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► **To cite this version:**

F Robin, S Cadiou, J-D Albert, G Bart, G Coiffier, et al.. Methotrexate osteopathy: five cases and systematic literature review. *Osteoporosis International*, 2021, 32 (2), pp.225-232. <10.1007/s00198-020-05664-x>. <hal-03001369>

HAL Id: hal-03001369

<https://hal.science/hal-03001369v1>

Submitted on 18 Dec 2020

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Methotrexate osteopathy. Five cases and systematic literature review.

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Mini-abstract

Methotrexate (MTX) osteopathy, described as a clinical triad: pain, osteoporosis and atypical stress fractures, while rare, must be known by the rheumatologist. Our cohort of 5 cases represent the largest series of the literature. Pathophysiological studies raised the question of a dose-dependent remnant effect of MTX on osteoforming bone cells.

Abstract

Introduction

Methotrexate (MTX) related osteopathy is rare, defined by the triad of pain, osteoporosis and "atypical fractures" when it was first described in the 1970s in children treated with high doses MTX for acute leukemia. Since then, several cases have been reported in patients treated with low-dose MTX for inflammatory diseases.

Methods

A systematic research of cases of MTX related osteopathy was performed in records of Rheumatology Department of Rennes University Hospital. Data collection focused on demographic data, corticosteroid doses, MTX doses and intake method, cumulative doses, year of diagnosis, fracture location, bone densitometry value and osteoporosis treatment if necessary. A literature review was also conducted to identify other cases in literature and try to understand the pathophysiological mechanisms of this rare entity.

Results

We report 5 cases identified between 2011 and 2019, which represents the largest cohort described excluding oncology cases. Fracture locations were atypical for osteoporotic fractures. All patients improved in the following months with MTX withdrawal. All patients except one were treated with antiresorptives (bisphosphonates, denosumab). Two patients, treated with bisphosphonates, had a recurrence of fracture, once again of atypical location. 25 cases were collected in literature with similar clinical presentation. The cellular studies that investigated the bone toxicity of MTX mainly showed a decrease in the number of osteoblasts, osteocytes and chondrocytes in the growth plate and an increase in the number and activity of osteoclasts. In vitro, consequences of mechanical stimulation on human trabecular bone cells in the presence of MTX showed an alteration in mechano-transduction, with membrane hyperpolarization, acting on the integrin pathway. In contrast with our report, the cases described in the literature were not consistently associated with a decrease in Bone Mineral Density (BMD).

Conclusion

MTX osteopathy while rare, must be known by the rheumatologist, especially when using this treatment for inflammatory conditions. The mechanisms are still poorly understood, raising the question of a possible remnant effect of MTX on osteoforming bone cells, potentially dose-dependent.

Introduction

Methotrexate (MTX) osteopathy was firstly described in young patients treated for acute leukemia[1]. This osteopathy was defined by a clinical triad: pain, osteoporosis and stress fractures. MTX is a cytotoxic drug commonly used at low dosage as a disease modifying drug in rheumatologic diseases, mainly in rheumatoid arthritis (RA) [2] and psoriasis [3]. A case of MTX induced osteopathy in rheumatology was firstly described in 1983, in a 72 years Caucasian man treated for widespread skin psoriasis and psoriatic arthritis; he developed spontaneously a stress fracture of the medial condyle of the right femur [4]. After this case, many cases, mostly isolated cases reports, were reported in the literature.

We identified and described here 5 new cases of osteopathy induced by long term MTX treatment, which represents to our knowledge, the largest cases series reported in the literature and we conducted a systematic review of the literature to identify other cases and try to understand the pathophysiological mechanisms of this rare entity.

Materials and methods

1) Cases collection:

A systematic research was performed in records of Rheumatology Department of Rennes University Hospital between the years 2005 and 2019. Data collection focused on demographic data, corticosteroid doses, MTX doses and intake method, cumulative doses, year of diagnosis, fracture location, bone densitometry value and osteoporosis treatment if necessary.

