VIEWPOINTS

Elevated blood pressure, antihypertensive medications and bone health in the population: revisiting old hypotheses and exploring future research directions

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Abstract

Blood pressure and bone metabolism appear to share commonalities in their physiologic regulation. Specific antihypertensive drug classes may also influence bone mineral density. However, current evidence from existing observational studies and randomised trials is insufficient to establish causal associations for blood pressure and use of blood pressure–lowering drugs with bone health outcomes, particularly with the risks of osteoporosis and fractures. The availability and access to relevant large-scale biomedical data sources as well as developments in study designs and analytical approaches provide opportunities to examine the nature of the association between blood pressure and bone health more reliably and in greater detail than has ever been possible. It is unlikely that a single source of data or study design can provide a definitive answer. However, with appropriate considerations of the strengths and limitations of the different data sources and analytical techniques, we should be able to advance our understanding of the role of raised blood pressure and its drug treatment on the risks of low bone mineral density and fractures. As elevated blood pressure is highly prevalent and blood pressure–lowering drugs are widely prescribed, even small effects of these exposures on bone health outcomes could be important at a population level.

Keywords Antihypertensive drugs · Blood pressure · Bone fracture · Bone mineral density · Osteoporosis

Introduction

For some years, a close link between cardiovascular and bone health has been hypothesised [1–5], given that there are similarities in the biological risk factors, lifestyle determinants and demographic profile associated with cardiovascular disease (CVD) and bone health conditions [1, 3, 6–10]. A fall in blood pressure (BP) level and use of antihypertensive drugs have been associated with increased risk of falls particularly in the elderly [11, 12], which may

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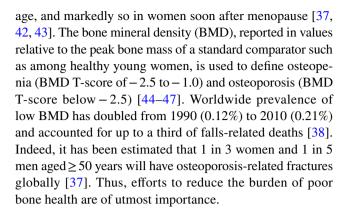
consequently increase the risk of bone fractures. Other pathways that may play a role in the pathophysiology of both atherosclerotic vascular disease and osteoporosis can include alterations in the regulatory mechanisms involved in calcium metabolism and homeostasis, stimulation of inflammatory response, and sympathetic nervous system activation [6–8, 13]. In particular, an association between hypertension and low bone mineral density (BMD) has been suggested [14], possibly as a result of calcium loss observed in people with raised BP [13, 15, 16]. The observation that BP may influence bone health is nothing new as many studies in the past few decades have examined associations between BP and BMD as well as fracture risk [17–21] and between BP-lowering drugs and the risk of osteoporosis and fractures [22–34]. These findings were largely based on observational studies and residual confounding could be an issue, so the likely causal role of BP or use of antihypertensive drugs on bone health outcomes remains to be established. Time trends suggest that age-adjusted mean BP and incidences of osteoporosis and fractures have been improving in some populations [35, 36], but the global burden of these conditions remains high [37–39] perhaps because of a demographic shift towards an ageing population. This ageing demographic trend underscores the importance of understanding the role of raised BP in the aetiology of osteoporosis and its important clinical consequence—bone fractures—as managing elevated BP could play a role in maintaining optimal bone health in the population.

In recent years, large-scale population-based cohorts with detailed clinical assessments, biological measures and genetic data are being used in epidemiologic and clinical investigations. Novel study designs and innovative analytical approaches have been developed, and collaborative studies that involve sharing of biomedical data of study cohorts have become a common practice. These research developments provide an opportunity to revisit hypotheses linking cardiovascular and bone health, and explore ways to answer questions that characterise and establish the causal role of raised BP on bone health outcomes in the population. To share our perspective, we describe some of the evidence linking BP with bone health, identify difficulties in establishing their causal relation from existing evidence and elucidate on research challenges and opportunities to help address these aetiological questions.

