Other high-income countries such as Italy and Germany had lower ranks in 2010 in terms of number of deaths attributable to these risk factors, with increasing importance of middle-income countries such as Brazil and Ukraine.

Discussion

More than 60% of worldwide deaths from cardiovascular diseases, chronic kidney disease, and diabetes in 2010 were attributable to four preventable cardiometabolic risk factors, with high blood pressure having the largest effect. Over time, high blood pressure has maintained its role as the leading risk factor while the mortality burdens of high BMI and glucose increased faster than that of high cholesterol, such that these two risks are now responsible for more deaths than high cholesterol. High serum cholesterol nonetheless remains the second leading risk factor for deaths from ischaemic heart disease.

At present, the mortality burden of most of these risk factors is largest in east and southeast Asia and Pacific and in central and eastern Europe and central Asia, where many people die of cardiovascular diseases (predominantly stroke in east and southeast Asia and Pacific and ischaemic heart disease in central and eastern Europe and central Asia); central and eastern Europe and central Asia also have high levels of most cardiometabolic risk factors compared with other regions.[8–11] The mortality burden has shifted from high-income to low-income and middle-income countries because of a combination of demographic factors (faster population growth and aging) and divergent epidemiological trends (decreasing blood pressure and cholesterol, and cardiovascular death rates in high-income countries while risk factors increased or remained unchanged in low-income and middle-income regions). Deaths attributable to these risk factors occurred in younger people in low-income and middle-income regions than in high-income countries.

Our study is the most detailed analysis of the worldwide mortality burden of cardiometabolic risk factors, and the only study to analyse trends in mortality burden over a period of three decades and to report the individual and combined effects of risk factors at the country level (panel). We used data for risk factor exposure, individual and joint associations of risk factors with disease-specific mortality, and cause-specific deaths from comprehensive up-to-date pooling studies.[1,3,8–11,14] We also quantified the uncertainties of our estimates.

Our study also has some limitations. Despite using much more data than previous analyses, risk factor exposures and deaths in some regions were affected by data shortages and had large uncertainty. Second, we used RRs from observational studies, which could have been affected by residual confounding. For high blood pressure and serum cholesterol, overwhelming evidence from randomised trials of antihypertensive and cholesterol-lowering drugs support the relative risks from observational studies.[17,33,34] The causal effects of high BMI are supported by follow-up of patients after bariatric surgery and randomised trials of lifestyle and diet interventions that have shown that weight loss helps to prevent diabetes.[35] Results of some randomised trials showed that intensive glucose lowering did not significantly reduce cardiovascular disease mortality of patients with diabetes.[36] The reasons for these findings might be that intensive glucose lowering was compared with usual care (rather than with placebo), participants were generally old and frail, patients had had diabetes for a long time at baseline, the high prevalence of existing atherosclerotic disease at trial entry, and low incidence of cardiovascular disease in the trial populations because of concurrent treatment with statins, aspirin, and antihypertensive drugs, which reduced the power of the trials to detect an effect.[36] Subsequently, several meta-analyses[37–39] of randomised trials of intensive versus moderate glucose lowering for patients with diabetes have shown that such treatment significantly reduces the risk of myocardial infarction and other major cardiovascular events. In particular, a meta-analysis of the four largest randomised trials concluded that highly intensive glucose lowering causes a modest but significant cardiovascular benefit in the short to medium term.[38] For these reasons, and in view of the overwhelming evidence from observational studies of the graded increase in risk of cardiovascular disease caused by impaired glucose metabolism, we included ischaemic heart disease and stroke as outcomes of high blood glucose. Nevertheless, for both high BMI and blood glucose, residual confounding remains a concern.

We used the same RRs for all countries. Although the results of large cohort pooling studies[3,7,14] suggest that RRs (and mediation of the excess risk of BMI by other cardiometabolic risk factors) are similar for populations in western and Asian cohorts, further evidence about the size of RRs would be useful—for example, from Africa and Latin America. In addition to mediation, the combined population attributable fractions for multiple risk factors depend on correlation of exposures and on effect size modification, for which we did not have data. In sensitivity analyses, our results were robust to correlations of risk factor exposures. We used serum total cholesterol to measure population exposure to high cholesterol because substantially more data were available for total cholesterol than for other measures such as LDL-cholesterol or non-HDL-cholesterol and for apolipoproteins.[11] Findings in countries with data for both total cholesterol and LDL-cholesterol (each with a corresponding RR) show that the estimated attributable deaths are comparable.[21] Similarly, we used BMI as our measure of adiposity to take advantage of decades of worldwide data for height and weight. However, measures of abdominal obesity, such as waist circumference and waist-to-hip ratio, seem to have independent effects on mortality even after accounting for BMI.[40]

Panel: Research in context

Systematic review

We searched PubMed with the terms "comparative risk assessment" AND ("cardiovascular disease" OR "chronic kidney disease" OR "diabetes") for articles in English published before April 9, 2014. We also identified articles thorough the references for comparative risk assessment studies. We found some articles that had reported the mortality burden of individual or multiple cardiometabolic risk factors for one or more countries (including subnationally), for specific diseases or all-cause mortality, for one or at most two points in time.[12,13,15,21,25-31]

Interpretation

Our study shows that more than 60% of deaths worldwide from cardiovascular diseases, chronic kidney disease, and diabetes are attributable to four cardiometabolic risk factors—high BMI, blood pressure, blood glucose, and serum cholesterol—which can be prevented through a combination of population-based and personal interventions. The largest mortality burden was caused by high blood pressure but mortality caused by high BMI and high blood glucose has increased more quickly since 1980 than those of the other two risks. Successful initiatives to reduce population blood pressure and cholesterol should be replicated on a wider scale, and effective and scalable interventions need to be developed to curb or reverse the rising trends of BMI and hyperglycaemia.[32] Periodic representative country data for cardiometabolic risk factors are needed to improve the estimates and monitor trends.

Our analysis focused on effects on only cardiovascular diseases, chronic kidney disease, and diabetes which are causally related. High BMI is also a risk factor for some types of cancer and responsible for an estimated 320 000 cancer deaths worldwide in 2010.[12] High glucose concentration is associated with increased risk of tuberculosis.[41] Finally, the remaining deaths caused by cardiovascular diseases, chronic kidney disease, and diabetes—which ranged from 20% to more than 50% in different countries—might be a result of factors not considered in our analysis, independently or in interaction with genetic factors. For example, more than 10% of all deaths caused by cardiovascular diseases are attributable to smoking,[42] which would make the combined effects of cardiometabolic risk factors and smoking about 70% worldwide. Unhealthy diets, insufficient physical activity, and harmful alcohol use are risk factors for cardiovascular diseases and diabetes, with their effects partly or fully mediated through the cardiometabolic factors covered in the present work. Fetal and early childhood undernutrition increases the risk of cardiovascular diseases and diabetes; infections and environmental pollutants are also risk factors for chronic kidney disease.[43] Inflammation, caused by infections and other environmental factors, is a risk factor for cardiovascular diseases, chronic kidney disease, and possibly diabetes.[44,45] There is increasing evidence that stress, insufficient sleep, and other psychosocial factors are independent risk factors for cardiovascular and other non-communicable diseases.

Our results have important implications for the prevention and control of non-communicable diseases throughout the world.[32] Interventions to lower blood pressure, such as reducing dietary salt and better diagnosis and treatment, have successfully reduced blood pressure in high-income countries,[46-48] which has in turn been an important determinant of the fall in deaths from cardiovascular diseases.[49] Interventions to reduce blood pressure are urgently needed for low-income and middle-income countries, where salt intake remains high and coverage of treatment with anti-hypertensive drugs is low.[50-52] Salt from packaged and prepared foods is a relatively small component of total salt intake in these countries, therefore alternative locally accepted approaches to reduce salt intake are needed.[53,54] Similarly, scaling up drug treatments requires a universal and high-quality primary care system as well as national guidelines for identification of people who are in need of intervention, either based on the presence of a single risk factor or on their absolute risk of an adverse event.[51,55]

High-income countries in Europe, north America, and Australasia have also reduced the prevalence of high serum cholesterol concentrations through a combination of replacing saturated fats with unsaturated fats and higher coverage of treatment.[11,56-58] Although high cholesterol had the lowest mortality burden of these risk factors worldwide, it has increased in east and southeast Asian countries such as Japan, China, and Thailand, possibly as a result of increased intake of meat, animal fats, and dairy.[11,59] The number of deaths from cardiovascular diseases attributable to high serum cholesterol increased by about 250% in the east and southeast Asia and Pacific regions between 1980 and 2010, more than those attributable to blood pressure and glucose but less than BMI. Dietary and health-care interventions for lowering serum cholesterol are needed in this region. Finally, access to and quality of health care is one of the most important determinants of variation in mortality caused by cardiovascular diseases, chronic kidney disease, and diabetes both across and within countries.