2) Systematic literature review:

A systematic research was performed on PubMed on September 10th using the following keywords: (fracture OR osteoporosis OR bone fragility) AND methotrexate. Preferred Reporting Items for Systematic Reviews and MetaAnalysis (PRISMA[®])[5,6] statement had been used to identify articles. Additional articles from references of previous articles had also been included. Cases of MTX-induced osteopathy and fractures were selected from title or abstract, with exclusion of articles involving MTX for hemopathy, especially in children. A systematic review was independently done by two rheumatologists of our team. Agreement on discordant cases was reached by consensus.

Results

1) Case Series:

Characteristics of patients with a diagnosis of MTX related osteopathy in the Rheumatology Department of Rennes University Hospital were summarized in **Table 1**.

Patients in this cohort were of hospital recruitment. All patients (n=5) were female, with a mean age of 55,8 years (minimum: 51 years, maximum: 64 years, SD: 4,96 years). Underlying disease was RA for 3 patients, skin psoriasis (n=1) and multiple sclerosis (n=1) for the others. Tibia involvement was

1 found in all cases, mainly at the metaphysis (proximal or distal). The typical appearance of the
2 fractures observed in our patients are shown in **Figure 1**. All patients except one had osteoporosis with
3 a low bone mineral density (BMD) and a T-score of at least one of the sites $< -2,5$. 2 patients (40%)
4 had been treated with bisphosphonates prior to fracture onset. Scintigraphy and MRI were useful for
5 diagnosis, whereas standard radiographs were most often non-informative (40% of the cases). In most
6 cases, MTX was stopped and anti-osteoporotic treatment was introduced (3 patients with
7 bisphosphonates, one patient with denosumab). Two patients (one with bisphosphonates and one with
8 denosumab) had a second BMD which revealed an improvement in bone density. In patient 1
9 (treatment with MTX discontinuation and risedronate), lumbar spine BMD (LS-BMD) was 0,766
10 g/cm^2 at diagnosis *versus* 0,820 after 3 years of treatment, with an increase of T-Score (-2,6 at
11 diagnosis *versus* -1,8). Femoral neck BMD (FN-BMD) was 0,566 g/cm^2 at diagnosis *versus* 0,585
12 after 3 years of treatment, with an increase of T-Score (-2,5 at diagnosis *versus* -2,3). In patient 2
13 (treatment with MTX discontinuation and denosumab), LS-BMD was 0,695 g/cm^2 at diagnosis *versus*
14 0,866 after 2 years of treatment, with an increase of T-Score (-3,2 at diagnosis *versus* -2,4). FN-BMD
15 was 0,464 g/cm^2 at diagnosis *versus* 0,543 after 2 years of treatment.

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Two patients experienced delayed bone healing with a prolonged fracture persistence and further fractures of the lower limbs, without other locations, especially at the classic locations of osteoporotic fractures.

2) Systematic literature review

a. Article selection:

The flow chart of selected articles is represented in **Figure 2**. Three hundred ninety-two articles were selected of which 362 were excluded after screening by title and abstract review. Thirty full-text articles were assessed for eligibility and 10 more articles excluded. Finally, twenty full-text articles were included in the analysis.

b. Cases reported in literature:

Twenty-five cases have been reported between 1983 and 2019. We analyzed, described and summarized these cases in **Table 2**. There was 84 % of women (21/25). Combining distal and proximal fractures, tibia was involved in 72% of the cases (18/25). RA and psoriasis (Pso) (cutaneous or articular) accounted for 92% of the underlying diseases. Pain was mainly described as mechanical. The summary of clinical and imaging characteristics of the 30 case reports (25 in the literature and 5 reported here) are presented in **Table 3**.

Interestingly, in some cases we noticed complications such as delayed fractures healing or the occurrence of other fractures with atypical locations [7–12], primarily during the year following the first fracture.

