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REVIEW

Oral creatine supplementation: A potential adjunct therapy for rheumatoid arthritis patients

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Abstract

Creatine is one of the most popular forms of protein supplements and is known to improve performance in healthy athletic populations *via* enhanced muscle mass and adenosine triphosphate energy regeneration. Clinical use of creatine may similarly benefit patients with rheumatoid arthritis (RA), an inflammatory condition characterised by generalised muscle loss termed "rheumatoid cachexia". The adverse consequences of rheumatoid cachexia include reduced strength, physical function and, as a consequence, quality of life. Whilst regular high-intensity exercise training has been shown to increase muscle mass and restore function in RA patients, this form of therapy has very low uptake amongst RA patients. Thus, acceptable alternatives are required. The aim of this review is to consider the potential efficacy of creatine as an anabolic and ergonomic therapy for RA patients. To date, only one study has supplemented RA patients with creatine, and the findings from this investigation were inconclusive. However, trials in populations with similar losses of muscle mass and function as RA, including older adults and those with other muscle wasting conditions, indicate that creatine is an efficacious way of improving muscle mass, strength and physical function, and may offer an easy, safe and cheap means of treating rheumatoid cachexia and its consequences.

Key words: Creatine supplementation; Nutritional supplement; Rheumatoid arthritis; Rheumatoid cachexia; Physical function

Core tip: Creatine supplementation primarily improves physical function by enhancing the re-synthesis of adenosine triphosphate *via* increased stores of phosphocreatine in the muscle. Through this pathway it provides greater levels of energy during physical activity and improves recovery. Creatine also augments muscle protein synthesis, thereby increasing muscle mass. These dual effects increase strength, reduce fatigue, and thereby improve function. In patients with conditions such as rheumatoid arthritis that are characterised by muscle loss and subsequent reductions in strength and physical function, creatine offers a potential therapeutic intervention for augmenting muscle mass and function that is safe, easy and inexpensive to administer.

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INTRODUCTION

Patients with rheumatoid arthritis (RA) often experience a substantial loss of muscle mass (cachexia), which results in significant adverse consequences such as decreased strength, impaired physical function, and a reduction in

quality of life. Unfortunately, current drug treatments for RA do not attenuate this muscle loss, nor fully restore physical function[1,2], and whilst exercise has been shown to be effective in restoring both muscle mass and function in RA patients (*e.g.*,[3]) the lack of uptake and adherence to sufficiently intense training means this form of therapy is unlikely to be widely adopted. Nutritional supplements offer a potential alternate therapeutic intervention that would be more easily adopted. One such nutritional supplement is oral administration of creatine (Cr). Creatine is a popular form of protein supplementation that has been widely demonstrated to improve physical function *via* enhanced energy regeneration and increased muscle mass[4]. Consequently, Cr supplementation potentially offers a low-cost and generally acceptable means for RA patients to restore muscle mass and functional capacity.

This article reviews the evidence regarding the potential of Cr as an adjunct treatment to improve muscle mass and function in RA patients. In the course of doing this, rheumatoid cachexia, its effect on patients, and the rationale for nutritional supplementation (such as Cr) to improve body composition and physical function will be discussed. Then the mechanisms and effectiveness of Cr in athletic populations will be described before we present a review of the existing evidence regarding the efficacy of Cr in RA-relevant clinical trials.

RHEUMATOID ARTHRITIS, CACHEXIA AND MUSCLE LOSS

Rheumatoid arthritis is an autoimmune disease predominantly affecting middle-aged and older females and is characterised by persistent synovitis, systemic inflammation, and the presence of specific autoantibodies[5]. This inflammation is associated with damage to the articular cartilage and bone[5], and a range of co-morbidities including cardiovascular disease[6], obesity[7], diabetes[8], osteoporosis[9], fatigue[10] and depression[11].

Additionally, RA is characterised by aberrant changes in body composition. The involuntary loss of muscle, often coupled with elevated adiposity, has been termed "rheumatoid cachexia"[12], and occurs in approximately 67% of patients[3,12-16] including those with controlled disease[12]. Much like sarcopenia (muscle loss due to ageing[17]), rheumatoid cachexia leads to a loss of strength[18] and reduced physical functioning[19,20] impairing performance of activities of daily living such as standing independently from a chair, walking, climbing stairs, and lifting and carrying[21]. Additionally, muscle wasting impairs immune function[22], and is a significant predictor of cardio-vascular disease and overall mortality[23-28].

The aetiology of rheumatoid cachexia is multifactorial and may involve increased production of excess inflammatory cytokines such as tumour necrosis factor-alpha (TNFα) and interleukins -1 and -6 (IL-1, IL-6) which are also implicated in the pathophysiology of RA itself[13,24-26]. On a cellular level, several key signalling pathways, such as nuclear factor-kappa B (NF-κB; catabolic) and insulin-growth factor- I (IGF- I ; anabolic), regulate protein synthesis and degradation in the muscle[27]. Changes to these pathways "tip" the metabolic activity from anabolic to catabolic, thereby inducing muscle wasting[22].

TREATMENTS OF MUSCLE WASTING

Interventions that are effective in increasing muscle mass have been shown to improve physical function, reduce disability, and enhance quality of life in RA patients[29]. However, efficacious and safe anabolic interventions which are widely acceptable to rheumatoid patients have yet to be identified.

Medication and drug treatments

Rheumatoid cachexia and relatively poor physical function remain prevalent even in RA patients with well-controlled disease activity (*i.e.*, approximately 20%-30% below the level seen in age- and sex-matched sedentary healthy controls[1,3]). Therefore, it is apparent that controlling disease activity alone is insufficient to restore body composition and function. Roubenoff *et al*[13] hypothesised that TNFα was central in causing rheumatoid cachexia, so it might be expected that anti-TNFα biologics would be the pharmaceutical anti-rheumatic treatment most likely to reverse rheumatoid cachexia. However, even these agents have proved ineffective in this regard[2,30,31]. In fact, in the trials conducted to date, anti-TNFα therapy have not only failed to increase lean mass in recent-onset[2,30] and established[31] RA patients, but appear to increase fat mass[2] and more disturbingly, trunk fat mass[31] relative to standard disease modifying anti-rheumatic drugs.

Similarly, yet to be published data from an on-going study by our group suggests that even in the current "Treat to Target" era, when disease activity is more tightly and successfully controlled, and clinical "remission" is regularly achieved, RA patients still experience significant loss of muscle (approximately 10%), increased adiposity (approximately 12%), and relatively poor physical function (approximately 20%-30% decreased), compared to age- and sex-matched healthy sedentary controls.

Progressive resistance training

High-intensity progressive resistance training (PRT) has been shown to substantially increase muscle mass, and as a consequence dramatically improve strength and restore normal levels of physical function in RA patients (*e.g.*,[3,16,32]). However, patient uptake of exercise is poor[33], and even patients who experience significant benefits of structured exercise cease training when supervision is withdrawn[34]. Thus, sustained exercise training is unlikely to be widely adopted as a therapy for reversing cachexia and restoring function.

Nutritional supplementation

Anabolic nutritional supplementation offers a potential treatment option that is easily administered, inexpensive, and makes limited demands of the patient. It has been

Table 1 Summary of the results from the meta-analysis by Nissen *et al*[37]

Supplement (n = studies)	Average dosage (maintenance dose)	Duration (wk)	Net lean mass change	Net strength change
Cr (n = 18)	19.4 g/d for 5.3 d (6.7 g/d)	7.5	+0.36%/wk[b]	+1.09%/wk[b]
HMB (n = 9)	3 g/d	8	+0.28%/wk[b]	+1.40%/wk[b]
Chromium (n = 12)	485 μg/d	11.2	+0.08%/wk	+0.25%/wk
Androstenedione (n = 3)	200 mg/d	10.7	+0.05%/wk	-0.06%/wk
Protein (n = 4)	1.15 g/kg per day	6.3	+0.12%/wk	-0.18%/wk
DHEA (n = 2)	125 mg/d	10	+0.12%/wk	+0.06%/wk

The net change is expressed as % change per week. Only Cr and HMB resulted in significant changes; [b]$P < 0.005$. Cr: Creatine; HMB: β-hydroxy-β-methylbutyrate; DHEA: Dehydroepiandrosterone.

reported that up to 75% of RA patients believe that food and nutrition may play an important role in their symptom severity, with up to 50% of RA patients reportedly trying some form of dietary manipulation in an attempt to attenuate symptomology[35]. Scientific evidence continues to suggest that diet should be part of routine care in those with wasting disorders (for review see Stamp[35]).

Our group previously investigated the effects of 12 wk of a mixture of β-hydroxy-β-methylbutyrate, glutamine and arginine (HMB/GLN/ARG) protein supplementation in 40 RA patients[15]. The results showed that both HMB/GLN/ARG and a control mixture of other, non-essential, amino acids (alanine, glutamic acid, glycine and serine) were effective in increasing muscle mass and improving physical function in RA patients. Thus it appears that protein per se is capable of significantly improving lean mass, total body protein and objective measures of physical function which reflect the ability to perform activities of daily living in RA patients.

Creatine, a combination of essential amino acids, has generally been shown to be more effective than other protein-based supplements in increasing lean mass. For example, Cribb *et al*[36] showed that Cr (1.5 g/kg per day for 11 wk) was able to significantly improve lean mass by +5.5%, compared to whey protein (+3.7%; $P < 0.05$) in 33 trained males. Further to this, in a meta-analysis[37] of 48 studies, both lean mass and strength gain were unaffected by whey protein and other supplementation such as androstenedione when compared to a placebo treatment, and only supplementation with either Cr or HMB resulted in a significant gains (Table 1). The superior gains in lean mass and strength from Cr relative to HMB, combined with the additional benefits of Cr to energy production and recovery identifies Cr as a potentially highly effective adjunct treatment for improving rheumatoid cachexia and physical function.

WHAT IS CREATINE?

Creatine, or methylguanidine-acetic acid, is a naturally occurring compound made from 3 amino acids; arginine, glycine, and methionine[4], and is synthesized within the body, primarily in the liver, kidney and pancreas[38].

Most (approximately 95%) of the total Cr pool is contained in skeletal muscle, with around 60% [75 mmol · kg dry weight (dw)$^{-1}$] in the phosphorylated form, phosphocreatine (PCr)[39,40], and the remaining 40% (50 mmol · kg dw^{-1}) existing as free Cr[41]. Muscle does not synthesize Cr itself but is dependent on Cr uptake through specific membrane sodium dependent transporters[42].

WHAT DOES CREATINE DO?

Changes in ATP energy synthesis

Creatine performs many roles in the body, the most important of which is in generating energy for the muscles. Muscle relaxation and contraction, and therefore the movement of the body, is fuelled by energy liberated from the dephosphorylation of adenosine triphosphate (ATP).

ATP ↔ adenosine diphosphate (ADP) + phosphate (P) + energy (catalysed by the enzyme ATPase)

The ATP stores in the body are limited (concentration in skeletal muscle approximately 24 mmol · kg/dw[40]), and without a means of resynthesizing ATP at an equally rapid rate, maximal exercise exhausts these stores within 1-2 s[43]. To overcome this storage limitation, the body is able to maintain a continuous ATP supply through different metabolic resynthesis pathways: either anaerobically in the cytosol, or aerobically in the mitochondrion.

As stated previously, Cr is primarily stored in the body in a phosphorylated form as PCr, with the muscle content of PCr 3-4 times higher than that of ATP[41]. In a process called dephosphorylation, some energy for ATP resynthesis comes directly from the hydrolysis (splitting) of phosphate from PCr[41].

PCr ↔ Cr + P + Energy [catalysed by the enzyme creatine kinase (CK)]

In this process, the liberated phosphate group can then combine with ADP in a reaction catalysed by CK to restore ATP levels[44] and maintain high cellular ATP/ADP ratios[45]:

ADP + P ↔ ATP + Cr (catalysed by CK)

As a consequence, it would be anticipated that increasing initial Cr stores and thereby delaying PCr depletion would enhance resynthesis of ATP and augment performance[46,47]. Ingestion of Cr supplements (20 g a day for 5 d) has been shown to increase the total Cr and PCr concentration of human skeletal (Table 2), and indeed, reduced blood lactate concentrations have been observed after high-intensity[48] and endurance exercise[49]; although these findings are not universal[50].

