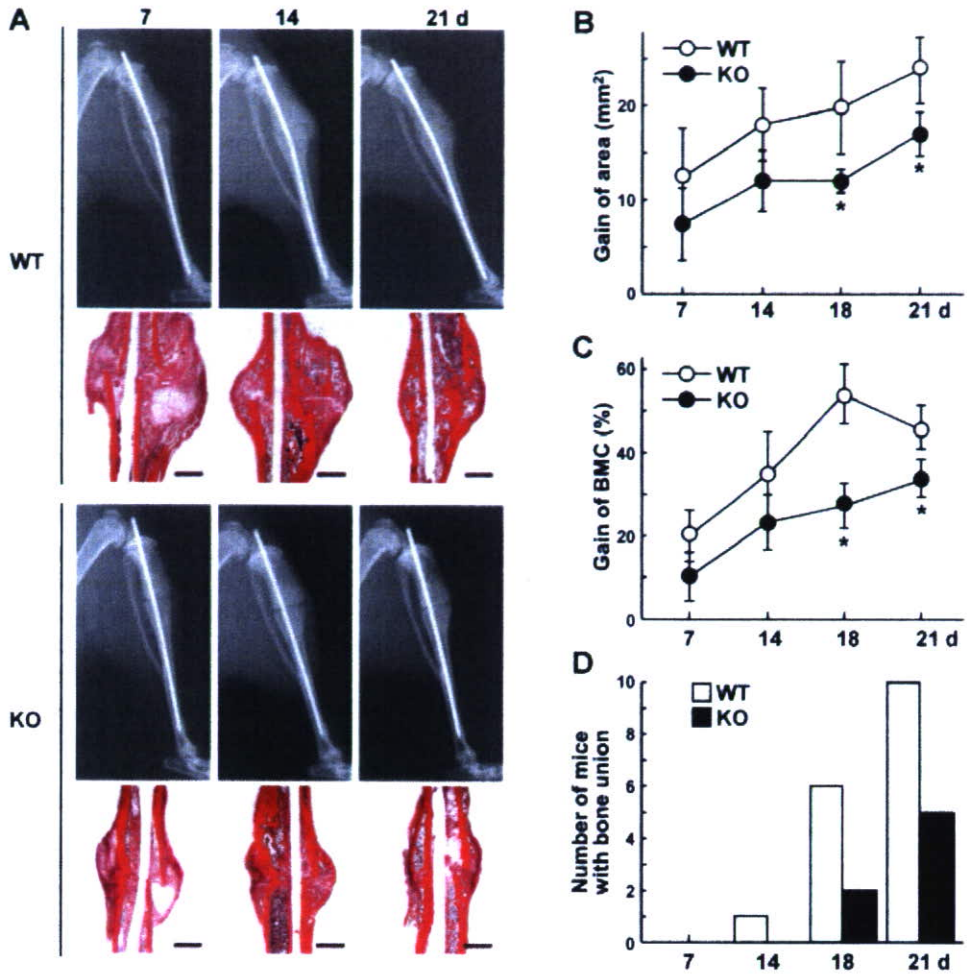

Figure 4. Bone fracture healing in KO (mPGES-1$^{-/-}$) mice and their WT littermates. **A,** Assessment by plain radiography and hematoxylin and eosin staining at 7, 14, and 21 days after fracture. Bar = 1 mm. **B** and **C,** Time course of the gain of area **(B)** and percent gain in bone mineral content (BMC) **(C)** in the fracture callus. The area and BMC of the entire tibias were measured bilaterally before and after the operation at the indicated time points (in days), and the difference between the right (fractured) and left (unfractured) tibias was calculated. Bars show the mean ± SEM of the gains as compared with the values before the operation, in 10 mice/group. * = $P < 0.05$ versus WT mice. **D,** Time course (in days) of the number of mice displaying bone union among 10 mice/group, determined by radiographic assessment of complete bony bridging at the fracture site. See Figure 1 for other definitions.

was compared between genotypes. The weight of the uterus was confirmed to be decreased by ovariectomy in both genotypes (Figure 2A). Similarly, the BMD was also decreased in both groups (Figure 2A), indicating that mPGES-1 does not contribute to bone loss caused by estrogen deficiency.

We then studied the role of this enzyme in bone loss induced by unloading, using the tail suspension model. Four weeks after tail suspension, radiologic and histologic analyses of the tibias were performed. Similar to the findings described above, both genotypes showed comparable decreases in BMD after hind limb unloading, as compared with the values in the loaded controls (Figure 2B). Histomorphometric analyses revealed that bone formation parameters were decreased, while bone resorption parameters were increased, by hind limb unloading, and that these changes were not affected by the mPGES-1 deficiency, which indicates that this enzyme is not essential for unloading-induced bone loss.

We then compared the susceptibility to OA in-

duced by knee joint instability between mPGES-1$^{-/-}$ and WT mice (Figure 2C), with cartilage destruction assessed using our original model and grading scheme (29). Safranin O staining showed that cartilage destruction progressed into the middle zone of the medial cartilage by 14 weeks after surgery, and this was evident in both genotypes. Quantification of cartilage destruction by our original grading system confirmed that the mPGES-1 deficiency does not affect OA induced by joint instability.

Expression of PGES enzymes and prostanoids in the fracture callus. To understand the involvement of PGES enzymes and PGE_2 in bone fracture healing, we created a fracture at the midshaft of the tibia in WT mice (Figure 3A) and examined the expression of mPGES-1, mPGES-2, and cPGES. Immunolocalization of mPGES-1 was visible 7 days after the fracture, in areas of both intramembranous and endochondral bone formation (Figure 3B). Among the 3 enzymes, only the mPGES-1 mRNA level increased, at 5 and 7 days after surgery, at the fracture callus of the right tibia, as compared with the sham-operated site of the left tibia (Figure 3C). In addition, the level of PGE_2 was confirmed to be higher at the callus 7 days after surgery, while the $PGF_{2\alpha}$ level at the fracture callus was comparable with that at the sham-operated site (Figure 3D).

Bone fracture healing in mPGES-1$^{-/-}$ mice. We then used the same fracture model as described above to compare the healing process in mPGES-1$^{-/-}$ and WT mice at 8 weeks of age and examine the effect of the mPGES-1 deficiency. In WT mice, a large soft callus had formed by 7 days after fracture and was thereafter reduced in size during ossification. Bony bridging was complete within 14–21 days (Figure 4A, top). In mPGES-1$^{-/-}$ mice, however, the size of the callus was smaller at 7 days after fracture, and fibrous tissue still remained in the fracture gap even at 21 days, indicative of a state of non–bone union (Figure 4A, bottom).

Evaluation of the time course of the gain of area (Figure 4B) and gain of BMC (Figure 4C) of the fracture callus revealed that, starting 7 days after fracture, impairment of callus formation became evident in mice with the mPGES-1 deficiency, with significant differences compared with WT mice by 18 days and thereafter. Determination of the number of mice with radiologic bone union revealed that 5 mPGES-1$^{-/-}$ mice remained in a non–bone union state even at 21 days after fracture, at which time all WT mice had achieved bone union (Figure 4D). Taken together, these findings reveal that the mPGES-1 deficiency probably caused an impairment of fracture healing from the early stage, when the required amount of soft callus must be formed.

Mechanism of impaired fracture healing by mPGES-1 deficiency. To examine the mechanism underlying the impaired fracture healing that occurs at an early stage and is attributable to mPGES-1 deficiency, we performed more detailed histologic analyses of the fracture callus at 7 days after surgery (Figure 5A). Toluidine blue staining revealed a decrease in the size of the soft callus in mPGES-1$^{-/-}$ mice, especially in the cartilaginous tissue. Moreover, in the tissue, BrdU-positive proliferative cells were abundant in the fracture callus of WT mice but were hardly detectable in that of the mPGES-1$^{-/-}$ mice, indicating that chondrocyte proliferation was markedly impaired by the mPGES-1 deficiency. In contrast, COL10 immunostaining and TUNEL staining, representing hypertrophic and apoptotic chondrocytes, were normally visible in the cartilaginous area of the callus of mPGES-1$^{-/-}$ mice, although the areas of positive staining were somewhat smaller than those in the callus of the WT mice, implying that these defects may be secondary to the impaired proliferation of mPGES-1$^{-/-}$ chondrocytes.

We then compared the functions of cultured chondrocytes isolated from WT and mPGES-1$^{-/-}$ costal cartilage. The growth curve at 7 days after seeding confirmed that the chondrocytes from mPGES-1$^{-/-}$ mice had impaired mitogenic ability. The number of cells in mPGES-1$^{-/-}$ mice was significantly lower than that in WT mice at 5 days and thereafter (Figure 5B). In contrast, chondrocyte differentiation, as determined by alkaline phosphatase and alizarin red staining, was similar between the 2 genotypes (Figure 5C). Thus, the impairment of bone fracture healing by the mPGES-1 deficiency may be due to a decrease in the mitogenic ability of chondrocytes, but not due to a decrease in the differentiation or survival of chondrocytes.

Finally, to determine whether the impaired healing was a tissue-autonomous effect of the mPGES-1 deficiency, we injected an adenovirus vector carrying the mPGES-1 gene (Ax-mPGES-1) or LacZ (Ax-LacZ) into the fracture site 2 days after the fracture (Figure 5D). Expression of the transgene was confirmed by X-Gal staining in and around the Ax-LacZ–injected fracture sites, as we have previously reported (32). Reintroduction of Ax-mPGES-1 into the fracture callus of mPGES-1$^{-/-}$ mice significantly restored both the area and the BMC 14 days after injection, indicating that the mPGES-1 deficiency was the cause of the impaired fracture healing, via a tissue-autonomous mechanism.

