sustained likelihood of fragility. Twin and house hold research studies have shown excess genetic influence in bone mineral density (BMD) as well as risk factors of fractures including bone composition, bone structure and bone turnover. Osteoporotic cracks have another generational aspect, although with age these decline as environmental factors like the potential to fall into action. Osteoporosis sensitivity is controlled by numerous gene variants and the ability to interact with environmental influences, such as diet and exercise. An analysis of rarities Mendelic bone disorders marked by primary defects in bone mass, in which large-impact variants are involved, has shown remarkable success in finding genes that control BMD. The repeated common variants of small-impact measures, leading to BMD control and potential fractures, have been reported in genome-wide interaction studies. Often the phenotypic traits and genetic mutations identified in such experiments were not identified as having a function in the metabolic processes of joints. While genomes and phenotypic traits which contribute to the control of BMD and injuries across the previous 15 years have increased greatly, many of the genetic markers which change certain genetic traits appear to still be identified.

INTRODUCTION

Osteoporosis is the product of decreased bone density, bone tissue degradation and deterioration of the bone microarchitecture that would lead to diminished bone density and a higher incidence of fracture [1].Osteoporosis may be the most common human bone malformation in Caucasians, girls and the elders.Osteoporosis is a causative factor to fracturing almost as hypertension is for stroke.It is a quiet illness that causes major secondary wellbeing and indeed mortality issues once fractures occur [2].More than 200 million sufferers with osteoporotic hip fractures have been estimated around the world [3].This has been recorded around 30 per cent of individuals in America and Europe are osteoporotic, with 40 per cent of post-menopausal females and 30 per cent of males expected to suffer osteoporotic fractures for the rest of their lives [4, 5].Through resorption and reconstruction the bone tissue is continually damaged and bone loss happens when the resorption rate reaches the forming limit.Bone mass is modelled from childhood to middle age: bone mass at adolescence reaches its peak called peak bone mass (PBM); bone mass loss then starts.Genetic variations, development fitness, diet, endocrine status, sexuality and physical exercise are the key determinants of PBM.Reward reconstruction that includes replacement of aging bones to add fresh bones can be used to fix mini-fractures in order not to become macro-fractures so that a healthy skeleton can be preserved.Menopause and advanced aging generate imbalances between certain resorption and the forming rate, increasing the chance of fracturing (resorption is greater than absorption).Several determinants rise

resorption rather than forming frequently, cause bone loss, exposing microarchitecture.Single trabecular plates are missing and a system architecturally compromised, with substantially reduced density, resulting in a significantly increased risk of fracturing, compounded by other reductions in functionality correlated with aging.An increase in scientific proof has indicated that accelerated bone remodelling (measured by bone resorption or bone formation biochemical markers) raises bone brittleness and rupture risk.Factors are correlated to an elevated risk of osteoporosis-related fractures.Which include overall factors linked to aged and sex hormone deficiencies, and also particular risk factors, such as glucocorticoids, causing lower bone growth and bone loss, decreased strength of the bone and damage to microarchitecture.Fractures arise if the bone becomes thin, often because of dropping or certain daily tasks [6].

BONE TURNOVER REGULATION

Bone seems to be a metabolic system which is constantly being restructured for a lifespan. After the maximum bone mass, the bone undergoes continuous remodelling by bone resorption followed by sequential forming at the simple multicellular bone unit called "Bone remodelling unit. “During bone resorption and formation, various biomolecules released into circulation are called BTMs [7].Bone resorption takes place in about 10 days under optimal physiological conditions, and bone formation takes about 3 months. It can be replaced by remodelling up to 20 per cent of the skeleton every year [8]. Bone turnover enzymes and non-enzyme peptides extracted from the bone cell and noncellular compartments are currently available as biochemical markers.

The BTMs are grouped into two categories based on the metabolic phase during which they are produced as:

a) Bone formation markers.

b) Bone resorption markers.

PATHOGENESIS OF FRACTURE

1) Hierarchical structure

Ruptures arise when the pressure of a bone reaches its strength. A bone, which is achieved by a hierarchical structure, must be solid and resilient with resistance to fracture. In a triple helical structure, collagen-1 fibrils are attached to non-collagenous proteins that help to prevent the rashing. Deposited on the collagen framework, the hydroxyapatite crystals contribute energy, specifically in compression. Cross-linkage between collagen fibrils with non-collagenous proteins is decreased in osteoporotic bone, main to decreased tensile power [9]. Additionally, greater crystals of hydroxyapatite are present in osteoporosis, which renders the bone more fragile and vulnerable to break [10].

2) Bone cells

The three main forms of bone cells are osteoblasts, osteocytes and osteoclasts. Osteoblasts enter bones andmay also occur as incorporated in the bone as developed osteocytes or live on surface as bone lining cells (including 90–95 per cent of the cells inside the bone). Osteoclasts are multi-nucleated bone resorption cells. Osteoblasts and osteoclasts function together on specific locations on the surface of the trabecular or cortical bone and form ' multicellular bone groups ' in a coordinated way. During bone formation, osteoblasts lay down new osteoid collagen matrix and for weeks to months, crystals of calcium hydroxyapatite structure on the collagen fibrils. In a process known as simulation, bones are laid down during development and reconstruction and by responding to mechanical mounting [11]. In comparison, the resorption and replacement of an intact bone require the regeneration process. Throughout designing and remodelling law, osteocytes play a vital role. The arrangement of the osteocytes around Haversian canals acts as a mechanosensory device and lets in verbal exchange each without delay between neighbouring osteocytes and through the launch of endocrine, paracrine and autocrine signalling factors to different bone cells. The specific mechanisms that are essential for controlling osteoblast and osteoclast function, such as the nuclear factor-kappa B receptor activator kappa B ligand (RANK – RANKL) and the signalling of Wnt are increasingly recognized as targets for anti-osteoporosis agents.

3) Changes in bone structure across the life course

The development and resorption process have a critical life-long effect on bone mass and strength. There is a favourable adolescence

balance until maximal bone mass in early adulthood is achieved with an adequate stable life and then with older adolescence destructive equilibrium, with the activity of osteoclast higher than that of osteoblast, resulting in bone loss [12].This cycle is intensified in women following menopause. The related cell processes and causes contribute to anatomical differences between men and women in the whole bone and shifts with advancing age. The cross-sectional bone region of males normally is bigger than females, and the post menopause of female cortical thickness is reduced significantly, leading to proven gender fracture risk disparities. The distribution of Trabeculae differs amongst sexes; young females tend to have fewer and thicker trabecular than young male and the trabecular numbers of women decreasing at maturity [13]. Cortical porosity thus develops more rapidly in aged women [14].