Changes in muscle mass and protein synthesis

Creatine is an osmotically active substance. Thus, as

Table 2 Changes in creatine and phosphocreatine levels following Cr supplementation

	Mean baseline Cr levels[1]	Increase after 20 g/d for 5 d
Creatine	Approximately 125 mmol·kg/dw[130] (90 to 160 mmol·kg/dw)[4]	+ 25 mmol·kg/dw (approximately 20%)[144]
Phosphocreatine	Approximately 50 mmol·kg/dw[41]	+ 8 mmol·kg/dw (approximately 15%)[132]

[1]Typical values for an average 70 kg male. Cr: Creatine.

skeletal muscle cell Cr and PCr concentrations rise, the cell will rapidly draw in extracellular water *via* osmosis in order to maintain equilibrium[51]. The uptake of Cr and water into the muscle accounts for the increases in body mass (approximately 1-2 kg) usually observed after a few days of supplementation (*e.g.*,[52]). Total body water has been reported to increase up to 3 litres (+9%)[45]; of which intra-cellular water has been shown to increase by between 0.77-3.0 litre (an increase of +3%-9% from baseline values) (*e.g.*,[53-56]) in the absence of changes in extra-cellular water[54].

The intramuscular uptake of Cr and the associated increase in intracellular water increases osmotic pressure, which in turn stimulates protein synthesis. Cellular hydration state is an important factor in controlling cellular protein turnover, *i.e.*, an increase in cellular hydration inhibits proteolysis and stimulates protein synthesis[57], whereas cell shrinkage has opposite effects[51,58-61]. However, it is unclear whether acute Cr supplementation augments muscle protein by this mechanism[62,63].

Creatine has also been shown to stimulate muscle hypertrophy by inducing expression of muscle myogenic factors such as MRF4, MyoD and myogenin[64].

Deldicque *et al*[65,66] showed that the muscle gene expression of IGF-I was raised following Cr supplementation. This finding was corroborated by Burke *et al*[67] who found increased muscle content of IGF-I as a result of Cr supplementation combined with 8 wk of PRT. These findings are highly relevant to Cr's anabolic potency as IGF-I produced locally in the muscle (mIGF-I) is thought to regulate adult skeletal muscle maintenance and hypertrophy[68]. Conversely, Cr supplementation in conjunction with PRT has been shown to lower serum levels of myostatin[69], a hormone that is highly expressed in RA synovial tissues and inhibits muscle growth by reducing myoblast (muscle) proliferation[70-72] and thus is associated with muscle atrophy[72] and joint destruction[73]. The anabolic response to Cr supplementation is particularly evident in type Ⅱ muscle fibres[60,74], which is particularly interesting because RA patients present with preferential atrophy of type Ⅱ fibres[75].

Reduction in inflammatory cytokines

Patients with RA exhibit high synovial levels and serum concentration of the cytokines TNFα and IL-1β[22]. These cytokines, in addition to causing synovial inflammation[76], also modulate the expression of enzymes controlling muscle protein degradation[27]. Bassit *et al*[77] investigated the effects of Cr supplementation (20 g/d for 5 d prior to competition) on plasma levels of the pro-inflammatory cytokines: TNFα, IL-1β, and prostaglandin E2 (PGE2) in triathletes after a half-ironman competition. These cytokines are typically raised following prolonged strenuous exercise[78], but Cr supplementation attenuated the increases in TNFα by 42% and 64%, IL-1β by 72% and 71%, and PGE2 by 85.5% and 91 %, 24 and 48 h post, respectively.

Creatine and bone degradation

RA patients are at 2-fold increased risk of having osteoporosis and approximately 28% of patients develop this condition[9,14]. In wheelchair-independent patients experiencing Duchenne dystrophy, Cr supplementation was able to enhance bone mineral density (+3%) and reduce urinary cross-linked N telopeptides of type I collagen (NTx) excretion, a marker for bone resorption[62]. In addition, Candow *et al*[79] also reported a reduction in NTx (-27%) *vs* placebo (+13%; $P < 0.005$), and similar findings were reported by Chilibeck *et al*[80] who showed that in elderly men, Cr was able to improve arm bone mineral density by +3.2% ($P < 0.001$) *vs* placebo (-1%) However, more research is needed in this area to understand the mechanisms behind this action.

Athletic performance

Creatine has repeatedly demonstrated efficacy in improving high-intensity short-term exercise performance and subsequent recovery. For example, in cycling, Cr supplementation has been shown to significantly enhance peak power output[48,81,82] and maximal work[39] during repetitive sprints. Similarly, runners who supplemented with Cr decreased their 100 m sprint time and total time for 6 m × 60 m sprint intervals[83], and highly trained football players improved their repeated sprint performance (6 m × 15 m sprints with 30 s recovery) and attenuated fatigue-induced decline in jumping ability following Cr supplementation[84]. Creatine supplementation has also been found to be effective in improving performance of a variety of sustained high-intensity activities (*e.g.*, kayaking for 5 min[85]; 1000 m rowing[86]; and running 300 and 1000 m intervals (3-4 min rest)[87]). These functional benefits are attributed to increased ATP resynthesis, heightened availability of PCr in type Ⅱ fibres, and increased total Cr stores[41]. These effects may be particularly beneficial to older adults or clinical populations who experience difficulty performing short-term, high intensity activities such as hurrying for a bus, crossing roads, climbing stairs, or digging in the garden.

Creatine has also been shown to improve strength related measures. In an analysis of 22 studies, athletes supplementing with Cr had an average +8% greater increase in muscle strength than placebo (for a review see Rawson *et al*[88]). Furthermore, Cr supplementation when combined with PRT has been shown to be more effec-

tive at increasing strength and weightlifting performance than PRT alone[89,90]. Improvements in strength translate into increased work capacity, and thus improved ability to perform activities of daily living such as walking, carrying shopping, doing housework, *etc*[16,19,21].

Although approximately 70%[91] of short-term studies on Cr supplementation report some ergogenic benefit, the responses are often variable amongst individuals[88], and supplementation generally does not result in improvements in endurance performance (*e.g.*, repeated 6 km treadmill and terrain run performance[48,58,92,93]).

CRITICAL REVIEW OF RELEVANT CLINICAL LITERATURE

Aim

The aim of this review is to examine existing evidence assessing the efficacy of Cr supplementation in improving muscle mass and physical function, with particular reference to its potential use in treating rheumatoid cachexia and its consequences. To achieve this we searched for, and extracted relevant data from published research papers in RA and other conditions for which findings are likely transferable to the RA population, *e.g.*, ageing population and other musculoskeletal and wasting diseases.

Search methods

Peer-reviewed research articles were included in this review provided they: (1) investigated the effects of Cr supplementation in RA patients or other populations deemed relevant to RA (*i.e.*, elderly populations (> 60 years) or musculoskeletal disorders featuring loss of muscle and physical function); (2) included body composition (muscle and/or fat mass) and/or physical function as outcome measures; and (3) conducted an intervention of any design in RA patients; or undertook a blinded placebo-controlled trial for non-RA populations, to ensure only evidence of higher certainty of evidence was included. As the purpose of this review is to investigate alternative treatments to high-intensity exercise for restoring muscle mass and physical function, data on the additive effects of Cr supplementation and PRT were excluded. Publications were also excluded if they were a literature review, thesis, abstract, or a letter or comment, and the search was limited to English language citations.

PubMed and Google Scholar were searched from April to May 2014 using the search term "creatine supplementation" combined with "cachexia"; "clinical"; "patient"; "older adults"; "elderly"; "sarcopenia" and "rheumatoid arthritis". In addition, the reference sections of the selected papers were hand-searched for relevant ancestral references. The title and abstract of each search result was first screened for relevance according to the inclusion criteria above, before full articles were obtained. Full-text articles were then screened before final inclusion in this review.

Search results

The initial search returned 758 articles, excluding duplicates, of which 21 met the inclusion criteria and were selected for this review. One trail investigating Cr supplementation of RA patients was found[94]. This study was not controlled in any way so is considered to provide evidence of low certainty. The body composition and physical function data extracted from trials in older adults are presented in Table 3, and data extracted from trials in other relevant clinical populations appear in Table 4.

Rheumatoid arthritis

Willer *et al*[94] was the only study identified that completed a trial of Cr in an RA population. Twelve RA patients were un-blinded to the Cr supplementation and no placebo group or control arm existed. Participants were given oral Cr supplementation for 21 d using recommended doses (day 1-5: 20 g/d; day 6-21: 2 g/d) and the effects on muscle strength, subjectively assessed function during activities of daily living (Health Assessment Questionnaire), and disease activity were examined. It was found that Cr supplementation increased muscle strength in 8 out of the 12 patients by an average of +14% ($P = 0.02$), as determined by the muscle strength index (the mean of 8 strength measurements during flexion and extension of the knee and elbow/max sample strength × 100[95]). This increase in muscle strength was not associated with changes in skeletal muscle Cr or PCr levels. Routine clinical measures of disease activity and subjectively evaluated physical function showed no changes.

The authors attributed the "limited effectiveness of Cr" to "alterations in the kinetics of Cr in patients with RA (*e.g.*, reduced transport into the muscle, increased metabolism and/or excretion)". However, this interpretation places emphasis on the subjectively assessed function, which was unchanged, rather than the objectively measured strength, which did improve significantly. It is known that the Health Assessment Questionnaire is weakly associated with objective measures of physical condition such as strength ($r = -0.35$) and joint mobility ($r = 0.27$)[96], and is often insensitive to changes in objective function (*e.g.*,[3,96]). Additionally, only 12 patients were used in the study, and with Cr supplementation reported to be ineffective in approximately 30% of individuals[46], it would be anticipated that only 8 of the RA patients in this investigation would see any benefit. Consistent with this prediction, strength increases were noted in 8 patients. Moreover, the study supplementation period only lasted 3 wk, much less than the 8-12 wk recommended by manufacturers and used by other studies. Thus, whilst the findings of Willer *et al*[94]'s trial are inconclusive, they do provide some indications that Cr may be effective in the RA population. Clearly more research is needed in this area.

Ageing and sarcopenia

Nine studies[55,97-104] were identified that investigated the effects of Cr supplementation in older adults and met the inclusion criteria. Four of these studies, reported that Cr increased body mass by 0.49-1.86 kg[55,98,100,102] and that

Table 3 Summary of studies investigating the effects of creatine supplementation on sarcopenia and function in older adults over 60 years

Treatment arm (mean age ± SD)	Supplementation period	Study design	Body composition changes	Physical function changes	Ref.
10 males (66.7 ± 1.9 yr)	20 g/d for 10 d followed by 4 g/d for 20 d	*vs* PL group (dextrose) (n = 10)	[2]Body density, [2]LM, [2]%BF	[1]Leg fatigue performance	[99]
9 males (65.0 ± 2.1 yr)	20 g/d for 5 d	*vs* PL group (sucrose) (n = 8)	[1]BM, [2]LM	[2]Strength	[100]
10 females (67.0 ± 6.0 yr)	0.3 g per kg/day for 7 d	*vs* PL group (n = 6)	No details	[1]Objective function tests, [2]Endurance capacity	[97]
10 males (65.4 ± 1.5 yr)	0.3 g per kg/day for 7 d	*vs* PL group (powdered cellulose) (n = 8)	[1]BM, [1]LM	[1]Strength, [1]Power, [1]Objective function tests	[55]
15 females (63.3 ± 1.2 yr)	0.3 g per kg/day for 7 d	*vs* PL group (powdered cellulose) (n = 12)	[1]BM, [1]LM, [2]%BF	[1]Strength, [1]Objective function tests	[98]
7 males and 8 females (74.5 ± 6.4 yr)	20 g/d for 7 d followed by 10 g/d for 7 d	Cross-over design	[2]BM	[1]Strength, [1]Endurance (cycling capacity at fatigue threshold), [2]Objective function tests	[101]
7 males (72.5 ± 2.5 yr)	20 g/d for 5 d	*vs* PL group (maltodextrin) (n = 5)	[1]BM, [2]LM	[2]MVC or contractile force	[102]
4 males and 4 females (71.0 ± 1.9 yr)	20 g/d for 5 d followed by 3 g/d for 8 wk	*vs* PL (glucose) (n = 8)	[2]Lower limb volume, [2]BM, [2]%BF	[2]Strength [2]Endurance	[103]
15 females (66.1 ± 4.8 yr)	20 g/d for 5 d followed by 5 g/d for 23 wk	*vs* PL (dextrose) (n = 15)	[1]LM, [2]FM	[1]Strength [1]Objective function tests	[104]

[1]Significant increase/improvement; [2]No significant change ([a]P < 0.05 for interaction between placebo and Cr group). Cr: Creatine; PL: Placebo; BM: Body mass; %BF: Percent body fat; FM: Fat mass; LM: Lean mass; MVC: Maximal voluntary contraction; No details: No details are specified or this measure was not made.

this gain was predominantly lean mass (LM), with increases in muscle mass of up to +2.22 kg[55]. In contrast, no significant changes in body mass or LM were found in the remaining five studies[99-101,103,104], although a trend of increased LM (+0.3%) following Cr supplementation relative to placebo (P = 0.062) was found by one of these[104]. As expected, no significant changes in % body fat subsequent to Cr supplementation in older subjects were reported[55,99,100].