Unlike national successes for reducing blood pressure and cholesterol, most countries have had increases of BMI and blood glucose;[8-11] a trend shown by the larger increase of their mortality burden than those of high blood pressure and cholesterol. Randomised studies of diet and lifestyle change have shown that moderate weight loss can be beneficial for up to 2 years,[60-62] and reduces diabetes incidence.[63] However, the long-term and community effectiveness of such interventions is not clear.[64] Simple advice and exercise alone have not been efficacious, even in randomised trials.[62] The rising burdens of high BMI and glucose, which can be only partly addressed through interventions to reduce blood

pressure and cholesterol, shows the urgent need for developing and testing new approaches to prevention of obesity. These approaches would have to go beyond health promotion at the individual level, and use fiscal and regulatory mechanisms to motivate changes in diet and lifestyle.[46,65] Actions to reduce exposure to cardiometabolic risk factors (and smoking) will also contribute significantly towards achieving the global 25×25 target for non-communicable disease mortality.[32]

Contributors

GD and ME designed the study. YL, GMS, EC, GAS, MC, FF, JKL, MMF, and MR analysed exposure and effect size data. YL and EC analysed attributable fractions and deaths. Collaborating group members contributed data for exposure and effect size. ME and GD wrote the first draft of the paper, with input from other members of the writing group and collaborating group. GD, SSL, and ME oversaw research.

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Declaration of interests

DM has received honoraria from Quaker Oats, Pollock Institute, and Bunge, has consulted for Foodminds, Nutrition Impact, Amarin, Astra Zeneca, Winston and Strawn, and Life Sciences Research Organization,

has sat on advisory boards for Unilever, and has received royalties from UpToDate. The other authors declare no competing interests. GAS, MJC, and LMR are staff members of the WHO. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy, or views of the WHO.

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Longitudinal Magnetic Resonance Imaging of Pseudotumors Following Metal-on-Metal Total Hip Arthroplasty

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ABSTRACT

The purpose of the study was to determine the natural history of pseudotumors following metal-on-metal total hip arthroplasty (THA) using magnetic resonance imaging (MRI). Initial MRI was conducted at a mean of 36 months postoperatively. Follow-up MRI was performed at a mean of 20 months after the detection of 24 asymptomatic pseudotumors. Pseudotumor size was determined on MRI. The mean pseudotumor size changed from 729 mm^2 to 877 mm^2. Pseudotumors increased in size in eight and decreased in six. Ten hips showed no changes. The bigger the pseudotumor size, the more likely the size would increase. In conclusion, pseudotumors frequently change in size. A single MRI study in the clinical decision-making process should be avoided and a longitudinal study should be performed.

Metal-on-metal bearings offer the theoretical advantages of decreased wear and increased functional outcome for younger and more active patients, but they have been associated with the development of pseudotumors [1–3]. Pseudotumors have been reported following metal-on-metal resurfacing or total hip arthroplasty (THA). These pseudotumors have been variously termed cysts, bursae, aseptic lymphocyte-dominated vasculitis-associated lesions (ALVAL) [4], adverse reactions to metal debris (ARMD) [5], and adverse local tissue reactions (ALTR) [6]. These lesions are the result of tissue reactions to metal debris with lymphocyte infiltration and soft tissue necrosis; however, their pathogenesis remains unclear. The prevalence of pseudotumors following metal-on-metal resurfacing or THA has been studied by a variety of investigators [7–13]. Recent studies demonstrated that pseudotumors can occur in asymptomatic hips after metal-on-metal hip resurfacing or THA [7,8,10,11]. In addition, the prevalence of pseudotumors is similar in well-functioning patients and patients with painful metal-on-metal hip implants [14]. Magnetic resonance imaging (MRI) provides sensitive screening of pseudotumors following metal-on-metal THA. MRI is ideally suited for assessment of these patients and complements standard clinical evaluation [15,16].

The natural history and longitudinal imaging findings of pseudotumors have yet to be fully analyzed. Our hypothesis was that pseudotumor size might change over time following metal-on-metal THA. This hypothesis was studied using serial MRI examinations. In addition, the relationships between the changes in pseudotumor size and serum cobalt and chromium ion levels were determined in these patients.

Patients and Methods

We performed large-diameter, metal-on-metal THAs using Cormet (Corin, Cirencester, UK) in 108 hips and Pinnacle (DePuy, Warsaw, IN, USA) in 80 hips. Screening for pseudotumors was performed using MRI after large-diameter, metal-on-metal THA. Every patient with metal-on-metal hip had a routine baseline screening MRI. MRI study was conducted on all subjects regardless of symptoms to ensure that asymptomatic pseudotumors could be detected. Thirty-six hips showed pseudotumors (24 Cormet and 12 Pinnacle). Twelve hips were revised after the first scan because of symptomatic pseudotumors. Subsequent MRI studies were performed only in the patients with pseudotumors at the index MRI. The patients without asymptomatic pseudotumors at the initial MRI did not undergo subsequent study. No patients were lost to follow-up between the index and subsequent study. Thus, 24 hips were studied longitudinally. Initial MRI was conducted at a mean of 36 months (range, 20–52 months) postoperatively. Follow-up MRI was performed at a mean of 20 months (range, 8–34 months) after the detection of 24 asymptomatic pseudotumors in 20 patients. There were 17 women and 3 men, with a mean age of 63 years and a mean body mass index (BMI) of 24.0 kg/m^2. The primary diagnoses were osteoarthritis in 18 patients and rheumatoid arthritis in 2 patients. A 1.5-Tesla scanner was used with T1-weighted spin-echo (SE), T2-weighted SE, and short tau inversion recovery (STIR) sequences (Signa; GE Medical Systems, Buckinghamshire, UK). Pseudotumors were classified as

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cystic (fluid), solid, and mixed types [10,17]. A minimum size of 10 mm was defined as pseudotumor. Fourteen hips were characterized as cystic type, and 10 hips were defined as mixed type. THA devices included 12 Cormet cup combined with CTi II stem (Corin) and 12 Pinnacle cup with S-ROM-A stem (DePuy). The Cormet cup was made of cobalt-chromium alloy with titanium porous coating for bone ingrowth. The CTi II stem, which was made of titanium alloy, had a proximal porous coating. The Pinnacle cup, which was made of titanium alloy, was a modular cup with titanium porous coating. Cobalt-chromium alloy liner was inserted in the cup. The S-ROM-A stem, which was made of a titanium alloy, was a modular stem with a proximal porous coating. The head was made of cobalt-chromium alloy in both implants. The mean head diameter of Cormet devices was 43 mm (40–48 mm). The head diameter for Pinnacle devices was 36 mm in all hips. The acetabular component inclination angle was measured on anteroposterior pelvic radiographs. The inclination angle was defined as the angle between the line joining the inferior teardrop points and the axis of the opening of the acetabular component. Acetabular anteversion was measured with computer software (Advanced CasePlan Digital Templating Planning Software; Stryker Orthopedics, Mahwah, NJ, USA) [18]. The mean inclination angle of the cup was 45° (30-57°) and the mean anteversion angle was 15° (4-22°).

Pseudotumor size was determined on MRI by manually outlining the greatest size of the mass. We measured the area of the pseudotumor using computer software (EV Insite Version 2.10.7.108; PSP Corporation, Tokyo, Japan). The scan areas were obtained from the same image for each comparison. Serum cobalt and chromium ion levels were measured in 9 patients with unilateral THA at the time of MRI. Blood samples (8 mL) were taken preoperatively and postoperatively using cobalt-free needles and glass tubes for trace metal analysis without additives for blood collection to avoid metal contamination. Cobalt levels were assayed using Inductively Coupled Plasma Mass Spectrometry (Perkin-Elmer SCIEX Elan 6100 DRC ICP-MS system; Perkin-Elmer Instruments, Norwalk, CT, USA) at Mayo Medical Laboratories (Rochester, MN, USA), and chromium levels were assayed using a graphite furnace atomic absorption spectrometer (Z-5700; Hitachi Ltd., Tokyo, Japan) with polarization-Zeeman absorption at Mitsubishi Chemistry Medience Co., Ltd. (Tokyo, Japan). Detection limits for each ion were 0.2 μg/L [19].