4) Clinical risk factors

Some factors, either by the bone mineral density (BMD) or by separate processes, impair the likelihood of fractures. These encompass age, glucocorticoid therapy, a preceding private history of fracture, a household history of hip fracture, present-day smoking practice, alcohol abuse and positive diseases associated with osteoporosis e.g. rheumatoid arthritis, diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), persistent malnutrition, malabsorption and continual liver disease, in terms of risk analysis, a program funded by the WHO of risk factors, with or without BMD calculation, has been integrated into the FRAX ® method to quantify a 10year likelihood of either hip fracture or severe osteoporotic fracture[15]. FRAX ® is by far the most commonly deployed method of this kind in the world, serving 75% of the world's population, and maybe related, as in the UK, to assessment algorithms to identify criteria for care intervention [16].

HERITABILITY OF OSTEOPOROSIS-RELATED TRAITS

Twin and relatives research have demonstrated that osteoporosis is particularly paternal, with a mainly genetic effect in families [17, 18]. It is true of a large number of phenotypes of osteoporosis, including BMD, bone turnover and skeletal proportions correlated with the risks of rising fractures, which is just as good as the danger of fracture itself [19]. Non-invasive assessment of bone microarchitecture has been thoroughly enabled. In particular, findings from animal models show that while a huge percentage of genetic variations can also be identified only through BMD tests, substantial information can be gathered using more detailed bone picking strategies such as comprehensive screening for computed tomography and magnet resonance imaging. For families with the relative risk of a comparatively first degree's fracture of 1.3-2.4, depending on the relative pair shape and fracturing location, the probability of fracturing is considered to occur [20, 21]. Rupture genetic risk work has often identified potential ancestry restriction in twins and families as compared to BMD, with one significant exception of hip fracture in younger populations (< 69 years of age). The fracture research overall shows that the fracture in particular among elderly people is less heritable than BMD. Thus, while it is obvious that it is important to determine whether or not bone fragility (the final question) is impaired by BMD-associated polymorphisms, the most effective method is to use a tentative monitor based on genes having an impact on BMD and then evaluating how significant such genes are for the fraction. The apparent drawback of this strategy is that if mutations affect bone fragility and the likelihood of fracturing independent of BMD, they will not be detected by this method. Nevertheless, the data from genes associated with BMD and fracture to date is that almost all genes associated with BMD are also correlated with the fracture.

GENETIC ARCHITECTURE OF OSTEOPOROSIS

The most significant medical consequence in osteoporosis is a fracture. In the past, through examining established GWAS BMD loci for interaction with fracture as mentioned above, most of the genes found to be correlated with fracture hazard have been identified. Two GWAS have been used as an endpoint to date utilizing vertebral fractures. One locus on chromosome 16q24 (rs11645938) was correlated with the possibility of radiographic vertebral fractures in the first meta-analysis, which was not repeated in 5720 cases and 21,791 controls [22]. A new meta-analysis found that a locus map of chromosome 2q13 was correlated strongly with medical vertebral fractures [23]. The

first GWAS research on non-vertebral osteoporotic fractures (N=700) was performed in elderly Chinese people and one fracture-associated locus within the ALDH7A1 gene was established[24]. However, in any of the larger European meta-analyses, this gene did not replicate. The largest GWAS on osteoporotic fractures to date was conducted. In 2018, consisting of 37,857 cases and 227,116 replicated cases in up to 300,000 individuals (147,200 cases). All in all, 15 fracture loci are found with moderate results[25]. Ironically, BMD loci are related to all defined loci. Together, the fracturing impact of these SNPs was weaker than the BMD effect. Therefore, through the genetic influence on BMD, the prevalence of any form of fractures in the general population is regulated. This is well illustrated by the BMD fracture hazard genetic associations. Also, only BMD had a significant causal effect on fracture across 15 medical factors examined (including vitamin D levels and dairy calcium intake) [25].

SINGLE GENE DISORDERS OF RELEVANCE TO OSTEOPOROSIS

The typical roles of osteoblast and osteoclasts are essential for the preservation of good bone tissue. Osteoclasts bone resorption and osteoclast formation are strongly interconnected on particular bone sites in continuous monotonous cycles and tactics are carefully managed by various regional systemic factors [26]. The bone function can be compromised through contact between osteoclast and osteoblast, which is necessary for healthy bone regeneration and deficiencies of both types. Osteoblasts express the receptor activator of nuclear issue kappa-B ligand (RANKL), which binds to its conjugate receptor RANK, on osteoclast cell surface [27,28]. It triggers osteoclastogenesis and resorption of the osteoclastic bone. Osteoblasts also secrete osteoprotegerin (OPG) that serves as a decoy receptor for RANKL to inhibit RANKL-RANK–binding, therefore downplaying RANKL's osteoclast genesis-promoting impact and, as it identifies implies, defending bone from over resorption [27, 28]. Recently, RANK used to be also referred to relay returned through vesicular trafficking from mature osteoclasts to osteoblasts to promote bone formation by way of reverse signalling [29]. The value of the RANK-RANKL–communication is portrayed in various monogenic stipulations with extraordinary bone mass ensuing from defective RANK-RANKL-OPG–axis: osteoclast-poor osteopetrosis with immoderate bone formation due to mutated RANKL, juvenile Paget's sickness with osteopenia and progressive skeletal deformity from mutated OPG, and familial expansile osteolysis (FEO) with osteolytic lesions and extended bone remodelling from mutated RANK [30, 31]. Alongside osteoblasts and osteoclasts, osteocytes have emerged as key regulators of bone turnover, mineral homeostasis and haematopoiesis [32]. Osteocytes are terminally differentiated osteoblasts embedded in the course of the mineralized matrix. They speak with each other and other cells through a huge community of lengthy cytoplasmic dendritic procedures and are thinking to orchestrate the interplay between osteoblasts and osteoclasts in bone modelling and remodelling through sensing mechanical loading and responding to endocrine factors, and blood calcium and phosphate concentrations [33]. Osteocytes express a range of proteins, such as dentin matrix protein 1 (DMP1), phosphate-regulating neutral end peptidase on chromosome X (PHEX), and matrix extracellular phosphoglycoprotein (MEPE), that are imperative for nearby matrix mineralization [34]. Osteocytes are the major source of sclerostin, RANKL, and fibroblast growth factor 23 (FGF23), through which osteocytes exert their endocrine functions in bone [32, 34]. In all facets of bone health, the WNT system has a key position: from the formation of the fetal skeleton to childhood bone mass accruing to the production of bone homeostasis and microarchitectural support [35]. WNTs function regionally with the assistance of paracrine activation of WNT adjacent cells: in developing phases, engage in a cross-discussion in bone marrow between osteoblasts and hematopoietic stem cells (HSCs) and facilitate the growth, differentiation and proliferation of bones in bone phones, and ultimately, osteoblastic bone-forming in mature individuals [35]. WNTs may also function autocrine with the same osteoblast or osteoclast lineage cell regulation [36]. The direction becomes anabolic to the skeleton, contributing to an increased structure of bones and a decreased reabsorption of the bones. The traditional route (WNT / b-catenin), the non-cationic, smooth, and shifting Polarity paths, and the non-cationic WNT / Ca2+path are known. Three separate WNT routes are established. While the two above, known also like the separate pathways of b-catenin, are implicated in different forms of growth and metabolism, the prevalent route for the