High population burden of osteoporosis and fractures

Osteoporosis is a systemic skeletal disease characterised by low bone mass and deterioration of the microarchitecture of bone tissue, which increases fragility of the bone and susceptibility to fractures [40, 41]. Its prevalence increases with age, and markedly so in women soon after menopause [37, 42, 43]. The bone mineral density (BMD), reported in values relative to the peak bone mass of a standard comparator such as among healthy young women, is used to define osteopenia (BMD T-score of − 2.5 to − 1.0) and osteoporosis (BMD T-score below − 2.5) [44–47]. Worldwide prevalence of low BMD has doubled from 1990 (0.12%) to 2010 (0.21%) and accounted for up to a third of falls-related deaths [38]. Indeed, it has been estimated that 1 in 3 women and 1 in 5 men aged ≥ 50 years will have osteoporosis-related fractures globally [37]. Thus, efforts to reduce the burden of poor bone health are of utmost importance.

Blood pressure may influence bone health

Elevated BP, or hypertension, is the leading cause of cardiovascular disease morbidity and mortality in many regions worldwide [48]. It is a condition that significantly raises the risks of coronary heart disease, stroke, and renal disease, and also the world's leading cause of premature death. Over 1.13 billion people globally have elevated BP, with two-thirds of them living in low- and middle-income countries [49]. The prevalence of raised BP increases with age, and in England, it has been estimated that over half of all adults aged ≥ 65 years in 2019 will have had hypertension [50]. There are public health preventive measures to reduce this burden [51]. Moreover, antihypertensive medications are effective, affordable and generally safe, and therefore widely prescribed for managing hypertension in many populations globally. Nevertheless, fewer than 1 in 5 people with hypertension globally have their BP levels under control [48]. In England, nearly a third of all adults have hypertension. More specifically, among all adults in the country, 10% have 'controlled' hypertension, 5% have uncontrolled hypertension and 12% have hypertension that remains untreated despite wide access to healthcare provision [50]. However, the continuing efforts for broader use of effective drugs to control and manage raised BP are showing an impact on encouraging trends towards more people with hypertension in England who are receiving treatment and whose raised BP are getting controlled.

Raised blood pressure, blood pressure reduction and bone health outcomes

While raised BP is an established risk factor of CVD, there are suggestions that it also affects long-term bone health. While the underlying mechanisms are not fully understood, elevated BP has been thought to alter calcium metabolism leading to increased calcium loss [15, 16]. Increased sympathetic nervous system activity, enhanced inflammation

response and alteration of parathyroid hormone regulation are pathways that have also been suggested to be involved [1, 6–8, 13]. This relation between raised BP and low bone mineral density could lead to enhanced bone fragility which may increase the risk of fracture, not least in some susceptible individuals such as among the elderly. There is also a suggestion that hypertension affects balance and mobility [52] thereby increasing the likelihood of falls and, consequently, fractures.

Few studies have examined the association between BP and BMD. In one small study, hypertensive women were shown to have lower BMD and higher 24-h urinary calcium excretion than normotensive women [17]. A meta-analysis of observational studies observed a heterogeneity in the association between BP and BMD depending on the anatomical location of the bone and ethnicity, although the study largely included cross-sectional studies [53]. In a prospective investigation based on repeated BMD measurements among 3000 elderly women, elevated BP was associated with increased bone loss in the femoral neck after 3 years of follow-up, independently of hormone replacement therapy and use of BP-lowering drugs [14]. It is uncertain if a similar observation can be seen in elderly men.

Limited data exist for investigating the impact of elevated BP on outcomes involving bone fractures. In a large case–control study, a 27% increased risk of any fracture was associated within 3 years of a diagnosis of hypertension, and 11% increase in risk in the longer term [19]. In a prospective study involving 1032 men and 1701 women aged ≥ 50 years, elevated BP was associated with increased risk of any or hip fracture in women, with similar but less precise estimates in men [21]. In another study, mean arterial pressure or hypertension was not shown to predict incident hip fracture, but the study was based only on 176 events in men and 458 in women, and did not account for the use of antihypertensive treatment [54].