Changes in pseudotumor size and serum metal ion levels were evaluated. Two hips in one female patient were revised simultaneously because of the development of hip pain after subsequent MRI. The in situ durations were 4 years and 8 months in her left hip and 4 years and 1 month in her right hip. She was revised 2 years and 10 months after her initial MRI. Femoral head diameter was 44 mm in bilateral hip. The cup inclination was 44° in bilateral hip and the cup anteversion was 9° in her left hip and 5° in her right hip. This study was approved by the ethics committee of our institution, and all patients provided their informed consent.

Statistical analysis was performed using the Kruskal–Wallis test and chi square test to compare age, gender, BMI, head diameter, cup inclination, cup anteversion, and pseudotumor type among changes of pseudotumor size. We compared the pseudotumor size for the three groups (increase in size, no change, decrease in size) using Kruskal–Wallis test and Mann–Whitney U test. Wilcoxon signed-rank test was used to compare median serum metal ion levels over time. A P value < 0.05 was considered significant. StatView Version 5.0 (SAS Institute Inc., Cary, NC, USA) was used.

Results

The mean ± standard deviation pseudotumor size changed from 729 ± 408 mm^2 to 877 ± 754 mm^2. The minimum and maximum sizes at initial MRI were 103 mm^2 and 1665 mm^2, respectively. The minimum and maximum sizes at subsequent MRI were 54 mm^2 and 3085 mm^2, respectively. The median size changed from 709 mm^2 to 509 mm^2. Among the 24 hips, pseudotumors increased in size in eight (three cystic and five mixed) and decreased in size in six (four cystic and two mixed). Ten hips showed no changes in size (seven cystic and three mixed, Table 1). We found no significant differences between changes of pseudotumor size and patient characteristics including age, gender, BMI, head diameter, cup inclination, cup anteversion, and pseudotumor type (Table 2). While it is not statistically significant due to the small numbers in this series, there is a trend toward the cystic pseudotumors either remaining the same size or decreasing (79%), while the mixed type pseudotumors tend to increase in size (50%). The mean initial size of pseudotumor was bigger in pseudotumors with increased in size (1002 ± 309 mm^2) than in those with decreased in size (542 ± 295 mm^2, $P = .020$) or no change (622 ± 448 mm^2, $P = .041$). Bone edema was not found in every patient. In the patient who underwent revision, the pseudotumor size in her left hip increased from 833 mm^2 to 1895 mm^2 (mixed type), and the size in her right hip showed no change (608 mm^2, cystic type). Serum cobalt and chromium levels at the time of revision were 2.3 μg/L and 1.9 μg/L, respectively. The median serum cobalt ion levels at initial and follow-up MRIs were 2.0 μg/L and 1.8 μg/L, respectively. The mean ± standard deviation (range) levels of cobalt at initial and subsequent MRIs were 17.6 ± 46.7 μg/L (0.9 – 142.0 μg/L) and 17.6 ± 46.3 μg/L (0.7 – 141.0 μg/L), respectively. The median serum chromium ion levels at initial and follow-up MRIs were 2.0 μg/L and 3.1 μg/L, respectively. The mean ± standard deviation (range) levels of chromium at initial and subsequent MRIs were 10.7 ± 26.0 μg/L (0.5 – 79.9 μg/L) and 11.8 ± 28.3 μg/L (0.3 – 87.0 μg/L), respectively. No significant differences were observed in the serum levels of either metal between the initial and subsequent MRIs.

Table 1
Changes in Pseudotumor Size Over Time.

Pseudotumor Size	Number of Hips	Types of Pseudotumor		
		Cystic	Solid	Mixed
Increased	8	3	0	5
Decreased	6	4	0	2
No change	10	7	0	3
Total	24	14	0	10

Discussion

A survey of pseudotumors after metal-on-metal hip resurfacing in Canadian academic centers demonstrated that a surgically confirmed pseudotumor developed after four of the 3432 arthroplasties, for a prevalence of 0.10% [9]. Pseudotumor prevalence, including asymptomatic cases, has been reported to range from 4% to 69% when patients are screened after metal-on-metal hip resurfacing or THA [7,9,10,12–14,20,21]. However, the use of routine imaging, metal ion testing, and indications for revision have not yet been established. A

Table 2
Comparison of the Patient Characteristics and Results Between Changes of Pseudotumor Size.

		Pseudotumor Size			P
		Increased	Decreased	No Change	
		n = 8	n = 6	n = 10	
Age	Mean (years)	63	57	66	0.085
Gender	% Female (%)	88	100	70	0.275
Body mass index	Mean (kg/m^2)	25.8	22.3	23.3	0.271
Head diameter	Mean (mm)	38.5	38.7	40.8	0.292
Cup inclination	Mean (°)	45.8	40.3	47.4	0.223
Cup anteversion	Mean (°)	14.4	17.4	13.4	0.323
Pseudotumor type	% Cystic (%)	38	67	70	0.340

longitudinal study of pseudotumors could be useful to understand their natural history. Therefore, the changes over time were assessed in patients with previously MRI-detected pseudotumors. Eight hips (33%) were found to continue to increase in size. Size reduction despite no intervention was seen in six pseudotumor masses (25%). It is difficult to explain why these masses increased or decreased in size. The present study demonstrated that the initial size of pseudotumor was bigger in pseudotumors with increased in size than in those with decreased in size or no change. We found that the bigger the pseudotumor size, the more likely the size would increase. And we might predict that bigger pseudotumors would tend to increase in size. In addition, the mixed type pseudotumors would tend to increase in size. A previous study showed that serum cobalt and chromium ion levels were significantly higher in hips with pseudotumor than in hips without pseudotumor [10]. Metal wear at the bearing surfaces and at the head and stem taper interface was the main source of metal ion debris. However, serum cobalt and chromium ion levels did not correlate with pseudotumor extent in this study.

The present study has some limitations. First, we studied the small number of patients. Second, natural history of pseudotumors could not be predicted absolutely. It would be desirable to identify the predictive value of a specific pseudotumor size threshold beyond which revision should be considered. Third, it is likely that in some patients with cystic pseudotumor its presence is not a result of an abnormal tissue reaction but rather fluid accumulation.

Ebreo et al [22] studied serial MRIs after small-diameter, metal-on-metal THA, and a total of 239 MRIs of 80 patients was classified as A (normal), B (infection), or C1–C3 (mild, moderate, severe metal-on-metal-related abnormalities). On subsequent MRIs, six initially normal scans (9.5%) showed progression to a disease state; 15 (15%) of 103 THAs with sequential scans demonstrated worsening disease on subsequent imaging. Almousa et al [23] performed follow-up ultrasound after the detection of 9 asymptomatic pseudotumors (six large-head, metal-on-metal THAs and three hip resurfacing arthroplasties). The pseudotumors increased in size in six (four solid and two cystic). Two pseudotumors (one solid and one cystic) disappeared completely. One solid pseudotumor decreased in size. In the large-head, metal-on-metal THA group, four pseudotumor masses (three solid and one cystic) increased in size. Two pseudotumors completely disappeared with no intervention. Nawabi et al [17] reported that pseudotumor size on MRI correlated with the histologic score (ALVAL score [24]) in patients with revised metal-on-metal hip prostheses. The patients with an ALVAL score of 5 or greater were more likely to have a mixed type of pseudotumor with higher maximal synovial thicknesses and synovial volumes.

Guidelines recommending follow-up of asymptomatic patients undergoing metal-on-metal hip arthroplasty have already been published [25]; however, indications for operative revision have yet to be established. A number of studies have suggested that pseudotumors are the result of an adverse response to metal wear debris and elevated metal ion levels in patients with metal-on-metal hip prostheses [2,10,26]. In contrast, other studies demonstrated that pseudotumors were not associated with increased wear or metal ion levels [27,28]. The present study failed to clarify the relationships between the changes in pseudotumor size and serum metal ion levels. Delay of revision may be associated with extensive soft-tissue damage and hence poor clinical outcomes [25]. It is desirable to assess the changes in pseudotumor size over time. The present study is the first, to the best of our knowledge, to examine the natural history of pseudotumors following large-diameter, metal-on-metal THA using MRI.

In conclusion, the present results suggest that pseudotumors frequently change in size in asymptomatic patients, and our hypothesis was verified. A single MRI study in the clinical decision-making process should be avoided, and a longitudinal study of pseudotumors with MRI, which could help clarify their natural history, should be performed.