maintenance of skeletal wellbeing is seen as the canonical WNT / a-catenin pathway [37]. WNT / b-catenin disordered signals cause multiple problems of skeleton for every lower and higher bone weight. Because of the X-chromosomal inheritance in male patients, osteoporosis is typically severe in early childhood. Medical symptoms in women with heterozygous PLS3 mutations differ between the subclinical osteopenia and the more extreme phenotype that of men [38]. The overall number of patients diagnosed remains scarce; the medical and genetic spectrum, the advancement of the illness and the excellent healing are therefore constrained. Despite the absence of a systematic study in all tissues, plastin 3 (also named plastin) is expected to be used in the mechanical transduction of bones, via roles in other tissues including the spinal cord, inner ear stereocilia and periodontic ligaments [39,40]. This is supported by the platinum 3 high expression of chicken osteocyte dendrites, especially during dendrite formation [41, 42]. These are favoured by medical research from biochemical findings and bone biopsy indicating that osteocytes are affected by PLS3 mutation-positive topics [43]. Eventually, current pathophysiologic model animal points out that osteoclastic malfunctions in PLS3 osteoporosis are involved [44]. The osteoporotic syndrome in the former and thickening cortical bone in the latter was examined in vivo and in vitro studies utilizing knockout and over-pressing Pls3. The regulating role of PLS3 in osteoclast genesis was tested on osteoclasts made from animals. Besides, osteoclast recreational dysregulation was observed in pls3-knockout cells, which was probably associated with a deficient podosome company because of lower actin regulation [44]. Such effects have still to be shown in people.

HUMAN LINKAGE STUDIES

Osteoporosis is a typical condition that occurs at a certain stage in life at least 30% of women and 12% of men [45]. In fact, as one in two girls and one in four men ages, a fragility split will be eventually encountered [46]. Females show a greater occurrence of every stress fracture earlier in life and fragility later on [47]. Bone degradation effects from bone mineral mass decline or/and skeleton microstructural transformations. Because of its use of dual-energy X-ray absorptiometry (DXA), the most commonly used and trustworthy scientific marker of an osteoporotic fracture remains the bone mineral density (BMD) and most genetical work on osteoporosis has in turn utilized BMD as a phenotype of concern[48]. Nevertheless, with any skeletal development gender dimorphism is identified and grows older, and is no longer restricted to BMD. Gender differences are evident in the structural factors of bone strength (e.g. skeletal size, cortical thickness), biomechanical reactions, mineral and turnover density and even trabecular microstructure. Skeleton and hierarchical sexual dimorphism is well established and forms the basis for archaeological and forensic intercourse examination. In Framingham's cohorts, for example, young males have lengthier femora, more obtuse angles of the neck shaft, longer and wider femoral necks, and greater BMD. Therefore, even after correcting for physical measurements, the increased likelihood of brittleness fractures with age advance in females, as compared to male, can also be largely defined by the decreased skeletal and bone mass of women [49]. Nevertheless, remember that the largest volumetric BMD is not gender-specific. While women, as well as men all, end up losing BMD and bone microstructure with a growing old because of endocrine, paracrine and cell factors, its effects are reported to be greater for women, in particular, a limited amount of cortical thickness, a limited number of sores and an increased placement among trabeculae compared with men. Fantastic acceleration with a rapid decline in estrogen levels after menopause [50]. Adaptation by periosteal apposition may be also smaller for women than men and lead further to structural dysfunction of the bones, which is hence symbolic of the life of a woman than of a man [51]. While sexual orientation-specific osteoporosis predisposition and the danger to fractures can also be checked in genes which determine both bone electrical structural and mineral components (and fragility). However, it should be noted that young boys are more vulnerable to childhood fractures than young girls, stressing the role of environmental (compartmental) differences between men and women in terms of the clinical expression of bone fragility (e.g., propensity to take dangers in boys)[52]. No purely gendered phenotype can be described, i.e. the numerous points of the male and female skeleton result from quantitative and qualitative variants of bone replication and reshaping, not now through absolutely extraordinary regulatory mechanisms. Even

estrogen may be as vital for reaching height bone mass in males as in females, as validated by using the decrease BMD in young ladies with late menarche as properly as in men with loss-of-function mutations in the estrogen receptor α gene and aromatase gene[53]. For males, decreases for BMD related to age are also directly linked to decreasing estradiol levels, which can also be even more distinct in getting older people than the BMD relationship with testosterone [54]. On the other hand, the androgen receptor often modulates the bone mass and shape in ladies, and in ladies, the periosteal enlargement of androgen, as seen in polycystic ovary syndrome (PCOS), may also prove more beneficial in males[55]. Such findings support the classification of genes in each system, including the Androgen Receptor (AR), the α (ESR1) and β (ESR2) estrogen receptors, and the Aromatase (CYP19), in the case of osteoporosis in men as well as females. In specific, variations in reaction to estrogens and testosterone were observed in men and woman chondrocytes, osteoblasts, myoblasts and separate cells and recently found that skeletal muscle-derived stem cell (MDSCs) from male mice had a greater expression of osteogenic genes and a higher pastime of alkaline phosphatase (ALP) when stimulating with bone morphogenic protein 4 (BMP4)[56]. This indicates that male MDSCs have a significantly greater osteoprogenic capacity, which can also provide a base for bone recovery with sexual dimorphism [60]. Gender differences in progesterone reactions were also indicated in cells originating from rat lumbar vertebras in a previous study. The above points offer evidence that several phenotypic determinants of bone strength (risk factors of bone vulnerability) include basic dimorphism. The problem is whether or not the ability is modulated in gender-based conditions such as access to gonadalhormones, variations in body function, and muscle strength by the production and penetration of similar genes.

LINKAGE STUDIES IN MODEL ORGANISMS: Animal models are used for studies through osteoporosis genetic basis. There were also early achievements in the use of GWAS methods in osteoporosis, however, genetic mapping in the mouse is likely to continue in genetic research in the bone biology sector. The freshly accessible populations of mouse genetic resources are somewhat more than ordinary mapping panels and the confirmatory use of such panels are already being effectively shown. Research on mouse model mapping should be a complement of, not contrary to, GWAS [57]. Recent work in genetic systems has led us to believe that genetic analysis and statistical analyses will quickly analyse ' hard ' genetic diseases. GWAS is seen as a more producing theory than as a final solution because of all its accomplishments. The assumption that biological dynamics are interdependent allows us to quantify and interpret data on a variety of scales with several stages of abstraction. Our task is to integrate these observations and inferences into the biological photograph, at a granularity level so that the deviations from everyday features found in a specific patient can be understood and corrected. This is not, of course, a simple task, but this aim can begin to be accomplished in the combination of genetic, biochemical, proteomic, physical, biomedical, and machine processes. For this factual revolution, skeletal science has been well secured because clinically significant bone quantification is convenient and more than one vertebrate design organism is traced in the computer community [57].