There are also other possible pathways by which elevated BP, or rather, its pharmacologic reduction, can influence bone health. Susceptible individuals may develop syncope or hypotension soon after initiating antihypertensive treatment, leading to injurious falls [12] and, consequently, to fractures [55]. Indeed, a history of a fall is a well-established predictor of future fractures [10]. Three randomised clinical trials (RCTs) with relatively long follow-up have separately reported on the effect of BP reduction on fracture outcomes (Table 1), but these trials only involved less than 500 fracture events collectively [56–58]. One trial [56] reported no difference in the risk of any fracture between comparison groups, while the other two trials [57, 58] showed suggestive reduction in fracture risk in the active BP-lowering treatment arm, but the confidence interval of the risk estimate included the null value. To our knowledge, no randomised trials have examined the effects of pharmacologic lowering of BP on BMD or osteoporosis outcomes.

Antihypertensive drug class and bone health outcomes

Other than the unintended effects of antihypertensive medications in lowering BP on falls, others have shown class-specific effects of antihypertensive drugs by affecting different pathways involved in bone remodelling (Table 2). Thiazide diuretics are widely prescribed drugs to manage elevated BP, and this drug can also modulate calcium homeostasis [59]. It has been reported that thiazides can reduce urinary excretion of calcium by 40% [60, 61] as well as stimulate the production of osteoblast differentiation markers and enhance bone calcium uptake by inhibiting thiazide-sensitive sodium chloride cotransporter which are expressed in human osteoblasts [62, 63]. In contrast, loop diuretics are associated with increased urinary calcium excretion and increase parathyroid hormone levels and bone-specific alkaline phosphatase, which could be indicative of accelerated bone remodelling [64, 65]. For both types of diuretics, their use may promote nocturia, which could increase the likelihood of a fall and/or fractures particularly in the elderly. β-Blockers have been suggested to inhibit osteoclastic activity thereby decreasing bone resorption [25, 66]. Selective β-blockers particularly inhibit signalling pathways via β_1-adrenergic receptors that are expressed in human bones [67]. The renin–angiotensin–aldosterone system not only has systemic effects but also local effects in several tissues including the bone which might explain some of the effects of angiotensin-converting enzyme inhibitors (ACEI) in improving bone mineral density, albeit similar effects are not seen for angiotensin-II receptor blockers (ARB) [59, 68]. There are, therefore, several plausible pathways by which antihypertensive drug classes—collectively or individually—can have an impact on important bone health outcomes.

Several observational studies have examined associations of specific BP-lowering drug classes with bone loss or fracture risk [59]. While some findings are inconsistent, many have suggested protective effects on BMD (and reduction in fracture risk) for thiazide diuretic [69–72], β-blocker [26, 73] and ACEI [68, 73, 74]. Loop diuretics have been reported to increase the risk of fracture [27, 70, 75, 76], with no or little evidence of any impact of the use of ARB and calcium channel blocker (CCB) on bone fractures [32, 70, 73, 74, 76]. Evidence from RCTs also remains limited. To date, only one long-term trial has investigated the effects of specific antihypertensive drug class on fracture risk [77]. Involving 22,180 participants and accruing 338 hip or pelvic fractures over 4 years of follow-up, thiazide treatment showed 20% reduction in fracture risk when compared to treatment with ACEI or CCB.

Table 1 Randomised clinical blood pressure–lowering treatment trials with long-term follow-up and have reported on the risk of fracture as an outcome

	Trial			
	ACCORD [58] (*N* = 3099)	**ALLHAT** [77] (*N* = 22,180)	**HYVET** [57] (*N* = 3845)	**SHEP** [56] (*N* = 4736)
Study population	Age ≥ 40 years with diabetes and increased CVD risk	Age ≥ 55 years with hypertension and other CVD risk factors	Age ≥ 80 years with sustained SBP ≥ 160 mmHg	Age ≥ 60 years with hypertension, and no previous treatment
Comparisons	More vs less intense treatment	Drug class comparison (thiazide vs ACEI, CCB or ACEI and CCB)	Placebo-controlled	Placebo-controlled
Drug intervention	Drug class available in clinical practice	Diuretic (chlorthalidone), CCB (amlodipine), and ACEI (lisinopril)*; additionally with atenolol, clonidine or reserpine if required	Diuretic (indapamide); additionally with ACEI (perindopril) if required	Diuretic (perindopril) and/or diuretic (indapamide)
Outcome, total *N* (%)	Non-spine fractures, 270 (8.7)	Hip or pelvic fracture, 338 (1.5)	First fracture, 90 (2.3)	Any fracture, 104 (2.2)
Active group, *N* (%)	116 (7.6)	135 (1.3)	38 (1.5)	57 (2.4)
Control group, *N* (%)	154 (9.8)	203 (1.7)	52 (2.0)	47 (2.0)
Risk estimate comparing active treatment vs control group	HR = 0.79 (95% CI 0.62 to 1.01)	HR = 0.78 (95% CI 0.63 to 0.97); HR = 0.75 (95% CI 0.58 to 0.98) if ACEI only as comparator; HR = 0.82 (95% CI 0.63 to 1.08) if CCB only as comparator	HR = 0.69 (95% CI 0.46 to 1.05); HR = 0.58 (95% CI 0.33 to 1.00) if adjusted for baseline predictors of fracture	z = 0.8 (p = 0.4)
Comment	Other site-specific fractures also reported	HR are age- and sex-adjusted; subgroup analysis consistent; post trial to 8 years similar but wide CI	Definite or probable fractures only	