Discussion

1 Methotrexate related osteopathy is a rare but possible complication of MTX treatment in
2 rheumatoid or psoriasis arthritis. Initially described with high-dose of MTX used in acute leukemia,
3 osteopathy can also appear with long-term low-dose, as used in inflammatory diseases. Usually, this
4 osteopathy is described as a clinical triad: pain, osteoporosis and stress fractures, of atypical
5 location[1].
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10 To our knowledge, our 5 cases collection is the largest reported in the literature. Most of the
11 studies on BMD failed to find a link between MTX use and osteoporosis [13–19]. However, *in vitro*
12 and *in vivo* models are consistent, on the one hand with a decrease in osteoblastic activity and the
13 number of osteoblasts [20–22], on the other hand with an increase in osteoclastic activity and the
14 number of osteoblasts, mainly at the metaphysis [20,23,24]. Even if the mechanisms remain unclear,
15 all these cellular changes are consistent with local bone loss, especially at the trabecular level
16 [22,25,26]. In addition, bones affected in MTX osteopathy seems to be mainly weight-bearing bones,
17 especially in metaphyseal area. In our cases, all patients had fractures in lower limb bones, mainly in
18 tibia (proximal or distal metaphyseal area). This observation is in agreement with literature, with
19 lower limb involvement in all cases and tibia involvement described in more than 70%.
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26 Several authors have suggested a link between the use of MTX and the development of
27 systemic osteoporosis assessed by Dual-energy X-ray Absorptiometry (DXA). However most of them
28 did not show any association with dose, duration or modality of MTX use and decreased BMD[13–
29 19]. A prospective, randomized, placebo-controlled study showed a greater decrease in lumbar BMD
30 in a group of patients treated with MTX and corticosteroids (≥ 5 mg/j) than in a corticosteroid-only
31 group at the same dose, raising the question of a possible role for MTX in potentiating corticosteroid-
32 related trabecular loss [27]. Nevertheless, BMD measurement is known to be imperfect to determine
33 the difference between trabecular and cortical bone damage and is not very accurate in assessing bone
34 microarchitecture damage. Other treatments used in inflammatory joint diseases, including biological
35 Dmards (bDmards), appear to have a protective effect on bone compared to methotrexate, including
36 tocilizumab[28] and anti-TNFs[29] on bone remodelling and bone mineral density. These results
37 remain to be put into perspective, as the use of these treatments is often associated with a decrease in
38 inflammation, disease activity and corticosteroids dose, well known risk factors for bone loss.
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48 Studies on animal models, mainly in rats, showed a decrease in bone formation: decrease in
49 bone osteoblast surface (ObS) [23], decrease in osteoblast proliferation [20,21], decrease in formation
50 markers (alkaline phosphatase and osteocalcin) [22]. There was also an increase in bone destruction:
51 increase in osteoclastic markers (OcS and OcS/BS) [25], increase in the number of osteoclasts at the
52 metaphyseal level [20,23,24], increase in urinary hydroxyproline levels [22]. Finally, there was a
53 decrease in the number of osteocytes in the primary spongiosa [21], associated with a modification of
54 the cellular structure, in particular with a decrease in the size of osteocytes “dendrites”[30]. Some of
55 the cellular damage could be resolved after the addition of folic acid [23,31,32]. The molecular
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1 mechanisms involved remain poorly identified, with a possible reorientation of precursors in the
2 adipocyte line in rat bone marrow (increase in PPAR γ a major nuclear transcription factor orienting
3 the mesenchymal stem cell in the adipocytic lineage, and decrease in Runx2 and Osterix, osteoblastic
4 transcription factors)[26]. In the same way, a decrease in the Wnt pathway has been found (decrease of
5 beta catenin and increase of DKK1 and sFRP1)[33], and an increase of NF κ B et TNF[24]. *In vivo*
6 studies in rats have underscored the predominant trabecular involvement, especially at the metaphysis
7 level, while the cortical bone appeared to be relatively unaffected [22,25,26].
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11 *In vitro* studies were in agreement with observations in animal models, with a toxicity of MTX
12 mainly on the quantity and function of osteoblasts, responsible for a decrease in bone
13 formation[34,35]. This toxicity was described in several studies as dose-dependent [36,37]. In
14 addition, MTX could decrease the trabecular bone's resistance to mechanical stimulation by
15 interrupting the integrin-dependent pathway [38].
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20 The role of osteocytes in MTX osteopathy is not well known yet. A daily injection of MTX
21 0,75mg/kg for 5 day in rats seemed to increase osteocytes apoptosis [21], mainly in primary
22 spongiosa, partially reversed after folinic acid supplementation [31]. In juvenile rat, MTX
23 chemotherapy induced an increase in the number of apoptotic osteocytes in tibial metaphysis
24 associated with an increase in the number of osteoclasts, and trabecular bone loss [30]. Osteocytes are
25 essential for bone homeostasis, regulating the basic multicellular unit (BMU) [39]. Apoptosis of
26 osteocytes caused by detection of a micro-crack in bone induces release of molecules from
27 neighboring viable osteocytes, including VEGF, which allows the flow of osteoclasts and the initiation
28 of bone remodeling [39]. In a context of imbalance between the number of osteoblasts and osteoclasts,
29 this step could appear as the starting point for bone loss. Moreover, osteocytes play a critical role, as a
30 mechanosensory cells, with a specific response to shear stress [40]. This response is partly enabled by
31 the lacuna-canalicular network woven between osteocytes. This network appeared to be altered *in vivo*
32 in presence of MTX, with a decrease in dendrite length of osteocytes [30]. In 2004, Elliot and al.
33 described *in vitro* that osteocyte mechano-transduction pathway in human bone cells was impaired by
34 MTX, with a decrease of cells hyperpolarization in response to mechanical stimulation [38].
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45 Osteocytes also play a role in fracture healing [41]. In the literature and in our cases, several
46 fractures were followed by repeated fractures, but also with delayed healing and persistent fracture
47 lines. This observation could be a sign, not of the remnant effect of MTX, but more importantly of an
48 increased time until recovery of the number and function of osteocytes.
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53 **Conclusion**