CANDIDATE GENES IDENTIFIED THROUGH GENOME-WIDE ASSOCIATION STUDIES (GWAS)

Like several genetic and environmental disorders, popular osteoporosis is often believed to induce phenotype effects in more than one variant [58]. Consequently, GWAS technological success has been fully integrated with the field once, and since 2008 was completed in conjunction with original studies and Meta-analyse, at least 29 low BMD and/or fractures GWAS were identified. As a consequence, several genes related to bone brittleness have previously been reported in these studies with a minimum of more than 70 loci and more than 90 genes respectively. Throughout the sample sizes 13,786 and 8,557 individuals and 5 primary genes, each: OPG, RANKL, LRP5, ESR1 and ZBT, were identified. As beforehand mentioned, OPG and RANKL alter osteoclast differentiation and activation, and LRP5 is an imperative mediator of Wnt signalling in bone formation. Long ESR1, which encodes the estrogen receptor, has long been considered an osteoporosis-candidate gene, mainly based on prior linking research and the distinctive physiological role of oestrogens in bone reshaping. A final locus recognized by rs 7524102 has been strongly

linked to every backbone, but evident applicant genes of its vicinity have not been found[59]. This locus was subsequently established by the GWAS in broader cohorts, with a p-value of 7.4x10-57 for hip BMD [60]. The association has been assigned ZBTB40, the closest gene, as these indicators map the intergenic region. To date, ZBTB40 has a largely unknown biological function in animal or human health. In 2012 GEFOS2, the largest reported GWAS consisted of > 80,000 BMD target figures and > 130,000 instances and controls of fracture [59]. When discovered only 56 BMD-related loci and 14 BMD-related loci were reported as a possibility of fracture, although the genetic contribution of femoral neck BMD should still be 5.8%. This is how GWAS ' remarkable strength in the discovery of genes in conjunction with common diseases is expressed in each of them, as well as their amazing limits, in describing the whole genetic variability of such diseases. In 2015, an innovative GWAS breakdown based primarily on whole-genome sequencing was used to discover the effectiveness of low-frequency variants, which are usually not found in genotype GWAS [62], with sufficient energy (minor allele frequency [MAF] between 1 and 5%). The latest EN1 gene was once established with this strategy, which is greatly related both to the BMD frequency and to the fracture risk. In vitro and animal fashions research highlight a workable role for EN1 in osteoblasts, this offers a thrilling opportunity to discover new bone formation mechanisms [61]. This information indicates, ultimately, that lower-frequency variants can also have a greater influence on BMD and fractures. A full description of the 95 main GWAS-recognized genes. Of interest are just 41 genes with proof of participation in bone physiology. The 54 ultimate genes were chosen primarily based on their physical closeness to the GWAS signal, and their association with bone fragility should, therefore, be further studied.

GENE-GENE INTERACTION: Numerous researchers investigating the connection among candidate gene polymorphisms and BMD combos, although we now know of the strengths of effect for common polymorphisms and osteoporosis-related phenotypes, all of those researcheswere underfunded [62]. Looking into the relationship of VDR and ESR1 polymorphisms for BMD in 171 post-menopausal women, people with aggregates of ESR1PvuII "PP" and VDR "bb" genotypes were investigated at all skeleton locations with very high average BMD values. Another finding of reveals that perhaps the combo of the genotypes of VDR and ESR1 identified sub-groups of men and women with highly undue and very low BMD in a postmenopausal Italian population[63]. In estimating the BMD in Belgian postmenopausal women, no major interactions among VDR and ESR1 genotypes were however found [64]. In the Rotterdam research, quite greater studies were conducted on candidate gene-gene interactions. For e.g. once VDR haplotypes and polymorphism COL1A1Sp1 were suggested to interact in this study to adjust fracture susceptibility in 1004 girls[65]. The riskiest allele carriers in each gene had a fracture threat of 4.4-fold relative to the reference group. In all other Rotterdam population assessments, it was mentioned that all the ESR1, ESR2 and IGFI interact with 6363 subjects in combination with BMD and aspects of the femoral neck structure, to modify sensitivity to osteoporotic fractures and different phenotypes[66]. The investigators recorded a substantial interplay between the three genes and the women's phenotype experiments, which continued despite the correction but had no implications for males. Two reports also examined the effects by integrating data from numerous alleles that were significantly related to BMD in GWAS research. In the British / Rotterdam Twins GWAS the TNFRSF11B and the LRP5 loci were compiled by chance information to enhance forecast of people with fractures and to identify sub-groups with very low or high BMD[67]. In a study, the cumulative findings of 20 unsafe alleles for BMD were evaluated based on comprehensive phenotypes, for each BMD and fracture, in a related yet greater giant assessment using the GEFOS meta-analysis [68]. It leads to the discovery of sub-groups with very small BMD (which bear a large number of dangerous alleles) and strong BMDs (which lift less hazardous alleles), with a defining range of BMD of up to 0.5 SD (femoral neck BMD) and 0.7 SD (femoral lumbar spine BMD). Likewise, an extended chance of breakage was found with non-vertebral and vertebral fractures, with odds of 2 and 4 for those subjects with an alloy of over 20 probability of BMD decreasing.

FUTURE PROSPECTS AND CLINICAL IMPLICATIONS

Fracture liaison services: Fracture Liaison Offerings (FLS) provide an extensive evaluation

and management model for people who are fragile [85]. FLS works cost-effectively, improve cure charges and adherence, lower re-fracture rates, and mortality when working according to high standards of practice [86]. FLS has been developed in many parts of the world, yet it represents only a small minority of fragile and broad-based individuals and is of paramount importance for the future.

a) Potential new treatments

BMD is strikingly but transiently promoting the production of romosozumab, a humanizing antibody that binds sclerostin and inhibits major Bone resorption [83]. Two research endpoint fractures have shown that starting a remedy for 12 months of romosozumab remedy observed with either denosumab (or alendronate), is finer than a remedy for either denosumab alone or alendronate alone (initiated after 12 months of placebo) [84]. In contrast to alendronate, an accelerated danger was once determined by cardiovascular unfavourable incidents with romosozumab but no longer by placebo. Regulatory review the results of those studies.