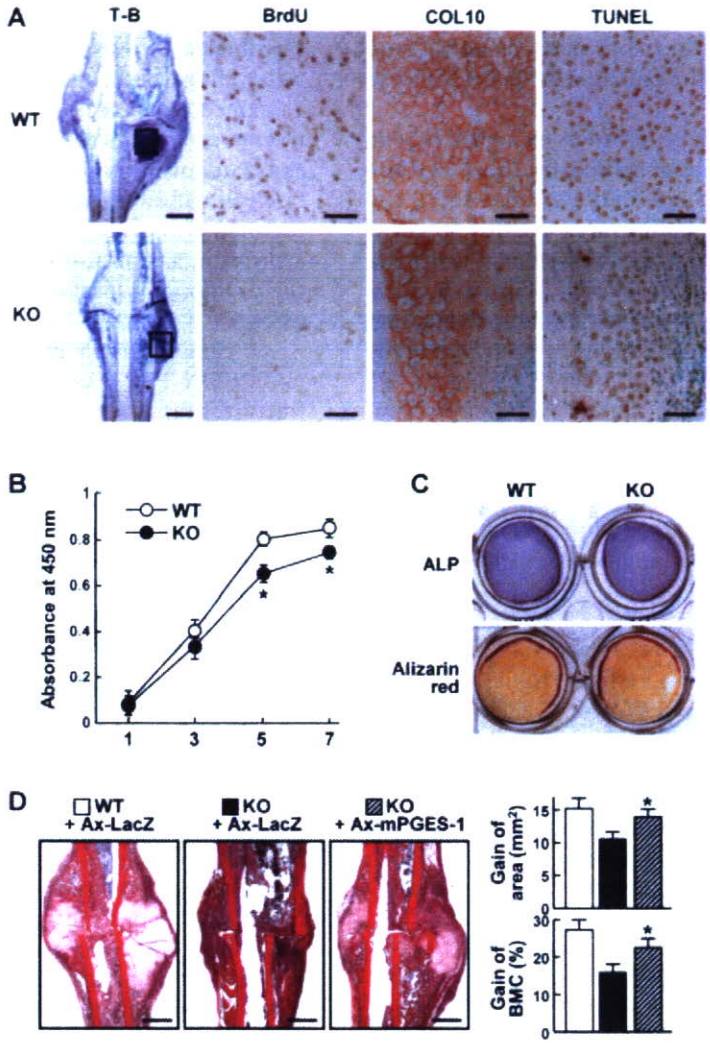

Figure 5. Mechanism of impaired fracture healing in mPGES-$1^{-/-}$ mice. **A,** Histologic and immunohistochemical findings in the fracture callus in WT and mPGES-$1^{-/-}$ mice 7 days after the fracture, using toluidine blue (T-B) staining, bromodeoxyuridine (BrdU) labeling, type X collagen (COL10) immunohistochemical staining, and TUNEL staining. Boxed areas in the T-B images are shown in higher magnification in the other images (T-B, bar = 1 mm; BrdU, COL10, and TUNEL, bar = 50 μm). **B,** Growth curves of cultured chondrocytes isolated from WT and mPGES-$1^{-/-}$ costal cartilage. Chondrocytes were incubated at a density of 5,000 cells/well in 96-multiwell plates, and the number of cells/well was determined by the absorbance at 450 nm at 7 days after seeding. Bars show the mean ± SEM of 8 wells/group. * = $P < 0.01$ versus WT mice. **C,** Differentiation of the costal chondrocytes, as determined by alkaline phosphatase (ALP) and alizarin red staining after 14 and 21 days of culture, respectively. **D,** Fracture callus formation by reintroduction of mPGES-1 using an adenoviral construct (Ax-mPGES-1) or the control LacZ (Ax-LacZ) in WT and mPGES-$1^{-/-}$ mice. Bar = 1 mm. Ax-mPGES-1 or Ax-LacZ was injected into the fracture site 2 days after surgery, and animals were killed 14 days after the injection. The gain of area and the percent gain of bone mineral content (BMC) of the fracture callus were measured as described above. Bars show the mean and SEM of 3 mice/group. * = $P < 0.05$ versus KO + Ax-LacZ. See Figure 1 for other definitions.

DISCUSSION

In accordance with the reports of previous studies indicating a lack of skeletal abnormalities in mPGES-$1^{-/-}$ mice under normal physiologic conditions (13–15), the present study confirmed this feature by detailed radiologic and histologic analyses (Figure 1). With regard to skeletal abnormalities under pathophysiologic conditions, we and others have previously reported that

mPGES-1$^{-/-}$ mice are resistant to CIA (14,15). Furthermore, another study of knockout mice showed a suppression of LPS-induced bone loss in mice with the mPGES deficiency (17).

Among the 4 skeletal disorders examined herein, only fracture healing was impaired by the mPGES-1 deficiency. This discrepancy indicates that there are differences in the contribution of mPGES-1 to these disorders, i.e., the enzyme plays an essential role in CIA, LPS-induced bone loss, and fracture healing but appears to be unnecessary for ovariectomy- or unloading-induced bone loss and OA induced by joint instability. This might be because the former 3 disorders are associated with inflammation while the latter are degenerative conditions, and both mPGES-1 and PGE_2 play important roles in inflammatory reactions. In fact, not only CIA and LPS-induced bone loss but also fracture healing are known to be initiated in response to regulatory factors associated with inflammation and the innate immune response (34).

Alternatively, the discrepancy in the effects of mPGES-1 deficiency might be attributable to differing compensatory mechanisms in response to the deficiency, similar to the observations in COX-2$^{-/-}$ mice indicating that primary hyperparathyroidism could develop (35,36). Since CIA, LPS-induced bone loss, and fracture healing progress more rapidly than ovariectomy- or unloading-induced bone loss and stress-induced OA, it is likely that any mechanism of compensation would not be adequate for the former disorders but would be sufficient to countervail the latter.

Following bone fracture, a sequence of events regulated by various molecules is induced to bring about endochondral and intramembranous bone formation (34). In fact, by creating the same model of bone fracture in knockout mice as used in the present study, we previously found that insulin receptor substrate 1, carminerin, and matrix metalloproteinase 13 had great effect on the stages of chondrocyte proliferation, calcification, and cartilage resorption, respectively, during endochondral bone formation (30,32,37). Although, in the present study, mPGES-1 was shown to be expressed during both endochondral and intramembranous bone formation (Figure 3B), the most prominent abnormality of the callus of mPGES-1$^{-/-}$ mice was the reduced quantity of cartilaginous tissue (Figure 5A).

In addition, further in vivo and ex vivo analyses showed that proliferation of mPGES-1$^{-/-}$ chondrocytes was suppressed; however, interestingly, the suppression was more conspicuous in vivo than ex vivo (Figures 5A and B). This might be due to differences in the nutritional environment, i.e., the in vivo chondrocytes were surrounded by avascular cartilage matrix, whereas cultured chondrocytes were in a nutritious medium that contained compensatory factors in response to the proliferation. The increase in mPGES-1 expression was associated with an increase in PGE_2 production in the fracture callus (Figures 3C and D), as we have also reported previously in conditions of LPS stimulation and arthritis induction (6), and PGE_2 is known to stimulate the proliferation of chondrocytes via the EP1 receptor (38).

Similar to our present findings in mPGES-1$^{-/-}$ mice, COX-2$^{-/-}$ mice are reported to exhibit impaired fracture healing (19,20). However, the mechanism underlying the impaired fracture healing in COX-2$^{-/-}$ mice is an unresolved issue, and may be different from that in mPGES-1$^{-/-}$ mice. It has been proposed that the mechanism of impairment is a suppression of terminal differentiation of chondrocytes during endochondral bone formation (20), whereas others have reported that the mechanism might be a reduction in osteoblastic differentiation from immature mesenchymal cells during both endochondral and intramembranous bone formation, induced via decreases in 2 essential genes, Runx2 and osterix (19). The present culture experiments revealed that differentiation of chondrocytes was not affected by the deficiency of mPGES-1 (Figure 5C). Moreover, in our preliminary culture experiment using mPGES-1$^{-/-}$ bone marrow stromal cells, we found that there were no abnormalities in osteoblastogenesis or in the expression of Runx2 and osterix (results not shown). Therefore, the critical cells or differentiation stages related to the contributions of COX-2 and mPGES-1 could be different, and would thus explain the differences in the way in which PGE_2 regulates bone formation (1).

In addition, the transcriptional mechanisms of induction of COX-2 and mPGES-1 are not identical. COX-2 is known to be induced by the transcription factors NF-κB, NF-IL6, activator protein 1, CCAAT/enhancer binding protein α (C/EBPα), C/EBPβ, cAMP response element, and Runx2 (39), while mPGES-1 is mainly transactivated by Egr-1 via MAPK pathways such as ERK-1/2 and p38 (40). Thus, even though COX-2 and mPGES-1 are stimulus-inducible and function sequentially in the same PGE_2-biosynthetic pathway, they appear to have less in common in their upstream and downstream signaling pathways.

Nonsteroidal antiinflammatory drugs (NSAIDs) and selective COX-2 inhibitors have recently been shown to inhibit bone repair in animal models and

clinical studies, although these findings have been obtained only retrospectively (41,42). More importantly, specific COX-2 inhibitors have been reported to increase the risk of cardiovascular events in patients in clinical trials, although whether this is a common risk factor of COX-2–selective agents or could be attributed to NSAIDs more generally is still under debate (43). The increase in cardiovascular events may be due to inhibition of PGI_2, which results in vasodilatory and platelet-inhibitory effects and can lead to detrimental effects on coagulation control (43).

Unlike NSAIDs and COX-2 inhibitors, which suppress not only PGE_2 but also other PGs that play essential roles in physiologic functions, specific mPGES-1 inhibitors are expected to function as highly selective agents in the management of several disorders. In fact, it has been observed that mPGES-$1^{-/-}$ mice exhibit no alterations in thrombogenesis or blood pressure, whereas selective COX-2 inhibitors have been associated with these effects (44). Furthermore, mPGES-$1^{-/-}$ mice lack the renal dysfunction and failure of the female reproductive system that has been seen in COX-$2^{-/-}$ mice (45).

These findings suggest that the mPGES-1 enzyme may represent a treatment target that could be manipulated without affecting important physiologic systems in which other PGs are involved. However, implementation of this treatment strategy will still require caution, because, in addition to its detrimental functions, PGE_2 also exerts homeostatic and defensive effects in several organs, such as the gastrointestinal tract, lung, and kidney, as well as in bone repair, as shown herein. Although selective mPGES-1 inhibitors have recently been developed (46) as a replacement for NSAIDs and COX-2 inhibitors, deliberate randomized and controlled clinical trials will be essential to determine the effectiveness of this new treatment approach.

AUTHOR CONTRIBUTIONS

Dr. Kawaguchi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Yamakawa, Kudo, Akira, Nakamura, Kawaguchi.

Acquisition of data. Yamakawa, Kamekura, Kamei, Murakami, Uematsu.

Analysis and interpretation of data. Yamakawa, Saegusa, Chung, Kawaguchi.

Manuscript preparation. Yamakawa, Kawamura, Kawaguchi.

Statistical analysis. Yamakawa, Kamekura.