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55 MTX osteopathy while rare, must be known by the rheumatologist, especially when using this
56 treatment for inflammatory conditions such as RA or psoriatic arthritis.
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58 However, the mechanisms are still poorly understood. In most cases, fractures occur in areas of load-
59 bearing stress in lower limbs, especially tibias. Clinical expression remains mainly mechanical pain.
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Even after MTX has been discontinued, fracture healing can be delayed and new fractures arise, raising the question of a possible remnant effect of MTX on osteoforming bone cells, potentially dose-dependent.

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Accepted manuscript

Legend:

Figure 1:

1) MRI of the right foot in coronal section (sequence T1 on the left and T2 on the right). Fracture of the distal metaphysis of the tibia. 2) Same image in sagittal section, T2 sequence. 3) Radiographic image in the same patient (front left and side right). 4) MRI of the right knee in coronal section (T2 sequence on the left and T1 sequence on the right). Fracture of the proximal tibial metaphysis.

Figure 2:

PRISMA[®] 2009 Flow Chart of selected articles in literature review. Flow chart design was described by Moher D. and al.

Accepted manuscript

- 1 Ragab AH, Frech RS, Vietti TJ. Osteoporotic fractures secondary to methotrexate therapy of
2 acute leukemia in remission. *Cancer* 1970;**25**:580–5. doi:10.1002/1097-0142(197003)25:3<580::aid-
3 cncr2820250313>3.0.co;2-m
- 4 Smolen JS, Landewé R, Bijlsma J, *et al.* EULAR recommendations for the management of
5 rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016
6 update. *Ann Rheum Dis* 2017;**76**:960–77. doi:10.1136/annrheumdis-2016-210715
- 7 Coates LC, Gossec L, Ramiro S, *et al.* New GRAPPA and EULAR recommendations for the
8 management of psoriatic arthritis: Process and challenges faced. *Rheumatology* 2017;:kew390.
9 doi:10.1093/rheumatology/kew390
- 10 Ansell G, Evans S, Jackson CT, *et al.* Cytotoxic drugs for non-neoplastic disease. *Br Med J*
11 (*Clin Res Ed*) 1983;**287**:762. doi:10.1136/bmj.287.6394.762-a
- 12 Liberati A, Altman DG, Tetzlaff J, *et al.* The PRISMA Statement for Reporting Systematic
13 Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and
14 Elaboration. *PLoS Med* 2009;**6**:e1000100. doi:10.1371/journal.pmed.1000100
- 15 Moher D, Liberati A, Tetzlaff J, *et al.* Preferred Reporting Items for Systematic Reviews and
16 Meta-Analyses: The PRISMA Statement. *PLoS Med* 2009;**6**:e1000097.
17 doi:10.1371/journal.pmed.1000097
- 18 Preston SJ, Diamond T, Scott A, *et al.* Methotrexate osteopathy in rheumatic disease. *Annals*
19 *of the Rheumatic Diseases* 1993;**52**:582–5. doi:10.1136/ard.52.8.582
- 20 Bologna C, Jorgensen C, Sany J. Possible role of methotrexate in the distal tibiae fractures in a
21 patient with rheumatoid arthritis. *Clin Exp Rheumatol* 1996;**14**:343–4.
