
Bone metabolism in rheumatoid arthritis

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ABSTRACT

In active RA, bone resorption is increased and bone formation is normal or reduced in comparison to healthy controls. This uncoupling of bone formation and resorption with a negative remodelling balance leads to generalized bone loss.

The pathogenesis of this altered bone metabolism is multifactorial, involving non-disease-specific factors (such as age, female sex and postmenopausal status) and disease-specific factors. Disease-specific factors are associated with disease activity (inflammatory cells and cytokines; hypogonadism), disease outcome (especially reduced mobility), and disease medication (e.g. corticosteroids).

Introduction

Local juxta-articular or periarticular osteoporosis is a well-recognized phenomenon in rheumatoid arthritis (RA) and is included in the 1987 American Rheumatism Association classification criteria. The hypothesis, based on the clinical observation that in active RA periarticular osteoporosis is more prominent than in inactive RA, is that inflammatory mediators and inflammatory cells cause local bone loss (1).

Most studies on bone density in RA indicate that RA is also associated with a generalized bone loss and that this loss is more evident at the hip and radius than at the spine (2-6). The etiology of this bone loss seems to be different from local periarticular bone loss. Generalized bone loss in RA is multifactorial, involving not only general, non-disease-specific factors, such as age, female sex, and postmenopausal status, but also disease-specific factors associated with disease activity, disease outcome and disease medication (corticosteroids, methotrexate?, cyclosporine?) (1,7). The absolute and relative importance of these risk factors is not exactly known, but most authors agree that bone loss in RA is most pronounced in steroid-treated patients, in

postmenopausal women, in elderly patients and in patients with more severe joint involvement. In addition to bone loss, patients with RA may have an increased risk of falls secondary to decreased general well-being (e.g. by anemia of chronic disease), functional impairment and muscle atrophy.

In this paper the focus is on altered bone metabolism in RA associated with disease activity and disease outcome, causing generalized bone loss. The topic of RA medication and bone (metabolism) will be addressed elsewhere in this issue.

Markers of bone metabolism in RA

In general, there are two types of biochemical markers of bone metabolism: (a) markers measuring the (enzyme) activity of osteoblasts or osteoclasts, and (b) markers released at the assembly or breakdown of bone matrix which assess bone formation or resorption, respectively. After a description of markers of bone metabolism, data from the literature on bone markers in RA are given.

Markers of bone formation

Serum alkaline phosphatase (sAP) is an enzyme originating from the membranes of osteoblasts; it is a marker of the activity of osteoblasts and therefore of bone formation. The use of sAP as a marker of bone formation is hampered, however, by its low sensitivity to change (8, 9); because sAP has a long half-life, it is not suitable for demonstrating rapidly occurring changes in bone formation. Another disadvantage is that in patients with severe osteomalacia, sAP can exhibit false-positive elevations without an increase in bone formation. Although alkaline phosphatase (AP) is also found in kidney, intestine and placenta, only the bone and liver isoenzymes are major contributors to serum levels in healthy adults. An ELISA has been developed for serum bone-specific alkaline phosphatase (sBAP) that is claimed to have low (5%) cross-reactivity with the liver isoenzyme;

thus its specificity as a marker of bone formation should be much higher than that of sAP.

Markers such as serum osteocalcin (sOC), also known as bone GLA protein and serum type 1 procollagen carboxy-terminal propeptide (sP1CP), are (in contrast to sAP, which is an enzyme) bone matrix components, released into the circulation during bone formation. sOC represents about 20% of the non-collagenous proteins. Its precise physiological role is as yet unresolved; it is also unknown which fraction of newly synthesized osteocalcin is incorporated into the bone matrix and which fraction is released into the circulation. sOC is increased in diseases with high bone turnover (primary hyperparathyroidism, Paget's disease) and is decreased in hypoparathyroidism (10).

Type 1 collagen accounts for 90% of the organic matrix of bone. It is synthesized in the form of a large protein, type I procollagen, with "propeptide" extensions at both ends; these extensions are removed by specific proteinases before the collagen molecules are assembled into collagen fibers. The part removed from the carboxyterminal end of the molecule can be found in blood (sP1CP), where its concentration reflects the rate of synthesis of type 1 collagen [11]. Theoretically, it is an advantage that the deposition of type 1 collagen in bone can be measured on a 1:1 stoichiometric basis with sP1CP, in contrast to sOC. When the data on sAP, sOC and sP1CP are compared, it appears that sOC discrimi-

nates best between a control group and a patient group with a metabolic bone disease (9). One disadvantage of both sOC and sP1CP is their diurnal variation: a difference of 50% has been described between values at night (high levels) and in the early afternoon (low levels). Thus, it is important to perform repeated measurements at the same time of the day. A comparison between the markers of bone formation is shown in Table I.