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Original Full Length Article

Determinants associated with bone mineral density increase in response to daily teriparatide treatment in patients with osteoporosis

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ABSTRACT

Introduction: Several factors associated with bone mineral density (BMD) increase are reported with daily teriparatide treatment, but there has been no systematic analysis to summarize these associations. The purpose of this study was to investigate the clinical determinants associated with BMD increase to daily teriparatide treatment.
Methods: This was a retrospective study. We performed an analysis of 306 patients diagnosed with osteoporosis. Teriparatide was administered at 20 μg/day for 12 months. The primary efficacy measure was a change in lumbar spine (LS) BMD from baseline at 12 months. To determine the response variables of BMD changes, we investigated the clinical determinants using univariate and multivariate analyses.
Results: There was a 9.8 ± 8.2% increase in LS BMD after 12 months. Prior bisphosphonate treatment and baseline procollagen type I N-terminal propeptide (PINP) concentration were significantly associated with LS BMD absolute response by univariate analyses. In the multiple regression model, patients with higher baseline PINP concentration had a significantly greater LS BMD absolute increase. Prior bisphosphonate use lost its correlation in the multiple regression models.
Conclusion: Our results showed that baseline PINP concentration was a useful predictor of LS BMD absolute increase regardless of prior treatment.

Introduction

Osteoporosis is a major public health problem characterized by low bone mass and microarchitectural deterioration of bone tissue, resulting in an increased risk of fracture [1]. Recombinant human parathyroid hormone (PTH) (1–34), teriparatide, is a bone anabolic agent indicated for the treatment of postmenopausal women and men with osteoporosis. Teriparatide administered on a daily basis is the only bone formation agent approved by the Food and Drug Administration and increases bone mineral density (BMD) through the formation of new bone [2–4]. Although the daily use of teriparatide in patients with osteoporosis has resulted in improved outcome, not all patients benefit equally. Studies have found associations between early treatment-related changes in bone formation markers, especially procollagen type I N-terminal propeptide (PINP), and subsequent changes in BMD [2,3,5–7]. However, a clinical problem still persists in that clinicians have little guidance for predicting improvements in BMD before initiation of teriparatide treatment.

Several determinants were reported to be associated with higher BMD increases, such as higher baseline PINP concentration [8], age (older [8–10]/younger [11]), and lower BMD [8,9]. In contrast, pretreatment with antiresorptives such as bisphosphonates, especially alendronate [9,12,13], reduced the efficacy of teriparatide treatment on BMD increase [9]. Furthermore, Orwoll et al. found that responses to teriparatide treatment were similar, regardless of age, gonadal status, smoking, or alcohol intake [14].

Although several factors have been associated with BMD increase in response to daily teriparatide treatment, there is no study which evaluated the consistency of these associations. Therefore, the objective of this study was to investigate the clinical determinants associated with BMD response to daily teriparatide treatment.

Materials and methods

Study subjects

We performed a retrospective analysis of 306 of 448 patients (68%) beginning with teriparatide treatment and completed 12-month

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teriparatide treatment. The reasons for the discontinued teriparatide treatment were as follows: lost to follow-up, 45 patients; loss of motivation for teriparatide treatment, 25 patients; discontinuation for illness unrelated to teriparatide treatment, 22 patients; relocation, 12 patients; dizziness, 7 patients; death of unrelated cause of teriparatide treatment, 7 patients; nausea, 5 patients; fatigue, 2 patients; hypercalcemia, 2 patients; expensive medical expenses, 2 patients; nettle rash, 2 patients; palpitation, 2 patients; dry mouth, 1 patient; diarrhea, 1 patient; itch, 1 patient; headache, 1 patient; loss of hair, 1 patient; bruising at the injection site, 1 patient; high level of serum alkaline phosphatase with unknown cause after one month (315 U/L at baseline → 2319 U/L at one month), 1 patient; and instruction by other doctor with incomprehensible reason, 1 patient. The inclusion criteria were postmenopausal females and males diagnosed with osteoporosis and at high risk of fracture. A high risk of fracture was defined when patients met at least one of the following criteria [15]: (1) BMD at lumbar spine (LS) L1–4 < 80% of the young adult mean (YAM; for all subjects reported in the Japanese Normative Female Database [16]) (approximate T-score - 1.9), with a minimum of one prevalent fragility fracture; (2) BMD at L1–4 < 70% of YAM (approximate T-score - 2.8) and age ≥ 65 years; (3) BMD at L1–4 < 65% of YAM (approximate T-score - 3.2) and age ≥ 55 years; or (4) more than three previous osteoporotic fractures. The exclusion criteria were patients with illnesses affecting bone and calcium metabolism or other bone disorders other than osteoporosis, as well as patients with serious cardiovascular, renal, or hepatic dysfunction. Patients with a high concentration of serum calcium (>11 mg/dl) at baseline were also excluded.

Measurements

We measured the BMD of the LS and femoral neck (FN) using dual-energy X-ray absorptiometry (DXA) on the DPX-BRAVO instrument (GE Healthcare, Madison, WI) at baseline and 12 months after treatment. Intra-observer coefficient of variation (% CV) for the DXA were 0.5% in LS and 1.0% in FN, respectively. Inter-observer % CV were 0.6% in LS and 0.9% in FN, respectively. The concentration of PINP at baseline was also measured by a radioimmunoassay (Orion Diagnostica, Espoo, Finland). Normal range are 21.9–71.9 μg/l in female patients and 19.0–83.5 μg/l in male patients. Intra-assay and inter-assay % CV for PINP were 3.5% and 4.2%, respectively. urinary N-telopeptide (uNTX) was measured by an enzyme-linked immunosorbent assay (ELISA; Alere Medical Co., Ltd., Tokyo, Japan). Normal range are 14.3–89.0 μg/l in female patients and 13.0–66.2 nmolBCE/mmol Cr in male patients. Intra-assay and inter-assay % CV for uNTX were 6.6% and 6.5%, respectively.

Determinants

The following possible determinants of response to teriparatide treatment were considered: age, gender, height, body weight, body mass index (BMI), body surface area (BSA) [17], prior bisphosphonate treatment, prior osteoporotic fractures, baseline LS BMD, baseline serum calcium concentration, baseline serum PINP, and uNTX concentration.

Statistical analysis

To determine the response variables of BMD changes, univariate analyses were performed by Spearman correlation coefficients and Mann–Whitney *U* test. Data were further analyzed by multiple regression analysis. The multiple regression model included gender and all determinants mentioned in the previous reports. As serum PINP and uNTX are bone turnover markers with strong relation between PINP and uNTX ($r = 0.79$, $p < 0.01$; Spearman rank correlation), multivariate analyses were performed using one bone turnover marker which was stronger relation to BMD change by Spearman rank correlation. In addition, to exclude the effect of confounding factors between baseline PINP concentration and prior bisphosphonate treatment, multivariate statistics were performed after stratification by prior bisphosphonate treatment.

The analyses were performed using the SAS software program, version 9.1 (SAS Institute, Inc., Cary, NC, USA). All data are expressed as means ± standard deviation (SD), unless otherwise indicated. p-Values <0.05 were considered statistically significant.

Compliance

The medication compliance was assessed at each visit. Participants were queried regarding the number of missed doses of medication and were considered compliant if they consumed ≥85% of the study drug.

The protocol was in compliance with the ethical principles stated in the Declaration of Helsinki and was approved by the Ethics Committee of Tomidahama Hospital. Written informed consent was obtained from the patients.

Results

Baseline characteristics

The age, gender, height, body weight, BMI, BSA, prior bisphosphonate treatment, prior osteoporotic fractures, baseline LS and FN BMD, serum calcium, serum PINP and uNTX concentrations are reported in Table 1. One hundred and thirty-four patients (44%) had been previously treated with antiresorptive agents for at least three months before switching to the teriparatide treatment. The antiresorptive agents

Table 1
Baseline clinical characteristics ($n = 306$).

Variable	Mean (SD), n (%)
Age (years)	78.1 ± 7.8
Gender, n (%)	
Females	271 (89%)
Males	35 (11%)
Height (cm)	150.5 ± 7.8
Body weight (kg)	47.9 ± 9.1
BMI (kg/m^2)	21.1 ± 3.6
BSA (m^2)	1.41 ± 0.14
Prior treatment, n (%), period (months)	Total 134 (44%)
Alendronate	86 (28%), 41 months (3–84 months)
Risedronate	23 (8%), 19 months (4–73 months)
Minodronate	5 (2%), 15 months (4–34 months)
SERM	20 (7%), 31 months (4–76 months)
Previous osteoporotic fractures, no of patients (%)	Total 221 (72%)
No of patients with multiple fractures	132 (43%)
Vertebral body	202 (66%)
Proximal femur	63 (21%)
Distal radius	18 (6%)
Proximal humerus	7 (2%)
BMD	
Lumbar spine (g/cm^2), T-score	0.822 ± 0.167 (g/cm^2), −2.5 ± 1.4
Femoral neck (g/cm^2), T-score	0.610 ± 0.120 (g/cm^2), −2.5 ± 1.0
Serum calcium (mg/dl), normal range 8.5–10.2 mg/dl	9.4 ± 0.6
Bone turnover marker	
serum PINP μg/l	54.0 ± 36.9
uNTX (nmolBCE/mmol Cr)	51.0 ± 37.0

SD: standard deviation; BMI: body mass index; BSA: body surface area; SERM: selective estrogen receptor modulator; BMD: bone mineral density; PINP: procollagen type I N-terminal propeptide; uNTX: urinary N-telopeptide.