REFERENCES

1. Kawaguchi H, Pilbeam CC, Harrison JR, Raisz LG. The role of prostaglandins in the regulation of bone metabolism. Clin Orthop Relat Res 1995;313:36–46.
2. Kobayashi T, Narumiya S. Function of prostanoid receptors: studies on knockout mice. Prostaglandins Other Lipid Mediat 2002;68-69:557–73.
3. Murakami M, Kudo I. Recent advances in molecular biology and physiology of the prostaglandin E_2-biosynthetic pathway. Prog Lipid Res 2004;43:3–35.
4. Murakami M, Naraba H, Tanioka T, Semmyo N, Nakatani Y, Kojima F, et al. Regulation of prostaglandin E_2 biosynthesis by inducible membrane-associated prostaglandin E_2 synthase that acts in concert with cyclooxygenase-2. J Biol Chem 2000;275: 32783–92.
5. Jakobsson PJ, Thoren S, Morgenstern R, Samuelsson B. Identification of human prostaglandin E synthase: a microsomal, glutathione-dependent, inducible enzyme, constituting a potential novel drug target. Proc Natl Acad Sci U S A 1999;96:7220–5.
6. Kamei D, Murakami M, Nakatani Y, Ishikawa Y, Ishii T, Kudo I. Potential role of microsomal prostaglandin E synthase-1 in tumorigenesis. J Biol Chem 2003;278:19396–405.
7. Naraba H, Yokoyama C, Tago N, Murakami M, Kudo I, Fueki M, et al. Transcriptional regulation of the membrane-associated prostaglandin E2 synthase gene: essential role of the transcription factor Egr-1. J Biol Chem 2002;277:28601–8.
8. Tanikawa N, Ohmiya Y, Ohkubo H, Hashimoto K, Kanagawa K, Kojima M, et al. Identification and characterization of a novel type of membrane-associated prostaglandin E synthase. Biochem Biophys Res Commun 2002;291:884–9.
9. Murakami M, Nakashima K, Kamei D, Masuda S, Ishikawa Y, Ishii T, et al. Cellular prostaglandin E_2 production by membrane-bound prostaglandin E synthase-2 via both cyclooxygenases-1 and -2. J Biol Chem 2003;278:37937–47.
10. Saegusa M, Murakami M, Nakatani Y, Yamakawa K, Katagiri M, Matsuda K, et al. Contribution of membrane-associated prostaglandin E_2 synthase to bone resorption. J Cell Physiol 2003;197: 348–56.
11. Tanioka T, Nakatani Y, Semmyo N, Murakami M, Kudo I. Molecular identification of cytosolic prostaglandin E_2 synthase that is functionally coupled with cyclooxygenase-1 in immediate prostaglandin E_2 biosynthesis. J Biol Chem 2000;275:32775–82.
12. Tanioka T, Nakatani Y, Kobayashi T, Tsujimoto M, Oh-ishi S, Murakami M, et al. Regulation of cytosolic prostaglandin E_2 synthase by 90-kDa heat shock protein. Biochem Biophys Res Commun 2003;303:1018–23.
13. Uematsu S, Matsumoto M, Takeda K, Akira S. Lipopolysaccharide-dependent prostaglandin E_2 production is regulated by the glutathione-dependent prostaglandin E_2 synthase gene induced by the Toll-like receptor 4/MyD88/NF-IL6 pathway. J Immunol 2002; 168:5811–6.
14. Trebino CE, Stock JL, Gibbons CP, Naiman BM, Wachtmann TS, Umland JP, et al. Impaired inflammatory and pain responses in mice lacking an inducible prostaglandin E synthase. Proc Natl Acad Sci U S A 2003;100:9044–9.
15. Kamei D, Yamakawa K, Takegoshi Y, Mikami-Nakanishi M, Nakatani Y, Oh-ishi S, et al. Reduced pain hypersensitivity and inflammation in mice lacking microsomal prostaglandin E synthase-1. J Biol Chem 2004;279:33684–95.
16. Okada Y, Lorenzo JA, Freeman AM, Tomita M, Morham SG, Raisz LG, et al. Prostaglandin G/H synthase-2 is required for maximal formation of osteoclast-like cells in culture. J Clin Invest 2000;105:823–32.
17. Inada M, Matsumoto C, Uematsu S, Akira S, Miyaura C. Membrane-bound prostaglandin E synthase-1-mediated prostaglandin E_2 production by osteoblast plays a critical role in lipopolysaccharide-induced bone loss associated with inflammation. J Immunol 2006;177:1879–85.
18. Paralkar VM, Borovecki F, Ke HZ, Cameron KO, Lefker B, Grasser WA, et al. An E_2 receptor-selective prostaglandin E_2

agonist induces bone healing. Proc Natl Acad Sci U S A 2003;100: 6736–40.
19. Zhang X, Schwarz EM, Young DA, Puzas JE, Rosier RN, O'Keefe RJ. Cyclooxygenase-2 regulates mesenchymal cell differentiation into the osteoblast lineage and is critically involved in bone repair [published erratum appears in J Clin Invest 2002;110:1211]. J Clin Invest 2002;109:1405–15.
20. Simon AM, Manigrasso MB, O'Connor JP. Cyclo-oxygenase 2 function is essential for bone fracture healing. J Bone Miner Res 2002;17:963–76.
21. Goldring MB, Berenbaum F. The regulation of chondrocyte function by proinflammatory mediators: prostaglandins and nitric oxide. Clin Orthop Relat Res 2004:S37–46.
22. Laufer S. Role of eicosanoids in structural degradation in osteoarthritis. Curr Opin Rheumatol 2003;15:623–7.
23. Hardy MM, Seibert K, Manning PT, Currie MG, Woerner BM, Edwards D, et al. Cyclooxygenase 2–dependent prostaglandin E_2 modulates cartilage proteoglycan degradation in human osteoarthritis explants. Arthritis Rheum 2002;46:1789–803.
24. Miwa M, Saura R, Hirata S, Hayashi Y, Mizuno K, Itoh H. Induction of apoptosis in bovine articular chondrocyte by prostaglandin E_2 through cAMP-dependent pathway. Osteoarthritis Cartilage 2000;8:17–24.
25. McCoy JM, Wicks JR, Audoly LP. The role of prostaglandin E_2 receptors in the pathogenesis of rheumatoid arthritis. J Clin Invest 2002;110:651–8.
26. Jacques C, Sautet A, Moldovan M, Thomas B, Humbert L, Berenbaum F. Cyclooxygenase activity in chondrocytes from osteoarthritic and healthy cartilage. Rev Rhum Engl Ed 1999;66: 701–4.
27. Kojima F, Naraba H, Miyamoto S, Beppu M, Aoki H, Kawai S. Membrane-associated prostaglandin E synthase-1 is upregulated by proinflammatory cytokines in chondrocytes from patients with osteoarthritis. Arthritis Res Ther 2004;6:R355–65.
28. Akune T, Ohba S, Kamekura S, Yamaguchi M, Chung UI, Kubota N, et al: PPARγ insufficiency enhances osteogenesis through osteoblast formation from bone marrow progenitors. J Clin Invest 2004;113:846–55.
29. Kamekura S, Hoshi K, Shimoaka T, Chung U, Chikuda H, Yamada T, et al. Osteoarthritis development in novel experimental mouse models induced by knee joint instability. Osteoarthritis Cartilage 2005;13:632–41.
30. Yamada T, Kawano H, Koshizuka Y, Fukuda T, Yoshimura K, Kamekura S, et al. Carminerin contributes to chondrocyte calcification during endochondral ossification. Nat Med 2006;12:665–70.
31. Kamekura S, Kawasaki Y, Hoshi K, Shimoaka T, Chikuda H, Maruyama Z, et al. Contribution of runt-related transcription factor 2 to the pathogenesis of osteoarthritis in mice after induction of knee joint instability. Arthritis Rheum 2006;54:2462–70.
32. Shimoaka T, Kamekura S, Chikuda H, Hoshi K, Chung UI, Akune T, et al. Impairment of bone healing by insulin receptor substrate-1 deficiency. J Biol Chem 2004;279:15314–22.
33. Van Griensven M, Lobenhoffer P, Barke A, Tschernig T, Lindenmaier W, Krettek C, et al. Adenoviral gene transfer in a rat fracture model. Lab Anim 2002;36:455–61.
34. Barnes GL, Kostenuik PJ, Gerstenfeld LC, Einhorn TA. Growth factor regulation of fracture repair. J Bone Miner Res 1999;14: 1805–15.
35. Xu M, Choudhary S, Goltzman D, Ledgard F, Adams D, Gronowicz G, et al. Do cyclooxygenase-2 knockout mice have primary hyperparathyroidism? Endocrinology 2005;146:1843–53.
36. Myers LK, Bhattacharya SD, Herring PA, Xing Z, Goorha S, Smith RA, et al. The isozyme-specific effects of cyclooxygenase-deficiency on bone in mice. Bone 2006;39:1048–52.
37. Kosaki N, Takaishi H, Kamekura S, Kimura T, Okada Y, Minqi L, et al. Impaired bone fracture healing in matrix metalloproteinase-13 deficient mice. Biochem Biophys Res Commun 2007;354: 846–51.
38. Brochhausen C, Neuland P, Kirkpatrick CJ, Nusing RM, Klaus G. Cyclooxygenases and prostaglandin E_2 receptors in growth plate chondrocytes in vitro and in situ: prostaglandin E2 dependent proliferation of growth plate chondrocytes. Arthritis Res Ther 2006;8:R78.
39. Chikazu D, Li X, Kawaguchi H, Sakuma Y, Voznesensky OS, Adams DJ, et al. Bone morphogenetic protein 2 induces cyclooxygenase 2 in osteoblasts via a Cbfal binding site: role in effects of bone morphogenetic protein 2 in vitro and in vivo. J Bone Miner Res 2002;17:1430–40.
40. Masuko-Hongo K, Berenbaum F, Humbert L, Salvat C, Goldring MB, Thirion S. Up-regulation of microsomal prostaglandin E synthase 1 in osteoarthritic human cartilage: critical roles of the ERK-1/2 and p38 signaling pathways. Arthritis Rheum 2004;50: 2829–38.
41. Giannoudis PV, MacDonald DA, Matthews SJ, Smith RM, Furlong AJ, De Boer P. Nonunion of the femoral diaphysis: the influence of reaming and non-steroidal anti-inflammatory drugs. J Bone Joint Surg Br 2000;82:655–8.
42. Gerstenfeld LC, Al-Ghawas M, Alkhiary YM, Cullinane DM, Krall EA, Fitch JL, et al. Selective and nonselective cyclooxygenase-2 inhibitors and experimental fracture-healing: reversibility of effects after short-term treatment. J Bone Joint Surg Am 2007;89: 114–25.
43. Dieppe PA, Ebrahim S, Martin RM, Juni P. Lessons from the withdrawal of rofecoxib. BMJ 2004;329:867–8.
44. Cheng Y, Wang M, Yu Y, Lawson J, Funk CD, Fitzgerald GA. Cyclooxygenases, microsomal prostaglandin E synthase-1, and cardiovascular function. J Clin Invest 2006;116:1391–9.
45. Langenbach R, Loftin C, Lee C, Tiano H. Cyclooxygenase knockout mice: models for elucidating isoform-specific functions. Biochem Pharmacol 1999;58:1237–46.
46. Riendeau D, Aspiotis R, Ethier D, Gareau Y, Grimm EL, Guay J, et al. Inhibitors of the inducible microsomal prostaglandin E_2 synthase (mPGES-1) derived from MK-886. Bioorg Med Chem Lett 2005;15:3352–5.

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ORIGINAL ARTICLE

Association between height loss and bone loss, cumulative incidence of vertebral fractures and future quality of life: the Miyama study

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Abstract
Introduction The study aimed to clarify associations between height loss, bone loss and the quality of life (QOL) score among general inhabitants of Miyama, a rural Japanese community. This population-based epidemiological study was conducted in Miyama, a village located in a mountain area in Wakayama Prefecture, Japan.

Methods A list of all inhabitants comprising 1,543 inhabitants (716 men, 827 women) born in this village between 1910–1949 was compiled. From the above whole cohort, a subcohort to measure bone mineral density (BMD) was recruited, consisting of 400 participants, divided into four groups of 50 men and 50 women each, and stratified into age decades by decade of birth-year (1910–1919, 1920–1929, 1930–1939 or 1940–1949). BMD measurement, physical measurements of height (cm) and body weight (kg) were taken, and body mass index (BMI; kg/m^2) were calculated. BMD and anthropometric measurements were repeated on the same participants at 3, 7 and 10 years after baseline measurement (1993, 1997 and 2000).

