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REVIEW

Bone: best papers of the year 2017

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Abstract

Summary An overview of selected papers related to bone published in 2017 is provided.

Purpose This paper accompanies a lecture at the 2018 Belgian Bone Club annual Clinical Update Symposium held in Brussels on January 20th, discussing the best papers (in the opinion of the author) published in the previous year.

Methods A PubMed search using the keyword "bone" and articles published in 2017.

Results Hot topics include screening for osteoporosis, novel anabolic drugs such as romosozumab and abaloparatide for osteoporosis and rare metabolic bone diseases, as well as long-term efficacy of denosumab and possible risk of multiple vertebral fractures following its discontinuation. Other selected articles cover effectiveness of bisphosphonates and changes in mineralization after long-term use, new guidelines for glucocorticoid- and aromatase inhibitor-induced osteoporosis, increasing use of high-dose vitamin D supplements despite lack of evidence for their widespread high-dose use, and cardiovascular safety concerns surrounding the use of calcium supplements. Other topics discussed are effects of diabetes on bone health, reciprocal crosstalk between bone cells and adipose tissue, and resistance exercise training to prevent bone loss and sarcopenia.

Conclusions These papers offer a hopeful outlook for a better treatment and management of patients with osteoporosis and other metabolic bone diseases anno 2018.

Keywords Osteoporosis · Screening · Bone anabolic drugs · Vertebral fractures · Vitamin D · Calcium supplements

Introduction

A PubMed search for "bone" yields more than 40,000 articles published in 2017, although the number has slightly declined since 2015 (Fig. 1). Obviously, it is impossible to read even just the titles of all of these articles. The selection of "best articles" is by no means based on a systematic review and merely represents the personal judgment of the author. In this paper, I focus mainly on articles published in core high-impact journals or those drawing considerable media attention. Rather than discussing single articles in depth, I aim to shortly present "hot topics" or themes highlighted by 2–3 key articles published online or in print in 2017. References are limited to the "top" articles themselves; I refer the reader to the individual articles for background, discussion, and related literature.

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Screening for osteoporosis

A topline paper describes the results of the Screening for Osteoporosis in Older women for the Prevention of fractures (SCOOP) study. This pragmatic trial randomized almost 12,500 women aged 70–85 years from general practices in the UK to either usual care or screening based on FRAX® with or without additional bone mineral density (BMD) measurement. After 5 years, screening significantly reduced the absolute risk of hip fractures (the risk of which was the treatment criterion and a secondary outcome) from 3.5 to 2.6% ($p = 0.002$), with a hazard ratio of 0.72 (95% confidence interval 0.59–0.89) [1]. However, the risk of osteoporotic fractures (the primary outcome), clinical fractures, or mortality was not significantly reduced. Notably, the recommendation to start anti-resorptive therapy was quite restrictive (in only 14% of screening group participants), in accordance with previous NOGG guidelines from 2008. The new UK NOGG guidelines also published last year [2] are however more in line with US NOF guidelines and install a fixed treatment threshold after 70 years, increasing the number of older people eligible for treatment. Results of a similar but smaller trial (SALT Osteoporosis Study) in the Netherlands are eagerly awaited.