b) Combining osteoporosis therapies

The use of two anti-resorptive agents has not, but has been validated in experiments now [82]. Bisphosphonates and teriparatides are no longer a significant advantage over monotherapy. Starting therapy for the effects of both teriparatide and Denosumab with better and more effective properties for BMD than both treatments by themselves, but whether this combined impact on greater fracture health is understood or not. On the other hand, sequence pills are encouraged to be used to perform long-term management. Estrogen and raloxifene in young postmenopausal women are outstanding and teriparatide and abaloparathy are ideal for those with a high risk of vertebral fracture. The continuation of bisphosphonate/denosumab therapy in patients with an excessive probability of fracture must be examined after each of these therapies.

c) Abaloparatide

Skeletal findings close to teriparatide are found by abaloparatide, a synthesized version of PTHrP. A daily administration of 80μg abaloparatide via subcutaneous injection has been compared to 20μg daily and placebo for the postmenopausal women with osteoporosis. The likelihood of vertebral and non-vertebral injuries was significantly reduced by 86 percentage and 43 percentage respectively after 18 months of abaloparatide treatment, as contrasted with placebo [80]. In abaloparatide-treated women, hypercalcemia was considerably less prevalent (3.4% vs6.4%). The medication was approved in the US but was refused approval in Europe because it had an impact of minimizing non-vertebral fractures and decreased cardiac rate and palpitations.

d) Teriparatide

The risk of vertebral and nonvertebral fractures decreased with teriparatide given every day through subcutaneous injections for 18–24 months [79]. In a randomized correlation report, teriparatide was considerably higher in postmenopausal women with fracture osteoporosis than previously risedronate[80]. In patients with hypercalcaemia, previous skeleton radiation remedies, skeletal illnesses or bone metastases, teriparatide should no longer be used and the use is limited to 18–24 months due to theoretical concerns over increased risk of osteosarcoma. When the therapy is discontinued, it is related to the maintenance or expansion of bisphosphonate or denosumab in BMD [81].

e) Selective oestrogen receptor modulators

An oestrogen agonist or antagonist, raloxifene is a sensitive antiresorptive agent reported in women with postmenopausal osteoporosis to reduce the risk for vertebral, non-vertebral or pulmonary fractures [75]. In women with danger caused by coronary heart disease (age average 67.5 years), the possibility of raloxifene may worsen warm flashes, bear an oestrogen-like chance of venous thrombosis and be associated to an increased risk of stroke death [76]. Nevertheless, it decreases the risk of invasive breast cancer dramatically. In addition to prominent vasomotor menopausal symptoms that are endangered for vertebral, but not for hip fractures, which are not hazardous for venous thrombosis, Raloxifene is an attractive therapeutic choice for young females with osteoporosis, especially those who are worried about breast cancers. As a patient's fracture for a while becomes a major scientific issue, it may be necessary to turn to a medication designed to reduce the risk of hip fractures. In girls with post-menopausal osteoporosis and their safety profile, the consequences of bazedoxifen on the risk of

fractures are similar to those of raloxifene [77]. In the US it is approved for postmenopausal Osteoporosis to be protected from aggregating conjugated oestrogen and bazedoxifen[78].

f) Hormone replacement therapy

Oestrogen therapy with or except for progestin correctly prevents postmenopausal females from bone loss and reduces the risk of vertebral and hip fractures by using 34% of the low-risk population in the Women's Health Initiative [72]. Initiating estrogen remedies for girls over ten years after menopause is no longer encouraged because of cardiovascular safety concerns, but the increase in cardiovascular hazard no longer appears to be linked soon after menopause [73]. Guidelines recommend the use of oestrogen in early menopause and as a treatment to avoid bone loss and reduce the danger of fracture in girls at high fracture risk where potential treatments are not appropriate for handling menopause signs and symptoms[74].

g) RANK ligand inhibitor

Denosumab, a monoclonal antibody entirely human, binds and inhibits RANK ligand which leads to significant but reversible bone remodelling inhibition [69]. Denosumab, per 6 months subcutaneous injected, reduces the likelihood of vertebral, non-vertebral and hip fractures, as well as the consequences within the first year of administering them[70]. BMD gradually increases over 10 years of treatments and for this time it is actively covered against fractures [71]. Denosumab is more regularly associated with skin rash and infection than placebo. In follow-up studies lasting up to 10 years, there was no theoretical problem about possible immune dysfunction and extended risk of serious pollution. In long-term therapy, the link between denosumab therapy period and these potential side effects was determined with very rare instances of odd femoral fractures and osteonecrosis of the jaw. After denosumab cures are stopped, bone remodelling indicators rise quickly over basic levels before the pre-treatment levels are returned. There have been significant reductions in the health of BMD and vertebral injuries, including numerous vertebral fractures 3–18 months since denosumab therapy has been stopped [72]. The significance of adherence to the ordinary cure system must be consulted with patients and their health care suppliers. Renovation of therapeutic benefits with any other anti-resorptive drugs should normally be indicated if treatment is stopped.

CONCLUSION

Osteoporosis is a relatively common serious disorder that places patients and community at a heavy cost of pain.Genetic osteoporosis findings have possible effects on clinical practice.In the field of genetics broadly and in particular osteoporosis, this is a time of great anticipation.This also demonstrated that the strategy that was embraced would address other complex quantitative characteristics such as osteoporosis. This stance is reinforced by the results of initial genome-wide osteoporosis interaction research. Genetic diagnostic research is projected to become a possibility over the next generation with the introduction of proven BMD predictive knowledge. The hope that the disappointments of the last few decades have shown the genetic group that the effectively detected genetic materials were mainly due to thorough phenotyping, advanced research design, appropriate cohorts and teamwork. We finally completed with the beginning, now we get to see how a prosperous future can be accomplished.

REFERENCES

1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. Jama 2001; 85:785-95.
2. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, Lindsay R. Clinician's guide to prevention and treatment of osteoporosis. Osteoporosis international. 2014; 25(10):2359-81.
3. Cooper C, Campion G, Melton L3. Hip fractures in the elderly: a world-wide projection. Osteoporosis international. 1992; 2(6):285-9.
4. Boonen S, Singer AJ. Osteoporosis management: impact of fracture type on cost and quality of life in patients at risk for fracture I. Current medical research and opinion. 2008; 24(6):1781-8.
5. Baek JH, Lee YK, Hong SW, Ha YC, Koo KH. Knowledge on osteoporosis in guardians of hip fracture patients. Journal of bone and mineral metabolism. 2013; 31(4):481-4.