Table 2
Univariate analyses[a] between baseline variables and LS BMD response at 12 months.

Parameter	Percent change		Absolute change	
	r	p value	r	p value
Age[b]	0.02	0.78	0.031	0.60
Gende[c]	-	0.64	-	0.48
Height (cm)[b]	0.02	0.69	0.07	0.25
Body weight (kg)[b]	−0.12	0.04	−0.01	0.81
BMI[b]	−0.16	<0.01	−0.07	0.21
BSA[b]	−0.08	0.18	0.03	0.67
Prior bisphosphonate use[c]	-	0.01	-	<0.01
Previous osteoporotic fractures[c]	-	0.66	-	0.79
Previous vertebral body fractures[c]	-	0.73	-	0.69
Baseline LS BMD[b]	−0.33	<0.01	−0.10	0.09
Baseline serum calcium[b]	−0.03	0.66	−0.03	0.63
Baseline PINP[b]	0.31	<0.01	0.31	<0.01
Baseline uNTX[b]	0.26	<0.01	0.24	<0.01

BMI: body mass index; BSA: body surface area; LS: lumbar spine; BMD: bone mineral density; PINP: procollagen type I N-terminal propeptid; uNTX: urinary N-telopeptide.
[a] Spearman correlation coefficients and Mann–Whiteney *U* test.
[b] Spearman correlation coefficients.
[c] Mann–Whitney *U* test.

used were alendronate (n = 86), risedronate (n = 23), minodoronate, a third generation bisphosphonate widely used in Japan (n = 5) [18–20], and selective estrogen receptor modulator (SERM) (n = 20).

Changes in BMD in response to teriparatide treatment

The LS BMD after 12 months of teriparatide therapy showed a 9.8 ± 8.2% increase, and the FN BMD showed a 2.2 ± 7.8% increase. The mean absolute LS BMD change of T-score was 0.60 ± 0.72, and FN BMD change was 0.08 ± 0.32. As the BMD response in FN was small, we performed subsequent analyses with a focus on LS BMD response.

Effects of the baseline data on BMD increase evaluated by univariate analyses

The effects of the baseline data on LS BMD increase were evaluated by univariate analyses. The results are shown in Table 2. Body weight, BMI, prior bisphosphonate use, baseline LS BMD, baseline PINP concentration, and baseline uNTX concentration were significantly associated with subsequent percent LS BMD response. In contrast, age, gender, height, BSA, previous osteoporotic fractures, previous vertebral body fractures, and baseline serum calcium were not associated with subsequent percent LS BMD response. With regard to absolute LS BMD increase, prior bisphosphonate use, baseline PINP concentration, and baseline uNTX concentration were significantly associated with subsequent LS BMD response. The highest correlation coefficient for the relationship between LS BMD response and determinants was for the percent change in LS BMD and baseline LS BMD ($r = -0.33$, $p < 0.01$). The second highest correlation coefficient was for the percent and absolute change in LS BMD and the baseline serum PINP concentration ($r = 0.31$, $p < 0.01$, both).

Effects of the baseline data on BMD increase evaluated by multivariate analyses

Data were further analyzed by multivariate analyses. The results are shown in Table 3. In the multiple regression model (which included age, BMI, prior bisphosphonate treatment, baseline LS BMD, and baseline PINP concentration), patients with higher baseline PINP concentration were significantly more likely to have greater percent and absolute LS BMD increase than patients with lower baseline PINP concentration. Interestingly, prior bisphosphonate use lost its correlation with subsequent LS BMD increase in the multiple regression models.

As there was a strong relation between the baseline PINP concentration and prior antiresorptive treatment, we confirmed the influence of prior antiresorptive treatment by stratification analyses. The results are shown Table 4. In brief, there was no apparent difference in each group except for the relation between baseline PINP concentration and absolute change in LS BMD. Therefore, we concluded that prior antiresorptive treatment did not strongly affect subsequent LS BMD increase.

Discussion

This study examined the relationship between various baseline determinants and LS BMD increase in response to teriparatide treatment. The present study is the first report to summarize various clinical determinants at baseline for subsequent percent and absolute LS BMD increase in patients under clinical practice. Our results showed baseline PINP concentration was a strong predictor of LS BMD increase regardless of prior bisphosphonate treatment.

Several clinical trials have suggested that response to treatment with antiresorptive agents may depend on the subjects' characteristics, such as baseline BMD and prevalent fractures [21,22]. Obermayer-Pietsch et al. showed that the effects of daily teriparatide treatment on BMD were greater in older patients, treatment-naïve patients, and those with lower BMD values at baseline [9]. Other reports showed that teriparatide response was greater in patients with higher baseline PINP concentrations [8]. In addition, age is reported to be associated with higher BMD increase [8,9,11]. In contrast, most studies concerning not only combination therapy with daily teriparatide and antiresorptives but also prior antiresorptives' use reduced the efficacy of teriparatide treatment in BMD increase [9,23,24].

Our results showed that both lower baseline LS BMD and higher baseline PINP concentrations predicted a greater percent LS BMD increase whereas only higher baseline PINP concentrations predicted a greater absolute LS BMD increase in multiple regression models. There is a possibility that the correlation between lower baseline LS BMD and greater percent LS BMD increase is at least in part an artifact of the very low baseline LS BMD. As to baseline PINP and subsequent LS

Table 3
Multivariate analyses[a] between baseline variables and LS BMD response at 12 months.

Parameter	Percent change $r^2 = 0.20$, F value = 15.01			Absolute change $r^2 = 0.07$, F value = 4.11		
	SPRC	t value	p value	SPRC	t value	p value
Age	0.01	1.88	0.06	0.08	1.38	0.17
BMI	−0.02	−0.26	0.80	−0.01	−0.07	0.95
Previous bisphosphonate treatment	0.04	0.66	0.51	0.04	0.59	0.56
Baseline LS BMD	−0.35	−6.21	<0.01	−0.01	−1.31	0.19
Baseline PINP	0.22	3.79	<0.01	0.20	3.18	<0.01

BMI: body mass index; BSA: body surface area; LS: lumbar spine; BMD: bone mineral density; PINP: procollagen type I N-terminal propeptide.
[a] Multiple regression model; SPRC: standardized partial regression coefficient.

Table 4
Stratification analyses[a] of prior treatment between baseline variables and LS BMD response at 12 months.

	Percent change						Absolute change					
	Prior bisphosphonate use (+) (n = 134) r^2 = 0.07, F value = 2.03			Prior bisphosphonate use (−) (n = 172) r^2 = 0.25, F value = 15.1			Prior bisphosphonate use (+) r^2 = 0.03, F value = 0.79			Prior bisphosphonate use (−) r^2 = 0.07, F value = 3.39		
Parameter	SPRC	t value	p value	SPRC	t value	p value	SPRC	t value	p value	SPRC	t value	p value
Age	0.06	0.63	0.53	0.11	1.77	0.08	0.08	0.79	0.43	0.08	1.12	0.26
BMI	0.04	0.37	0.72	−0.05	−0.66	0.51	0.02	0.23	0.82	−0.02	−0.25	0.81
Baseline LS BMD	−0.22	−2.18	0.03	0.40	−5.67	<0.01	−0.01	−0.14	0.89	−0.11	−0.145	0.15
Baseline PINP	0.19	1.99	<0.05	0.18	2.80	<0.01	0.14	1.43	0.16	0.20	2.76	<0.01

BMI: body mass index; LS: lumbar spine; BMD: bone mineral density; PINP: procollagen type I N-terminal propeptide.
[a] Multiple regression model; SPRC: standardized partial regression coefficient.

BMD response, Yamamoto et al. reported that patients with a higher baseline PINP concentration had greater percent and absolute LS BMD increase, which is consistent with our results [4]. Ma et al. also pointed out that bone turnover at baseline may be related to the number of new remodeling cycles, an index to show how many new basic multicellular units (BMUs) are initiated [25]. There was a correlation between baseline PINP and absolute LS BMD change in this study, which might suggest that PINP reflects the BMUs stimulated by teriparatide. Our results supported Ma's opinion because higher baseline PINP concentration, which reflects both present and subsequent BMU activation, is correlated with subsequent LS BMD increase.