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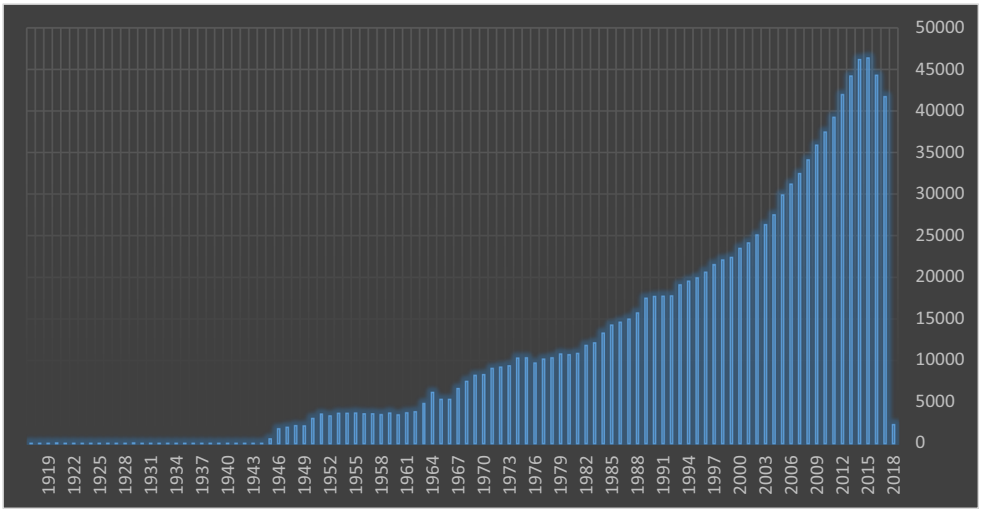

Fig. 1 Number (*Y*-axis) of PubMed-indexed articles returned after a search for "bone," per year (*X*-axis) over the last 100 years (1918–2018, with the last year (2018) still incomplete)

New anabolic therapies: romosozumab and abaloparatide

One of the most discussed papers last year was the ARCH trial, in which $n = 4093$ post-menopausal women were randomized to monthly s.c. romosozumab or weekly oral alendronate for 1 year, followed by 2 years of alendronate in both groups [3]. Not only did romosozumab reduce the risk of vertebral fractures after 12 months but also in the 24 months thereafter the risk of new vertebral fractures was reduced by 48% ($p < 0.001$). The risk of non-vertebral (− 19%) and hip fractures (− 38%) was also reduced in the romosozumab-to-alendronate vs. the alendronate-alendronate group. Thus, there was further evidence that initial bone anabolic therapy with romosozumab reduces fracture risk compared to an initial anti-resorptive strategy. These favorable outcomes can be explained by the superior increase in BMD with the anti-sclerostin antibody vs. alendronate, which is accompanied by increased bone formation and reduced bone resorption markers. Similarly, another trial of romosozumab vs. teriparatide in prior oral bisphosphonate users showed superior BMD increases at the lumbar spine and hip with sclerostin inhibition [4]. However, commentators largely focused on an imbalance in cardiac ischemic and cerebrovascular events in the ARCH trial. The latter was however not observed in the much larger placebo-controlled FRAME trial. The reasons for this discrepancy remain unclear, but the authors speculated that a baseline higher cardiovascular risk in ARCH trial participants or a cardioprotective effect of alendronate could be involved. In response to these results, the US Food and Drug Administration has not yet decided on romosozumab's regulatory application, and has meanwhile requested that the dossier be resubmitted including cardiovascular safety data from the FRAME, ARCH, and another trial in male osteoporosis (BRIDGE).

Extension data were also published from the ACTIVE trial of abaloparatide, an analogue of teriparatide with a more favorable safety and efficacy profile. After 18 months of abaloparatide or placebo, participants from both arms of this trial received 6 months of weekly oral alendronate. During these 6 months, no new vertebral fractures occurred in participants previously treated with abaloparatide vs. seven incident vertebral fractures in alendronate users, which was however not a significant difference. Overall, the significant reduction of vertebral, non-vertebral, and clinical fractures observed during the 18-month study phase was maintained during the 6-month extension [5]. Nevertheless, clinicians will have to take the high cost and reimbursement criteria of this new osteoanabolic drug into consideration.

On a side note, phase 2 clinical trials evaluated another anti-sclerostin monoclonal antibody (BPS804) for the treatment of adults with osteogenesis imperfecta [6] and hypophosphatasia [7]. More therapeutic options for patients with rare metabolic bone diseases are expected in the coming years.

What's new with bisphosphonates and denosumab?