Results and discussion Among 299 of 400 participants, changes in height over 10 years for men in their 40s, 50s, 60s and 70s were −0.7 cm, −0.5 cm, −1.2 cm and −1.5 cm, respectively, compared with −0.7 cm, −1.4 cm, −2.1 cm and −3.7 cm in women, respectively. No significant relationships between change in height and rate of change in BMD at the lumbar spine and femoral neck after adjustment for age in men (lumbar spine, β=0.058, standard error of the mean (SE)=0.031, P=0.501, R^2= 0.038; femoral neck, β=0.100, SE=0.038, P=0.228, R^2= 0.121) were identified. By contrast, among women, a significant positive association was identified between height change and change rate of BMD at the lumbar spine after adjusting for age (β=0.221, SE=0.039, P=0.012, R^2= 0.069), while no significant relationship was found between height change and change rate at the femoral neck (β=0.107, SE=0.039, P=0.229, R^2=0.048). No significant relationship was noted between vertebral fractures (VFx) and height at baseline in men and women (men: odds ratio (OR) 0.93, 95% confidence interval (CI) 0.81–1.05, P=0.24; women: OR 0.97, 95% CI 0.87–1.08, P=0.58) or between VFx and height loss

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(men: OR 1.31, 95% CI 1.00–1.71, P=0.051; women: OR 1.20, 95% CI 0.94–1.53, P=0.14). In both men and women, no significant relationship was identified between utility of the EuroQol EQ5D questionnaire and height at baseline (men: β=−0.148, SE=0.003, P=0.202, R^2=0.076; women: β=0.127, SE=0.004, P=0.235, R^2=0.048), and height change (men: β=−0.078, SE=0.008, P=0.452, R^2=0.065; women: β=0.053, SE=0.010, P=0.608, R^2=0.038).

Keywords Bone mineral density · Cohort study · Height loss · Osteoporosis · Quality of life · Vertebral fractures

Introduction

Osteoporotic fracture is one of the leading reasons for the elderly becoming bedridden in Japan [1, 2]. Among fractures associated with osteoporosis, hip fracture results in confinement to bed and markedly impaired quality of life (QOL) in aged individuals. The number of patients with femoral neck fracture has almost doubled over the past 15 years from 1987 to 2002 [3, 4]. Prevention of osteoporosis and osteoporotic fracture is, therefore, an urgent issue for maintaining QOL in the elderly and containing the medical costs of their care.

For the prevention of osteoporosis, the importance of risk assessment must be emphasized. As a risk factor of osteoporosis and osteoporotic fractures, anthropometric measurements no doubt have an important role to play. Particularly among anthropometric measures, light weight [5–8], weight loss [9, 10], and low body mass index (BMI) [11–13] suggest a risk of osteoporosis and osteoporotic fractures. However, data are scarcer on relationships between height loss and subsequent rate of changes in bone mineral density (BMD) or osteoporotic fractures. In addition, few reports have assessed relationships between height loss and subsequent loss of QOL.

To clarify associations between height or height loss and bone loss, osteoporotic fractures focused on vertebral fractures and QOL scores among general inhabitants, the present study was performed as a postal survey on the cohort established in Miyama, a rural Japanese community.

Methods

Establishment of baseline cohort

This population-based epidemiological study was initiated in 1990 in Miyama, a mountain village in Wakayama Prefecture, Japan. As the Miyama cohort has been profiled in detail elsewhere [14, 15], subject characteristics are summarized here briefly. A list of all inhabitants born in this village between 1910–1949, and therefore aged 40 to 79 years, was compiled from the register of residents as of the end of 1989. A cohort of 1,543 inhabitants (716 men, 827 women) was identified, all of whom completed a self-administered questionnaire covering daily activities, such as dietary habits, smoking habits, alcohol consumption and physical exercise (125 items) (the whole cohort).

From the above whole cohort, a BMD cohort was recruited, consisting of 400 participants, divided into four groups of 50 men and 50 women each, and stratified into age decades by decade of birth-year (1910–1919, 1920–1929, 1930–1939, 1940–1949). An interviewer administered a second questionnaire to these 400 participants, covering items of past medical history, family history, calcium intake, dietary habits, physical exercise, occupational activities and sun exposure, in addition to reproductive variables for women.

BMD and anthropometric measurements

The baseline measurement of BMD was made in 1990. Dual energy X-ray absorptiometry (DXA:Lunar DPX, Madison, WI, USA) was used for the measurement of BMD, providing antero-posterior images at lumbar vertebrae L2–4 and the proximal femur (femoral neck, Ward's triangle, trochanter, and total hip). In addition to BMD, physical measurements of height and body weight were taken, and BMI (kg/m^2) was calculated. Height and weight at each visit were all measured by the same well-trained public health nurse (TT).

BMD measurements were repeated on the same participants at 3, 7 and 10 years after baseline measurement (1993, 1997 and 2000). Rates of change in BMD and height change were calculated over the 10-year period, classified by sex and age stratum. BMD measurements at all visits were performed by the same well-trained medical doctor (NY).

To control for precision of DXA, the equipment was checked every examination in 1990, 1993, 1997 and 2000 using the same phantom, and BMD of the phantom was regulated to 1.270 ±0.025 g/cm^2 (2%) during examinations. In addition, to control for observer variability, all participants were examined by the same medical doctor. Intra-observer variability of DXA (Lunar DPX) in vitro and in vivo had been measured for a prior study [16], using the same doctor, and CV% for L2–4 in vitro was determined as 0.35%, while CV% for L2–4, proximal femur, Ward's triangle and trochanter, examined in vivo in five male volunteers, were 0.61–0.90%, 1.02–2.57%, 1.97–5.45% and 1.77–4.17%, respectively.

Radiography

Radiographic examination of the spine was performed on all participants in 1990. Anteroposterior and lateral images

of thoracolumbar vertebrae Th5-L5 were used for diagnosis (Initial X-ray survey). Radiographic examination was again performed on subjects who provided consent after 10 years. Lateral images of thoracolumbar vertebrae Th5-L5 were again used for diagnosis (2nd X-ray survey). Lateral spinal radiographs were examined for the presence of one or more vertebral fractures (VFx) between Th5–L5, using the criteria determined by the Japan Bone and Mineral Society (Fig. 1) [17]. According to these criteria, measurement of anterior, middle and posterior heights on lateral radiography of the thoracic and lumbar spine is required, to determine ratios defining the anterior wedge, biconcave and compound dimensions of the vertebral bodies. Diagnosis of VFx on all radiographs was performed by the same experienced orthopedic doctor (HK). In the present study, cumulative incidence over 10 years was detected by dividing the number of incident cases by the number of participants in the follow-up study, and cases with previous VFx were excluded from both numerators and denominators. In this analysis, cumulative incidence of cases with first VFx was detected.

QOL postal survey

The QOL questionnaire postal survey was performed in 2002. To select QOL items, the Euro Qol EQ5D questionnaire [18] translated into Japanese was used, comprising the following two parts: a 5-dimensional health state classification; and a visual analogue scale (VAS) called the "thermometer" [19]. The 5-dimensional healthcare classification included questions on the status of morbidity, self-care, usual activities, pain/discomfort and anxiety/depression. Participants were asked to indicate current health status by ticking the most appropriate of three statements about each of five QOL dimensions. Each statement represents an increasing degree of severity. These results were coded and converted to a score of utility using the tables of values. The VAS "thermometer" represents a self-rated scale of current health-related QOL. The endpoint of 100 at the top indicates the best imaginable health state, and 0 at the bottom indicates the worst imaginable health state at that time.

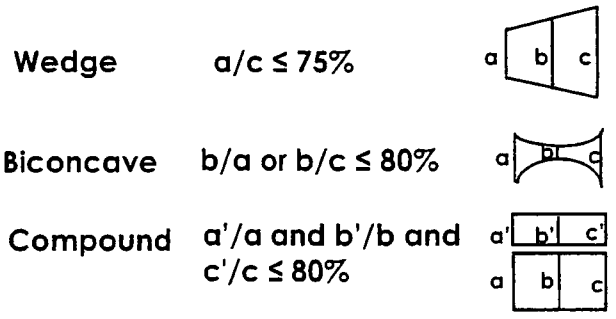

Fig. 1 Diagnostic criteria of vertebral fractures

Statistical analysis

Statistical analyses were performed using SPSS statistical software (SPSS, USA) and STATA software (STATA, USA). Differences were tested for significance using ANOVA for comparison among multiple groups and Scheffe's LSD test for pairs of groups. Significant items were selected, and multiple regression analysis was performed with adjustment of suitable variables.

Results

Eligible participants

From the whole cohort of 1,543 inhabitants (716 men, 827 women), 50 men and 50 women in each decade age group between 40–79 years (a total of 400 participants) were recruited for baseline bone densitometry in 1990 (baseline BMD cohort).

To evaluate the representativeness of subjects in the baseline BMD cohort compared to the whole cohort, the prevalence of 125 items of the self-administered questionnaire, results of physical measurements and blood examination were compared between members of the BMD and whole cohorts [14]. As a result, prevalence of lifestyle factors such as smoking and drinking were identical among BMD and whole cohorts. In addition, no significant differences existed in frequency distribution of the following items favorable to the maintenance of good health among BMD and whole cohorts: sleeping 7–8 h/day; exercise and sports >1 h/day; walking >30 min/day; eating regularly; reduction of salt intake compared with age 30; less stress; less anger. Regarding medical examinations, no significant differences in blood pressure classified by age and sex were seen between cohorts. Moreover, no abnormal values in serum calcium or phosphorus were observed. In view of these findings, subjects in the BMD study were considered to have been selected adequately from the whole cohort.

A total of 299 of 400 participants (137 men, 162 women; 74.8%) completed the follow-up survey after 10 years. Loss of 101 participants was due to following: death, n=55 (37 men, 18 women); moved away from Miyama, n=16 (8 men, 8 women); illness, n=13 (4 men, 9 women); busy, n=8 (8 men); refused to participate further, n=5 (5 men); and away from the area at the time of follow-up, n=4 (1 man, 3 women). Analysis was performed on the 299 subjects who had participated in all surveys performed in 1990, 1993, 1997 and 2000.

A comparison of physical characteristics between completers and non-completers has been described elsewhere [20], and is briefly summarized here. Height, weight and

BMI classified by age-strata and sex were identical between completers and non-completers, while mean age of female completers in their 70s was significantly younger than that of female non-completers (completers, 71.7 years (standard deviation (SD), 1.8 years) vs. non-completers 75.1 years (SD; 2.8 years); $p<0.001$).

Table 1 shows the characteristics including anthropometric factors and BMDs at the time of baseline measurement for participants who completed the 10-year follow-up (Table 1). Mean height and weight of the remaining participants were smaller according to age, while BMI did not differ significantly for both men and women in all age groups except men in their 70s.

Height loss and bone loss

Table 2 shows mean change of height, weight, BMI and change rate of BMDs over 10 years by age and gender (Table 2). Height and weight of men and women decreased in all age strata, and these decreases were greatest in subjects in their seventies. BMI in the 50s, 60s and 70s were decreased over 10 years in both genders, but no significant differences were seen among age-strata. BMDs at the lumbar spine and femoral neck decreased except for BMD at the lumbar spine in men.

To clarify associations between height, height change and changes in BMD, multiple regression analysis was performed. Rate of change of BMD (%/year) was used as an objective factor and height at baseline (cm) or change of height (cm/10 years) were used as explanatory factors. Analysis was performed after adjustment for age and female menstrual status at baseline (0, regular; 1, irregular; 2, menopause). In both men and women, no significant relationship was identified between bone loss and height at baseline (lumbar spine: men, $\beta=-0.046$, standard error of the mean (SE)=0.011, P=0.653, $R^2=0.036$; women, $\beta=-0.042$, SE=0.014, P=0.652, $R^2=0.032$; femoral neck: men, $\beta=0.143$, SE=0.014, P=0.149, $R^2=0.125$; women: $\beta=0.078$, SE=0.014, P=0.397, $R^2=0.043$).