ACCORD Action to Control Cardiovascular Risk in Diabetes, *ALLHAT* Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attacks Trial, *HYVET* Hypertension in the Very Elderly Trial, *SHEP* Systolic Hypertension in the Elderly Program, *ACEI* angiotensin-converting enzyme inhibitor, *CCB* calcium channel blocker, *HR* hazard ratio, *CI* confidence interval

*An α-blocker (doxazosin) trial arm was terminated early

So far, we see that much of the existing findings on BP level or BP-lowering drug classes on bone health outcomes have been based on observational studies, with only a handful using a prospective study design. Since both hypertension and osteoporosis and fractures are influenced by similar factors as age, body size, physical activity level and co-existing chronic conditions, these factors need to be considered and will pose analytical challenges when establishing the causal relation between raised blood pressure and bone health outcomes using data from observational studies. As exposure to these drugs in these studies is mainly based on self-reports, details on timing of prescription as well as the dose and duration of drug treatment are often missing, which limits characterisation of exposure to these drugs. Given how common hypertension is and how widely antihypertensive drugs are being prescribed, even small effects of these exposures could be relevant at the population level. It is therefore crucial to determine the causal relation between BP and

BP-lowering drugs with bone health, as it will improve our understanding of the additional implications of BP control in the promotion of optimal bone health. Since the prevalence of raised BP and use of antihypertensive medications increase with age, and those at risk to suffer from metabolic bone disorders and fractures are also more likely to be older, understanding the nature of the associations is important for maximising the benefits and reducing the risks associated with BP control and treatment.

Advancing research into blood pressure and bone health in the population: current opportunities

Developments in population-based research in recent years have opened up opportunities to address fundamental questions on the role of elevated BP in the aetiology of

Table 2 Blood pressure–lowering drugs and hypothesised effects and mechanisms on bone health and fracture risk (adapted and modified from Ghosh and Majumdar [59])

Medications	Potential mechanisms affecting bone health	Effect on bone mineral density	Effect on fracture risk
All blood pressure–lowering drugs	Blood pressure reduction leading to syncope, hypotension and falls	↔	↑
	Reduction in sympathetic nervous system stimulation	↑	↓
By drug class			
Thiazide diuretic	Direct stimulation of osteoblasts	↑	↓
	Bone formation	↑	↓
Loop diuretic	Increased urinary calcium loss	↓	↑
	Falls	↔	↑
Spironolactone	Inhibition of aldosterone receptors	↑	↓
β-Blocker	Inhibition of β_2-adrenergic receptors in osteoblast	↑	↓
ACE-inhibitor	Inhibition of ACE in local RAAS in bone	↑	↓
ARB	Direct blockade for angiotensin-II receptor	↔	↔
CCB	Inhibition of voltage-gated calcium channel	↔	↔
Nitrates	Donates nitric oxide	↑	↓
	Suppression of osteoclast	↑	↓

↑, increase; ↓, decrease; ↔, probably no discernible impact; *ACE* angiotensin-converting enzyme, *RAAS* renin–angiotensin–aldosterone system, *ARB* angiotensin-II receptor blocker, *CCB* calcium channel blocker

osteoporosis and fractures. Access to databases providing detailed health data for large numbers of people allows us to investigate associations between BP and bone health outcomes prospectively and with sufficient statistical power. Further, advances in study designs and innovative analytical techniques have drawn us towards making causal inference with more credence. There is also an increasing trend among research communities across disciplines towards working collaboratively and sharing research data and expertise, which have opened up new ways to re-examine old, unanswered questions using novel ideas and perspectives.