This study has several limitations that should be kept in mind when interpreting the results. First, the investigation was not large enough to examine the relation between baseline determinants and fracture outcomes. However, the determinants related to a greater BMD increase would lead to a greater fracture risk reduction. Second, in routine medical practice, the background of patients may vary more widely than that in the patients of this study. For instance, patients who have suffered a fracture just before beginning teriparatide treatment may exhibit differences in their baseline PINP concentration. Future studies in a larger number of patients with more diverse backgrounds will be needed. Third, we evaluated only serum PINP and uNTX among several bone turnover markers. There is a possibility that other bone turnover markers might be more strongly associated with BMD response.

In conclusion, we recommend that physicians should keep these results in mind in clinical practice so that they can make more accurate treatment decisions and improve utilization of daily teriparatide.

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Disclosure statement

The authors have nothing to disclose.

Conflicts of interest

None.

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ORIGINAL ARTICLE

Prevalence of hallux valgus and risk factors among Japanese community dwellers

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Abstract
Background To investigate the prevalence and severity of radiographically detected hallux valgus (HV) as well as associated risk factors among Japanese residents of Miyagawa, a mountain village located in the center of Mie Prefecture.
Methods The height, weight and body mass index (BMI) of 403 participants (male $n = 135$, female $n = 268$) recruited from among the residents of Miyagawa Village, Japan aged ≥65 years were measured, and baseline data, including age, sex and medical history were obtained from interviews and questionnaires. Knee osteoarthritis (KOA) was determined from radiographs of the feet and knees, and osteoporosis was determined by measuring bone mineral density. Hallux valgus, defined as angulation of the big toe at the first metatarsophalangeal joint of >20°, was classified as: mild (20°–30°), moderate (30°–40°) or severe (>40°). Risk factors for HV were calculated using multivariate logistic regression analysis that included age, sex, obesity (BMI ≥25), KOA, osteoporosis, Heberden's nodes and low back pain as variables.
Results The overall prevalence of definite radiographic HV was 22.8 % (184/806), and mild, moderate and severe HV was found in 66.3, 27.2 and 6.5 % of the participants, respectively. Hallux valgus was found in at least one foot in 120 (29.8 %) of the participants and the prevalence significantly differed between females with and without HV and KOA (odds ratios: 2.54 and 1.71, respectively).
Conclusions The prevalence of definite radiographic HV was 29.8 %. Female sex and KOA were significantly associated with increased risk for radiographic HV.

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Introduction

Hallux valgus (HV) is a common deformity in adults that is characterized by abnormal angulation, rotation and lateral deviation of the big toe at the first metatarsophalangeal joint [1, 2]. Wearing footwear causes individuals with HV pain and difficulty in walking [3], and many such patients require orthosis and/or surgery [4, 5]. Understanding the associated risk factors is very important to prevent HV and determine the ratio of individuals with HV. However, the community prevalence of HV estimated by epidemiological studies varies between 21 and 70 % [6–10]. This variation is partly attributable to differences in study populations and unclear definitions of HV, with the terms "hallux valgus" and "bunion" specifically causing confusion. Most epidemiological HV studies have used a self-check sheet or footprint rather than X-rays to detect HV [11] and very few community-based studies have incorporated such radiographic imaging [12]. We initiated a cohort study in 1997 to investigate the epidemiology of knee osteoarthritis (KOA) [13–15] and osteoporosis [16]. The present study of HV started from the seventh (2009) and eighth (2011) biennial examinations.

The present cross-sectional study investigates the prevalence of radiographic HV and associated risk factors

among Japanese inhabitants of Miyagawa. Whether having radiographic HV affected their quality of life (QOL) was determined using the Japanese version of the EuroQol 5D (EQ-5D) questionnaire [17, 18].

Materials and methods

Individuals aged ≥65 years were recruited from among the inhabitants of Miyagawa, a mountain village located in the center of the Mie Prefecture, Japan. The population of this village was 3,364 in the year 2012, and 1,522 residents met the age criterion. The study that started in 1997 was designed to determine factors associated with KOA and osteoporosis by analyzing data from a representative sample of a rural elderly population every 2 years. The present study analyzes data from the seventh and eighth biennial examinations in 2009 and 2011, respectively.

The Ethics Committee for Human Research at our institution approved this study, and written informed consent was obtained from all participants before enrollment.

Baseline data were obtained at one-to-one interviews using standard questionnaires designed by orthopedic surgeons. These data included information about age, sex, medical history, cigarette smoking, and health-related QOL determined from the EQ-5D questionnaire. Height and body weight were measured, and body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2) at the baseline assessment. Obesity was defined as BMI >25. Bunions and callosities were identified by palpation. Pain was determined by applying pressure to the bunion. The location of callosities was categorized from maps of the soles of the feet. Heberden's nodes were located by visual inspection and palpation.

The EQ-5D is a standardized, characterized instrument for assessing the course of health processes [17] that was translated into Japanese for the present study. The EQ-5D contains a self-assessment section in which participants provide a description of their health status from the viewpoints of mobility, self-care, daily activities, pain (discomfort and anxiety) and depression. They selected the most appropriate of three statements about each of the five QOL dimensions to indicate their current health status. Each statement represents an increasing degree of severity. The results were coded and converted to utility scores using a table of values [18].

Other medical examinations consisted of radiography of the feet and knees and measurement of bone mineral density (BMD) at the distal third of the non-dominant side radius using dual energy X-ray absorptiometry (DCS-600EX; Aloka, Tokyo, Japan). Osteoporosis was defined as 2.5 standard deviations (SD) of BMD below that of the young adult mean (YAM) of a healthy young adult of the same sex.

Fully extended anteroposterior (AP) radiographs of both knees while standing were scored for radiographic KOA according to the Kellgren Lawrence (K/L) grading system [19]. Confirmed radiographic KOA was defined as a K/L grade of ≥2.

Foot X-rays were taken from participants standing upright with both feet on the cassette as described by Saltzman [20]. The standardized radiographic projection was indicated for weight-bearing views, in which the X-ray beam was inclined at 20° at a distance of 40 in., and centered between the bilateral feet. The hallux valgus angle (HVA), which is formed by the bone axes of the first metatarsal and the first proximal phalanx, and the M1-M2 angle formed by the bone axes of the first and second metatarsals on all radiographs, were consistently measured by the same examiner (AN) [21] and analyzed using Image J version 1.37 software (National Institutes of Health, Bethesda, MD, USA). The HVA value was taken as the mean of three determinations.

Hallux valgus was defined as an HV angle >20°, according to the Japanese Orthopaedic Society criteria and severity was classified as mild (20°–30°), moderate (30°–40°) or severe (>40°) [22].

Statistical analysis

Means ± standard deviations (SD) were calculated for variables unless otherwise noted. Risk factors for HV were determined from multivariate logistic regression analysis that included age, sex, obesity, KOA, osteoporosis, Heberden's nodes and low back pain as variables. The relationship between HVA and the M1-M2 angle was assessed using Pearson's correlation coefficient. The relationship between the severity of HV and of KOA (except total knee arthroplasty) was assessed using the Spearman rank correlation coefficient. Risk factors for HV are summarized as odds ratios (OR) with 95 % confidence intervals (CI). The EQ-5D values for normal feet or for each grade of HV were determined using a one-way ANOVA with Dunnett's post hoc test.

Significance at the level of 5 % was taken for all tests. All data were statistically analyzed using PASW Statistics for Windows version 18 (SPSS Inc, Chicago, IL, USA).

Results

A total of 314 (105 men, 209 women) and 221 (74 men, 147 women) elderly residents participated in the seventh and eighth Miyagawa studies, respectively, of whom 130 participated in both. Two residents declined X-ray examinations, and thus data from 403 (overall mean age: 75.5 ± 6.4 years, range: 65–94 years, female: 75.8 ± 6.6 years, male: 75.4 ± 6.3 years) participants (806 feet) who fulfilled the study criteria were analyzed. None of the participants had a history of surgically treated HV.

Table 1 shows the distribution of HV severity in the 806 feet. The overall prevalence of definite radiographic HV was 22.8 % (184/806), and 11.6 % (28/270) and 41.1 % (156/536) in men and women, respectively. The ratios of residents with mild, moderate and severe HV were 66.3 % (122/184), 27.2 % (50/184) and 6.5 % (12/184), respectively. The HV was bilateral in 64 (15.9 %), unilateral in 56 (13.9 %), and on at least one side in 120 (29.8 %) of the participants.