Regarding the association between height loss and bone loss over 10 years, no significant relationship was identified between height change and rate of change of BMD at the lumbar spine and femoral neck after adjusting for age in men (lumbar spine: $\beta=0.058$, SE=0.031, P=0.501, $R^2=0.038$; femoral neck: $\beta=0.100$, SE=0.038, P=0.228, $R^2=0.121$). In contrast, among women, significant positive associations were noted between height change and change rate of BMD at the lumbar spine after adjusting for age ($\beta=0.221$, SE=0.039, P=0.012, $R^2=0.069$), while no significant relationship was noted between height change and change rate at the femoral neck ($\beta=0.107$, SE=0.039, P=0.229, $R^2=0.048$).

Height loss and vertebral fractures

As reported elsewhere [21], 32 men and 35 women had suffered from previous VFx at the initial survey. Cumulative incidences of first VFx at follow-up for subjects in their 40s, 50s, 60s and 70s were thus 2.9%, 2.8%, 8.6% and 21.1% in male completers, respectively, and 2.1%, 7.0%, 18.9% and 31.3% in female completers, respectively. Cumulative incidence of first VFx among participants during follow-up increased with age in both men and women, and was higher in women than in men in all age-strata except the 40s.

Table 3 shows differences in height at baseline and height loss between the incident group and non-fracture group. Both height and height loss over the 10 years were

Table 1 Characteristics at the baseline measurement of participants completed 10-year follow-up

				Anthropometric factors			Bone mineral density (g/cm^2)	
Birth cohort	Age strata	N	Age (years)	Height(cm)	Weight(kg)	BMI (kg/m^2)	L2-4	Femoral neck
Men								
1940–1949	40–49	36	44.1 (3.1)	166.5 (5.9)	64.4 (8.9)	23.1 (2.3)	1.19 (0.17)	0.98 (0.16)
1930–1939	50–59	41	53.9 (2.6)	162.0 (5.7)[a]	60.2 (8.0)	22.9 (2.4)	1.15 (0.20)	0.90 (0.18)
1920–1929	60–69	38	63.2 (2.8)	159.4 (5.4)[a]	56.1 (7.5)[a]	22.0 (2.4)	1.03 (0.19)[a]	0.82 (0.12)[ab]
1910–1919	70–79	22	73.2 (2.7)	155.3 (6.5)[ab]	50.0 (8.4)[ab]	20.6 (2.6)[ab]	1.03 (0.20)[a]	0.79 (0.11)[ab]
Women								
1940–1949	40–49	49	44.7 (3.1)	152.5 (4.7)	53.3 (8.4)	22.9 (2.8)	1.18 (0.16)	0.88 (0.12)
1930–1939	50–59	46	54.8 (2.6)	149.6 (5.3)	50.3 (7.4)	22.4 (2.8)	0.99 (0.18)[a]	0.75 (0.12)[a]
1920–1929	60–69	40	64.4 (2.8)	147.4 (5.1)[a]	47.4 (6.8)[a]	21.8 (3.0)	0.86 (0.20)[ab]	0.69 (0.11)[ab]
1910–1919	70–79	27	71.7 (1.8)	143.1 (5.5)[ab]	45.4 (7.7)[a]	22.1 (3.0)	0.79 (0.16)[ab]	0.65 (0.09)[ab]

Mean (SD)

a: Significantly different from values of the birth cohort group born in 1940–1949

b: Significantly different from values of the birth cohort group born in 1930–1939

Table 2 Changes in height, weight, BMI and change rate in bone mineral densities over 10 years by age and gender

Age at initial survey	Change rate of anthropometric factors			Change rate of bone mineral density	
Age strata (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	L2–4 (%/year)	Femoral neck (%/year)
Men					
40–49	−0.73 (2.21)	−0.21 (5.09)	0.17 (2.20)	0.17 (0.69)	−0.26 (0.86)
50–59	−0.54 (2.09)	−0.83 (3.69)	−0.18 (1.38)	0.55 (0.58)	−0.13 (0.84)
60–69	−1.19 (2.41)	−3.01 (4.80)	−0.86 (1.84)	0.01 (0.89)[b]	−0.75 (0.97)[b]
70–79	−1.54 (1.72)	−3.05 (3.88)	−0.84 (1.65)	−0.16 (0.68)[b]	−1.17 (1.09)[ab]
Women					
40–49	−0.69 (1.21)	−0.33 (3.22)	0.06 (1.39)	−0.87 (0.71)	−0.53 (0.70)
50–59	−1.37 (1.18)	−1.74 (3.64)	−0.35 (1.69)	−0.83 (0.75)	−0.53 (0.71)
60–69	−2.06 (2.08)[a]	−2.44 (3.55)[a]	−0.58 (1.69)	−0.48 (0.71)	−0.50 (0.87)
70–79	−3.65 (2.83)[abc]	−3.09 (3.48)[a]	−0.42 (1.76)	−0.48 (1.48)	−1.16 (1.32)[abc]

Mean (SD)
a: Significantly different from values of the age-group in their 40s
b: Significantly different from values of the age-group in their 50s
c: Significantly different from values of the age-group in their 60s

also greater in the group with VFx than without VFx. To clarify associations between height or height change and incidence of VFx after excluding the effects of age, logistic regression analysis was performed. We utilized new VFx over 10 years (1: yes; 0: no) as an objective factor and height at baseline (cm) or change of height (cm/10 years) as explanatory factors. Analysis was performed after adjusting for age and female menstrual status at baseline (0: regular; 1: irregular; 2: menopause). After logistic regression analysis, no significant relationship was identified between VFx and height at baseline in men and women (men: odds ratio (OR) 0.93, 95% confidence interval (CI) 0.81–1.05, P=0.24; women: OR 0.97, 95% CI 0.87–1.08, P=0.58). Furthermore, a non-significant relationship was seen between cumulative incidence of VFx and height loss in men and women (men: OR 1.31, 95% CI 1.00–1.71, P=0.051; women: OR 1.20, 95% CI 0.94–1.53, P=0.14).

Table 3 Comparison of height (cm) at baseline and height loss between the group with new vertebral fractures and the no fracture group

		VFx* over 10 years		
		No (n=116)	Yes (n=9)	P (Yes vs. No)
Men	Height (cm)	161.8 (6.49)	156.4 (7.76)	0.014
	Height loss (cm/10 years)	0.87 (2.08)	2.59 (2.23)	0.019
		No (n=128)	Yes (n=16)	
Women	Height (cm)	149.7 (5.75)	145.9 (6.43)	0.015
	Height loss (cm/10 years)	1.33 (1.78)	2.88 (2.26)	0.002

*VFx: vertebral fractures

Height loss and QOL

Among the 299 subjects who participated in the latest follow-up survey in 2000, 212 answered the QOL questionnaire distributed in 2002 (94 men, 118 women; 70.9%).

Figures 2 and 3 show mean values for utility in EQ5D health states and VAS scores classified by age and gender. Mean utility for EQ5D in men in their 40s (n=30), 50s (n=33), 60s (n=25) and 70s (n=6) were 0.95, 0.87, 0.88 and 0.83, respectively, compared to 0.90, 0.85, 0.81 and 0.77 in women in their 40s (n=42), 50s (n=32), 60s (n=31) and 70s (n=13). VAS values in men were 76.6, 75.1, 72.4 and 63.8, respectively, compared to 77.6, 73.9, 67.6 and 71.7, respectively, in women. Utility of EQ5D decreased according to age in both men and women, while mean VAS scores were lowest for women in their 60s.

We utilized multiple regression analysis using utility of EQ5D health states or VAS scores as an objective factor and height at baseline (cm) or change of height (cm/10 years) as explanatory factors to clarify associations between height and QOL. Analysis was performed after adjusting for age and female menstrual status at baseline

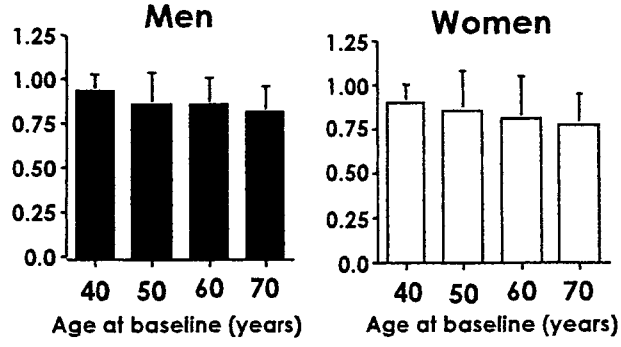

Fig. 2 QOL score classified by age and gender

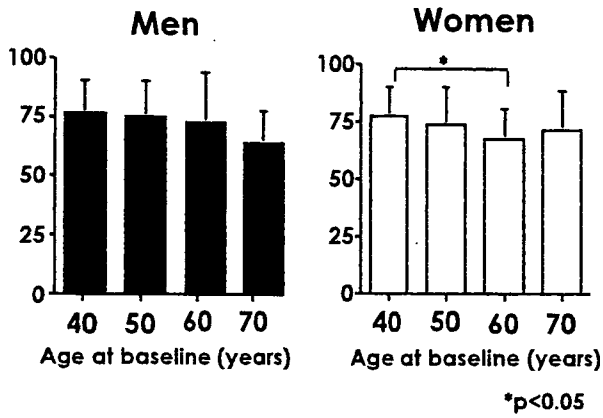

Fig. 3 VAS scores classified by age and gender

(0: regular; 1: irregular; 2: menopause). In both men and women, no significant relationship was identified between utility of EQ5D and height at baseline (men: β=−0.148, SE=0.003, P=0.202, R^2=0.076; women: β=0.127, SE=0.004, P=0.235 R^2=0.048), and height change (men: β=−0.078, SE=0.008, P=0.452, R^2=0.065; women: β=0.053, SE=0.010, P=0.608, R^2=0.038). Regarding VAS scores, height at baseline among men and women was not significantly associated VAS scores (men: β=−0.148; SE=0.003, P=0.202, R^2=0.076; women: β=0.066, SE=0.255, P=0.532, R^2=0.092). In addition, no significant associations were identified between utility of VAS scores and height change (men: βa=−0.148, SE=0.003, P=0.202, R^2=0.076; women: β=0.142, SE=0.698, P=0.160, R^2=0.105).

Discussion

The present study clarified associations between height, height change and bone loss and cumulative incidence of VFx. Furthermore, we assessed the usefulness of height and height change as predictors of future QOL. As a result, we identified significant positive associations between height change and change rate of BMD at the lumbar spine in women after adjusting for age and menstrual status, while no significant relationships were found between height or height change at the femoral neck in either men or women. Regarding associations between height, height change and cumulative incidence of first VFx, both height and height loss over the 10 years were also greater in the group with VFx than in the group without VFx, but the association was less significant in logistic regression analysis after adjusting for age. No significant relationships existed between height, height change and future QOL in men or women.