- 22 Maenaut K, Westhovens R, Dequeker J. Methotrexate osteopathy, does it exist? *J Rheumatol*
23 1996;**23**:2156–9.
- 24 Singwe M, Le Gars L, Karneff A, *et al.* Multiple stress fractures in a scleroderma patient on
25 methotrexate therapy. *Rev Rhum Engl Ed* 1998;**65**:508–10.
- 26 Günay TY, GariP Y, Bodur H. Methotrexate Osteopathy in a Patient with Rheumatoid
27 Arthritis: Case Report. 2014;:4.
- 28 Tjl T, Wls H, Yh T. Sequential Proximal Tibial Stress Fractures associated with Prolonged
29 usage of Methotrexate and Corticosteroids: A Case Report. *MOJ* 2015;**9**:65–7.
30 doi:10.5704/MOJ.1511.010
- 31 Carbone LD, Kaeley G, McKown KM, *et al.* Effects of Long-Term Administration of
32 Methotrexate on Bone Mineral Density in Rheumatoid Arthritis. *Calcified Tissue International*
33 1999;**64**:100–1. doi:10.1007/s002239900585
- 34 Cranney AB, McKendry RJ, Wells GA, *et al.* The effect of low dose methotrexate on bone
35 density. *vitamin D* 2001;:6.
- 36 Patel S. Effect of low dose weekly methotrexate on bone mineral density and bone turnover.
37 *Annals of the Rheumatic Diseases* 2003;**62**:186–7. doi:10.1136/ard.62.2.186
- 38 Tascioglu F, Oner C, Armagan O. The effect of low-dose methotrexate on bone mineral
39 density in patients with early rheumatoid arthritis. *Rheumatology International* 2003;**23**:231–5.
40 doi:10.1007/s00296-003-0298-z
- 41 Di Munno O, Mazzantini M, Sinigaglia L, *et al.* Effect of low dose methotrexate on bone
42 density in women with rheumatoid arthritis: results from a multicenter cross-sectional study. *J*
43 *Rheumatol* 2004;**31**:1305–9.
- 44 Minaur NJ. Methotrexate in the treatment of rheumatoid arthritis. II. In vivo effects on bone
45 mineral density. *Rheumatology* 2002;**41**:741–9. doi:10.1093/rheumatology/41.7.741
- 46 Vestergaard P, Rejnmark L, Mosekilde L. Methotrexate, Azathioprine, Cyclosporine, and Risk
47 of Fracture. *Calcif Tissue Int* 2006;**79**:69–75. doi:10.1007/s00223-006-0060-0
- 48 Wheeler DL, Vander Griend RA, Wronski TJ, *et al.* The short- and long-term effects of
49 methotrexate on the rat skeleton. *Bone* 1995;**16**:215–21. doi:10.1016/8756-3282(94)00032-U
- 50 Xian CJ, Cool JC, Scherer MA, *et al.* Cellular mechanisms for methotrexate chemotherapy-
51 induced bone growth defects. *Bone* 2007;**41**:842–50. doi:10.1016/j.bone.2007.07.021
- 52 May KP, West SG, Mcdermott MT, *et al.* The Effect of Low-Dose Methotrexate on Bone
53 Metabolism and Histomorphometry in Rats. *Arthritis & Rheumatism* 1994;**37**:201–6.

doi:10.1002/art.1780370208

23 Fan C, Cool JC, Scherer MA, *et al.* Damaging effects of chronic low-dose methotrexate usage on primary bone formation in young rats and potential protective effects of folinic acid supplementary treatment. *Bone* 2009;**44**:61–70. doi:10.1016/j.bone.2008.09.014

24 King TJ, Georgiou KR, Cool JC, *et al.* Methotrexate Chemotherapy Promotes Osteoclast Formation in the Long Bone of Rats via Increased Pro-Inflammatory Cytokines and Enhanced NF- κ B Activation. *The American Journal of Pathology* 2012;**181**:121–9. doi:10.1016/j.ajpath.2012.03.037