Figure 1 shows that HVA significantly correlated with the M1-M2 angle (Pearson's correlation coefficient $(r) = 0.762$, $p < 0.001$).

Table 2 shows relationships between each risk factor and the prevalence of HV. The prevalence of females significantly differed between groups with and without HV ($p = 0.003$, OR: 2.54, 95 % CI: 1.38–4.66) and KOA ($p = 0.028$, OR: 1.71, 95 % CI: 1.06–2.76).

The incidences of bunions on normal feet and on feet with mild, moderate and severe HV were 2.7 % (17/622), 28.7 % (35/122), 54.0 % (27/50), and 91.7 % (11/12), respectively (Fig. 2a). The incidences of painful bunions on normal feet and on feet with mild, moderate and severe HV were 0.3 % (2/622), 5.7 % (6/122), 8.0 % (4/50), and 16.7 % (2/12), respectively. The rate of painful bunions on all those with HV was 6.5 % (12/184). The incidences of callosities located on the balls (the first metatarsal head) of both normal feet and on feet with mild, moderate and severe HV were 3.2 % (20/622), 7.4 % (9/122), 2.0 % (1/50), and 0 % (0/12), respectively. On the other hand, the incidences of callosities located on the second, third, and fourth metatarsal heads of normal feet and of feet with mild, moderate and severe HV

Table 1 Distribution of hallux valgus severity

Participants	Normal	Mild	Moderate	Severe
Men	242	22	5	1
Women	380	100	45	11
Total	622	122	50	12

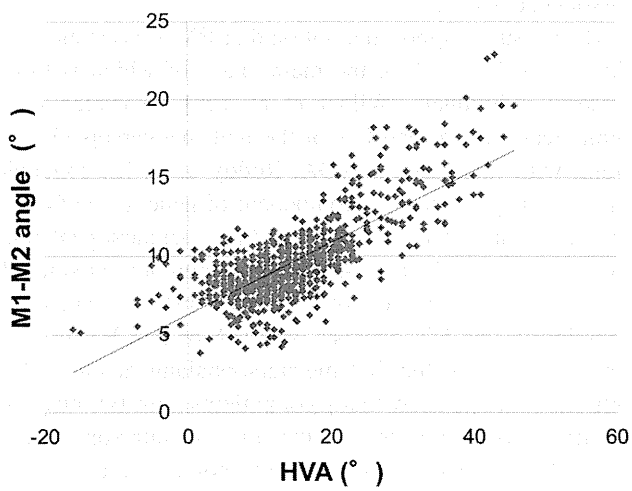

Fig. 1 Relationship between hallux valgus (*HVA*) angle and M1-M2 angle

Table 2 Comparison of individuals with and without radiographic hallux valgus

	HV ($n = 120$)	No HV ($n = 283$)	p	95 % CI	OR
Age (years)	76.1 ± 6.9	75.3 ± 6.1	0.66	0.97–1.05	1.01
Gender	M21; F99	M114; F169	0.003*	1.38–4.66	2.54
Obesity	+30/−90	+81/−282	0.23	0.38–1.22	0.73
KOA	+73/−47	+115/−168	0.03†	1.06–2.76	1.71
Osteoporosis	+66/−54	+123/−160	0.80	0.65–1.74	1.07
Heberden's nodes	+67/−53	+118/−165	0.13	0.90–2.27	1.43
Low back pain	+53/−67	+146/−137	0.10	0.44–1.08	0.68

HV hallux valgus, *KOA* knee osteoarthritis, *CI* confidence interval, *OR* odds ratio. Age is shown as mean ± SD. * $p < 0.01$, † $p < 0.05$

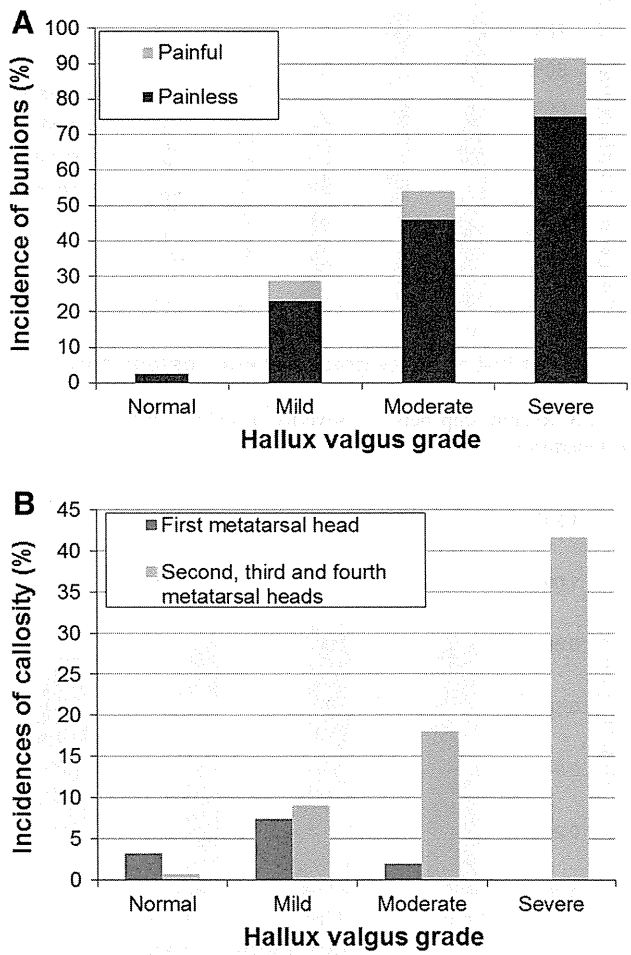

Fig. 2 Incidence of painful (*gray*) and painless (*black*) bunions (**a**) and callosities (**b**)

were 0.6 % (4/622), 9.0 % (11/122), 18.0 % (9/50) and 41.7 % (5/12), respectively (Fig. 2b).

Figure 3 shows that the severity of HV and of KOA significantly correlated ($\rho = 0.228$ and $p < 0.001$).

The EQ-5D utility scores of individuals with normal feet and with mild, moderate and severe HV were 0.855, 0.872, 0.809 and 0.769, respectively, with no significant differences among the groups (Fig. 4).

Discussion

The results of this cross-sectional study indicated a 29.8 % prevalence of radiographic HV among residents in a single village. Roddy et al. [2] reported a 28.4 % prevalence of self-reported HV among 4,249 patients in two general practices. On the other hand, Cho et al. [12] found radiographic HV in 364 (64.7 %) of 563 individuals. The reason for this higher value is their wider definition of radiographic HV as >15°, compared with our definition of >20°. Severe HV (>25°) was also found in 48 (13.2 %) individuals. Given these diagnostic criteria for HV, the prevalence was similar in both studies.

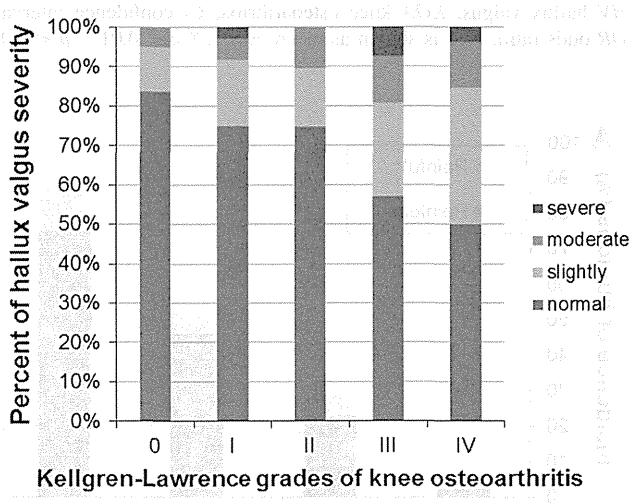

Fig. 3 Relationship between severity of hallux valgus and of knee osteoarthritis

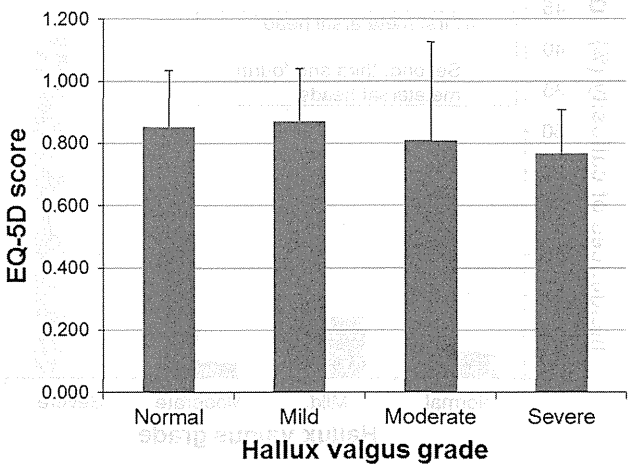

Fig. 4 EQ-5D utility scores of hallux valgus severity. Severity does not significantly differ between groups

Badlissi [11] identified HV in 37.1 % of 784 individuals in a community-based study and found no association with foot pain or function, whereas 9.9 % of individuals studied by Cho et al. [12] reported foot pain. On the other hand, Menz et al. [23] identified foot pain in 20–30 % of community-dwelling elderly individuals. Although foot pain was not assessed in the present study, bunions and callosities, which are the main cause of pain associated with HV, were investigated. The rate of painful bunions on all those with HV in the present study was 6.5 % (12/184), which closely correlated with the severity of HV. The rates of painful bunions and callosities were higher in feet with HV than in normal feet. The locations of callosities changed from the ball of the foot to the second, third and fourth metatarsal heads according to the severity of HV. The likely reason for this is that the load center of the foot moves from the ball of the foot to the second, third and fourth metatarsal heads as HV severity progresses.