Big data from large-scale cohort studies and healthcare databases

Routinely collected healthcare data have become increasingly an important resource to generate and test hypotheses in clinical research. Anonymised data are extracted from electronic health records (EHRs), such as the United Kingdom (UK) Clinical Practice Research Database [78]. These EHRs provide rich datasets that include time-stamped information on clinical measures, diagnoses and prescriptions and are linked to various national databases that further enrich the datasets to incorporate information on hospitalisations and vital status. These linkages at individual level allow investigations on the prospective associations of hypertension and antihypertensive drug use on bone health outcomes including osteoporosis and fractures. As drug dose and duration can be estimated from these medical records, detailed characterisation of drug exposure is possible to conduct in this context. In the UK, where 97% of the population are registered with the National Health Service, EHRs provide clinical data that are generalisable to the population [79]. Similar possibilities exist in other countries using their national healthcare or prescription databases [80–82]. By linking prescriptions with other administrative health records, it is possible to create anonymised records of prescriptions and relevant health data at individual level.

In addition, several cohorts involving large numbers of participants have collected detailed information on personal characteristics, medical history, lifestyle factors, biological samples, genetic data and clinical measures such as bone densitometry and heel bone ultrasound. For example, in the UK Biobank, these data have been collected for nearly 0.5 million individuals, including calcaneal ultrasound measures for the whole cohort and total dual-energy X-ray absorptiometry in a large subset of the study population [83–85]. Similar detailed phenotypic and genetic data have been collected in other cohorts, such as the population-based Trøndelag Health Study with genetic information combined with phenotypic data that include BMD measurements and prospectively recorded fracture information [86]. Indicators of bone health as well as diagnoses of osteoporosis and fractures are collected in these cohort studies. Data from EHR and well-characterised cohort studies have detailed health information that allows analyses that account for the potential effects of confounding factors. With large numbers of participants and long follow-up, health outcomes will accrue in sufficient numbers and allow conducting stratified analysis to investigate associations in important subgroups, such as by age and sex.

Trials investigating the effects of antihypertensive drugs involving large numbers of participants with relatively long follow-up have been conducted for many years. Findings from these RCTs, particularly by pooling evidence from across these trials, have helped establish the causal role of elevated BP in the aetiology of cardiovascular disease and clearly demonstrated the efficacy of antihypertensive drugs in reducing cardiovascular disease risk [87]. In recent years, collaborative efforts of trialists have allowed pooling of evidence based on individual-level data, which further provided evidence into the efficacy of BP-lowering treatment across important patient subgroups and clinical characteristics [88]. While bone health conditions are not the primary outcomes of these trials, adverse events and other unintended consequences of antihypertensive drug treatments are commonly collected, which may include information on hypotension, falls and fractures. The Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) (www.bplttc.org) is one such collaboration which recently has been investigating the efficacy and safety of antihypertensive drug treatment [89]. As many of the trials in the collaboration have collected safety data, it could be an important resource to provide randomised evidence for the effects of BP reduction and specific effects of antihypertensive drug classes on fracture risk.

Methodological and analytical innovations

Epidemiological investigations

Designing studies and analysing data to examine associations between an exposure (e.g. raised BP or specific classes of BP-lowering drugs) and an outcome (e.g. low BMD or fracture) in cohort studies require careful consideration as associations based on observational data are prone to biases, confounding and reverse causation. As bone health outcomes are likely to affect the elderly, analysis should account for competing risk such as from other causes of death. While using relevant study designs may help establish temporality of the association of the exposure with the outcome and confounding factors could be adjusted for by employing appropriate statistical methods, residual confounding remains a possibility due to unmeasured or imprecisely measured confounders. When the exposure of interest involves pharmacologic treatments, confounding by indication is an important issue as the clinical indication for the drug treatment in itself may affect the outcome of interest. Some have also suggested that osteoporosis is associated with an increased risk of cardiovascular disease [3, 90], so reverse causation is also a possibility. However, a number of large-scale cohort studies are well-characterised and extensively phenotyped, allowing for potential confounders to be accounted for in the analyses. Data from repeat measurements provide estimates of variability that can be used to correct for imprecision