25 Liu Y, Cui Y, Chen Y, *et al.* Effects of dexamethasone, celecoxib, and methotrexate on the histology and metabolism of bone tissue in healthy Sprague Dawley rats. *CIA* 2015;:1245. doi:10.2147/CIA.S85225

26 Georgiou KR, Scherer MA, Fan C-M, *et al.* Methotrexate chemotherapy reduces osteogenesis but increases adipogenic potential in the bone marrow. *J Cell Physiol* 2012;**227**:909–18. doi:10.1002/jcp.22807

27 Buckley LM, Leib ES, Cartularo KS, *et al.* Effects of low dose methotrexate on the bone mineral density of patients with rheumatoid arthritis. *J Rheumatol* 1997;**24**:1489–94.

28 Chen Y-M, Chen H-H, Huang W-N, *et al.* Tocilizumab potentially prevents bone loss in patients with anticitrullinated protein antibody-positive rheumatoid arthritis. *PLoS ONE* 2017;**12**:e0188454. doi:10.1371/journal.pone.0188454

29 Ozen G, Pedro S, Wolfe F, *et al.* Medications associated with fracture risk in patients with rheumatoid arthritis. *Ann Rheum Dis* 2019;**78**:1041–7. doi:10.1136/annrheumdis-2019-215328

30 Shandala T, Shen Ng Y, Hopwood B, *et al.* The role of osteocyte apoptosis in cancer chemotherapy-induced bone loss. *J Cell Physiol* 2012;**227**:2889–97. doi:10.1002/jcp.23034

31 Xian CJ, Cool JC, Scherer MA, *et al.* Folinic acid attenuates methotrexate chemotherapy-induced damages on bone growth mechanisms and pools of bone marrow stromal cells. *J Cell Physiol* 2008;**214**:777–85. doi:10.1002/jcp.21274

32 Fan C-M, Foster BK, Hui SK, *et al.* Prevention of Bone Growth Defects, Increased Bone Resorption and Marrow Adiposity with Folinic Acid in Rats Receiving Long-Term Methotrexate. *PLoS ONE* 2012;**7**:e46915. doi:10.1371/journal.pone.0046915

33 Georgiou KR, King TJ, Scherer MA, *et al.* Attenuated Wnt/ β -catenin signalling mediates methotrexate chemotherapy-induced bone loss and marrow adiposity in rats. *Bone* 2012;**50**:1223–33. doi:10.1016/j.bone.2012.03.027

34 Uehara R, Suzuki Y, Ichikawa Y. Methotrexate (MTX) inhibits osteoblastic differentiation in vitro: possible mechanism of MTX osteopathy. *J Rheumatol* 2001;**28**:251–6.

35 May KP, Mercill D, McDermott MT, *et al.* The effect of methotrexate on mouse bone cells in culture. *Arthritis & Rheumatism* 1996;**39**:489–94. doi:10.1002/art.1780390317

36 Van Der Veen MJ, Scheven BAA, Van Roy JLAM, *et al.* Effects of Methotrexate on Human Articular Cartilage and Bone-Derived Osteoblasts. *Rheumatology* 1996;**35**:342–9. doi:10.1093/rheumatology/35.4.342

37 Scheven BAA, van der Veen MJ, Damen CA, *et al.* Effects of methotrexate on human osteoblasts in vitro: Modulation by 1,25-dihydroxyvitamin D3. *J Bone Miner Res* 1995;**10**:874–80. doi:10.1002/jbmr.5650100608

38 Elliot KJ. Effects of methotrexate on human bone cell responses to mechanical stimulation. *Rheumatology* 2004;**43**:1226–31. doi:10.1093/rheumatology/keh296

39 Tresguerres FGF, Torres J, López-Quiles J, *et al.* The osteocyte: A multifunctional cell within the bone. *Annals of Anatomy - Anatomischer Anzeiger* 2020;**227**:151422. doi:10.1016/j.aanat.2019.151422