Particularly among anthropometric measurements, light weight [5–8], weight loss [9, 10] and low BMI [11–13] could suggest a risk of osteoporosis and osteoporotic fractures. Conversely, few investigations have reported that height and height loss are associated with low BMD or bone loss. We have already reported that tall height is associated with greater bone loss over 3 years [22]. Twiss et al. [23] reported that actual height loss is associated with risk factors of osteoporosis, while Thornton et al. [24] evaluated relationship between height change and bone mineral density among 168 healthy women at 50- to 65-years-old, and reported no significant relationships between height change and BMD. Kantor [25] reviewed cross-sectional data from 2,108 women referred for a bone density scan and reported that a height loss of ≥2 inches offers a highly significant predictor of osteoporosis at the hip [25]. As mentioned, investigations into associations between height and bone loss have yielded controversial results, and no data from follow-up studies over periods as long as 10 years have been available. The present study clarified that greater height loss was associated with greater bone loss at the lumbar spine in women. This means that height loss might offer a predictor for greater bone loss, thus indicating a potential high-risk group for future osteoporosis in women. Conversely, the present study failed to identify any significant association between height loss and bone loss at the lumbar spine in men, which is artificial due to the difficulties in measuring BMD at the lumbar spine in men. As observed in the BMD cohort, 35.1% of men and 13.3% of women were diagnosed with osteophytosis more than grade 3 according to Nathan's classification [26, 27]. Such osteophytes might lead to overestimation of BMD in men.

Regarding the relationship between height loss and osteoporotic fractures, Meyer et al. [11] compared mean height among participants of population-based cohort studies established in different countries in Europe, and found that participants in Oslo were taller than those in other European countries. They noted that the taller height of community-dwelling inhabitants might contribute to the higher incidence of hip fracture in Finland, although this suggestion was based on ecological data. Fujiwara et al. [28] suggested that the presence of more than one column of VFx will lead to a decrease of about 2 cm in height. The present study found both height and height loss over the 10 years were also greater in the group with VFx than in the group without VFx, but failed to identify any statistically significant association between height loss and VFx. This might be because the sample size of the BMD cohort was insufficient to detect a significant association. However, height loss (cm/10 years) tended to increase the OR of VFx in both men and women. Loss of height may represent an important clinical sign of vertebral deformation and/or fracture in postmenopausal women and elderly men. Relationships between BMD at the femoral neck and hip fracture were not able to be analyzed because of the low numbers of new hip fractures in subjects. A larger

epidemiological study would be needed to clarify associations between height loss and future osteoporotic fractures.

Regarding relationships between QOL, height and height loss, Martin et al. [29] found that height loss and kyphosis in women are significantly associated with increased physical difficulty in activities of daily life. In addition, some reports have described the influence of osteoporotic VFx on QOL [30–32]. These investigations have shown that patients with higher grades of vertebral deformities displayed low QOL, suggesting that the results of VFx such as height loss are related to QOL, but the direct influence of height loss on QOL remains unclear. The present study could not find any significant association between height loss and QOL, so we concluded that QOL in patients with osteoporosis is impaired by postural deformities, particularly by whole kyphosis, and that spinal mobility exerts a strong effect on QOL in these patients.

Conclusions

The present study identified significant positive associations between height change and change rate of BMD at the lumbar spine in women, while no significant relationships were found between height, height change, cumulative incidence of VFx and future QOL.

In conclusion, changes in measured height might offer a cost-saving indicator of bone loss. Measurement of height should be considered as one potential component in determining risk of comprehensive osteoporosis, but further consideration is required before utilizing this approach as a predictor of future osteoporotic fracture and QOL.

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References

1. Hosoda Y, Fujiwara S (1992) The epidemiology of osteoporosis in Japan. J Epidemiol 2(suppl):205–213
2. Hashimoto T, Sakata K, Yoshimura N (1997) Epidemiology of osteoporosis in Japan. Osteoporos Int 7(suppl):99–102
3. Orimo H, Hashimoto T, Sakata K, Yoshimura N, Seino Y, Emi M, Hada A, Suzuki T, Hosoi T, Miyao M, Research Group for Risk Factors for Prevention of Osteoporosis, Longevity Science General Research Project, Ministry of Health and Welfare, (Director Orimo H) (1999) Results of the 3rd nation-wide survey of femoral neck fracture. Estimation of the number of new patients in 1997 and changes during the past 10-year period. Nihon Iji Shinpo (Japan Medical Journal) 3916:46–49 (in Japanese)
4. Yosihmura N, Suzuki T, Hosoi T, Orimo H (2005) Epidemiology of hip fracture in Japan: incidence and risk factors. J Bone Miner Metab 23:78–80
5. Wardlaw GM (1996) Putting body weight and osteoporosis into perspective. Am J Clin Nutr 63 (3 Suppl):433–436
6. Yoshimura N, Hashimoto T, Morioka S, Sakata K, Kasamatsu T, Cooper C (1998) Determinants of bone loss in a rural Japanese community. The Taiji Study. Osteoporos Int 8:604–610
7. Dennison E, Eastell R, Fall CH, Kellingray S, Wood PJ, Cooper C.(1999) Determinants of bone loss in elderly men and women: a prospective population-based study. Osteoporos Int 10:384–391
8. Wildner M, Peters A, Raghuvanshi VS, Hohnloser J, Siebert U (2003) Superiority of age and weight as variables in predicting osteoporosis in postmenopausal white women. Osteoporos Int 14:950–956
9. Nguyen TV, Sambrook PN, Eisman JA. (1998) Bone loss, physical activity, and weight change in elderly women: the Dubbo Osteoporosis Epidemiology Study. J Bone Miner Res 13:1458–1467
10. Tsunenari T, Yamada S, Kawakatsu M, Negishi H, Tsutsumi M (1995) Menopause-related changes in bone mineral density in Japanese women. A longitudinal study. Calcif Tissue Int 56:5–10
11. Meyer HE, Falch JA, O'Neill T, Tverdal A, Varlow J (1995) Height and body mass index in Oslo, Norway, compared to other regions of Europe: do they explain differences in the incidence of hip fracture? European Vertebral Osteoporosis Study Group. Bone 17:347–350
12. Nguyen TV, Center JR, Eisman JA (2000) Osteoporosis in elderly men and women: effects of dietary calcium, physical activity, and body mass index. J Bone Miner Res 15:322–331
13. Korpelainen R, Korpelainen J, Heikkinen J, Vaananen K, Keinanen-Kiukaanniemi S (2006) Lifelong risk factors for osteoporosis and fractures in elderly women with low body mass index-A population-based study. Bone 39:385–391
14. Kasamatsu T, Morioka S, Hashimoto T, Kinoshita H, Yamada H, Tamaki T (1991) Epidemiological study on bone mineral density of inhabitants in Miyama Village, Wakayama Prefecture (Part 1). Background of study population and sampling method. J Bone Miner Metabol 9(suppl):50–55
15. Kinoshita H, Danjoh S, Yamada H et al (1991) Epidemiological study on the bone mineral density of inhabitants in Miyama Village, Wakayama Prefecture (part II) Bone mineral density of the spine and proximal femur. J Bone Miner Metab 9(suppl):56–60
16. Yoshimura N, Kakimoto T, Nishioka M, Kishi T, Iwasaki H, Niwa T, Morioka S, Sakata T, Hashimoto T (1997) Evaluation of reproducibility of bone mineral density measured by dual energy X-ray absorptiometry (Lunar DPX-L). J Wakayama Medical Society 48:461–466
17. Yoshimura N, Kinoshita H, Danjoh S, Yamada H, Tamaki T, Morioka S, Kasamatsu T, Hashimoto T, Inoue T (1995) Prevalence of vertebral fractures in a rural Japanese population. J Epidemiology 5:171–175
18. EuroQol Group (1990) EuroQol: A new facility for the measurement of health-related quality of life. Health Policy 16:199–208
19. Ikeda S, Ikegami N (on behalf of the Japanese EuroQol Tariff Project) (1999) Health status in Japanese population, Results from Japanese EuroQol Study. Iryou-to-Kagaku 9:83–92 (in Japanese)
20. Yoshimura N, Kinoshita H, Danjoh S, Takijiri T, Morioka S, Kasamatsu T, Sakata K, Hashimoto T (2002) Bone loss at the lumbar spine and the proximal femur in a rural Japanese community, 1990–2000: The Miyama study. Osteoporos Int 13:803–808
21. Yoshimura N, Kinoshita H, Oka H, Muraki S, Mabuchi A, Kawaguchi H, Nakamura K (2006) Cumulative incidence and changes in prevalence of vertebral fractures in a rural Japanese

community: a 10-year follow-up of the Miyama Cohort. Archives Osteoporosis, DOI 10.1007/s11657-006-0007-0
22. Yoshimura N (1996) Incidence of fast bone losers and factors affecting changes in bone mineral density - A cohort study in a rural Japanese community-. J Bone Miner Metab 14:171–177
23. Twiss JJ, Dillon AL, Konfrst JM, Stauffer J, Paulman A (2002) The relationship of actual height loss with health-seeking behaviors and risk factors in perimenopausal and menopausal women. J Am Acad Nurse Pract 14:131–137
24. Thornton MJ, Sedlak CA, Doheny MO (2004) Height change and bone mineral density: revisited. Orthop Nurs 23:315–320
25. Kantor SM, Ossa KS, Hoshaw-Woodard SL, Lemeshow S (2004) Height loss and osteoporosis of the hip. J Clin Densitom 7:65–70
26. Nathan H (1962) Osteophytes of the vertebral column, an anatomical study of their development according to age, race, and sex with considerations as to their etiology and significance. J Bone and Joint Surg 44:243
27. Yoshimura N, Saika A, Oka H (2006) The study on the causality between osteoporosis and osteoarthritis. Osteoporos Jpn 14:691–695 (in Japanese)
28. Fujiwara S (2006) Clinical sign-height loss and vertebral deformity. Nippon Rinsho 64:1610–1614 (in Japanese)
29. Martin AR, Sornay-Rendu E, Chandler JM, Duboeuf F, Girman CJ, Delmas PD (2002) The impact of osteoporosis on quality-of-life: the OFELY cohort. Bone 31:32–36
30. Fechtenbaum J, Cropet C, Kolta S, Horlait S, Orcel P, Roux C (2005) The severity of vertebral fractures and health-related quality of life in osteoporotic postmenopausal women. Osteoporos Int 16:2175–2179
31. Miyakoshi N, Itoi E, Kobayashi M, Kodama H (2003) Impact of postural deformities and spinal mobility on quality of life in postmenopausal osteoporosis. Osteoporos Int 14:1007–1012
32. Tanaka K, Yoshizawa M, Yoh K (2005) Improvement of QOL in osteoporotic patients by calcitonin treatment. Clin Calcium 15:174–178 (in Japanese)

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Original article

High tibial osteotomy using two threaded pins and figure-of-eight wiring fixation for medial knee osteoarthritis: 14 to 24 years follow-up results

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Abstract

Background. High tibial osteotomy (HTO) is an established surgical treatment for medial knee osteoarthritis (OA). Several studies have reported the deterioration of clinical results with time, especially after more than 10 years. The purpose of this study was to evaluate the long-term results after HTO using our originally developed fixation method and to clarify the factors affecting the long-term clinical outcome.

Methods. Sixty-eight HTO treatments in 55 patients were evaluated. Eighteen patients were unable to be analyzed, thus reducing the study to 48 knees in 37 patients. The follow-up rate of the knee joint was 70.6% and the mean follow-up period was 17.1 years. The first evaluation was performed at a mean of 6.5 years postoperatively, and the most recent evaluation was done at more than 10 years postoperative follow-up. A closing-wedge osteotomy was performed, and the osteotomy site was fixed with two threaded pins and a figure-of-eight wiring technique. The Japanese Orthopaedic Association knee rating score (JOA score) was used for the clinical assessment. The change of the femorotibial angle (FTA) and progression of knee OA were radiographically analyzed. The whole knees were subsequently divided into two groups, satisfactory group and unsatisfactory group, according to the JOA score at the most recent follow-up.