Final results from the 10-year extension of the FREEDOM trial showed that denosumab continuous to increase BMD over one decade of therapy [8]. Attention was drawn however by a post hoc analysis of this trial, focusing on the risk of multiple vertebral fractures after discontinuation of denosumab [9]. The term "rebound-associated vertebral fractures" was coined to indicate the potential risk of multiple vertebral fractures, usually 8–16 months after the last denosumab s.c. injection, when BMD in bisphosphonate-naïve patients reverts to pre-treatment levels and bone

turnover markers (BTMs) rebound above baseline levels [10]. In the FREEDOM trial, the rate of multiple vertebral fractures after stopping denosumab increased quickly towards (both not above) the risk seen after stopping placebo. Nevertheless, in those subjects who did experience vertebral fractures, there was a borderline significantly higher proportion that such vertebral fractures were multiple ($n = 34$, 61% after stopping denosumab vs. $n = 12$, 39% after stopping placebo, $p = 0.049$) [9]. Taken together, the benefits of long-term continuation and possible risks of discontinuation will likely influence clinical decision making during long-term management of these patients.

Two large Swedish retrospective epidemiological studies reported that oral alendronate was associated with a reduced risk of hip fractures, either in older glucocorticoid users [11] or in the oldest-old [12]. Since there is no evidence from randomized trials on hip fracture risk reduction in these populations, these observations offer reassurance.

Several studies also investigated matrix and mineralization changes during long-term bisphosphonate use, reporting higher matrix mineralization [13], and presence of larger crystals [14]. A case report of three sisters who sustained bisphosphonate-associated atypical femoral fractures suggested that mutations in *GGPS1* or other enzymes in the mevalonate pathway constitute a new genetic basis for these fractures [15]. Although these studies shed more light on the pathophysiology of this rare adverse event, it should not be overlooked that bisphosphonates prevent far more fractures than they cause.

The American College of Rheumatology released new guidelines for the prevention of glucocorticoid-osteoporosis [16], while several societies published a joint position statement on the management of aromatase inhibitor-associated bone loss in post-menopausal breast cancer patients [17]. Also in the field of bone metastasis, a study demonstrated the non-inferiority of longer dosing intervals of zoledronic acid every 12 instead of 4 weeks, offering a more attractive therapeutic options for many patients [18]. Finally, a systematic review concluded that there is still a large gap of evidence concerning the benefits and harms of osteoporosis medications in patients with chronic kidney disease [19].

Calcium and vitamin D

A score of trials published in 2017 could not demonstrate benefits of high doses of calcium, vitamin D, or dairy products. These include lack of a significant difference of higher than usual dairy intake on bone mass in early puberty [20], of calcium and vitamin D supplements for the prevention of cancer [21], or of vitamin D on insulin sensitivity or secretion [22], cardiovascular disease [23], mortality in heart failure patients [24], or on viral upper respiratory tract infections in children [25]. Although a smaller trial ($n = 107$) reported that high-dose (100,000 IU vitamin D_3 monthly) reduced the risk of acute respiratory tract infections in older long-term care residents, this benefit was entirely outweighed by a significant increase in falls risk [26]. Nevertheless, the use of vitamin D supplements of both ≥ 1000 and ≥ 4000 IU/day has grown exponentially in the USA (and probably elsewhere too), in all age groups but particularly in the elderly [27]. Importantly, in a randomized trial in overweight elderly comparing 1000 mg of calcium citrate with either low (600 IU) or high (3750 IU) dose vitamin D_3, there was no significant difference in BMD or BTMs [28]. Thus, any benefit from these increasingly popular high doses remains to be demonstrated. Nevertheless, these findings should not distract from the proven fracture prevention benefits of regular calcium and vitamin D supplements in deficient and/or elderly subjects, as well as in combination with anti-resorptive or osteoanabolic drugs. A case report also lent further credence to the possibility of hypervitaminosis D associated with tanning bed use [29].

Finally, a large Mendelian randomization study showed that genetic variants associated with genetically determined higher serum calcium levels (particularly a single nucleotide polymorphism near the calcium-sensing receptor, *CASR*) were also associated with a significantly higher risk of coronary artery disease as well as myocardial infarction [30]. These findings draw attention to the risk of cardiovascular calcifications in hypercalcemic disorders (e.g., familial hypocalciuric hypercalcemia), although they add little new information to the debate surrounding possible cardiovascular risks of calcium supplements.