6. Riggs BL, Wahner HW, Seeman E, Offord KP, Dunn WL, Mazess RB, Johnson KA, Melton LJ. Changes in bone mineral density of the proximal femur and spine with aging: differences between the postmenopausal and senile osteoporosis syndromes. The Journal of clinical investigation. 1982; 70(4):716-23.
7. Shetty S, Kapoor N, Bondu JD, Thomas N, Paul TV. Bone turnover markers: Emerging tool in the management of osteoporosis. Indian journal of endocrinology and metabolism. 2016;20(6):846.
8. Seibel MJ. Molecular markers of bone turnover: biochemical, technical and analytical aspects. Osteoporosis International. 2000; 11(18):S18-29.
9. Saito M, Marumo KM. Collagen cross-links as a determinant of bone quality: a possible explanation for bone fragility in aging, osteoporosis, and diabetes mellitus. Osteoporosis international. 2010; 21(2):195-214.
10. Boskey A. Bone mineral crystal size. Osteoporosis international. 2003; 14(5):16-21.
11. Kanis JA, Svedbom A, Harvey N, McCloskey EV. The osteoporosis treatment gap. Journal of Bone and Mineral Research. 2014; 29(9):1926-8.
12. Hernandez CJ, Beaupre GS, Carter DR. A theoretical analysis of the relative influences of peak BMD, age-related bone loss and menopause on the development of osteoporosis. Osteoporosis international. 2003; 14(10):843-7.
13. Macdonald HM, Nishiyama KK, Kang J, Hanley DA, Boyd SK. Age-related patterns of trabecular and cortical bone loss differ between sexes and skeletal sites: a population based HR pQCT study. Journal of Bone and Mineral Research. 2011; 26(1):50-62.
14. Zebaze RM, Ghasem-Zadeh A, Bohte A, Iuliano-Burns S, Mirams M, Price RI, Mackie EJ, Seeman E. Intracortical remodelling and porosity in the distal radius and post-mortem femurs of women: a cross-sectional study. The Lancet. 2010; 375(9727):1729-36.
15. Kanis JA, Johnell O, Odén A, Johansson H, McCloskey EF. FRAX™ and the assessment of fracture probability in men and women from the UK. Osteoporosis international. 2008; 19(4):385-97.
16. Compston J, Bowring C, Cooper A, Cooper C, Davies C, Francis R, Kanis JA, Marsh D, McCloskey EV, Reid DM, Selby P. Diagnosis and management of osteoporosis in postmenopausal women and older men in the UK: National Osteoporosis Guideline Group (NOGG) update 2013. Maturitas. 2013; 75(4):392-6.
17. Slemenda CW, Turner CH, Peacock M, Christian JC, Sorbel J, Hui SL, Johnston CC. The genetics of proximal femur geometry, distribution of bone mass and bone mineral density. Osteoporosis international. 1996; 6(2):178-82.
18. Flicker L, Faulkner KG, Hopper JL, Green RM, Kaymakci B, Nowson CA, Young D, Wark JD. Determinants of hip axis length in women aged 10–89 years: a twin study. Bone. 1996; 18(1):41-5.
19. Deng HW, Mahaney MC, Williams JT, Li J, Conway T, Davies KM, Li JL, Deng H, Recker RR. Relevance of the genes for bone mass variation to susceptibility to osteoporotic fractures and its implications to gene search for complex human diseases. Genetic Epidemiology: The Official Publication of the International Genetic Epidemiology Society. 2002; 22(1):12-25.
20. Fox KM, Cummings SR, Powell-Threets K, Stone K, Study of Osteoporotic Fractures Research Group. Family history and risk of osteoporotic fracture. Osteoporosis international. 1998; 8(6):557-62.
21. Deng HW, Chen WM, Recker S, Stegman MR, Li JL, Davies KM, Zhou Y, Deng H, Heaney R, Recker RR. Genetic determination of Colles' fracture and differential bone mass in women with and without Colles' fracture. Journal of Bone and Mineral Research. 2000; 15(7):1243-52.
22. Oei L, Estrada K, Duncan EL, Christiansen C, Liu CT, Langdahl BL, Obermayer-Pietsch B, Riancho JA, Prince RL, van Schoor NM, McCloskey E. Genome-wide association study for radiographic vertebral fractures: a potential role for the 16q24 BMD locus. Bone. 2014; 59:20-7.

23. Alonso N, Estrada K, Albagha OM, Herrera L, Reppe S, Olstad OK, Gautvik KM, Ryan NM, Evans KL, Nielson CM, Hsu YH. Identification of a novel locus on chromosome 2q13, which predisposes to clinical vertebral fractures independently of bone density. Annals of the rheumatic diseases. 2018; 77(3):378-85.
24. Guo Y, Tan LJ, Lei SF, Yang TL, Chen XD, Zhang F, Chen Y, Pan F, Yan H, Liu X, Tian Q. Genome-wide association study identifies ALDH7A1 as a novel susceptibility gene for osteoporosis. PLoS genetics. 2010; 6(1):e1000806.
25. Trajanoska K, Morris JA, Oei L, Zheng HF, Evans DM, Kiel DP, Ohlsson C, Richards JB, and Rivadeneira F. Assessment of the genetic and clinical determinants of fracture risk: genome wide association and Mendelianrandomization study. Bmj. 2018; 362:k3225.
26. Rucci N. Molecular biology of bone remodeling. Clinical cases in mineral and bone metabolism. 2008; 5(1):49.
27. Khosla S. Minireview: The opg/rankl/rank system. Endocrinology. 2001; 142(12):5050-5.
28. Zuo C, Huang Y, Bajis R, Sahih M, Li YP, Dai K, Zhang X. Osteoblastogenesis regulation signals in bone remodeling. Osteoporosis international. 2012; 23(6):1653-63.
29. Ikebuchi Y, Aoki S, Honma M, Hayashi M, Sugamori Y, Khan M, Kariya Y, Kato G, Tabata Y, Penninger JM, Udagawa N. Coupling of bone resorption and formation by RANKL reverse signaling. Nature. 2018; 561(7722):195.
30. Wright HL, McCarthy HS, Middleton J, Marshall MJ. RANK, RANKL and osteoprotegerin in bone biology and disease. Current reviews in musculoskeletal medicine. 2009; 2(1):56-64.
31. Polyzos SA, Cundy T, Mantzoros CS. Juvenile Paget disease. Metabolism. 2018; 80:15-26.
32. Divieti Pajevic P. Recent progress in osteocyte research. Endocrinology and Metabolism. 2013; 28(4):255-61.
33. Uda Y, Azab E, Sun N, Shi C, Pajevic PD. Osteocyte mechanobiology. Current osteoporosis reports. 2017; 15(4):318-25.
34. Plotkin LI, Bellido T. Osteocytic signaling pathways as therapeutic targets for bone fragility. Nature Reviews Endocrinology. 2016; 12(10):593.
35. Baron R, Kneissel M. WNT signaling in bone homeostasis and disease: from human mutations to treatments. Nature medicine. 2013; 19(2):179.
36. Maeda K, Takahashi N, Kobayashi Y. Roles of Wnt signals in bone resorption during physiological and pathological states. Journal of molecular medicine. 2013; 91(1):15-23.
37. Sugimura R, Li L. Noncanonical Wnt signaling in vertebrate development, stem cells, and diseases. Birth Defects Research Part C: Embryo Today: Reviews. 2010; 90(4):243-56.
38. Laine CM, Wessman M, Toiviainen-Salo S, Kaunisto MA, Mayranpaa MK, Laine T, et al. A novel splice mutation in PLS3 causes X-linked early onset low-turnover osteoporosis. J Bone Miner Res. (2015) 30:510–8.
39. Oprea GE, Krober S, McWhorter ML, Rossoll W, Muller S, Krawczak M, Bassell GJ, Beattie CE, Wirth B. Plastin 3 is a protective modifier of autosomal recessive spinal muscular atrophy. Science. 2008; 320(5875):524-7.
40. Van der Pauw MT, Klein-Nulend J, van den Bos T, Burger EH, Everts V, Beertsen W. Response of periodontal ligament fibroblasts and gingival fibroblasts to pulsating fluid flow: nitric oxide and prostaglandin E2 release and expression of tissue non-specific alkaline phosphatase activity. J Periodontal Res. (2000) 35:335–43.
41. Tanaka Kamioka K, Kamioka H, Ris H, Lim SS. Osteocyte shape is dependent on actin filaments and osteocyte processes are unique actin rich projections. Journal of Bone and Mineral Research. 1998; 13(10):1555-68.
42. Bacabac RG, Smit TH, Van Loon JJ, Doulabi BZ, and Helder M, Klein-Nulend J. Bone cell responses to high-frequency vibration stress: does the nucleus oscillate within the cytoplasm. The FASEB journal. 2006; 20(7):858-64.
43. Wesseling-Perry K, Makitie RE, Valimaki VV, Laine T, Laine CM, Valimaki MJ, et al. Osteocyte protein expression is altered in low-turnover