Risk factors for HV in some countries have been reported. Our results concurred with the findings of many reports indicating that female sex increases risk for HV [2, 12, 24–26], but contradicted those of Roddy et al. [2], who reported that HV is closely associated with age. However, their study participants were much younger than those in the present study (>30 vs >65 years). Our results suggested that HV is less likely to occur in the elderly. We also found that osteoporosis, which is considered a typical musculoskeletal disease of the elderly, and low back pain, which is associated with osteoporosis, were not associated with HV.

Our results support the notion that HV is associated with knee pain [2, 12, 27], the main cause of which is OA in elderly individuals. Wilder et al. [28] associated radiographically confirmed OA of the first metatarsophalangeal joint with radiographic KOA. Roddy et al. [2] concluded that HV appears to be a component of generalized OA and a likely marker of OA of the first metatarsophalangeal joint. However, the cross-sectional design of their study did not allow confirmation of this relationship ahead of the possibility that HV coexists with OA or that HV is a precursor of OA of the first metatarsophalangeal joint. Other reports [29, 30] show that most patients with HV also have cartilage degeneration of the first metatarsophalangeal joint. Knee OA has a genetic association [34], as well as a phenotypic association with factors such as weight loading (obesity) [12]. A deformity (especially of the varus type) of a person with a genetic background of KOA might proceed

gradually, according to weight loading. On the other hand, valgus stress affects the first MTP joint very little when walking barefoot, but the effect is considerable when wearing shoes, especially those with pointed toes or high heels. Not all people who wear such shoes develop HV, so we believe that those who develop HV have internal factors that are related to KOA. On the other hand, Heberden's nodes that are considered hand OA [31] are thought to indicate a systemic predisposition to generalized OA [32]. However, our data showed that HV is related to KOA, but not to Heberden's nodes. Cicuttini et al. [33] found poor agreement between Heberden's nodes and radiological distal interphalangeal osteophytes in the same finger of the same hand. Heberden's nodes were defined in the present study only by inspection and palpation, and such a relationship might be revealed by X-rays of the hand. Further study is needed to clarify this issue.

Cho et al. [12] associated a high BMI with HV, whereas Roddy et al. [2] and Abhishek et al. [35] did not. The present study supports the latter finding, as an association between HV and BMI >25 (obesity) was not identified. Race, lifestyle or socioeconomic background might be involved in this contradiction.

Abhishek et al. [35] suggested that self-reported HV and big toe pain are associated with an impaired QOL, whereas HV alone is not. They also considered that the influence of HV on QOL could be explained by impaired balance [36] and gait [23]. Cho et al. [12] reported that participants with at least moderate HV (HVA >25°) had impaired general functional status on the physical function domain of the SF-36. They also found even lower general functional status among participants who had HV with foot pain than those without. Both moderate and severe HV tended to be a relatively lower EQ-5D score in the present study, but not significantly with QOL (EQ-5D). We considered only HV angle and not foot pain. This could explain the discrepancy between the previous and present results.

The present study has several potential limitations. We did not question participants about the types of shoes they wore when they were young, and so could not clarify the relationship between HV and type of shoes worn in youth. However, many inhabitants were engaged in forestry and/or agriculture because Miyagawa is a mountain village. Thus, most of them probably wore Japanese tabi socks and/or Japanese zori sandals when they were young. Both tabi socks and zori separate the big toe from the other toes and they do not have a heel. Shoes with pointed toes and high heels are risk factors for HV according to the Japanese guidelines [22]. Thus, people who wore tabi and zori in their youth might be less likely to develop HV, and because the younger generations did not wear tabi and zori even when they were young and often wore high-heeled shoes, the prevalence of HV might increase in the near future as they age. Participants who could visit the hospital were generally healthier than non-participants. The statistical significance of the risk factors might be relatively low. The EQ-5D is a standardized instrument used as a measure of health outcome, so it is not foot-specific like the self-administered foot evaluation questionnaire (SAFE-Q) [37], which might reveal significant differences. This study was cross-sectional and not longitudinal. Only two of the 130 participants who participated in both the seventh and eighth Miyagawa studies were free of HV (HVA <20) at the seventh study but had HV by the eighth (data not shown). Thus, a longitudinal study was impossible at this time. Further investigations of more participants over a longer term are planned, as the study will continue every 2 years.

Conclusion

This cross-sectional epidemiological study identified a 22.8 % prevalence of definite radiographic HV in a rural Japanese village. The ratios of mild, moderate and severe HV were 66.3, 27.2 and 6.5 %, respectively, and 15.9 and 13.9 % of participants had bilateral and unilateral HV, respectively. Furthermore, both female sex and KOA were identified as risk factors for radiographic HV.

Conflict of interest The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

An algorithm using the early changes in PINP to predict the future BMD response for patients treated with daily teriparatide

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Abstract
Summary About two thirds of patients with a procollagen type I N-terminal propeptide (PINP) increase of >80 μg/l at 1 month after starting teriparatide therapy showed a ≥10 % increase in lumbar spine (LS) bone mineral density (BMD) from baseline at 12 months. We recommend this algorithm as an aid in the clinical management of patients treated with daily teriparatide.
Introduction An algorithm using PINP is provided in osteoporotic patients with teriparatide treatment. The correlations between the early changes in PINP and the subsequent BMD changes after daily teriparatide therapy were studied to develop an algorithm to monitor patients.
Methods We evaluated whether early changes in PINP correlated with the changes in BMD at 12 months and developed an algorithm using the early changes in PINP to predict the upcoming BMD increases.
Results The highest correlation coefficient for the relationship between PINP and LS BMD response was determined for the absolute change in PINP at 1 month and the percent change in LS BMD at 12 months (r=0.36, p <0.01). Using a receiver operator curve analysis, we determined that an 80 μg/l increase in PINP was the most convenient predictor of a 10 % increase in LS BMD from baseline (area under curve=0.72). Using a cut-off value of 80 μg/l, the positive predictive value for predicting a 10 % increase in LS BMD from baseline to 12 months was 65 %.
Conclusion Greater short-term changes in PINP with teriparatide therapy are associated with greater 12-month increases in LS BMD. About two thirds of patients with a PINP increase of >80 μg/l at 1 month after starting treatment showed a ≥10 % increase in LS BMD from baseline at 12 months. We recommend this algorithm as an aid in the clinical management of patients treated with teriparatide.

Keywords BMD · Clinical trials · Osteoporosis · PINP · Teriparatide

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Introduction

Fractures in patients with osteoporosis are a global burden for both individuals and health-care systems. Among postmenopausal females aged 60 years and older, the mortality-adjusted residual lifetime risk of fractures has been estimated to be 44–65 % [1]. Fractures in the elderly are associated with high morbidity and mortality; pain and immobility lead to a loss of quality of life and an increase in general frailty. Daily injection of teriparatide [human parathyroid hormone PTH(1-34) is known to increase the bone mineral density (BMD) and markers of bone formation, and to reduce the fracture risk. The vertebral fracture risk was reduced in the teriparatide group by 84 % compared to the placebo group [2]. Miyauchi et al. [3] assessed the efficacy of teriparatide in Japanese males and females with osteoporosis during a 12-month period, and reported that teriparatide significantly increased BMD at the lumbar spine (LS) by 10.0 % and BMD at femoral neck (FN) by 2.2 %.

Bone turnover markers provide information on the rates of bone formation and resorption, and correlate with the rate of bone loss. Bone turnover markers also have the potential to provide early feedback on the progress of the patient, and allows for changes to be made in the management of