Results. The mean JOA score was 59.1 before HTO and 83.1 at the most recent evaluation. In comparing the satisfactory and unsatisfactory groups, the JOA score before HTO was the same, but the JOA score of the unsatisfactory group was significantly lower at the first evaluation. The FTA in the unsatisfactory group was the same as in the satisfactory group preoperatively, but it was significantly larger after HTO. The radiographic OA was significantly progressed at the most recent evaluation, but no difference was observed in the distribution of the preoperative OA grade between the two groups.

Conclusions. HTO with two threaded pins and figure-of-eight wiring fixation showed an acceptable clinical outcome, but careful attention was needed for correction loss in early postoperative periods. In addition, the proper correction angle is necessary in order to achieve satisfactory long-term results.

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Introduction

Osteoarthritis (OA) is the most common form of degeneration of the joints. The knee joint is the key structure in the lower extremity and has much influence on the activity of daily life (ADL) and the quality of life (QOL) in elderly persons. These include standing, walking, running, jumping, stair climbing, deep knee bending such as squatting or Japanese-style sitting, and other lower extremity tasks. Approximately 10% to 15% of people aged 60 years and older have symptomatic knee OA.[1] Therefore, knee OA is a major source of chronic disability and is becoming a serious public health problem.

High tibial osteotomy (HTO) is one of the successful surgical treatments for medial compartment knee OA. HTO was first described by Jackson and Waugh,[2] and it is now widely accepted as an attractive procedure with good pain relief and preservation of knee function. Previous studies of early to midterm results of HTO have shown excellent outcomes in more than 80% of cases.[3–5] However, several studies with long-term follow-up reported that the results of HTO deteriorated with time, especially after more than 10 years. Several factors have been identified as affecting the results of HTO, but they remain controversial. These include sex, age at surgery, body weight, preoperative severity of knee OA, method of osteotomy and fixation, correction angle, amount of preoperative adduction moment, and postoperative period.[6–14]

Among these factors, the type of fixation following osteotomy remains important, and, in the past, the following methods have been reported: bone staples, blade plate with screws, one third tubular plate with a cortical screw (tension bend principle), L-buttress plate, and external fixator.[3,15–20] We developed a fixation method using two threaded pins and figure-of-eight wire and used this method for our consecutive HTO cases.

The purpose of this retrospective study was to assess the long-term results after HTO using our fixation method and to clarify the factors affecting the long-term clinical outcome.

Subjects and methods

Our indications for HTO were basically as follows: (1) degenerative change was mainly located in medial compartment (medial knee osteoarthritis), (2) normal or mild degeneration in lateral and patello-femoral compartment, (3) patient was younger than 70 years old and had relatively high activity in ADL, and (4) good range of motion and no remarkable knee joint instability. Between 1980 and 1990, HTO was performed in 68 consecutive knees in 55 cases by our senior surgeon (Y. K.). Seven patients died, 6 patients were unable to be evaluated due to the presence of other severe medical illnesses, and 2 patients were lost to follow-up. Three knees in 3 patients were converted to total knee arthroplasty (TKA) at 10 years, 12 years, and 15 years after HTO, respectively. Therefore, the remaining 48 knees in 37 cases were available for the present study, and the follow-up rate of the knee joint was 70.6%. There were 43 knees in 33 women and 5 knees in 4 men. The mean age at HTO was 59 years with a range from 40 to 69 years. The mean follow-up period was 17.1 years, but individual follow-up ranged from 14 to 24 years. The preoperative diagnosis was medial compartment knee OA in all the cases, and the preoperative Kellgren-Lawrence classification[21] showed grade II in 8 knees, grade III in 35 knees, and grade IV in 5 knees. All of the patients were evaluated initially in 1993, with a mean follow-up of 6.5 years, and evaluated at more than 10 years follow-up postoperatively. All of the patients were fully informed about the procedures and gave their informed consent.

Operative procedures and postoperative regimen

In all knees, the closing-wedge interlocking osteotomy through a lateral approach was performed according to the technique described by Ogata.[22] The correction angle was preoperatively determined to allow the mechanical axis, which is the line connecting the center of the femoral head and the ankle joint, to pass through the midpoint of the lateral compartment. The preoperative planning was performed using non-weight-bearing supine radiograph of the whole lower extremity according to Ogata et al.[23] Ogata mentioned that the relative angle of the articular surface (condylar-plateau angle) in the weight-bearing knee changed after osteotomy, and this might give unpredictable results postoperatively. He also found that the condylar-plateau angle in the postoperative standing radiograph was very similar to that seen in the non-weight-bearing supine condition, and recommended that a non-weight-bearing supine radiograph was better for preoperative planning. The femorotibial angle (FTA) that met this condition was around 165° to 168° in the majority of cases. The fibula was resected at the mid portion of the shaft. The osteotomy site was fixed with two threaded pins and a figure-of-eight wiring technique. First, two threaded pins, 2.4 or 3.0 mm in diameter, were inserted from distal and lateral of the osteotomy site to the medial corner of the proximal tibia passing through the medial half of the osteotomy line. Next, figure-of-eight wiring, 0.8 to 1.0 mm in diameter, was placed between the distal end of the pins and lateral wall of the proximal tibia. After the osteotomy site was fixed, leg alignment was checked by X-ray and cancellous bone fragments harvested from the resected bone wedge were grafted to the osteotomy site (Fig. 1). Postoperatively, the knee joint was immobilized with a cast for 6 weeks. Range-of-motion exercise was started after the cast was removed. Partial weight bearing was started 4 weeks after HTO and full weight bearing was allowed at 8 to 10 weeks postoperatively.

Clinical evaluation

All of the patients were directly interviewed and examined. The clinical result was evaluated using the Japanese Orthopedic Association knee rating score (JOA score).[24] The JOA score consisted of four categories and 100 points as full marks: pain and walking (30 points), pain and ascending or descending stairs (25 points), range of motion (35 points), and joint effusion (10 points). In this study, the preoperative JOA score was compared with the JOA score at the first evaluation in 1993 and at the most recent follow-up. Subsequently, the results of the JOA score were classified as excellent if the most recent score was 91 to 100, good if 81 to 90, fair if 71 to 80, and poor if the most recent score was less than 70 points. Furthermore, all knee joints were divided into two subgroups according to the result of the most recent follow-up. The patients who were classified as excellent and good were referred to as the satisfactory group, and the patients who were classified as fair and poor were referred to as the unsatisfactory

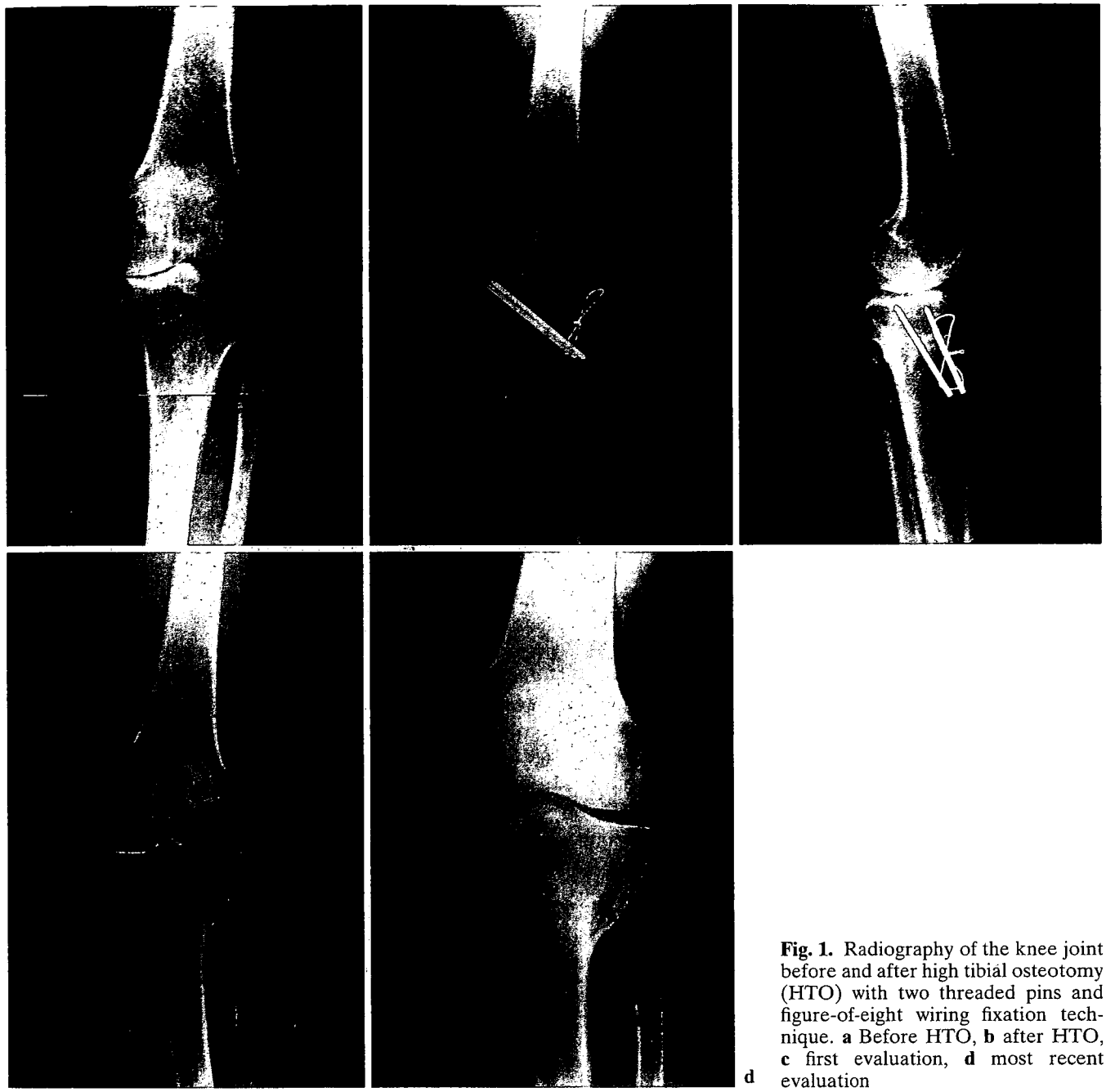

Fig. 1. Radiography of the knee joint before and after high tibial osteotomy (HTO) with two threaded pins and figure-of-eight wiring fixation technique. **a** Before HTO, **b** after HTO, **c** first evaluation, **d** most recent evaluation

group. Thirty-seven knees in 22 patients (1 male, 21 female) were included in the satisfactory group, with an average age at surgery of 57.9 ± 5.0 years and average follow-up period of 14.0 ± 2.9 years. On the other hand, 11 knees in 10 patients (3 male, 7 female) were included in the unsatisfactory group, with an average age at surgery of 60.1 ± 8.7 years and average follow-up period of 14.3 ± 3.1 years. No statistical difference was observed in the demographic data between the two groups.

Radiographic evaluation

The change of FTA and the grades of knee OA according to the Kellgren-Lawrence classification were analyzed with a standing whole-leg X-ray taken before surgery, at 1 to 3 weeks after HTO, and at each follow-up point.