Markers of bone resorption

Serum tartrate-resistant acid phosphatase mirrors the enzyme activity of osteoclasts; it is not sensitive to changes in bone resorption, however. Urinary excreted calcium (uCA), hydroxyproline (uHP), pyridinoline (uPyr), deoxypyridinoline (uDpyr) and serum type 1 collagen carboxyterminal telopeptide (s1-CTP) are breakdown products of bone matrix. Fasting urinary excretion of calcium, corrected for creatinine excretion, is inexpensive but lacks sensitivity (8). Although uHP is useful for monitoring large changes in bone resorption, such as in patients with Paget's disease treated with bisphosphonates (12), it generally is not sensitive enough to measure small changes, e.g. to distinguish between normal pre-menopausal and osteoporotic postmenopausal women (9). Other drawbacks of uHP are that: (a) it originates from all types of collagen and not only type 1 collagen, the type of collagen found in bone; (b) it is also a breakdown product of the C1q fraction of complement; (c) it is metabolized by the liver;

and (d) measurement can be influenced by diet, especially meat or gelatin containing foods, such as ice cream and bananas.

Collagen fibrils in mature collagen are stabilized by pyridinoline and deoxypyridinoline cross-links. They are released during bone resorption. Pyridinolines (Pyr) are also found in cartilage, blood vessels, ligaments, intestine and muscles (13). Urinary excretion of Pyr is derived mainly from bone, however, because bone is remodelled faster than the other connective tissues and because of the high volume of bone. Approximately 40% of the Pyr are excreted in free form, while the remaining 60% are incorporated into peptides of various lengths (14).

It is possible to measure the free fraction of the Pyr by immunoassay. Two types of immunoassay exist: with antibodies against free uPyr and/or uDpyr and with antibodies against N-telopeptide or C-telopeptide from the cross-linking part of type 1 collagen. Pyr and deoxypyridinoline (DPyr) are not metabolized and measurement of the uPyr and uDpyr is not influenced by diet. It has been shown that the urinary excretion of cross-links is not only a more specific but is also a more sensitive marker of bone resorption than uHP (8, 15). The discriminative power of both uPyr and uDpyr is higher than that of uHP:(40), e.g. in women with postmenopausal osteoporosis, uPyr, uDpyr and uHP were increased in 61%, 40% and 25% of them, respectively, in comparison to healthy women (16).

The carboxyterminal telopeptide region of type 1 collagen is cross-linked by Pyr bridges and liberated during the degradation of type 1 collagen (17). This peptide is found in an immunochemically intact form in the blood (s1CTP), an advantage over the other markers of bone resorption, assessed in urine. Measurement of urinary excretion may be inaccurate because of low patient compliance or collection errors. However, s1CTP does not seem to be very sensitive to changes in bone metabolism.

From these data it is clear that at present uPyr and uDpyr are currently the best available parameters of bone resorption. However, important disadvantages are

Table I. Characteristics of some of the markers of bone formation*.

	sAP	sOC	sP1CP
Origin	Bone/liver (mainly)	Bone	Type 1 collagen
Discriminates between increased/normal bone formation	+	+	+
Discriminates between normal and osteoporotic situation	-	+	-
Subject to diurnal variation	-	+	+
Renal excretion	-	+	-
Specificity	-	+	+
Method	Autoanalyzer	RIA	RIA

* Serum alkaline phosphatase (sAP), serum osteocalcin (sOC) and serum type 1 procollagen carboxy-terminal propeptide (sP1CP).

their diurnal variation and the fact that urinary excretion has to be measured. A comparison of the markers of bone resorption is presented in Table II.

Studies

Several studies show disturbances in markers of bone metabolism in RA, but the results are not always equivalent. A problem in the interpretation of these studies is that various assays have been used for similar bone markers, and that different patient groups with RA were included; in some studies patients on corticosteroids were also included. The studies relevant to the subject of this paper will here be briefly reported.