of measurements and adjust for regression dilution [91], an issue particularly relevant for blood pressure [92]. The long follow-up of these cohorts also allows for time-stratified analysis, which permits exploring reverse causality, such as by excluding outcomes occurring during the early years of follow-up. Another important consideration is body weight or body mass index (BMI), which is positively associated with blood pressure and inversely associated with bone density [93, 94] and risk of hip fracture [95–97]. It is therefore important to take into account the impact of BMI when studying the association between BP and bone health.

Analysis using data extracted from EHRs faces similar issues on bias and confounding [98] as analysis using data from observational cohort studies. However, an important issue to consider when using EHR is missing data [99]. Since EHR data are collected primarily for administrative rather than research purpose, information relevant to the study may be missing for many individuals. Thus, to account for these missing data, imputation techniques can be employed to address this problem [99–101]. As EHRs include detailed information on drug prescriptions for a large number in the population, it would be an important resource for addressing questions on the effects of antihypertensive drug classes that are unlikely to be answered reliably by BP-lowering trials, perhaps because some outcomes, such as osteoporosis, take a long time to develop and get diagnosed, and most BP-lowering treatment trials do not actively follow up study participants beyond 5 years [102]. While comparing drug treatment effects without randomisation is prone to bias and confounding, methodological developments in designing studies using EHR could address these potential issues. It has been proposed that a target randomised trial can be emulated using large-scale EHR data, and a framework has been developed to serve as a guide when designing such investigations [103–106]. For example, the effects of statin treatment on cardiovascular disease and cancer tend to show contrasting findings obtained from RCTs and observational studies. However, by designing the study using observational data to 'mimic' the target RCT study population and comparison groups, findings from this trial emulation were shown to be consistent with the trial [103]. Using this relatively novel design to conduct studies using EHR data may be useful in this particular context to enable to address questions on BP treatment and bone health that are not ordinarily feasible to be answered using evidence from existing randomised trials.

Mendelian randomisation studies

Naturally randomised genetic variants associated with specific phenotypes are increasingly being applied in epidemiologic analysis to investigate unconfounded associations between an exposure and an outcome of interest [107, 108].

This approach is based on Mendel's second law which follows the principle of the random assortment of alleles during meiosis involving the transfer of deoxyribonucleic acid from parent to offspring during gamete formation. Inheriting a particular genetic variant by an individual is independent of other characteristics. When these individuals are grouped together in the population according to a specific genotype that is associated with a particular phenotype, they should be similar other than for the genetically determined phenotype. If the genetic variant alters or reflects the biological effects of the phenotype, such as BP, the effects of the phenotype can be predicted by the genetic variant for the phenotype. The inheritance of a particular set of alleles could be thought of as a form of naturally occurring randomisation to different levels of exposures. Thus, Mendelian randomisation (MR) is a form of instrumental variable analysis that uses genetic variants as instruments, which could be used in an analysis to diminish issues on confounding and reverse causality in exposure-outcome associations [107, 109]. Multiple single nucleotide polymorphisms (SNPs) associated with a specific phenotype can be combined and used as an instrument in MR analysis [110]. Recent genome-wide association studies (GWAS) have identified over 270 single nucleotide polymorphisms associated with systolic BP in over a million people of European ancestry [111–113]. These variants have been used and validated on coronary heart disease and stroke outcomes and showed findings to be consistent with the randomised evidence from BP-lowering trials [114], suggesting that these SNPs are valid instruments for MR analyses to examine a causal association between BP and bone health outcomes.