40 Bonewald LF. The amazing osteocyte. *Journal of Bone and Mineral Research* 2011;**26**:229–38. doi:10.1002/jbmr.320

41 Choy VMH, Wong RMY, Chow SKH, *et al.* How much do we know about the role of osteocytes in different phases of fracture healing? A systematic review. *Journal of Orthopaedic Translation* 2019;:S2214031X18302080. doi:10.1016/j.jot.2019.07.005

Sex	Age*	Underlying Disease	Dose* (mg/w)	CM (g)	CTC* (mg/d)	Route	MTX Duration (years)	Fractures location	X-Ray	Scintigraphy	MRI	T-Score (DS)/BMD (g/cm ²) LS	T-Score (DS)/BMD (g/cm ²) FN	T-Score (DS)/BMD (g/cm ²) TH	Treatment
F	51	MS	10	7.7	No	O	15	Bilateral Distal Tibial Metaphysis	Yes	Yes	Yes	-2.6/0.766	-2.5/0.566	-2.2/0.674	Stop MTX/BP
F	55	RA	15	10.8	2	O	15	Distal Femoral Metaphysis and Proximal Tibia	No	ND	Yes	-3.2/0.695	-3.5/0.464	-3.6/0.508	Stop MTX/Denosumab
F	56	RA	25	9.6	3	SC	10	Bilateral Distal Tibial Metaphysis	No	ND	Yes	-1.7/0.834	-2.8/0.530	-2.2/0.647	Stop MTX/BP
F	64	RA	20	10.6	No	SC	11	Unilateral Proximal Tibial Metaphysis	Yes	Yes	ND	-2.3/0.797	-3.3/0.480	-3.0/0.580	Stop MTX/BP
F	53	Psoriasis	25	4.8	No	SC	4	Bilateral Proximal Tibial Metaphysis	Yes	ND	Yes	-1.1/ND	-1.7/ND	-1.7/ND	Stop MTX

* At diagnosis

Table 1: Characteristics of cases reported in this study. F: Female, MS: Multiple Sclerosis, RA: Rheumatoid Arthritis, CTC: Corticoids (prednisone), CM: cumulative dose, O: Oral, SC: Sub-Cutaneous, ND: No Data, LS: Lumbar Spine, FN: Femoral Neck, TH: Total Hip, BP: Bisphosphonates.