Biochemical parameters of bone metabolism were investigated in 105 ambulant, non-steroid treated patients with RA and compared with parameters of disease activity. uCa and uHP excretion, as parameters of bone resorption, and sAP, as a parameter of bone formation, were all positively related to parameters of disease activity, but sOC, another parameter of bone formation, was not. This suggests that in RA patients bone metabolism is related to disease activity. Patients with active RA had significantly higher uCa and uHP excretion and slightly higher sAP and sOC levels than patients with inactive RA. This suggests that in active disease, bone resorption is increased more than bone formation, which may lead over time to bone loss (18).

sOC and sP1CP as markers of bone for-

mation and remodelling were measured in 119 women with RA (aged 30-66 years) and in 47 healthy female controls matched for age. sOC and sP1CP concentrations were significantly decreased in RA patients compared with the controls, suggesting reduced bone formation and bone remodelling in RA. The lowest values were found in patients with recent onset RA (19).

uPyr and uDPyr were assessed in 62 non-steroid treated patients with early RA and compared with the values in 56 healthy controls. uPyr and uDPyr were significantly increased in the patients compared with the controls; uPyr (but not uDPyr) was associated with disease activity but not with disability and was correlated with bone mineral density loss at the femoral neck (20).

One hundred and six RA patients were divided into two groups: those who were taking (St+) (n = 35) and those who were not taking low-dose steroids (St-) (n = 71), and then were randomly allocated to receive HRT or calcium for 2 years. Bone formation markers included sOC and sBAP, and the resorption markers included uDPyr and urinary crosslaps (uCx). sOC levels were significantly lower in both the St+ and St- groups compared with 112 healthy control subjects, but were similar in the two St groups; sOC was negatively correlated with parameters of disease activity. uDPyr and uCx levels were elevated in the St+ group compared with the St-

group, but were similar between the St-group and controls. After HRT, uCx excretion decreased significantly in the whole RA group. Three-month changes in uCx correlated with 2-year changes in spinal BMD. It was concluded that bone formation appears to be reduced, partly reflecting disease activity, whereas resorption is increased only in steroid users (21).

In 17 consecutive patients with active RA, bone formation was quantified by the measurement of sAP, sOC, and sP1-CP and bone resorption by the measurement of uCA, uHP, (free and total) uDPyr and uPyr, and s1CTP. sOC, sAP and sP1-CP were within normal limits, while uDPyr, uPyr and s1CTP were increased, suggesting that in active RA bone resorption is increased, while bone formation is normal. uDPyr and uPyr levels correlated with both the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP); s1CTP correlated with CRP but not with ESR; and sOC and sP1CP correlated neither with ESR nor with CRP. These results suggest that in active RA, bone metabolism is altered more than in inactive RA (22).

The effects of menopause and disease activity on bone metabolism in RA were studied by using biochemical markers of bone metabolism. sOC, sBAP, urinary total Pyr and DPyr, and urinary free DPyr were measured in 78 female patients with RA (39 pre- and 39 postmenopausal) and in 54 female normal controls (28 pre-and

Table II. Characteristics of some of the markers of bone resorption*.

	uHP	uPyr	uDPyr	s1CTP
Origin	All collagens, complement, diet	Several connective tissues	Several connective tissues(mainly bone)	Type 1 collagen
Discriminates between normal and increased bone formation	+	+	+	+
Discriminates between normal and osteoporotic situation	-	+	+	-
Affected by diet	+	-	-	-
Released only during collagen breakdown	-	+	+	+
Metabolized by the liver	+	-	-	-
Measurement in serum	-	-	-	+
Method	Colorimetric	HPLC/ELISA	HPLC/ELISA	ELISA

*Urinary excretion of calcium (uCa), hydroxyproline (uHP), pyridinoline (uPyr), deoxypyridinoline (uDPyr) and serum type 1 collagen carboxyterminal telopeptide (s1CTP)

26 postmenopausal). In premenopausal RA, bone formation was equal to that in premenopausal normal controls, but bone resorption was increased. In postmenopausal RA, bone formation was lower while bone resorption was higher than in postmenopausal normal controls. The high disease activity RA subgroup showed higher bone turnover than the low disease activity RA subgroup. Therefore, these results indicate that in premenopausal RA osteopenia is caused by an increase in bone resorption and in postmenopausal RA by an uncoupling between bone formation and resorption, and that high disease activity induces a high bone turnover (23).