osteoporosis caused by mutations in WNT1 and PLS3. J Clin Endocrinol Metab. (2017) 102:2340–8.
44. Neugebauer J, Heilig J, Hosseinibarkooie S, Ross BC, Mendoza-Ferreira N, Nolte F, et al. Plastin 3 influences bone homeostasis through regulation of osteoclast activity. Hum Mol Genet. (2018) 27:4249–62.
45. Ralston SH, de Crombrugghe B. Genetic regulation of bone mass and susceptibility to osteoporosis. Genes & development. 2006; 20(18):2492-506.
46. Burge R, Dawson Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis related fractures in the United States, 2005–2025. Journal of bone and mineral research. 2007; 22(3):465-75.
47. McGrother CW, Donaldson MM, Clayton D, Abrams KR, Clarke M. Evaluation of a hip fracture risk score for assessing elderly women: the Melton Osteoporotic Fracture (MOF) study. Osteoporosis International. 2002; 13(1):89-96.
48. AL-Homood IA, Sheshah I, Mohammed AG, Gasim GI. The prevalence and risk factors of osteoporosis among a Saudi female diabetic population. Open access Macedonian journal of medical sciences. 2017; 5(2):177.
49. Curran D, Maravic M, Kiefer P, Tochon V, Fardellone P. Epidemiology of osteoporosis-related fractures in France: a literature review. Joint Bone Spine. 2010; 77(6):546-51.
50. Ahlborg HG, Rosengren BE, Jarvinen TL, Rogmark C, Nilsson JÅ, Sernbo I, Karlsson MK. Prevalence of osteoporosis and incidence of hip fracture in women-secular trends over 30 years. BMC musculoskeletal disorders. 2010; 11(1):48.
51. Kim BT. Mosekilde L, Duan Y, Zhang XZ, Tornvig L, Thomsen JS, Seeman E. The structural and hormonal basis of sex differences in peak appendicular bone strength in rats. J Bone Miner Res. 2003; 18:150-5.
52. Khosla S, Westendorf JJ, Oursler MJ. Building bone to reverse osteoporosis and repair fractures. The Journal of clinical investigation. 2008; 118(2):421-8.
53. Javaid MK, Holt RI. Understanding osteoporosis. Journal of Psychopharmacology. 2008;22(2_suppl):38-45
54. Brown JP, Fortier M, Frame H, Lalonde A, Papaioannou A, Senikas V, Yuen CK, Henneberg E, Capistran C, Oman J. Canadian consensus conference on osteoporosis, 2006 update. Journal of Obstetrics and Gynecology Canada. 2006; 28(2):S95-112.
55. Manolagas SC, Jilka RL, Kousteni S, Bellido T, Weinstein RS, O'Brien CA, Plotkin L, Han L. Response to Windahl et al. The Journal of clinical investigation. 2006; 116(11):2834-.
56. Karasik D, Ferrari SL. Contribution of gender-specific genetic factors to osteoporosis risk. Annals of human genetics. 2008; 72(5):696-714.
57. Ackert-Bicknell CL, Hibbs MA. The need for mouse models in osteoporosis genetics research. BoneKEy reports. 2012; 1.
58. Richards JB, Zheng HF, Spector TD. Genetics of osteoporosis from genome-wide association studies: advances and challenges. Nature Reviews Genetics. 2012; 13(8):576.
59. Estrada K, Styrkarsdottir U, Evangelou E, Hsu YH, Duncan EL, Ntzani EE, Oei L, Albagha OM, Amin N, Kemp JP, Koller DL. Genome-wide meta-analysis identifies 56 bone mineral density loci and reveals 14 loci associated with risk of fracture. Nature genetics. 2012; 44(5):491.
60. Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, McCarthy MI, Ramos EM, Cardon LR, Chakravarti A, Cho JH. Finding the missing heritability of complex diseases. Nature. 2009; 461(7265):747.
61. Zheng HF, Forgetta V, Hsu YH, Estrada K, Rosello-Diez A, Leo PJ, et al. Whole-genome sequencing identifies EN1 as a determinant of bone density and fracture. Nature. 2015; 526:112-7.
62. Willing M, Sowers M, Aron D, Clark MK, Burns T, Bunten C, Crutchfield M, D'Agostino D, Jannausch M. Bone mineral density and its change in white women: estrogen and vitamin D receptor

genotypes and their interaction. Journal of Bone and Mineral Research. 1998; 13(4):695-705.