In addition, SNPs that encode proteins relating to the functions of specific antihypertensive drug classes have also been identified. For example, selective β-blocker acts by inhibiting the activation of adrenergic receptor $β_1$ ($ADRβ_1$) which results in reduced myocardial contractility and heart rate leading to a fall in BP [115]. The $ADRβ_1$ gene encodes for this receptor which could then be used as a surrogate for exposure to selective β-blockers. Indeed, genetic variants that could be used to evaluate the effects of antihypertensive drug classes, particularly for thiazides, ACEI, ARB, β-blocker and CCB, have been identified [116, 117]. It is, therefore, possible to conduct MR studies to examine associations between specific classes of antihypertensive drugs and bone health outcomes. However, unlike the number of SNPs associated with BP, the number of variants associated with BP-lowering drug classes is limited, and single cohort studies may lack sufficient power to conduct MR analyses in this context. To address this limitation, methods have been developed to allow conducting MR association studies by using summary data from large-scale GWAS without the need for individual-level data at the same time increasing statistical power [118]. In a two-sample MR, the instruments will include all the BP-related variants identified in a separate and independent GWAS, and the outcome will be based on the estimates obtained from the GWAS estimates of bone health outcomes. Given that separate GWAS have been conducted for the exposure (e.g. BP and antihypertensive drug class [111–113]) and for the outcome (e.g. BMD, osteoporosis and fractures) [119–123]), two-sample MR investigations could be conducted. It is worth noting that the UK Biobank contributes genetic data to some of these collaborative studies. Thus, it is important to consider the data being used for exposure (e.g. BP GWAS) are separate from the outcome data [124]. This two-sample MR technique is an approach increasingly being used [114, 125]. Since this analysis does not require individual-level data, it circumvents some of the limitations of genomic data access and sharing.

There are, of course, issues to consider when conducting MR analysis, primarily, the issue of pleiotropy [107, 108, 126]. Although findings remain valid with 'vertical pleiotropy', when the association with the phenotype is representing the downstream effects of the genetic variants on the exposure, 'horizontal pleiotropy' needs to be considered particularly in settings when multiple variants are being used as instruments. However, there are tools to assess the impact of this bias and still allow calculation of valid causal estimate even when horizontal pleiotropy exists [126, 127]. Additionally, the GWAS on BP phenotype also mainly include participants from Western populations; hence, their generalisability to other populations remains uncertain.

Individual participant-level data meta-analysis

As mentioned earlier, there were very few RCTs that reported on the effects of BP-lowering treatment and effects of antihypertensive drug class on risk of fractures. Each individual trial does not have sufficient statistical power to examine the effects of BP-lowering treatment on bone health outcomes. However, several RCTs of BP-lowering treatment have previously collaborated to pool individual participant-level data (IPD) to examine important clinical questions. Since the inception of BPLTTC in 1995, it has provided reliable evidence on the efficacy of BP-lowering drugs in reducing major cardiovascular disease events and mortality [89]. In its current phase, the collaboration includes 52 trials and over 350,000 randomised participants [102]. Many of these trials have routinely collected information on fractures as well as predisposing events, such as syncope, hypotension and falls. As the BPLTTC provides the largest IPD on BP-lowering treatment currently available, this resource offers an opportunity to investigate the effects of pharmacologic effects of BP-lowering on the risk of fractures. There are well-established methods for conducting IPD meta-analysis which could be used to examine the impact of drug

treatments to lower BP on bone health outcomes [128, 129]. While it is common to conduct meta-analysis based on published or aggregate data, this method is evidently of limited use because most trials have not reported findings on fracture risk, and, by design, it is not possible to conduct stratified analysis, such as by age and sex.

Summary

The association between BP and bone health is certainly not a new observation. Yet their plausible biologic link is certainly intriguing and deserves further scrutiny. Given the high prevalence of elevated BP and wide use of BP-lowering drugs, the impact of these exposures on bone health may be important in the population. However, for these associations to have relevance in informing clinical practice and public health policy, the causal nature of the relation between BP and bone health has to be established. It is unlikely that a single source of evidence or study design can provide a definitive answer. For population studies, what is likely needed is to combine epidemiologic, genetic and randomised evidence to provide detailed and nuanced understanding of the importance of controlling BP levels to improve bone health of the population.

Data availability Not applicable.

Code availability Not applicable.

Declarations

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