Statistical analysis

The obtained data were expressed as the mean values ± standard deviation (SD). The relationships of analyzed parameters were determined using the paired *t*-test and the Wilcoxon signed rank test. In all analyses, a *P* value of less than 0.05 was considered to be significant.

Results

Clinical results

The mean JOA score of all patients improved significantly from 59.1 ± 7.6 before HTO to 86.3 ± 6.5 at the first evaluation (Table 1). At the most recent follow-up, the JOA score had slightly declined to 83.1 ± 9.3 but this change was not significant. In each category of JOA scores in all patients, the pain and walking score improved from 14.5 ± 5.2 before HTO to 26.6 ± 5.6 at the most recent evaluation, the pain and stairs score from 12.7 ± 6.6 to 20.2 ± 4.9, the score for range of motion from 25.6 ± 4.8 to 27.8 ± 4.6, and the score for joint effusion from 6.3 ± 5.7 to 8.5 ± 4.3. The mean range of motion was 9.3° ± 8.0° fixed flexion to 133.0° ± 18.1° of flexion before HTO, and 2.6° ± 4.3° to 132.5° ± 16.2° of flexion at the most recent evaluation. In comparing the satisfactory group and the unsatisfactory group, the mean JOA score was similar before HTO, but at the first and the most recent evaluation, the JOA score of the unsatisfactory group was significantly lower than that of the satisfactory group. Furthermore, in the unsatisfactory group, the JOA score had significantly declined from first evaluation to the most recent follow-up (Table 1). In the current study, there were two postoperative complications. One patient had peroneal nerve palsy and spontaneously recovered in 3 months after surgery. Another patient had delayed union and autologous iliac bone graft was performed. Final bone union was obtained at 7 months after HTO. These complications did not affect the clinical results.

Radiographic results

The mean FTA of all patients was corrected from 185.4° ± 4.4° before HTO to 168.2° ± 2.9° postoperatively, and this alignment was maintained at the most recent evaluation. In the satisfactory group, the change of FTA was almost same as the results of all patients. In contrast, the FTA of the unsatisfactory group changed from 185.3° ± 2.1° preoperatively to 170.2° ± 2.3° after HTO, and gradually increased at first evaluation and increased even more at the most recent follow-up. The FTA of the unsatisfactory group was the same as the satisfactory group preoperatively, but was significantly larger at each time of postoperative evaluation (Table 2). Seven of the unsatisfactory group (63.6%) had an FTA larger than 168° (170°: 3 cases, 172°: 3 cases, 173°: 1 case). The radiographic OA of all patients before HTO were classified as follows: 8 knees as Grade II, 35 knees as Grade III, and 5 knees as Grade IV. At the most recent evaluation, the distributions were 1 knee as Grade II, 18 knees as Grade III, and 29 knees as Grade IV. The number of Grade IV OA at the latest evaluation was significantly greater than that of before HTO (Table 3). In comparing the satisfactory group and the unsatisfactory group, no statistical difference was observed in the distribution of preoperative radiographic OA grade (Table 4). At the latest evaluation, the distributions of OA in the satisfactory group were 1 knee in Grade II, 18 knees in Grade III, and 18 knees in Grade IV. On the other hand, in unsatisfactory group, all knees were classified as Grade IV OA.

Table 1. Japanese Orthopaedic Association (JOA) score before high tibial osteotomy (HTO), at the first evaluation, and at the latest evaluation

Classification	Number of knees	JOA score		
		Before HTO	First evaluation[a]	Latest evaluation[b]
All Patients	48	59.1 ± 7.6	86.3 ± 6.5	83.1 ± 9.3
			**	
Satisfactory group	37	59.1 ± 9.1	90.0 ± 5.4	87.3 ± 4.3
			**	* **
Unsatisfactory group	11	59.1 ± 5.8	82.2 ± 7.2	69.1 ± 5.8
			**	*

Data given as mean ± standard deviation
* $P < 0.05$; ** $P < 0.01$
[a] Mean follow-up 6.5 years
[b] Mean follow-up 17.1 years

Table 2. Femorotibial angle (FTA) before HTO, at the first evaluation, and at the latest evaluation

Classification	Number of knees	FTA (degrees)			
		Before HTO	After HTO	First evaluation[a]	Latest evaluation[b]
All Patients	48	185.4 ± 4.4	168.2 ± 2.9	169.1 ± 4.5	169.8 ± 5.2
Satisfactory group	37	185.5 ± 4.8	167.6 ± 2.8 *	168.0 ± 4.1 *	168.4 ± 4.4 **
Unsatisfactory group	11	185.3 ± 2.1	170.2 ± 2.3 *	172.7 ± 3.8 *	174.4 ± 5.2 **

Data given as mean ± standard deviation
* $P < 0.05$; ** $P < 0.01$
[a] Mean follow-up 6.5 years
[b] Mean follow-up 17.1 years

Table 3. Distribution of the radiographic osteoarthritis (OA) grade before HTO and at the latest evaluation

Classification	Number	OA grade[a]		
		Grade II	Grade III	Grade IV
Before HTO	48	8	35	5
Latest evaluation[b]	48	1	18	29**

** $P < 0.01$
[a] Radiographic OA grade according to the Kellgren-Lawrence classification
[b] Mean follow-up 17.1 years

Table 4. Distribution of the preoperative radiographic OA grade between the satisfactory group and the unsatisfactory group

Classification	Number	OA grade[a]		
		Grade II	Grade III	Grade IV
All Patients	48	8	35	5
Satisfactory group	37	8	26	3
Unsatisfactory group	11	0	9	2

[a] Radiographic OA grade according to the Kellgren-Lawrence classification

Discussion

The first purpose of this study was to evaluate our fixation methods. We used two threaded pins and figure-of-eight wire, and the basic concept of this procedure was similar to a tension band or modified tension band fixation as previously described.[17,18] Generally speaking, rigid fixation and early rehabilitation is important for good clinical outcome after HTO,[15,25] and there have been several studies concerning the primary stability of the implants for HTO.[26–28] Flamme et al.[27] tested the initial stability of the following devices: one third tubular plate with a cortical screw, blade plate with screws (Giebel's plate), bone staples, and external fixator. In their study, the highest stability was achieved by the bone staple and external fixator, while Giebel's plate and one third tubular plate were less stable. Recently, we biomechanically evaluated the initial stability of our fixation method and compared it with the bone staple, Giebel's plate, and L-buttress plate. The results of this study indicated that our method showed similar stability to Giebel's plate and the bone staple against compression and bending stress except rotational force.[29] In the present study, we additionally used cast immobilization after HTO in consideration of initial stability of our fixation method, and we clinically experienced 11 of 48 unsatisfactory cases. Furthermore, 7 of the unsatisfactory cases showed correction loss in early postoperative periods. The main reason for this early correction loss is thought to be combination of the lack of initial stability especially against rotational stress and the bone quality of the osteotomy site. Thus, we think the two threaded pins and figure-of-eight wiring fixation is an acceptable fixation procedure for HTO; however, careful attention should be paid to correction loss in the early postoperative periods.

The second purpose of the present study was to evaluate the long-term clinical results after HTO and to determine the factors related to the outcome. There are many studies about the clinical results after HTO. The

majority of authors have reported satisfactory results in the short to midterm, but these results gradually deteriorated over time, especially at more than 10 years after surgery. The reported probability of a good or excellent result after HTO was 75% to 96% after 6 years, 45% to 94% after 10 years, and 46% to 90% after more than 15 years.[3–14] In the current study, the percentage of satisfactory results (excellent or good) after HTO was 93.7% after 6 years and 77.1% after 17 years. Our results had the same tendency of deterioration over a long period as the other studies, but still maintained a favorable result up to 17 years after HTO. We think the main reason for the good clinical outcome in spite of the progression of radiographic OA is that good alignment was maintained in the majority of cases during the follow-up period and the ADL of the patients slowly deteriorated with time. Recently, Koshino et al.[14] evaluated 75 knees with a mean follow-up of 19 years and reported good or excellent results in 90% of their series. Good alignment was described as the most important factor for good long-term clinical results.[14]

There is still considerable discussion about which factors affect the long-term outcome of HTO, and the present study focused on the correction angle at the surgery and the preoperative severity of knee OA. As for the correction angle, previous studies have reported that the optimum clinical outcomes were associated with a correction of 6° to 16° valgus, and an undercorrection less than 5° was strongly related to a high failure rate.[5,8–14] In this study, the mean FTA after HTO was 167.6° in the satisfactory group and 170.2° in the unsatisfactory group. In addition, in the unsatisfactory group, progressive varus recurrence was found at the follow-up. We believe that the most important concept for HTO is to shift the loading axis from the medial compartment to the lateral compartment, and this will lead good long-term clinical outcomes in HTO. In order to achieve this safely, we recommend that we should target a valgus correction of at least 10° for medial compartment knee OA.

In western countries, the patients with advanced knee OA were primarily indicated for total knee arthroplasty. Therefore, there have been few studies that evaluate the relationship between the preoperative severity of the knee OA and the clinical result of HTO. Holden et al.[30] followed 51 knees for 10 years and found no correlation between the clinical results and the radiographic severity of the knee OA preoperatively. Rinonapoli et al.[10] evaluated 60 knees with an average follow-up of 15 years and their multivariate analysis indicated that the length of follow-up and the amount of preoperative osteoarthritis affected the clinical results. On the other hand, there have been many studies about this issue in Japan, because the preservation of range of motion is important for ADL in Japanese people. Yasuda et al.[8] found no statistical difference between the preoperative OA stage and the clinical results, but also described that no stage IV patients obtained good results. Sasazaki et al.[31] compared HTO in mild to moderate OA with advanced OA, and found no clinical difference between the two groups. They also indicated that overcorrection was effective for HTO in advanced OA cases.[31] In this study, the radiographic OA grade of the knee joint was significantly deteriorated at the mean follow-up of 17 years, but no statistical difference was observed regarding the preoperative severity of the radiographic knee OA between the satisfactory and the unsatisfactory group. Furthermore, three of five patients with preoperative Grade IV OA were included in the satisfactory group at the recent follow-up. Therefore, we agree that the mild to moderate stage is expected to have better results after HTO, but we could also expect good clinical outcomes for the advanced stage if the cartilaginous condition of the lateral compartment is acceptably preserved and the proper postoperative alignment is achieved.

We believe that there are two limitations in this study. The first limitation is that this is a retrospective study and the 70.6% follow-up rate is perhaps low even for the long-term periods of more than 10 years. The second limitation is that we used the JOA score for clinical evaluation. The JOA score is a good scoring system and is popular in Japan. In addition, several recent studies about HTO using this scoring system have been published in international journals.[24,32,33] However, even though the JOA score is not a worldwide universal measuring system, we believe that we can compare the result of this study with other clinical reports.

In conclusion, HTO with two threaded pins and figure-of-eight wiring fixation showed an acceptable and good clinical outcome for an average of 17 years of follow-up. The present study also suggests that the proper correction angle is necessary to achieve satisfactory long-term clinical results and HTO is considered to be indicated for the patients with a moderate to advanced stage of medial knee OA.

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References

1. Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. Arthritis Rheum 1998;41:1343–55.
2. Jackson JP, Waugh W. Tibial osteotomy for osteoarthritis of the knee. J Bone Joint Surg Br 1961;43:746–51.
3. Coventry MB. Osteotomy of the upper portion of the tibia for degenerative arthritis of the knee. A preliminary report. J Bone Joint Surg Am 1965;47:984–90.