63. Gennari L, Becherini L, Masi L, Mansani R, Gonnelli S, Cepollaro C, Martini S, Montagnani A, Lentini G, Becorpi AM, Brandi ML 1998 Vitamin D and estrogen receptor allelic variants in Italian postmenopausal women: evidence of multiple gene contribution to bone mineral density. J Clin Endocrinol Metab 83:939–944
64. Vandevyver C, Vanhoof J, Declerck K, Stinissen P, Vandervorst C, Michiels L, Cassiman JJ, Boonen S, Raus J, Geusens P 1999 Lack of association between estrogen receptor genotypes and bone mineral density, fracture history, or muscle strength in elderly women. J Bone Miner Res 14:1576–1582
65. Uitterlinden AG, Weel AE, Burger H, Fang Y, van Duijn CM, Hofman A, van Leeuwen JP, Pols HA 2001 Interaction between the vitaminDreceptor gene and collagen type Iα1 gene in susceptibility for fracture. J Bone Miner Res 16:379–385
66. Rivadeneira F, van Meurs JB, Kant J, Zillikens MC, Stolk L, Beck TJ, Arp P, Schuit SC, Hofman A, Houwing-Duistermaat JJ, van Duijn CM, van Leeuwen JP, Pols HA, Uitterlinden AG 2006 Estrogen receptor (ESR2) polymorphisms in interaction with estrogen receptor (ESR1) and insulin-like growth factor I (IGF1) variants influence the risk of fracture in postmenopausal women. J Bone Miner Res 21:1443–1456
67. Richards JB, Rivadeneira F, Inouye M, Pastinen TM, Soranzo N, Wilson SG, Andrew T, Falchi M, Gwilliam R, Ahmadi KR, Valdes AM, Arp P, Whittaker P, Verlaan DJ, Jhamai M, Kumanduri V, Moorhouse M, van Meurs JB, Hofman A, Pols HA, Hart D, Zhai G, Kato BS, Mullin BH, Zhang F, Deloukas P, Uitterlinden AG, Spector TD 2008 Bone mineral density, osteoporosis, and osteoporotic fractures: a genome-wide association study. Lancet 371:1505–1512
68. Rivadeneira F, Styrka´ rsdottir U, Estrada K, Halldo´ rsson BV, Hsu YH, Richards JB, Zillikens MC, Kavvoura FK, Main, Aulchenko YS, Cupples LA, Deloukas P, Demissie S, Grundberg E, Hofman A, Kong A, Karasik D, van Meurs JB, Oostra B, Pastinen T, Pols HA, Sigurdsson G, Soranzo N, Thorleifsson G, Thorsteinsdottir U, Williams FM, Wilson SG, Zhou Y, Ralston SH, van Duijn CM, Spector T, Kiel DP, Stefansson K, Ioannidis JP, Uitterlinden AG 2009 Twenty bone-mineral-density loci identified by largescale meta-analysis of genome-wide association studies. Nat Genet 41:1199–1206
69. Cummings SR, Martin JS, McClung MR, Siris ES, Eastell R, Reid IR, Delmas P, Zoog HB, Austin M, Wang A, Kutilek S. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. New England Journal of Medicine. 2009; 361(8):756-65.
70. Bone HG, Wagman RB, Brandi ML, Brown JP, Chapurlat R, Cummings SR, Czerwiński E, Fahrleitner-Pammer A, Kendler DL, Lippuner K, Reginster JY. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomized FREEDOM trial and open-label extension. The lancet Diabetes & endocrinology. 2017; 5(7):513-23.
71. Cummings SR, Ferrari S, Eastell R, Gilchrist N, Jensen JE, McClung M, Roux C, Tarring O, Valter I, Wang AT, Brown JP. Vertebral fractures after discontinuation of denosumab: a post hoc analysis of the randomized placebo controlled FREEDOM trial and its extension. Journal of Bone and Mineral Research. 2018; 33(2):190-8.
72. Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, LeBoff M, Lewis CE, McGowan J, Neuner J, and Pettinger M. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. Jama. 2003; 290(13):1729-38.
73. Hodis HN, Mack WJ, Henderson VW, Shoupe D, Budoff MJ, Hwang-Levine J, Li Y, Feng M, Dustin L, Kono N, Stanczyk FZ. Vascular effects of early versus late postmenopausal treatment with estradiol. New England Journal of Medicine. 2016; 374(13):1221-31.
74. Pinkerton JA, Aguirre FS, Blake J, Cosman F, Hodis H, Hoffstetter S,

Kaunitz AM, Kingsberg SA, Maki PM, Manson JA, Marchbanks P. The 2017 hormone therapy position statement of the North American Menopause Society. Menopause. 2017; 24(7):728-53.

75. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 1999; 282: 637–45.
76. Lewiecki EM, Miller PD, Harris ST, Bauer DC, Davison KS, Dian L, Hanley DA, McClung MR, Yuen CK, Kendler DL. Understanding and communicating the benefits and risks of denosumab, raloxifene, and teriparatide for the treatment of osteoporosis. Journal of Clinical Densitometry. 2014; 17(4):490-5.
77. Silverman SL, Christiansen C, Genant HK, Vukicevic S, Zanchetta JR, de Villiers TJ, Constantine GD, Chines AA. Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3 year, randomized, placebo, and active controlled clinical trial. Journal of bone and mineral research. 2008; 23(12):1923-34.
78. Lindsay R, Gallagher JC, Kagan R, Pickar JH, Constantine G. Efficacy of tissue-selective estrogen complex of bazedoxifene/ conjugated estrogens for osteoporosis prevention in at-risk postmenopausal women. Fertil Steril 2009; 92: 1045–52.
79. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. New England journal of medicine. 2001; 344(19):1434-41.
80. Kendler DL, Marin F, Zerbini CA, Russo LA, Greenspan SL, Zikan V, Bagur A, Malouf-Sierra J, Lakatos P, Fahrleitner-Pammer A, Lespessailles E. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicenter, double-blind, double-dummy, randomized controlled trial. The Lancet. 2018; 391(10117):230-40.
81. McClung MR. Using osteoporosis therapies in combination. Curr Osteoporosis Rep 2017; 15: 343–52.
82. Miller PD, Hattersley G, Riis BJ, Williams GC, Lau E, Russo LA, Alexandersen P, Zerbini CA, Hu MY, Harris AG, Fitzpatrick LA. Effect of abaloparatide vs. placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. Jama. 2016; 316(7):722-33.
83. McClung MR, Grauer A, Boonen S, Bolognese MA, Brown JP, Diez-Perez A, Langdahl BL, Reginster JY, Zanchetta JR, Wasserman SM, Katz L. Romosozumab in postmenopausal women with low bone mineral density. New England Journal of Medicine. 2014; 370(5):412-20.
84. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, Hofbauer LC, Lau E, Lewiecki EM, Miyauchi A, Zerbini CA. Romosozumab treatment in postmenopausal women with osteoporosis. New England Journal of Medicine. 2016; 375(16):1532-43.
85. Mclellan AR, Wolfowitz SE, Zimovetz EA, Beard SM, Lock S, McCrink L, Adekunle F, Roberts D. Fracture liaison services for the evaluation and management of patients with osteoporotic fracture: a cost-effectiveness evaluation based on data collected over 8 years of service provision. Osteoporosis international. 2011; 22(7):2083.
86. Walters S, Khan T, Ong T, Sahota O. Fracture liaison services: improving outcomes for patients with osteoporosis. Clinical interventions in aging. 2017; 12:117.