In another study, 48 patients with RA (mean disease duration 11 years), of whom 30 were not on corticosteroid therapy, and age- and sex-matched controls were studied. When the analysis was confined to the patients not on corticosteroid therapy, the levels of the marker of bone resorption s1CTP were significantly elevated in the patients as compared with the controls, whereas no significant differences were found for the markers of bone formation sOC, sP1CP and serum type 1 procollagen N-terminal propeptide (sP1NP). s1CTP levels were correlated with age, the Health Assessment Questionnaire score, and the ESR. These data suggest that RA (especially active RA) is associated with increased bone resorption (24).

In another study 318 RA patients (disease duration > 2 years; mean 9 years) were divided into those with joint destruction and those without. Bone formation was assessed by sOC levels and bone resorption by serum type I collagen C-telopeptide breakdown products (s1CTx). sOC levels were significantly lower in both the destructive and non-destructive RA groups compared with 319 healthy gender- and age-matched control subjects, but were similar in the two arthritis groups. s1CTx levels were increased in the patients with destructive RA compared with controls, but were not different between patients with non-destructive RA and controls. In patients with joint destruction, there was a greater decrease in the bone formation rate in those on steroids compared with those not on steroids, as demonstrated by the

lower sOC levels in the steroid users. s1CTx levels, but not sOC levels, were positively correlated with indices of disease activity and, moreover, of joint destruction. These results indicate that bone formation is reduced in both patients with and those without joint destruction, whereas resorption is increased only in patients with joint destruction in relation to disease activity (25).

In 25 female patients with active RA, 25 female patients with RA suppressed by medication, and 25 age-matched healthy female controls, sOC as a parameter of bone formation, and s1CTP and spot urine concentrations of crosslinked N-telopeptides of type 1 collagen (uNTx) and uPyr as parameters of bone resorption, as well as serum intact parathyroid hormone (iPTH) and serum concentrations of interleukin 6 (IL-6), were measured. Patients with active RA had significantly higher concentrations of IL-6 compared to both patients with suppressed RA and healthy controls, as was to be expected. In the patients with active RA, iPTH and sOC were significantly lower and s1CTP, uNTx and uPyr were significantly higher compared to patients with suppressed RA and the controls. There were no significant correlations, however, between serum IL-6 and s1CTP or uNTx, nor between iPTH and s1CTP in the patients with active RA (26).

In 74 postmenopausal women with RA, IL-6 showed a positive correlation with the urinary excretion of DPyr collagen cross-links; the urinary excretion of Pyr and DPyr-collagen cross-links showed a positive correlation with CRP. It was concluded that IL-6 is a determinant of increased bone resorption in postmenopausal RA women with high disease activity (27).

In 184 patients with inactive RA, as defined by the preliminary criteria for clinical remission of the American College of Rheumatology, and in 118 healthy controls, bone resorption was investigated by assessing uPyr, uDPyr, and the urinary excretion of N- and C-telopeptides. All markers were significantly higher in the patients than in controls, suggesting that even in inactive RA, bone resorption and the inflammatory process are not completely absent (28).

Thus, from the studies on bone markers in RA, it can be concluded that bone resorption seems to be increased and bone formation is normal or reduced (Table III). This uncoupling of bone formation and resorption might, especially in postmenopausal patients, be responsible for bone loss.

Bone histomorphometry in RA: Studies

In bone biopsies, anatomical features reflect bone metabolism. For instance, the mean trabecular bone volume is an indicator of the amount of bone, the mean wall thickness reflects the amount of bone formed per remodelling unit, the mean interstitial bone thickness is related to resorption depth, and the extent of trabecular surface covered by osteoid reflects the number of remodelling units. After double tetracycline labeling (two doses of a tetracycline derivate, given to the patient within a pre-defined interval), the distance between the two labels in the biopsy, divided by the labeling time interval, is a measure of the rate of bone formation. Biopsies of bone distant from inflamed joints, such as the iliac crest, relate to the generalized effects of RA on bone. Several studies have been performed and are described here (Note: studies which included steroid-treated patients but which did not give separate results for the steroid-treated and the non-steroid treated patients are not described here, as the results could have also been due to steroid treatment).

In 48 non-steroid treated patients with RA, transiliac bone biopsies were taken and compared with those of age- and sex-matched control subjects. The mean trabecular bone volume was significantly lower in the patients than in the controls. This result, combined with the findings of unchanged mean trabecular plate separation and density in the patients, indicates increased bone loss in RA on the basis of trabecular thinning (29).