Three of the six studies that measured muscle strength changes reported improvements following Cr supplementation[55,98,101]. Gotshalk *et al*[55] reported strength increases of both maximal leg press (+7%-8%), knee extensor (+9%) and knee flexor muscles (+15%) in older males, whilst in females increases in leg press (+3.4% or 5.2 kg) and bench press (+4.4% or 1.7 kg) were found[98]. In a cross-over design, Stout *et al*[101] found that Cr significantly increased maximal isometric grip strength by +6.7%[101]. Conversely, Jakobi *et al*[102] found that 5 d of Cr supplementation was unable to increase elbow flexor maximal voluntary strength or any other muscle contractile properties (twitch and tetanic recordings from electrical stimulation of the muscles). Similar findings were reported by Rawson *et al*[100], who found no significant effect on isometric elbow flexor strength after 5 d supplementation, and Bermon *et al*[103] who found no increase in chest or strength compared to a placebo (P > 0.05).

All studies assessing short-term physical function reported significant improvements in lower-extremity functional tests such as the sit-to-stand in 30 s (SST-30) by up to 12%[55,97,98,105], and a tandem gait test by 6%[55] to 9%[98] following Cr supplementation. Lower body power (as assessed by a 10-s Wingate test) was shown to improve by +11%[55] and Rawson *et al*[99] reported that leg fatigue (as expressed as a % change in the total peak torque generate and assessed by 5 × 30 s knee extensions at 180° on an isokinetic dynamometer) was reduced by 9% (compared to a 5% increase in the placebo group, P < 0.05). Similar findings by Stout *et al*[101] showed lower body muscle endurance (cycling capacity at fatigue threshold) was improved by 15.6% compared to the placebo group. However, assessments of endurance capacity (*i.e.*, 1-mile walk test; and gross mechanical efficiency, ventilatory threshold, and peak oxygen intake determined during cycle ergometry) were not significantly improved following Cr supplementation[97].

Trials in other clinical populations

One study[106] trialled Cr supplementation in osteoarthritis (OA). OA is the most common form of arthritis, and as with RA, is characterised by joint damage, muscle weakness, poor physical function[107], and predominantly affects females[108]. In this investigation, Roy *et al*[106] reported limited effects of Cr supplementation in OA patients recovering from total knee arthroplasty, despite a significant increase in serum Cr concentration, with no improvements in muscle strength (handgrip, dorsiflexion and quadriceps strength, 30-foot timed walk and 4-step climb) observed after 40 d (10 d pre surgery and 30 d post-surgery) of Cr supplementation relative to placebo.

One trial[109] reported the use of Cr supplementation in fibromyalgia, another chronic syndrome of unknown etiology, characterized by some similarities in symptomology to RA, including pain, muscle dysfunction, disability and fatigue[110]. Some of the fibromyalgia symptoms such as muscle dysfunction and fatigue could, in theory, be due to low muscle levels of ATP and PCr[109]. A randomised controlled trial of Cr supplementation in fibromyalgia

Table 4 Summary of clinical trials investigating the effects of creatine supplementation on body composition and physical function

Condition	Treatment arm	Supplementation period	Control arm	Body composition changes	Physical function changes	Other effects	Ref.
Osteoarthritis	n = 18	10 g/d pre surgery; 5 g/d for 30 d post-surgery	*vs* PL (n = 19) (dextrose)	[2]% BF, [2]FM, [3]LM (CSA), [3]BW	[3]Strength	[3]PCr	[106]
Fibromyalgia	n = 16	20 g/d for 5 d followed by 5 g/d for 16 wk	*vs* PL (n = 16) (dextrose)	Not measured	[1]Strength	[3]QoL scores, [3]Pain, [3]Cognition, [1]PCr	[109]
Cancer (cachexia)	n = 16 (colorectal cancer)	20 g/d for 5 d followed by 5 g/d for 8 wk	*vs* PL (n = 15) (cellulose)	[3]LM	[1]Strength	[3]QoL scores	[118]
	n = 9 (adolescents with leukaemia (acute lymphoblastic)	2 sets of 8 wk (with a 6 wk wash out in-between)	*vs* control "natural history group" (n = 50)	[3]LM, [2]%BF	No details	[3]Bone mineral content	[119]
Duchenne muscular dystrophy	n = 18 (adolescents)	5 g/d for 8 wk	*vs* PL (n = 15) (vitamin C)	No details	[1]Strength	[1]PCr	[113]
	n = 15 (adolescents)	5 g/d for 24 wk	*vs* PL (n = 16) (cocoa powder)	No details	[3]Strength, [3]Objective function tests		[116]
	n = 30 (adolescents)	0.10 g per kg/d for 16 wk	Cross-over design (PL group dextrose)	[1]LM	[1]Strength	[2]Bone breakdown markers	[112]
	n = 15 (adolescents) (12 with DMD and 3 with Becker dystrophy)	3 g/d for 13 wk	Cross-over design (PL group maltodextrin)	No details	[1]Strength (MVC), [1]Fatigue resistance		[62]
Mytonic muscular dystrophy 1 (DM1)	n = 34	5 g/d for 36 wk	Cross-over design (PL group dextrose)	[3]LM	[3]Strength, [3]Objective function tests		[115]
	n = 34	10.6 g/d for 10 d followed by 5.3 g/d for 45 d	Cross-over design (PL group cellulose)	[3]LM	[3]Strength	[3]ADL, [3]QoL scores	[114]
Mytonic muscular dystrophy 2 (DM2)	n = 10	10 g/d for 13 wk	*vs* PL (n = 10)	No details	[3]Strength	[3]QoL scores	[117]

[1]Significant increase/improvement; [2]Significant decrease/reduction; [3]No significant change ([a]$P < 0.05$ for interaction between placebo and Cr group). Cr: Creatine; PL: Placebo; CSA: Cross sectional area; ADL: Activities of daily living; PCr: Phosphocreatine; QoL: Quality of life; MVC: Maximal voluntary contraction; BM: Body mass; FM: Fat mass; LM: Lean mass; PRT: Progressive resistance training; No details: No details are specified or this measure was not made.

patients[109] found that muscle PCr content increased and muscle strength improved relative to the placebo group (leg-press by 9.8%, $P = 0.02$; chest-press by 1.2%, $P = 0.02$; and isometric hand-grip strength by 6.4%, $P = 0.07$) in the Cr group.

Myopathy is a muscle wasting disorder which primarily affects skeletal muscle. Much like rheumatoid cachexia seen in RA patients, this can cause a variety of complaints including progressive weakness and wasting of skeletal muscle, and fatigue (for a review see Kley *et al*[111]). Seven trials of Cr supplementation in populations with myopathies were found, with these investigations finding mixed results on the efficacy of oral Cr. In a cross-over design trial in 30 Duchenne muscular dystrophy (DMD) adolescents[112], the Cr supplementation phase increased lean mass by +0.7 kg and grip strength by approximately 20% compared to the placebo phase. In a similar design, Cr supplementation improved maximal strength and fatigue resistance in 15 other patients with DMD[62]. Further to these trials, improvements in muscle PCr/P ratio and preservation of calf muscle strength were also reported by Banerjee *et al*[113] in 18 DMD patients.

In contrast, in cross-over design trials of patients with Mytonic muscular dystrophy 1 (DM1), Cr failed to induce any changes in muscle strength, lean mass or disease symptoms[114,115], or improve function or strength in DMD patients[116] or patients with myotonic dystrophy type 2 (DM2)[117].

Two studies[118,119] were found that reported trials of Cr supplementation in cancer patients. Up to 80% of cancer patients have associated muscle wasting which is termed "cancer cachexia"[120]. Like other forms of cachexia, this is characterised by a preferential loss of skeletal muscle mass (with or without a loss of fat mass) which cannot be reversed through conventional methods of nutrition[121]. In patients with cancer, Cr supplementation improved handgrip strength by 5.5% ($P = 0.019$)[118] and reduced body fat accumulation (-3.5%; $P < 0.05$) relative to a placebo group[119].

Review conclusions

Around 70% of RA patients are middle-aged or elderly females[122], and the existing evidence indicates that Cr can be successful in countering the effects of sarcopenia

in older populations independent of exercise training[123], specifically in older females[124,125]. Of nine included trials that have supplemented the elderly with Cr, only three[100,102,103] found no beneficial effect on lean mass, strength, or physical function. However, the magnitude of effect appears to be reduced relative to that observed in young healthy individuals[126], and the limited number of studies indicates that further work is needed to fully evaluate the role of Cr supplementation[127].

Creatine has been shown to be effective in a range of clinical conditions[128] including muscle wasting disorders[62,112,113], and cancer cachexia[118]. Despite the inconclusive findings of the solitary RA study[94], of the twelve clinical trials identified, six showed positive effects of Cr on muscle mass and/or strength and function measures.

FACTORS AFFECTING CREATINE EFFECTIVENESS IN CERTAIN INDIVIDUALS OR POPULATIONS

Apart from inadequate supplement duration or dose, various other factors influence Cr effectiveness. It has been reported that 20%-30% of individuals do not respond to Cr supplementation; when "non-responsiveness" is defined as an increase in resting total muscle Cr of < 10 mmol · kg/dw following 5 d loading at 20 g per day[46,88]. Syrotuik *et al*[129] found that based on pre-existing biological and physiological factors, "responders" (defined in that study as ⩾ 20 mmol · kg/dw increase in intramuscular Cr) possessed a biological profile of (1) low initial levels of total Cr or PCr (approximately < 110 mmol · kg/dw); (2) higher percentage of type Ⅱ fibres (> 63.1%); and (3) a higher preload muscle fibre cross-sectional area (CSA) (approximately > 1500 μm^2). For individuals whose initial muscle Cr concentrations approach 150 mmol · kg/dw, Cr supplementation does not appear to augment muscle Cr uptake, increase PCr resynthesis, or improve performance[4,129,130]. Not surprisingly, optimal responses to Cr supplementation are generally observed in groups with reduced serum and muscle levels of Cr such as vegetarians and low meat eaters, which include many older individuals[58,125,130,131].

Although the majority of the studies reviewed found benefits of Cr supplementation in the elderly, it has been suggested that uptake of Cr into muscle is reduced in older adults (> 60 years) relative to younger subjects[99,132], and that subsequently older adults may require a longer Cr treatment period[56].

SAFETY OF CREATINE

Concerns about possible side effects of Cr supplementation have been raised in lay publications, mailing lists and online forums. However, none of the studies included in this review reported any adverse incidents during the trials ranging from 5 d to 36 wk. This is consistent with other studies of long term (10 mo to 5 years) (*e.g.*,[53,133,134]) or high dose Cr supplementation (10 g/d) (*e.g.*,[135,136]) that have reported no adverse side effects. According to Walliman[137], current evidence does "not hint towards any negative health effects of Cr". Therefore, the anecdotal reports remain unsubstantiated and may be unrelated to Cr supplementation[44].