What's new for the endocrinologist? Testosterone and diabetic bone

A trial of transdermal testosterone replacement in hypogonadal men showed increases in volumetric BMD as well as estimated strength, which were more pronounced in trabecular than in cortical bone and more pronounced at the spine, while changes in areal BMD were not significant at the hip [31]. Still, evidence that testosterone replacement in older men reduces fracture risk remains lacking, while possible cardiovascular risks remain lurking. Another analysis from the MrOS study showed that while guidelines recommend measurement of testosterone in male osteoporosis and low estradiol and high sex hormone-binding globulin are associated with greater bone loss and fracture risk in older men, none of these measurements have clinical utility beyond BMD, FRAX®, or their combination [32]. Given these data, current guidelines may need to be reconsidered.

Bone health in subjects with diabetes mellitus is also gaining attention. An elegant series of studies showed that

both type 1 diabetes [33] as well as insulin resistance at the age of peak bone mass [34] are associated with cortical bone size deficits. These clinical findings are also of interest in light of preclinical studies on the link between bone and whole-organism energy metabolism (see the Preclinical and translational studies: fat bones and senescent cells section below).

Exercise and sarcopenia

Obesity is a pandemic health issue, but weight loss unfortunately leads to not only loss of adipose tissue but also of muscle and bone mass. A randomized trial showed that BMD loss is greatest in dieting older adults who perform aerobic exercise, while resistance training maintains bone and muscle mass as well as strength [35]. Similarly, the LIFTMOR trial showed that high-intensity supervised resistance training in post-menopausal osteopenic women improved hip and lumbar spine BMD, all physical performance measures, and even prevented height loss [36]. Further trials are needed to investigate the effects of physical training regimens on frailty, sarcopenia, and patient-reported outcomes using, e.g., the recently developed sarcopenia-related quality of life assessment tool (SarQoL®) [37].

Preclinical and translational studies: fat bones and senescent cells

A set of preclinical papers further strengthened the notion that bone could play a role in the pathophysiology and treatment of obesity. Kousteni's group identified lipocalin 2 as an osteoblast-derived hormone promoting insulin secretion and sensitivity and suppressing appetite via the hypothalamic melanocortin 4 receptor [38]. Another paper contributed to PNAS suggests that osteocytes through sensation of gravitational bodily loading act as a "gravitostat" to impede body weight loss (a novel variant of the so-called *ponderostat* hypothesis) [39]. However, this thought-provoking study requires confirmation in different models (e.g., partial unloading). Furthermore, a novel mechanism by which parathyroid hormone signaling regulates bone metabolism is by directing bone marrow mesenchymal precursor cells to commit to either the adipocyte or the osteoblast lineage [40]. Another study reported that in mice, a polyclonal antibody which blocks the β–subunit of the follicle stimulating hormone, not only increases bone mass but also reduces adiposity, offering a potential simultaneous therapeutic avenue for obesity and osteoporosis [41].

The largest genome-wide association study yet performed in the bone field ($n = 142{,}487$ individuals from the UK Biobank) tripled the number of loci associated with heel ultrasound-estimated BMD, and by phenotyping more than 100 knock-out mice identified several potential novel osteoporosis treatment targets including glypican 6 (*GPC6*) [42].

Last but certainly not least, investigators from the Mayo Clinic reported that targeting senescent cells by genetic or pharmacological means prevents age-related bone loss in mice [43].

Collectively, I believe these papers offer a hopeful outlook for a better treatment and management of patients with osteoporosis and other metabolic bone diseases anno 2018.

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Compliance with ethical standards

Conflicts of interest MRL is a member of the Board of the Belgian Bone Club and has received consultancy fees from Alexion, Novartis, and Sandoz and lecture fees from Amgen. The opinions in this work represent the sole view of the author and not of the Belgian Bone Club.

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