In 45 non-steroid treated patients with RA, the mean wall thickness, the mean interstitial bone thickness and the extent of trabecular surface covered by osteoid were assessed in iliac crest biopsy specimens. The mean wall thickness was significantly reduced in the patient group when compared with controls matched

Table III. Studies on markers of bone metabolism in non-steroid treated RA*.

Patients	Controls	Bone formation	Bone resorption	Ref.
Active RA, n = ? (whole study population: n = 105)	Inactive RA, n = ?	slightly		[18]
Women with RA, n = 119	Healthy females, age-matched, n = 47			[19]
Early RA, n = 62	Healthy, n = 56			[20]
RA, n = 71	Healthy, n = 112		normal	[21]
Active RA, n = 17	Historical	normal		[22]
RA, pre-menopausal, n = 39	Healthy, pre-menopausal, n = 28	normal		[23]
RA, post-menopausal, n = 39	Healthy, post-menopausal, n = 26			[23]
Longstanding RA, n = 30	Healthy, gender & age matched	normal		[24]
Established RA, n = 318 (102 using steroids)	Healthy, gender & age matched		in destructive RA	[25]
Women with active RA, n = 25	Age-matched healthy women			[26]
Inactive RA, n = 184	Healthy, n = 118			[28]

* = decreased, = increased.

Of the studies which also included patients on corticosteroids, if it was possible, subgroups of non-steroid treated patients are reported in this table.

for age and sex, but there were no significant differences between patients and controls in the mean interstitial bone thickness or the osteoid surface. This study, in line with the studies on bone markers, also found uncoupling of bone formation and resorption, but suggests that reduced bone formation at the remodeling unit level is the predominant mechanism of bone loss in RA (30).

Transiliac bone biopsies were performed in 17 patients with early RA (mean duration 3.5 years) treated with nonsteroidal anti-inflammatory drugs alone, and in age- and sex-matched controls. The biopsies of the RA patients demonstrated reduced trabecular bone volume and an increased eroded surface compared with the controls. In addition, the metacarpal indices were reduced in the RA patients and correlated with the iliac crest bone volume. This study suggests increased bone resorption as a systemic effect of RA (3).

In 37 non-steroid treated RA patients, quantitative histomorphometric analyses were performed on iliac crest biopsies after tetracycline labeling, using semi-automated computerised techniques. The median disease duration was 4 years (range 1-25 yrs.). Biopsies were processed without decalcification and compared with those of age- and sex-matched

controls. Of the parameters of bone formation, the mineralisation perimeter (%), bone formation rate ($\mu\text{m}^2/\mu\text{m}/\text{day}$) and the activation frequency (year^{-1}) were significantly decreased compared with the controls, but the mineral apposition rate ($\mu\text{m}/\text{day}$) was not. Of the parameters of bone resorption, the mean eroded depth (μm), maximum eroded depth (μm), eroded area (μm^2) and eroded surface (%) were also significantly decreased compared with the controls, but the number of cavities (per mm) was not. This study suggests that reduced bone formation is the most important mechanism of bone loss in RA (31).

Therefore, about half of the histomorphological studies suggest, in agreement with the studies on bone markers, that increased bone resorption is the major cause of bone loss in RA, while the other studies suggest that reduced bone formation is the most important mechanism. It is not easy to explain why the results of some of the histomorphological studies contrast in this way with the results of the studies on bone markers. Obviously, this could be due to differences in the patients selected for study. That RA influences bone in several ways and that for different individuals some mechanisms might be more important than other mechanisms, depending on each

individual's disease activity and outcome, will now be discussed.

Disease activity and bone metabolism: Mechanisms

In the studies on bone markers in RA, there is uncoupling of bone formation and resorption; bone resorption seems to be increased, especially in active RA. This is in line with the following findings. 1. Prostaglandin E2 produced by rheumatoid synovium has bone resorption-stimulating activity (32). 2. IL-4, having anti-inflammatory properties, inhibits bone resorption (33). 3. IL-6 is a determinant of increased bone resorption in postmenopausal RA patients with high disease activity (1, 27). 4. Synovial macrophages and monocytes from patients with RA can differentiate into mature osteoclasts (34, 35). 5. Several cytokines and inflammatory mediators can induce recruitment, differentiation and activation of osteoclasts, including IL-1, tumor necrosis factor (TNF)- α and TNF- β , macrophage colony stimulating factor, IL-6, IL-11, IL-17 and parathyroid hormone-related peptide (1).