Concerns about the long-term safety of Cr have specifically been related to kidney function. Theoretically, the high nitrogen content (approximately 32%) of Cr could place additional strain on the kidney if taken in large excess for a long period of time[133]. Glomerular filtration rate (GFR) is widely accepted as the best overall measure of kidney function, with serum and urine creatinine levels the most commonly used markers for estimating GFR[136]. However, since Cr is converted to creatinine[47], it is normal for individuals who take Cr supplements to have elevated creatinine levels[138], thus falsely suggesting renal function impairment. Use of alternative GFR markers such as Cystatin C has shown that Cr supplementation does not promote renal dysfunction[136].

There is currently limited research on the effects of Cr supplementation in patients with exiting low GFR. A prospective report[139] suggests that short-term (35 d) Cr supplementation (5 d of 20 g/d followed by 5 g/d) does not affect kidney function in individuals with a single kidney and mildly decreased GFR. However, more research is needed in this area. Similarly, no evidence has emerged that Cr supplementation results in impaired liver function or liver damage[41,44,140,141].

PRESCRIPTION OF CREATINE TO PATIENTS

Type

Creatine supplements are usually taken as a tablet or powder (mixed with water), and exist in a variety of forms including Cr ethyl ester, Cr hydrochloride and the most commonly available Cr monohydrate (Cr complexed with a molecule of water). No differences in effectiveness have been found between these different Cr forms[142].

"Loading" dosage

Cr should be "loaded" into the muscle (using a high dose) for the first few days followed by a lower maintenance dose[41]. The most common "loading" dosage recommendation for Cr supplementation is 20 g/d (in four 5 g doses) for 5 d, as stores appear to be maximised within 5 to 6 d at this dose[130]. Alternate loading phases exist including daily doses based on body mass such as 0.25 g/kg[41] or 0.15 g/kg[143]. However, a constant dose of 3 g/d, without an intensive loading phase, achieved an increase in total Cr levels equal to a standard 5 d loading protocol and subsequent maintenance phase after 28 d[144].

"Maintenance"and frequency

Total muscle Cr can be maintained for at least 4-6 wk after the initial loading phase by the ingestion of small daily Cr doses of 2-5 g[41,144]. This period of low dosage is called the "maintenance phase". Here, Cr is usually taken

in 8 to 12 wk cycles, with a 4 to 5 wk "washout" period in between to allow serum Cr to return to baseline levels.

CONCLUSION

RA is characterised by a loss of muscle which causes reduced strength and physical functioning. Current anti-rheumatic pharmaceutical treatments are unable to reverse the effects of cachexia, and although high intensity exercise is highly effective in rectifying body composition and restoring physical function, uptake of, and adherence to, exercise training by RA patients is poor. Thus, other treatment options need investigation. Oral Cr supplementation offers a potentially efficacious, cheap and widely acceptable therapy for achieving these outcomes in RA patients. Creatine works primarily by enhancing the re-synthesis of ATP *via* increased stores of PCr in the muscle, and thus improving recovery during and after physical activity. Creatine also augments muscle protein synthesis thereby increasing muscle mass.

This review found only one study in which RA patients were supplemented with Cr[94] and its findings, whilst promising, were inconclusive. However, trials in populations with similar presentation to RA (*i.e.*, reduced muscle mass and impaired physical function), including older females, indicate that Cr is an efficacious way to improve muscle mass, strength and physical function. Therefore, additional studies in RA populations are advocated, as confirmation of the efficacy of Cr supplementation would provide an easy, safe and effective means of reversing the effects of rheumatoid cachexia in the majority of the RA population.

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REVIEW

Gender differences in axial spondyloarthritis

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Abstract

Within the concept of axial spondyloarthritis (axSpA), relevant differences between men and women have been described for patients with the radiographic disease form [ankylosing spondylitis (AS)]. The subjective perception of disease activity (spinal and peripheral pain, fatigue, morning stiffness) has been shown to be higher in female than in male patients. Moreover, women experience more functional limitations and a lower quality of life, despite lower degrees of radiographic spinal damage. Peripheral clinical involvement (arthritis and enthesitis) is, additionally, more predominant in women. On the other hand, a higher level of objective signs of inflammation (C-reactive protein, erythrocyte sedimentation rate, magnetic resonance imaging of sacroiliac joints and spine) has been reported in men. Whether these differences might explain the better response to treatment with anti-tumor necrosis factor agents observed in male patients remains unclear. The underlying causes of the discrepancies are still unknown and genetic, environmental, cultural and/or societal factors may be involved. While AS is still more prevalent in men in a ratio of 2-3:1, the prevalence of males and females in patients with axSpA without radiographic sacroiliac damage is similar. Gender differences in this subgroup of patients have not been adequately addressed, and are particularly needed to further validate the Assessment of SpondyloArthritis international Society classification criteria.

Key words: Axial spondyloarthritis; Ankylosing spondylitis; Classification; Gender; Outcome

Core tip: In comparison to men, women with ankylosing spondylitis (AS) experience a higher subjective burden of disease despite lower objective signs of systemic inflammation and less spinal radiographic damage. A better response to treatment with tumor necrosis factor inhibitors has been demonstrated in male AS patients.

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INTRODUCTION

Ankylosing spondylitis (AS) is still considered the prototype disease of a group of inflammatory rheumatic conditions, referred to as spondyloarthritides (SpA), and characterized by inflammation of the sacroiliac joints (SIJ), the spine, as well as peripheral joints and enthesis[1,2]. It was traditionally associated with a long diagnostic delay[3], as the defining radiographic changes of the SIJ, described by the modified New York criteria[4], usually develop gradually over several years. It is now regarded as part of a disease continuum, referred to as axial SpA (axSpA), defined by the 2009 Assessment of SpondyloArthritis international Society (ASAS) classification criteria[5]. Within this concept, AS, also called radiographic axSpA, is opposed to nonradiographic (nr-) axSpA[6,7]. In the absence of definite radiographic SIJ damage, patients can be classified as having nr-axSpA either in the presence of sacroiliitis on magnetic resonance imaging (MRI) plus at least one SpA feature or in the presence of human Leukocyte Antigen (HLA)-B27 plus at least two SpA

features[5]. Relevant differences between men and women have been delineated for the AS subgroup and this review will particularly focus on new data published after the extensive 2008 survey by Lee *et al*[8]. Recent studies have also highlighted differences in sex distribution between AS and nr-axSpA[9-12]. Data on gender differences in the nr-axSpA subgroup are, however, only beginning to emerge[13].

GENDER DIFFERENCES IN ANKYLOSING SPONDYLITIS

Distribution

AS was believed to affect predominantly men, with a ratio of 10 males for every female patient[14]. It remained a relevant example of sex biased research for many decades as it was often carried out in military or veteran's hospitals. Underestimation of disease prevalence in the female population might have additionally been due to differences in disease phenotype, reluctance to perform X-rays of the pelvis and lumbar spine in women of child-bearing age, gender differences in the act of seeking a doctor's advice or a faster investigative approach in men with back pain and stiffness in physically demanding jobs. Studies conducted in the last decade reported a much smaller sex distribution difference, still favoring males, in the order of 2-3:1, also reflecting progress in imaging technologies and changing gender roles[9,11,15]. A recent systematic analysis of 13 cross-sectional population studies revealed a mean gender ratio of 3.4:1 and some differences between geographic regions (3.8:1 in Europe and 2.3:1 in Asia)[16].

Pathogenesis

The strong genetic association of AS with HLA-B27, discovered by Brewerton and Schlosstein in 1973[17,18], was subsequently shown to presumably not be implicated in the unequal sex distribution, as the prevalence of HLA-B27 was similar in women and men[19]. These findings should be confirmed in larger population studies, as the proportion of HLA-B27 positivity was significantly lower in women than in men in recent treatment studies[20,21] and in the Swiss Clinical Quality Management (SCQM) axSpA cohort[22]. While only a quarter of the genetic susceptibility to AS is currently explained by HLA-B27, sex differences have not been addressed in other discovered major histocompatibility complex (MHC)- or non-MHC genetic associations involved in the innate immune stimulation, the interleukin-23 pathway or peptide presentation[23]. Potential sex differences have been described for the *ANKH* gene, coding for a protein regulating the cellular export of inorganic pyrophosphate[24]. The association of *ANKH* with disease susceptibility remains, however, controversial[25,26]. By contrast, no evidence for an involvement of the X-chromosome in the development of AS could be detected[27].

Genetic factors may also have an indirect impact on disease susceptibility by interacting with environmental factors influenced by gender. HLA-B27 is particularly interesting in this regard, as it might interact with bacterial antigens[28]. The triggering role of Chlamydia trachomatis is clearly established for the development of reactive arthritis after urogenital infection with this bacterium and the disease has an important male predominance (up to 20:1)[29]. A significant proportion of HLA-B27-positive patients with Chlamydia-induced SpA will eventually develop AS and Chlamydia trachomatis has also been detected by polymerase chain reaction in synovial tissues from patients with other SpA forms[30].

Smoking represents another environmental and societal factor potentially influencing gender differences in rad-axSpA. Although studies linking smoking with incident AS are lacking, smoking was demonstrated to be associated with increased disease activity, impaired function and poorer quality of life in cross-sectional analyses[31-38]. Furthermore, it was associated with future radiographic spinal progression in longitudinal studies[39,40], probably through an amplifying effect of disease activity on radiographic damage[41]. While the prevalence of smoking is higher in men than in women with AS[38,42], a causal effect between smoking and gender differences in disease outcome, as depicted below, remains to be established.

No differences in gonadal and adrenal sex hormones have been identified in male and female patients with AS in comparison to healthy controls[42]. A recent analysis of 448 women using the oral contraceptive pill in comparison to 123 female non-users failed to demonstrate any effect of the use of exogenous estrogens on the initiation or on the severity of AS[43].

Disease onset and diagnostic delay

The age at symptom onset was similar in women and men with AS in most of the studies available to date, while a longer duration from disease onset to diagnosis has been detected in women[3,44]. However, HLA-B27 has been shown to have a strong effect not only on the age at symptom onset[9,21], but also on diagnostic delay[15], and was not available in all patients. Additional investigations are therefore needed. We found an earlier disease onset in male patients in a large cohort of 1199 patients with AS (mean age at onset 26.3 years in men *vs* 29.3 years in women, $P < 0.001$)[22]. The documented differences in HLA-B27 prevalence in men and women in this study (see above) may not fully account for the gender difference in disease onset, as women were on average 1.8 years older than men at the beginning of back pain in the subgroup of HLA-B27-positive patients[22].

Signs and symptoms

A multitude of comparisons of male and female patients with AS have provided data on women having more pain at the level of the cervical spine and in peripheral joints, with the hip joints being more often involved in men[45-56]. The intensity of symptoms (spinal pain, peripheral joint pain and swelling, areas of localized tenderness, fatigue, morning stiffness) was substantiated with the patient-reported Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[57] in the more recent literature. Women

presented with higher BASDAI, global pain, nocturnal pain, joint pain and fatigue scores in comparison to men[58-66]. As these common symptoms overlap with the clinical features of fibromyalgia, which is more prevalent in women with AS than in men[67-69], additional objective parameters to assess disease activity seem advisable. Whether the use of the recently defined Ankylosing Spondylitis Disease Activity Score (ASDAS) will prove helpful in this regard, as its calculation includes acute phase reactants [erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)] in addition to patient-reported parameters[70], remains to be established.

Clinical findings

The report of women being more often treated with methotrexate, sulfasalazine and prednisone in an North American cohort suggested a higher prevalence of peripheral arthritis in women with AS[56]. When analyzing the presence of current or previous peripheral synovitis, these gender differences with regard to the presence of peripheral arthritis in AS have been substantiated[62,71]. In the Swiss SCQM axSpA Cohort (826 men and 373 women with AS), a significantly higher percentage of women had peripheral synovitis as well as a higher number of swollen joints at inclusion, while no differences have been observed with regard to the percentage of men and women with previous peripheral arthritis (unpublished results). The discrepancies might be explained by longer disease duration in men in this cohort, allowing for more clinical manifestations to accumulate. As demonstrated in another registry, the presence of peripheral arthritis seems to delay spinal radiographic progression (see below), independently of other confounding factors, including gender[72].