First author, country & Year of Publication		Number of patients	Sex	Age	Fracture Location	Underlying Disease	Disease Duration	MTX Duration	Cumulative MTX doses	Way	Type of Pain	Swelling	Treatment	Improvement
Ansell and al. (GB)	1983	1	M	59	MC Knee	Psoriasis	ND	ND	14 g	SC	Mechanical	ND	ND	ND
Preston and al. (Australia)	1993	2	F	58	Distal/Prox Tibia	Psoriasis	ND	5 years	6 g	ND	Mechanical	ND	Stop MTX	Yes
			F	75	Distal Tibia	RA	15 years	6 years	2.8 g	ND	Mechanical	Yes	Stop MTX	Yes
Shapira and al. (Israel)	1995	1	M	74	Distal Tibia	RA	15 years	5 years	1.8 g	ND	Mechanical	ND	Immobilization	Yes
Bologna and al. (France)	1996	1	F	62	Distal Tibia	RA	15 years	5 years	2.48 g	O	ND	Yes	Immobilization	Yes
Zonneveld and al. (Neth.)	1996	3	F	61	Distal Tibia	Psoriasis	17 years	4 years	0.67 g	O	ND	Yes	Stop MTX	Yes
			F	56	Distal Tibia	Psoriasis	43 years	4 years	2.95 g	O	Mechanical	Yes	Stop MTX	Yes
			F	78	Distal Tibia	RA	30 years	8.5 years	3.5 g	O	Inflammatory	Yes	Stop MTX	Yes
Maenaut and al. (Belgium)	1996	2	F	57	2 th Metatarsal	RA	6 years	8 months	0.24 g	O	Mechanical	Yes	Immobilization	No
			F	76	Distal Tibia	RA	18 years	3 years	1.8 g	O	ND	No	Immobilization	No
Singwe and al. (France)	1998	1	F	65	Cotyle/MC Knee	Scleroderma	15 years	5 years	2.32 g	O	ND	ND	Stop MTX/BP	Yes
Stevens and al. (Neth.)	2001	1	F	63	Distal Tibia	RA	5 years	5 years	3.0 g	ND	ND	Yes	Stop MTX	Yes
Wijnands and al. (Neth.)	2001	1	F	42	Distal Tibia	Psoriasis	25 years	5 years	3.6 g	ND	Inflammatory	Yes	Diminution MTX	Mild
Rudler and al. (France)	2003	1	F	36	Pelvis	JA	27 years	2 months	0.09 g	O	Mechanical	No	Stop MTX	ND
Alonso and al. (Spain)	2006	2	F	69	Distal Tibia	RA	5 years	1 year	0.5 g	ND	Mechanical	No	Stop MTX/BP	Yes
			F	61	Distal Tibia	RA	5 years	2.5 years	1.6 g	ND	Mechanical	No	Stop MTX/BP	Yes
Meier and al. (Neth.)	2010	3	F	51	Prox Tibia	Psoriasis	ND	12 years	8.6 g	ND	ND	No	Stop MTX	Yes
			F	77	Prox Tibia	RA-Psoriasis	ND	11 years	13.2 g	SC	Mechanical	Yes	Stop MTX	Yes
			M	68	Prox Tibia	RA	35 years	9 years	10.8 g	SC	ND	ND	Stop MTX	Yes
Günay and al. (Turkey)	2014	1	F	69	5 th Metatarsal	RA	15 years	12 years	11.5 g	ND	Mechanical	Yes	Stop MTX	Yes
Mansoor and al. (Pak.)	2014	1	F	56	Distal Tibia	RA	20 years	3 years	1.8 g	ND	Mechanical	Yes	Immobilization	Yes
Tjl and al. (Singapore)	2015	1	M	65	Prox Tibia	Psoriasis	ND	4 years	2.88 g	SC	Mechanical	No	Immobilization	No
Hooghof and al. (Neth.)	2016	1	F	52	MC Knee	RA	10 years	10 years	12.0 g	ND	Mechanical	No	Stop MTX	Yes
Rajeev and al. (GB)	2018	1	F	68	Calcaneus	RA	ND	20 years	ND	ND	Mechanical	No	BP	Mild
Rolvien and al. (Ger.)	2019	1	F	64	Distal Tibia	Lupus	10 years	10 years	4.8 g	ND	ND	No	Stop MTX	Yes
Total		25	F: 21/25	m: 62.5	Distal Tibia: 14/25 Tibia: 18/25	RA: 15/25 Pso: 8/25	m RA: 15 m Pso: 28	m RA: 7 m Pso: 7	M: 8.3 g		Mechanical: 15/25	11/25	Stop MTX: 16/25	Yes: 18/25

Table 2: Characteristics of cases described in the literature. M: Male, F: Female, MC: medial condyle, Prox: Proximal, Pso: Psoriasis, RA: Rheumatoid Arthritis, JA: Juvenile Arthritis, ND: No Data, O: Oral, SC: Sub-Cutaneous, BP: Bisphosphonates, GB: Great Britain, Neth.: Netherlands, Pak.: Pakistan, Ger.: Germany.

Table 3. Summary of clinical and imaging characteristics of 30 case reports of MTX related osteopathy

General characteristics	
Women, n (%)	26/30 (87)
Age (years) mean \pm SD	61 \pm 10
<i>Underlying disease, n (%):</i>	
• Rheumatoid arthritis	18 (60)
• Psoriasis	9 (30)
• Other	3 (10)
Duration of underlying disease (in year) \pm SD	16 \pm 10
MTX osteopathy features	
<i>Fracture location n (%)</i>	
• Lower limb	30 (100)
<i>Fracture location n (%)</i>	
• Distal tibia	16 (53)
• Proximal Tibia	8 (27)
• Metatarsal bones	3 (10)
<i>Clinical presentation n (%)</i>	
• Mechanical pain	20 (67)
• Swelling	14 (47)
<i>MTX-treatment</i>	
• Mean duration of treatment (years) \pm SD	7.1 \pm 4.8
• Cumulative MTX doses (grams) \pm SD	5.4 \pm 4.4
• Oral way n (%)	10 (33)
• Subcutaneous way n (%)	7 (23)