Another recently described mechanism of bone loss in RA is the following (36). Osteoclast differentiating factor (ODF) is a new member of the TNF family and is also known as TNF-related activation-

induced cytokine, TRANCE, RANK-L or osteoprotegerin ligand. It induces the differentiation and maturation of osteoclast precursor cells into osteoclasts and causes bone loss (37). ODF soluble decoy receptor (named osteoprotegerin or osteoclastogenesis-inhibitory factor) is a member of the TNF-receptor superfamily and is produced by many different cells; it blocks ODF action by binding to it (36). In healthy people, osteoclastic activity probably is regulated by a delicate balance between ODF and osteoprotegerin. ODF is expressed on stimulated T-cells and in this way, activated T-cells seem to play an important role in bone loss in arthritis (37). Interestingly, osteoprotegerin has indeed been shown to prevent bone loss in adjuvant arthritis (36, 37).

Next to these mechanisms involving inflammatory cells and mediators, active RA probably induces bone loss in another way. There seems to be an androgen disorder in RA (38, 39). Low levels of gonadal and adrenal androgens have been found in the body fluids (i.e., blood, synovial fluid, salivary fluid) of male and female RA patients (40). Hypo-androgenism and testosterone deficiency are considered to be an integral part of RA disease activity. The mechanism has not been fully elucidated, but may be due to altered steroidogenesis pathways, to deficient testicular steroid synthesis, and/or to chronically low gonadotropin stimulation (41, 42). In RA patients treated with glucocorticoids, the use of low dose prednisone may result in decreased gonadal hormone concentrations such as decreased testosterone levels in male RA patients (43, 44).

Therefore disease activity in RA leads to bone loss via the negative influence of pro-inflammatory cytokines, osteoclast activating factors and hypogonadism, leading to increased bone resorption and decreased bone formation.

Disease outcome and bone metabolism: Mechanisms

The mechanical strain theory predicts that load-bearing strain on bone will result in an osteogenic response with increased bone mass and strength (45, 46). The rapidly remodelling trabecular bone is probably more sensitive to an increase

in mechanical loading than cortical bone. Load-bearing at the spine and femoral neck can be obtained with weight-bearing exercise; brisk walking indeed increases bone mass at those sites (47). Load-bearing at the wrist cannot be obtained with weight-bearing exercise; muscle strengthening at the forearm, however, does result in a load-bearing strain on bone at the wrist and increases bone mass (47). The mechanism of how bone load-bearing strain leads to increased bone strength and bone mass has not fully been elucidated, but within a few days after applying mechanical strain, the osteoblasts on the bone surface show an active appearance (48). Conversely, it is reasonable to suggest that bone formation is impaired in patients with RA, in whom as a consequence of the disease, physical ability, mobility and muscle strength are impaired, and therefore the bone load-bearing strain is reduced. Next to impaired bone formation, immobilization also increases bone resorption; this can be concluded from increased parameters of bone resorption, e.g. uHP and uCA, with the increased risk of nephrolithiasis (49). Another way in which immobility may lead to decreased strength of bone could be decreased exposure to sunlight causing osteomalacia. Apart from the decreased strength of bone, physically disabled RA patients of course have an increased risk of falling, leading to fractures (50).

What is the evidence that these mechanisms based on physical disability and decreased mobility indeed apply in RA? Disability and impaired grip strength have been shown to be associated with fractures in RA (51) and disability was found to be a major determinant of both spinal and femoral bone mass in RA patients (5). In line with these data is the finding that cortical bone distant from inflamed joints is conserved more successfully in RA patients who achieve higher levels of physical rehabilitation than in patients who do not (52).

Thus, in RA physical disability and immobility as a long-term consequence of the disease may lead to impaired bone formation and accelerated bone resorption, with the consequence of decreased bone strength and mass.

Conclusion

In RA patients, bone resorption is increased and bone formation is normal or reduced in comparison to healthy controls. This uncoupling of bone formation and resorption leads to bone loss. The global negative remodelling balance associated with uncoupling is, apart from non-disease-specific factors, due to the inflammatory process with its circulating cytokines and hypogonadism and to the disease outcome, which leads to physical disability and immobility.

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