Peripheral enthesitis evaluated by the Maastricht Ankylosing Spondylitis Enthesitis Score was also more frequently found in women in comparison to men with AS[62,73]. The finding might be confounded by a potential overlap between enthesitic and fibromyalgia tender points.

Spinal mobility, as assessed by different clinical parameters, such as the tragus-to-wall distance, the Schober' s test or the Bath Ankylosing Spondylitis Metrology Index in more recent studies, was consistently more greatly impaired in women in comparison to men. Spinal mobility cannot be used as a proxy for radiographic damage in an individual patient[74], as both inflammation and structural damage have been shown to contribute to its impairment[75].

With regard to extra-articular manifestations - acute anterior uveitis, psoriasis and inflammatory bowel disease-only bowel inflammation was positively associated with the percentage of women in the evaluated AS studies of a systematic review and meta-analysis of 156 selected articles[76].

Imaging studies

Radiographic differences between genders in AS have been analyzed in numerous studies[34,45,46,48,49,51-56,62,77]. After adjustment for age and disease duration and using either the Bath Ankylosing Spondylitis Radiography Index or the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) in the more recent literature, men consistently presented with more important spinal changes on X-rays in comparison to women. This was confirmed in a recent 12-year prospective follow-up analysis, especially in the presence of HLA-B27 positivity[78].

Male sex was also associated with MRI inflammation of the SIJ in several studies of patients with axSpA, including patients with AS, while HLA-B27 was an independent predictor of future MRI positivity[21,79,80].

Laboratory findings

While ESR and CRP levels have been demonstrated to be higher in women in comparison to men in the general population[81-83], acute phase reactants were either similar, or slightly more elevated in male patients with AS in comparison to females, suggesting a higher level of systemic inflammation in men[20,59-61,84,85]. Elevated CRP was shown to be associated with radiographic progression in AS[39]. As smoking is associated with pro-inflammatory effects and may raise CRP levels in a non-specific manner[86], it remains unclear, whether higher acute phase reactant levels in AS might be explained in part by the higher prevalence of smokers in the male AS population.

Disease activity and radiographic progression

Higher disease activity, as measured by the ASDAS, which includes both patient-reported outcomes and acute-phase reactants, led to more spinal structural damage, especially syndesmophyte formation, in a recent 12-year longitudinal study[78]. The authors highlighted the fact that the ASDAS outperformed all other disease activity measures (BASDAI and CRP, patient-reported global activity and CRP, back pain and CRP) in this analysis. A significant interaction was found between ASDAS and gender: the effect of ASDAS on the change in mSASSS was higher in males versus females (0.98 *vs* -0.06 units per 2 years and per additional unit of ASDAS). Whether an association exists between important mechanical forces acting on the spine (observed in male-dominated more intensive occupational activities) and formation of syndesmophytes, should be confirmed in future studies.

Functional outcomes

Self-reported functional ability in performing daily activities is usually assessed with the Bath Ankylosing Spondylitis Functional Index. A similar level of functional impairment has been demonstrated in women and men with AS[20,56,61,64]. After adjustment for the level of radiographic spinal damage, however, the disability observed was more pronounced in female in comparison to male patients[56]. The documented higher level of peripheral symptoms (arthritis and enthesitis) in women might be regarded as a confounder in this analysis[87].

Quality of life

Health-related quality of life encompasses the individual

well-being considering social, emotional and physical aspects, as well as the effect of disease on a patient's well-being, mainly measured by the Short-Form Health Survey (SF-36) and the Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL). It is significantly impaired in AS[88]. In unadjusted analyses, women reported a significantly worse quality of life and a greater reduction in vitality than men[88-90]. However, after adjustment for the normal differences in men and women's self-assessment of their health in the general population, the crude effect of AS on the quality of life was greater in men[88].

Work disability

Analyses of gender differences with regard to work disability in AS led to conflicting results due to differences in economic environment, social security system, disability compensation system in different countries as well as comorbidities, disease duration and proportions of patients with manual jobs in the respective studies[91-100]. The contributing factors to absenteeism (impossibility to attend work, either due to temporary sick leave or permanent worker disability) and presenteeism (reduced performance or productivity at work due to health reasons) in AS patients have been analyzed recently[101]. Female sex, an impaired health-related quality of life and helplessness (a personal factor) were associated with presenteeism, while at-work limitations and lower quality of life contributed to sick leave.

Family life

In a US analysis, patients with AS were more likely to have never been married and men were more likely to divorce, especially in longstanding disease[102]. In the same study, women with AS were less likely to have children than women in the general population, in contrast to men. The authors postulate that women might be more sensitive to the concern about having children with AS. The quality of marital life was shown to be characterized by a higher global distress and a higher probability of aggression from their partner in female SpA patients from Korea[103]. Furthermore, in comparison to healthy individuals in Europe, a higher proportion of women with SpA was shown to be single or divorced[104]. Disease activity was, moreover, higher in divorced than married female SpA patients. With regard to inheritance, a higher prevalence of AS among children and siblings of female index cases has been demonstrated, suggesting that women may require a higher genetic load to develop the disease[44, 105]. The higher prevalence of a family history of SpA found in female patients with axSpA[13,56,62,64], would be compatible with this hypothesis.

Response to treatment

Tumor necrosis factor (TNF) inhibitor treatment is recommended in patients with highly active AS and insufficient response to non-steroidal anti-inflammatory drugs[106]. Elevated acute phase reactants have been shown to represent the most important predictor of treatment response[84,107-113]. Gender differences in response to TNF inhibition or treatment survival have also been identified in most studies, which were, however, not adjusted for all known confounding factors. In the Groningen Leeuwarden AS observational cohort, male gender was a predictor of treatment response, while female gender predicted treatment discontinuation independently of other parameters[111]. Female gender was also a predictor of anti-TNF-agent discontinuation in the South Swedish Arthritis Treatment Group Register and in the Danish nationwide DANBIO register[84,113]. In a study of pooled data from four clinical control trials of etanercept, sulfasalazine or placebo in AS, female patients had less improvement in ASDAS than male patients[20]. In contrast, female gender was an independent predictor of improvement in BASDAI and the Bath Ankylosing Spondylitis Functional Index in the British Society of Rheumatology Biologics Register[110], while gender did not influence treatment responses in other studies[107,112,113].

Mortality

An increased mortality was found in men but not women with AS (standard mortality rate 1.63 *vs* 1.38, $P < 0.001$) in a cohort of 677 patients followed since 1977, with circulatory disease being the most frequent cause of death[114]. A trend towards increased mortality in women was only found after longer disease duration (35-40 years). The authors postulate that a larger study population with a longer time span of observation might be necessary to demonstrate excess mortality in women with AS. The finding that the increased mortality in AS was related to the degree of disease activity, however, points to a really existing gender difference in this regard.

GENDER DIFFERENCES IN NONRADIOGRAPHIC AXIAL SPONDYLOARTHRITIS

The most striking differences between patients with axSpA fulfilling or not fulfilling the modified New York classification criteria (AS *vs* nr-axSpA) are the unequal gender distribution (1:1 in nr-axSpA and favoring men in a ratio of 2-3:1 in AS) and the higher level of CRP in AS compared to nr-axSpA[9-12]. Women as well as patients with low systemic inflammation might have a lower risk to develop radiographic spinal damage and remain longer in the nonradiographic disease stage. The risk of misdiagnosis in patients with other reasons for back pain in context of HLA-B27 positivity[115] would represent an alternative, mutually not exclusive explanation for the higher prevalence of women in the nr-axSpA group. Comparisons between women and men with nr-axSpA, as well as between women with AS and women with nr-axSpA, along with prospective longitudinal data are therefore needed. Tournadre *et al*[13] have analyzed the differences between female and male patients in the French cohort Devenir des Spondylarthropathies Indifférenciées Récentes of patients classified as having axSpA. Data are also presented in the subgroup of patients classified by the imaging and

the clinical arms of the ASAS classification, respectively. Only patients in the clinical arm are available for analysis of gender differences in nr-axSpA in this study, as both patients with AS and patients with nr-axSpA are present in the imaging arm by definition. Higher self-reported disease activity parameters and functional impairment were found in women. Multivariate regression models confirmed the relationship between higher levels of BASDAI, ASDAS-CRP, fatigue and ASQoL and female gender[13].

CONCLUSION

Female AS patients experience higher levels of pain and other self-reported disease activity parameters, a greater impairment of health-related quality of life and a reduced treatment response upon TNF inhibition. On the other hand, male AS patients present with higher objective measures of disease activity (acute phase reactants, inflammation of SIJ on MRI) and a more important radiographic spinal damage. The causes underlying these relevant differences remain largely unknown.

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REVIEW

Muscle wasting in rheumatoid arthritis: The role of oxidative stress

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Abstract

Rheumatoid arthritis (RA), the commonest inflammatory arthritis, is a debilitating disease leading to functional and social disability. In addition to the joints, RA affects several other tissues of the body including the muscle. RA patients have significantly less muscle mass compared to the general population. Several theories have been proposed to explain this. High grade inflammation, a central component in the pathophysiology of the disease, has long been proposed as the key driver of muscle wasting. More recent findings however, indicate that inflammation on its own cannot fully explain the high prevalence of muscle wasting in RA. Thus, the contribution of other potential confounders, such as nutrition and physical activity, has also been studied. Results indicate that they play a significant role in muscle wasting in RA, but again neither of these factors seems to be able to fully explain the condition. Oxidative stress is one of the major mechanisms thought to contribute to the development and progression of RA but its potential contribution to muscle wasting in these patients has received limited attention. Oxidative stress has been shown to promote muscle wasting in healthy populations and people with several chronic conditions. Moreover, all of the aforementioned potential contributors to muscle wasting in RA (*i.e.*, inflammation, nutrition, and physical activity) may promote pro- or anti-oxidative mechanisms. This review aims to highlight the importance of oxidative stress as a driving mechanism for muscle wasting in RA and discusses potential interventions that may promote muscle regeneration *via* reduction in oxidative stress.

Key words: Rheumatoid arthritis; Oxidative stress; Muscle wasting; Inflammation; Cytokines; Exercise

Core tip: Muscle wasting is common in rheumatoid arthritis (RA) and associates with significant health burden. To date several theories have been proposed to explain why RA patients loose muscle mass but the exact underlying mechanisms are not clear. Oxidative stress is a key driver of muscle wasting in the general population; however, its potential role in muscle wasting in RA has not been studied. As it arises from this review, oxidative stress seems to contribute to muscle wasting in RA. Further research on the subject is warranted, especially focusing on the underlying mechanisms and potential interventions.

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INTRODUCTION

Rheumatoid arthritis (RA) is the most common inflammatory arthritis, with a prevalence of approximately 1% in Europe and North America[1]. It is an autoimmune disease affecting mainly synovial joints[2] and associates with high-grade inflammation characterised by high levels of circulating pro-inflammatory cytokines, including tumour necrosis factor alpha (TNF-α), and the interleukins (IL) 1 and 6. These cytokines are produced in the inflamed synovium and are implicated in joint swelling, pain, and eventually destruction[3]. As the condition progresses, patients very frequently lose their jobs[4], functional ability (movement)[1] and eventually their independence[5]. Apart from this physical and psychological personal burden, RA has significant costs for the health and social care system[6]. Thus, the efforts of the scientific community have focused on the identification and elimination of the potential causes of RA as well as effective treatments. Despite significant therapeutic progress in recent years a cure remains elusive[1].

Apart from the joints, RA affects several other tissues of the body leading to systemic involvement and significant extra-articular manifestations[7]. It is these extra-articular manifestations, and not RA itself, that significantly shorten the life of RA patients and add extra layers of morbidity. Cardiac and vascular conditions are especially common among these patients. Heart disease in RA is both more prevalent and more likely to lead to death than in the general population[8]. The exact cause for this remains unknown, however genetic predisposition[9-12], classical cardiovascular disease risk factors[13,14] and the effects of systemic inflammation on the vasculature[15,16] are all thought to contribute. Other extra-articular manifestations are observed in the skin, eyes, lungs, renal, nervous and gastrointestinal systems[17].

The reasons for the development of such manifestations are not fully understood. It is believed that the endocrine functions of the pro-inflammatory cytokines (mainly TNF-α, IL-1 and IL-6) initiate a cascade of destructive processes in distant tissues, with reactive oxygen species playing a central role in cell membrane destruction and cellular death[18].

OXIDATIVE STRESS IN RA

Free radicals and inflammation

Free radicals, such as reactive oxygen species (ROS), have been proposed to play a significant role both in the development and progression of inflammation, as well as its deleterious effects on cell structure and function at the site of the inflammation and in distant tissues[19,20]. Free radicals, formed as by-products of normal biological processes - such as cellular metabolism in the mitochondrial electron transport chain and reperfusion injury - are highly reactive agents that can cause physiological damage[21]. Free radicals can damage all cellular components such as lipids, proteins and DNA. In the general population, they are counterbalanced by effective antioxidant defence mechanisms. However, in inflammatory conditions these defence mechanisms seem to be weakened[22]. It is not clear which is the sequence of events but it seems likely that inflammation reduces the anti-oxidant response, thereby increasing the accumulation of free radicals[19]. These further activate pro-inflammatory nuclear pathways (specifically Activator Protein one - AP-1 and nuclear factor kappa β - NFκB) that transcribe cytokines and adhesion molecules involved in the modulation of inflammation[23] resulting in further production of free radicals. Nitric oxide (NO) has a role in the regulation of vascular tone, superoxide free radical ($O_2^{\cdot-}$) in fibroblast proliferation and hydrogen peroxide (H_2O_2) in the activation of pro-inflammatory transcription factors. Other control mechanisms which may be perturbed in inflammation include: the oxidative modification of low density lipoprotein, the oxidative inactivation of alpha-1-protease inhibitor, DNA damage, lipid peroxidation and heat shock protein formed with the activation of neutrophil, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and endothelial cell xanthine dehydrogenase, which associate with oxidative stress and contribute significantly to the inflammatory process[19,22,23].

Oxidative stress and RA activity

Oxidative stress is frequently reported in patients with RA. Cells present in inflamed joints (*e.g.*, macrophages, neutrophils and lymphocytes), have the ability to produce free radicals[24,25]. These liberate superoxide radical, hydrogen peroxide, elastase, hypochlorus acid and eicosanoids[26]. Another source of free radicals in RA is hypoxic reperfusion injury from elevated synovial cavity pressure during joint movement. A fivefold increase in mitochondrial ROS production in whole blood and monocytes of patients with RA compared with healthy subjects suggests that oxidative stress is a significant factor in RA[26].

Free radicals are implicated in joint damage both indirectly (*via* increasing inflammation as described above) and directly. They can degrade joint cartilage, by attacking proteoglycans (integral components of structural tissues) and inhibiting proteoglycan synthesis[27]. Indeed in patients with RA, serum and synovial fluid contain end products of lipid peroxidation which correlate with disease severity and activity[28]. In parallel, anti-oxidant capacity in patients with RA seems to be significantly reduced[29]. This low antioxidant status has been associated with low levels of tocopherols, beta-carotene and retinols and low activities of glutathione reductase and superoxide dismutase[26]. RA has also been linked to low levels of reduced glutathione- an intracellular antioxidant- in synovial fluid T cells[30]. Reduced glutathione, is among the most prominent defences against reactive oxygen species. It is a substrate for glutathione peroxidases, several trans-

ferases and several other enzymes and acts as a general radical quencher in cells by removing superoxide anions and hydrogen peroxide[26]. Serum concentrations of anti-oxidative vitamins A, C and E are also significantly reduced in RA[19,23,31].

MUSCLE WASTING IN RA

A significant but little studied extra-articular manifestation of RA is rheumatoid cachexia (RC). RC is characterised by a high rate of muscle mass and strength loss, typically with preservation or slight increase in fat mass[32]. RC differs from other forms of cachexia such as those observed in cancer, chronic heart failure, kidney disease or chronic infection as it is rarely accompanied by a net weight loss[33]. RC also differs from sarcopenia (age-related reduction in muscle mass observed in the elderly) as it occurs at a younger age and muscle mass loss progresses at a substantially higher rate[34]. The prevalence of RA in the United Kingdom is 0.8%[5]. The exact prevalence of RC is not known today as there is no consensus on its definition and assessment. However, at least 10%-20% of patients with controlled RA[35,36] and > 40% of patients with active RA[37] suffer from muscle wasting. This makes it one of the most common complications of RA.

RC has been shown to associate with poorer disease outcomes including reduced quality of life, more fatigue and increased overall morbidity and mortality[34,38,39], although the independent nature and directionality of many of these associations remain uncertain and require further study. Low muscle mass also associates with dysmetabolic states such as insulin resistance and type II diabetes[40,41] and thus may be partly responsible for the increased cardiovascular risk observed in RA[33,35,42]. Inflammation associated with the disease is consistently identified as the potential cause of these manifestations. Indeed, inflammatory cytokines produced at the site of the disease (*i.e.*, the joints) have endocrine functions and act on distant tissues such as the muscle[43].

Mechanisms of muscle wasting in RA

Inflammation: High plasma concentrations of the inflammatory cytokines implicated in RA pathophysiology (TNF-α, IL-1 and IL-6) are thought to trigger muscle wasting[34,44]. TNF-α-induced activation of the classical NFκB pathway is now generally accepted to lead to inhibition of skeletal muscle differentiation and regeneration in a variety of muscle diseases, although this has not been confirmed yet as a mechanism of muscle wasting in RA patients. IL-1 among other cytokines has been shown to prevent the anabolic effect of insulin growth factor 1 (IGF-1) on myoblast differentiation, muscle protein synthesis, and myogenin expression[44,45], while intravenous infusion of IL-6 in healthy volunteers led to net muscle protein degradation in healthy individuals[46]. In RA patients, short term (3-6 mo) anti-TNF-α medication led to significant reduction of disease activity but did not improve body composition and had no effect of muscle mass[47,48] suggesting that cytokines might not be the most significant contributors to muscle wasting in RA.

Physical inactivity: Physical inactivity is the strongest predictor of fat mass in RA[49], while resistance exercise interventions may result in increased muscle mass and strength and partial reversal of muscle wasting in patients with RA[50,51]. Therefore muscle wasting in RA seems to be a consequence of a negative spiral between the metabolic and functional consequences of inflammation which enhance muscle catabolism and the premature adoption of an increasingly sedentary lifestyle in which the anabolic stimulus of regular exercise is missing[49] with consequent increase in fat mass. In line with this hypothesis is the observation that obesity is a common feature of RA and adds to the high risk for the metabolic syndrome and cardiovascular disease[34,52,53].

Adiposity: It is reasonable to assume that there are parallels between the mechanisms that lead to sarcopenia in healthy sedentary elderly individuals and the mechanisms that lead to muscle mass loss in RA patients. It is also reasonable to assume that there are parallels between the impact of obesity on the rate of sarcopenia and the potential role that obesity plays in the mechanisms that lead to muscle wasting in RA. An inherent consequence of the adoption of a sedentary life-style, without a reduction in energy intake, is a gradual increase of the subcutaneous and visceral adipose tissue mass[54]. Adipose tissue (especially visceral) is a well-known source of inflammation. In addition to adipocytes, pre-adipocytes and fibroblasts, up to 50% of the cell mass in adipose tissue of obese individuals are inflammatory cells such as monocytes and macrophages[55,56]. Adipocytes and macrophages both are a source of inflammatory cytokines[55,56]. In addition, the large adipose tissue stores in obese individuals are a constant source of lipolysis and lead to high circulatory concentrations of fatty acids and triglycerides. High plasma concentrations of inflammatory cytokines, FA and triglycerides contribute to the insulin resistance of skeletal muscle and its microvasculature[54-56] *via* mechanisms outlined below.

Insulin resistance: The most striking change in skeletal muscle through a sedentary lifestyle is a reduction of the mitochondrial density[54] and, therefore, of oxidative capacity of blood-borne fatty acids (NEFA's). Sedentary muscles also have a reduced capacity to oxidize the lipid droplets that are stored in the muscle in the vicinity of the mitochondria[54,57,58]. This, combined with an increased supply of plasma fatty acids and triglycerides, leads to the accumulation of fatty acid metabolites (long-chain fatty acyl-coenzyme A, diacylglycerols and ceramides). Both these fatty acid metabolites and the exposure of the muscle to inflammatory cytokines activate serine kinases that lead to serine phosphorylation of insulin receptor substrate 1 (IRS-1) and prevent downstream activation of the insulin signalling cascade and, therefore, impair

glucose transporter type 4 translocation and glucose uptake[58]. Insulin resistance (IR) also leads to an imbalance between protein synthesis and degradation[59] and is a major cause of the muscle mass loss in sedentary obese elderly individuals.

Endothelial dysfunction: The overload of the muscle with fatty acids, triglycerides and inflammatory cytokines also leads to major impairments in its associated vasculature. The endothelial cells that cover the luminal wall of feeding arteries, resistance arteries, and terminal arterioles (which control blood supply to the capillaries) normally dilate if they are exposed to meal-induced increases in insulin concentration[54,60]. Insulin in endothelial cells activates the enzyme eNOS [endothelial nitric oxide (NO) synthase] and the resultant NO leads to dilation of the smooth muscle layer in arteries and arterioles. This mechanism ensures that in the period after meal ingestion maximal amounts of glucose, amino acids and insulin are channelled to the muscle to maximize glucose uptake, increase protein synthesis and reduce protein degradation[54,60]. Vascular overload with lipids and inflammatory cytokines also leads to endothelial IR and reduces the supply of blood and nutrients to muscles of obese individuals[54,60].

POTENTIAL ROLE OF OXIDATIVE STRESS IN MUSCLE WASTING IN RA

To our knowledge, there is no study today investigating the associations of oxidative stress with muscle wasting in RA. However, there are numerous reports in the general population and several other conditions showing that oxidative stress may be a very important underlying mechanism that drives muscle wasting.

Endothelial function and oxidative stress

Experiments in obese Zucker rats and incubated endothelial cells have shown that high concentrations of long-chain fatty acylCoA and diacylglycerol activate protein kinase C (PKC)-β in aortic endothelium[61] and prevent insulin-induced activation of IRS-1, Akt, eNOS phosphorylation and increases in NO production. A high lipid and cytokine load (*via* PKC-activation) also leads to induction of NADPH oxidase in the vasculature of patients with the metabolic syndrome, hypertension or cardiovascular disease[54]. High NADPH oxidase activity will lead to excess production of superoxide anions (O_2-) which will scavenge NO thereby reducing basal and insulin-induced NO-production. Superoxide anions react with NO resulting in the formation of peroxynitrite and reducing the amount of NO available for vasodilation[62].

Muscle disuse and oxidative stress

Physical inactivity, in a population with constantly high grade inflammation, such as those with RA, may lead to significant intramuscular accumulation of ROS, as is the case for muscle disuse (*e.g.*, due to limb immobilization or bed rest) in the general population[63]. Muscle atrophy from disuse is mainly attributed to oxidative stress, *i.e.*, reduces anti-oxidant capacity and increased ROS production[64,65]. Mitochondria are the site for excessive ROS production[65,66]; and ROS production, such as H_2O_2, is increased by up to 100% following 14 d of limb immobilization[67]. Moreover, xanthine oxidase and NADPH oxidase contribute but to a lesser degree to ROS production in muscle disuse[68,69]. Similarly, lipid peroxidation has been shown to associate with muscle atrophy[70].

These affect the balance between protein synthesis and degradation[71,72]. Specifically, disturbed redox balance due to intramuscular ROS accumulation, such as that of H_2O_2[73,74], may activate transcriptional factors that increase expression of apoptotic pathways, such as the NF-κβ pathway and Foxo leading to severe protein degradation[68,75]. Moreover, oxidative stress may activate calpain and caspase-3, further increasing proteolytic processes[68,76]. Oxidation of muscle proteins themselves makes them susceptible to proteolytic damage[77].

ROS accumulation may also inhibit signalling pathways controlling protein synthesis[78,79]. It seems that ROS inhibit mRNA translation at an early stage; this reduces the ability of senescent satellite cells to become active and infiltrate the muscle cell[79,80]. However, these studies where performed in cell cultures, and it is not clear if these processes also occur *in vivo*.

Aging and oxidative stress

Muscle wasting is commonly observed in the elderly, affecting their quality of life and independence[81]. Oxidative stress has long been associated with aging related processes[82]. The elderly exhibit increased concentrations of oxidative by-products compared to younger individuals[83,84]. In normal aging, ROS participate in a number of processes aiding the transmission of signals within the muscle and affect gene expression[85,86]. As is the case with disuse atrophy, in aging mitochondria are also the main site for ROS production. Aging mitochondria seem to produce larger amounts of ROS, and especially H_2O_2, compared to younger ones[87]. The wasting effect of H_2O_2 seems to be mediated by the presence of the Copper and Zinc containing superoxide dismutase (Cu,ZnSOD)[88,89]. Cu,ZnSOD has been shown to decrease with aging[90]. In animal studies, SOD1 (gene encoding Cu,ZnSOD) knockout mice exhibited a form of rapid muscle wasting with similar characteristics to that of aging, including oxidative stress and weakness[91].

PREVENTION OF OXIDATIVE STRESS IN RA

Nutritional interventions

The vast majority of studies in this field have focused on the use of exogenous anti-oxidative agents, such as the administration of vitamins (A, C, E) and omega-3 fatty acids. Vitamin E seems to uncouple joint inflammation and joint destruction in the transgenic KRN/NOD

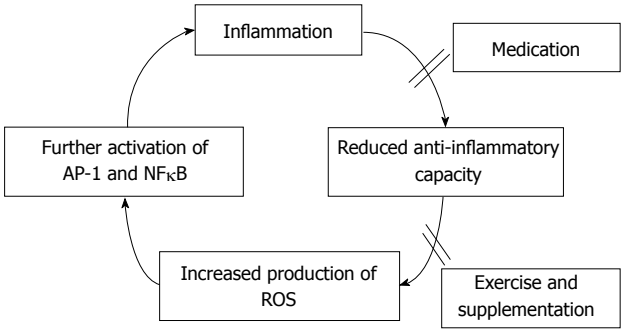

Figure 1 Hypothesis: Inflammation reduces anti-oxidant capacity which increases reactive oxygen species concentration, further activating pro-inflammatory pathways, entering the body into a vicious circle. Control of inflammation *via* medication might increase anti-inflammatory capacity of the body while exercise and supplementation may lead to increased anti-oxidant capacity both resulting in reduced oxidative stress and preserve muscle mass. ROS: Reactive oxygen species. AP: Activator protein; NFκB: Nuclear factor kappa β.

mouse model of RA, with a beneficial effect on joint destruction[92]. Some studies have even attributed therapeutic value to antioxidant supplementation as they reported better control[93] and improvement of RA-related symptoms[94]. Dietary interventions have been suggested to improve plasma levels of vitamin C, retinol and uric acid, which inversely correlate with variables related to disease activity[95]. Moreover, proper dietary antioxidant nutrient intake may reduce generation of free radicals and improve antioxidant status in RA patients[96]. Finally, intake of certain antioxidant micronutrients particularly beta-cryptoxanthine, supplemental zinc, and possibly diet in fruits and cruciferous vegetables have been suggested to protect against the development of RA[97].

Increasing anti-oxidant capacity in RA is a very attractive and potentially effective intervention. In current clinical practice, vitamin and micronutrient supplementation is frequently prescribed. However, we now know, that polypharmacy (prescription of a large number of medications) is one of the most significant reasons why patients forget to take their pills[98]. However, the most important question concerning use of antioxidants, is that of suicidal oxidative stress[19]. In certain conditions, such as presence of transition metals, antioxidants can act as pro-oxidants[99]. Similarly, high concentrations of anti-oxidants can cause the cell to undergo severe oxidative stress ultimately resulting in suicidal cell death[100].

Medication

In very recent years, the anti-oxidant potential of anTiTNF therapy has also been investigated. Infliximab plays an essential role as an anti-oxidative agent against advanced glycation end-product formation, oxidative DNA damage and lipid peroxidation[101], whereas etanercept acts as a regulator against pentosidine formation, oxidative DNA damage, and lipid peroxidation in RA patients[102].

Exercise and oxidative stress

In the general population, exercise has been shown to increase anti-oxidant capacity. Working *via* the physiological concept of hormesis (an ancient practice where the induction of a sub-lethal dose of toxin was used to increase tolerance of the organism to withstand higher doses of toxins) acute exercise increases free radical production[103], in a dose-response fashion (*i.e.*, increasing intensity, increases free radical production). This exercised-induced increase in free radicals is due to the increased electron leak from the mitochondria as well as the alterations in blood flow and oxygen supply that occur in response to exercise[104,105].

However, it has been consistently observed that trained individuals have high levels of antioxidant enzymes and certain nonenzymatic antioxidants in muscle[106] and demonstrate greater resistance to exercise-induced or -imposed oxidative stress[107,108]. Most likely, these adaptations result from cumulative effects of repeated exercise bouts on the gene expression of anti-oxidant enzymes. However, the attenuation of oxidative stress by exercise is reduced in the aging muscle, warranting concomitant nutritional supplementation with anti-oxidants to elicit the greatest potential benefits[109].

EXERCISE IN RHEUMATOID ARTHRITIS

Exercise is a useful tool, with constantly increasing clinical relevance to several conditions. In recent years, a large number of studies have investigated the safety of different exercise modalities in RA. Despite the common misconception that it may increase joint pain and damage, all of the studies indicate that properly designed exercise interventions are safe and beneficial for RA patients[110]. de Jong *et al*[111-113] have investigated the safety of intensive aerobic exercise (in the form of cycling) in > 200 RA patients; they concluded that all patients were able to achieve the pre-determined intensity targets. However, they pointed out that patients with severe joint damage may need attention[114]. Along similar lines, resistance training improved body composition and muscle mass without any adverse effects on disease activity[50]. Finally, we have recently completed a randomised trial looking at the effects of intensive aerobic exercise on cardiovascular risk factors in RA patients[115]. From these and other studies[116-120], it is clear that exercise is a safe intervention for RA patients and its use in the clinical setting is gaining significant support. Moreover, it is evident that exercise is able to reverse muscle wasting and increase muscle mass in RA patients. Indeed, the regenerative capacity of the RA muscle seems to be unaffected as the number of satellite cells (muscular stem cells that are utilised for muscular regeneration) present in it are preserved[121] but the stimulus for their activation (*i.e.*, exercise) is absent.

CONCLUSION

The role of oxidative stress in muscle wasting has been clearly demonstrated in several studies. However, to date there is no study looking at this in RA patients. We suggest that there is significant scope for such research in RA as the potential mechanisms by which oxidative stress

drives muscle wasting have been already described in other populations. Identification of specific mechanisms induced by RA-associated inflammation could significantly aid towards improvement of pharmacological and non-pharmacological interventions aiming to counteract oxidative stress in RA. In addition to effective control of inflammation *via* medication, exercise and nutrition may prove significant aids towards the reduction of oxidative stress (Figure 1).

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REVIEW

Diagnosis and pharmacologic management of neuropathic pain among patients with chronic low back pain

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Abstract

Chronic low back pain consists of both nociceptive and neuropathic mechanisms and can be classified as a mixed pain syndrome. Neuropathic component of chronic low back pain has often been under-recognized and under-treated by the physicians. Recent studies have demonstrated that approximately 20%-55% of chronic low back pain patients have neuropathic pain symptoms. An altered peripheral, spinal, and supraspinal processing of pain arising as a result of a lesion affecting the nerves system are the major contributor to neuropathic low back pain. The clinical evaluation is still the gold standard for assessment and diagnosis of neuropathic low back pain. Although diagnosis can be difficult due to the lack of reliable gold standard diagnostic test for neuropathic low back pain, screening tools may help non-specialists, in particular, to identify potential patients with neuropathic low back pain who require further diagnostic evaluation and pain management. Several screening tools for neuropathic pain have been developed and tested with different patient populations. Among the screening tools, the painDETECT questionnaire and the Standardized Evaluation of Pain are validated in patients with low back pain. The Standardized Evaluation of Pain may lead to more effective in discriminating between neuropathic and nociceptive pain in patients with low back pain according to the higher rate of sensitivity and its validity in patients with low back pain. However, the most appropriate approach is still to combine findings on physical and neurologic examinations and patient's report in distinguishing neuropathic pain from nociceptive pain. The clinical examination including bedside sensory tests is still the best available tool for assessment and diagnosis neuropathic pain among patients with chronic low back pain. Due to the fact that chronic low back pain consists of both nociceptive and neuropathic mechanisms, a multimodal treatment approach is more rational in the management of patients with chronic low back pain. Therefore, combination therapy including drugs with different mechanisms of action should be given to the patients with chronic low back pain.

Key words: Low back pain; Neuropathic; Pharmacotherapy; Screening; Questionnaire

Core tip: Neuropathic component of chronic low back pain has often been under-recognized and under-treated by the physicians. Recent studies have demonstrated that approximately 20%-55% of chronic low back pain patients have neuropathic pain symptoms. The clinical examination including bedside sensory tests is still the best available tool for assessment and diagnosis neuropathic pain among patients with chronic low back pain. Combination therapy including drugs with different mechanisms of action should be given to the patients with chronic low back pain.

Yavuz F, Guzelkucuk U. Diagnosis and pharmacologic management of neuropathic pain among patients with chronic low back pain. *World J Rheumatol* 2014; 4(3): 54-61 Available from: URL: http://www.wjgnet.com/2220-3214/full/v4/i3/54.htm DOI: http://dx.doi.org/10.5499/wjr.v4.i3.54

INTRODUCTION

Chronic low back pain (LBP) is defined as pain and disability lasting more than 3 mo. In adults, the incidence of chronic LBP is estimated about 6%-15%[1]. Although there are multiple causes of LBP, about 85% of LBP patients have non-specific LBP. If the cause of LBP is not due to a specific pathology such as infection, tumor, osteoporosis, inflammatory disorders, disc pathologies, then it can be called non-specific LBP. About 10%-15% of the patients with non-specific LBP will go on to develop chronic, disabling LBP[2,3]. The most common pain generator in chronic LBP is the facet joint (40%), the intervertebral disc (26%) and the sacroiliac joint (2%), respectively[4].

Chronic LBP consists of both nociceptive and neuropathic mechanisms and can be classified as a mixed pain syndrome[5,6]. Non-specific nociceptive pain is caused by an inflammatory response to tissue injury and usually described as a sharp or aching pain, while neuropathic pain is caused by damage to nerve tissues and usually described as a burning or heavy sensation, or numbness along the dermatom of the affected nerve[7,8]. Neuropathic component of chronic LBP has often been underrecognized and under-treated by the physicians. Therefore, recent studies have demonstrated that approximately 20%-55% of chronic LBP patients have neuropathic pain symptoms[6,9-11]. The presence of a neuropathic pain component is associated with more severe pain[6], a greater number of comorbidities[5], reduced quality of life[12] and higher healthcare utilization costs[13].

Mechanical and chemical pathophysiological mechanisms are thought to be responsible for neuropathic LBP. Mechanical pathomechanism consist of nerve root compression due to spinal stenosis or intervertebral disc herniation and lesions of nociceptive sprouts within the degenerated intervertebral disc. In chemical pathomechanism, chemokines and cytokines originating from the degenerative disc have been elucidated[5,14-16]. In addition, the theoretical consideration of nerve roots as the only cause of neuropathic pain in chronic LBP is incorrect. Regarding the pathogenesis of degenerative and painful discs, it was reported that intervertebral discs have nerve ingrowth into the inner layers of the annulus fibrosis; as such, the intervertebral disc itself can be a source of neuropathic pain in patients with chronic LBP[14]. Some various nerve-damaging mechanisms were shown in generating a neuropathic pain component in patients with chronic LBP[5]. An altered peripheral, spinal, and supraspinal processing of pain arising as a result of a lesion affecting the nerves system are the major contributor to neuropathic LBP[17-20].

SCREENING TOOLS FOR NEUROPATHIC PAİN AMONG PATIENTS WİTH CHRONIC LBP

Since neuropathic LBP requires specific treatment, favouring the use of drugs with proven efficacy in the treatment of neuropathic pain such as opioids, tricyclic antidepressants and anticonvulsants[21], identifying neuropathic pain from nociceptive pain is important. It is assumed that the treatment directed against the specific cause or particular pain mechanisms will induce better treatment response in the patients. Therefore, physicians should consider chronic LBP not only with nociceptive component but also with neuropathic component. The clinical evaluation is still the gold standard for assessment and diagnosis of neuropathic LBP. The diagnostic workup should include neurological and psychosocial evaluation. Although diagnosis can be difficult due to the lack of reliable gold standard diagnostic test for neuropathic LBP, screening tools may help to identify neuropathic pain component in patients with chronic LBP[5]. An ideal screening tools should be brief, simple, valid, and sensitive. Several screening tools for neuropathic pain such as the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)[10], the Douleur Neuropathique en 4 questions (DN4)[22], the ID-Pain[23], the Neuropathic Pain Questionnaire (NPQ)[24], the Standardized Evaluation of Pain (StEP)[25], and the painDETECT questionnaire (PD-Q)[11] have been developed and tested with different patient populations. These tools contain some weak and strong features, and they are insufficient to diagnose neuropathic pain in 10%-20% of the patients. However, providing immediate information and their ease of use for both clinicians and patients makes these screening tools attractive[26].

Among the screening tools, the PD-Q and the StEP are validated in patients with LBP[11,25]. The PD-Q consists of graduation of pain, pain course pattern and radiating pain. The graduation of pain subscale consists of seven items, and patients are asked to answer each item using a 6-point scale. The PD-Q score is calculated by addition of the each score in the questionnaire, with a maximum score of 38. Scores 19 or greater indicate that neuropathic mechanisms are likely to be involved in the pain; scores between 13 and 18 are uncertain but a neuropathic pain component may be present; scores of $\leqslant$ 12 are suggestive of nociceptive pain. Approximately 80% sensitivity and specificity have been found for the PD-Q. The StEP consists of six interview questions and ten physical tests[25]. The StEP achieves higher sensitivity (92%) and specificity (97%) than the PD-Q which consists only interview questions in distinguishing neuropathic pain from nociceptive pain in patients with LBP. Straight-leg-raising test (Lasegue's sign), a reduced response to cold sensation and a reduced pinprick sensation are the most discriminatory StEP indicators for neuropathic pain[27].

Although the other screening tools except for the PD-Q and the StEP are also used in some clinical studies for distinguishing neuropathic pain from nociceptive pain in patients with LBP[10,28-31], none of them has been validated in patients with LBP. The LANSS scale[10] and the DN4 questionnaire[22] are another screening tools consist of physical tests such as sensation examination and interview questions. The LANSS comprises a seven-item

pain scale, including the sensory descriptors and items for sensory examination, with a maximum score of 24. Scores less than 12 indicate that neuropathic mechanisms are unlikely to be involved in the pain and scores 12 or greater indicate the opposite. The LANSS demonstrated sensitivity of 83% and specificity of 87% in distinguishing neuropathic pain from nociceptive pain. In the DN4 screening tool, three physical tests were using for determining light touch sensation, pinprick sensation and painful response[25]. A score of at least 4/10 in this screening tool is indicative of neuropathic pain, with high sensitivity and specificity (82.9% and 89.9%, respectively).

The ID-Pain[23] and the NPQ[24] rely only on interview questions, and they don't include physical examinations. The ID-Pain is a six-item screening tool, scores ranged from 1 to 5, with a higher score indicative of pain that contains a neuropathic component. The NPQ consists a 12-item questionnaire form, and this scale demonstrated sensitivity of 66.6% and specificity of 74.4% in distinguishing neuropathic pain from nociceptive pain.

Based on the above mentioned clinical studies, it seems plausible that the StEP may lead to more effective in discriminating between neuropathic and nociceptive pain in patients with LBP according to the higher rate of sensitivity and its validity in patients with LBP. However, the most appropriate approach is still to combine findings on physical and neurologic examinations and patient's report in distinguishing neuropathic pain from nociceptive pain.

BEDSIDE SENSORY TESTS

The Neuropathic Pain Special Interest Group of the International Association for the Study of Pain recommend the sensory bedside examination which consists of touch, pinprick, pressure, cold, heat, and vibration sensations for patients presenting with possible neuropathic pain[32]. In order to demonstrate sensory abnormalities in patients with chronic LBP, sensory symptoms and signs should be investigated carefully in the affected dermatome. Thus, these tests will help to physicians confirming or denying the presence of neuropathic pain. A piece of cotton wool can be used in touch sensation examination. Thermal sensation can be assessed by warm and cold objects. Vibration sense can be assessed by a 128-Hz tuning fork[5,33]. The findings in the painful area should be compared with the findings in the non-painful area in contralateral side. The reported responses of the patient are recorded as the same, increased, or decreased, as compared with the normal area. Temporal summation, hypoalgesia to pinprick, allodynia to brush and cold, and hypoesthesia to light touch are discriminant findings for the neuropathic pain. The bedside sensory tests were also found more sensitive than quantitative sensory testing[34,35]. In order to show a lesion of the somatosensory system suggesting possible neuropathic pain, careful clinical examination should be made. However, there is no gold standard finding to label a specific pain within an area of sensory abnormalities as neuropathic pain.

PHARMACOLOGIC MANAGEMENT OF NEUROPATHIC PAIN AMONG PATIENTS WITH CHRONIC LBP

In the treatment of neuropathic pain among patients with chronic LBP, there are many treatments consist of non-pharmacological and pharmacological. Thus, it is difficult for physicians to decide on convenient treatment method. In recently, some treatment guidelines which suggest a multimodal approach for the treatment of neuropathic pain have been developed[36-40]. In the present review, we will only focus on pharmacological treatment of neuropathic pain among patients with chronic LBP. First-line medications recommended for neuropathic pain include tricyclic antidepressants, anticonvulsants, and opioid analgesics.

Antidepressants

Tricyclic antidepressants (TCAs) show their analgesic effect *via* some mechanisms in the central and peripheral nervous systems, including: reuptake inhibition of noradrenaline and serotonin neurotransmission; actions on opioid, adrenergic, serotonin, gamma-aminobutyric acid and N-methyl-D-aspartate receptors; and activation some ion channels[41]. Their analgesic effects are independent of their antidepressant effect. TCAs are recommended in the NICE guidelines for patients with chronic LBP who showed inadequate treatment response to other drugs[42]. TCAs have several side-effects such as sedation, dry mouth, blurred vision, and urinary retention. All of these side-effects are often due to their anticholinergic properties. Especially, elderly patients may be more susceptible to some of these effects. Therefore, TCAs should be used carefully in elderly patients[43]. Data on the efficacy of antidepressants other than TCAs such as serotonin noradrenaline reuptake inhibitors-duloxetine and venlafaxine- and selective serotonin reuptake inhibitors (SSRIs)in chronic LBP are conflicting[44-48].

In a systematic review by Staiger *et al*[49], TCAs were found to produce moderate pain reductions for patients with chronic LBP while SSRIs were not found effective in pain reducing in patients with chronic LBP. In addition, conflicting results were found about the antidepressants whether they improve functional status of patients with chronic LBP. In the Cochrane review of 10 placebo-controlled clinical trials including antidepressants, the authors conclude that "there is no clear evidence that antidepressants are more effective than placebo in the management of patients with chronic LBP"[50]. In randomized placebo controlled trial involving duloxetine, the reduction in weekly mean pain observed with duloxetine was significantly greater at higher doses (120 mg) than with placebo. However, there were no differences between duloxetine 20 or 60 mg and placebo. Although duloxetine 120 mg showed significant effect on reduc-

ing pain level, adverse reactions were found significantly higher than placebo[44]. In contrast to this study, further clinical studies showed that duloxetine 60 mg provided significantly greater pain reductionsthan placebo in patients with chronic LBP[45,46].

Anticonvulsants

Anticonvulsant agents such as pregabalin and gabapentin show their analgesic effects by binding to the α2-γ subunit of N-type voltage-gated calcium channels which leads to decreased release of neurotransmitters[51]. Gabapentin is initiated at 300 mg/d and up titrated in 300-mg increments every 3-7 d according to tolerability, to a target dose of 1800-3600 mg/d in three divided doses. Pregabalin is initiated at 150 mg/d in two divided doses. After 7 d, the dose was elevated to target dose of 300-600 mg/d. The main side effects of these drugs include somnolence, dizziness and peripheral oedema, and caution is advised in patients with renal insufficiency[37].

To date, there is no systematic reviews of anticonvulsants for chronic LBP. However, there are two clinical trials of gabapentin for chronic LBP[52,53]. As the result of these studies, gabapentin showed small improvements in pain scores compared with placebo. There was no difference between gabapentin and placebo in according to the rates of adverse reactions. In the treatment of chronic LBP, there is no evidence to support the use of pregabalin. In two randomized trials, there were no significant difference between pregabalin and placebo groups in according to the reduction in weekly mean pain score. In addition, when the patients with treatment-refractory neuropathic pain, including those with chronic LBP had taken pregabalin as a monotherapy, pain relief and improvement in quality of life were found significantly lower than those patients with either oxycodone controlled release (CR) alone or the combination of oxycodone CR and pregabalin[54,55].

Opioid analgesics

These drugs show their analgesic effect with binding to opioid receptors in the central nervous system, thus they regulate the pathways involved in the generation, transmission, and modulation of pain impulses[56]. In clinical practice, the most important factors for the restriction of an opioid using are drug tolerability issues and adverse reactions. The most common adverse reactions are dry mouth, nausea, constipation, dizziness, drowsiness, pruritis and vomiting[57]. In addition, the other concerns about opioids using in chronic non-malignant pain management are development of analgesic tolerance and dependence in susceptible patients. However, the short-term using of opioids is recommended in those patients with nociceptive and neuropathic pain who have unresponsive to first-line treatment and in those patients who have moderate to severe pain[58]. Due to the absence of high-quality published trials, there are few meta-analyses and systematic reviews investigating opioids in the chronic pain setting.

In higher-quality trial, sustained-release oxymorphone or sustained-release oxycodone was found to be superior than placebo in the treatment of chronic LBP [59]. In another study conducted by Schnitzer *et al*[60] tramadol was found more effective than placebo for short-term pain relief in the patients with chronic LBP. Two other trials of tramadol found that there were no significant differencesin benefits or harms between sustained-release and immediate-release tramadol for chronic LBP[61,62]. There is no trial comparing tramadol with acetaminophen or opioid monotherapy, or with other NSAIDs. Another open-label, randomized multicenter study showed that transdermal fentanyl and sustained-release oral morphine provided similar pain relief in patients with chronic LBP[63]. The meta-analysis investigating the use of opioids in chronic non-cancer pain, including chronic LBP reported that opioids were more effective than placebo for both nociceptive and neuropathic pain[64]. Controversy exists as to whether opioids are effective for neuropathic component of chronic LBP.

Other drugs

Tapentadol is a centrally acting analgesic used to treat moderate to severe acute pain. This drug show its analgesic effect *via* acting as μ-opioid receptor agonist and providing noradrenaline re-uptake inhibition[65]. In phase 3 studies, patients with chronic LBP showed good clinical results to tapentadol prolonged release (PR)[66,67]. In these studies, tapentadol PR demonstrated similar analgesic efficacy compared with oxycodone CR. Gastrointestinal tolerability and the incidence of drug discontinuations were lower in patients using tapentadol PR than those patients using oxycodone CR[68,69]. In another phase 3b study, the effectiveness and safety of tapentadol PR *vs* a combination of tapentadol PR and pregabalin were compared for the management of severe, chronic LBP with a neuropathic component. The authors found that tapentadol PR showed comparable improvements in pain intensity and quality-of-life measures to combination of tapentadol PR and pregabalin, with improved drug tolerability[69]. Ascorbic acid (Vitamin C) is an *anti-oxidant*. This means it lowers the amount of free radicals produced from oxidation, like the reactive oxygen species (ROS). ROS are critically involved in the development and maintenance of neuropathic pain. So, free radical scavengers like ascorbic acid could be useful for treatment of neuropathic pain[70]. However, there is no clinical study investigating tilidine and ascorbic acid in the management of neuropathic pain among patients with chronic LBP.

COMBINATION THERAPY

Since chronic LBP consists of both nociceptive and neuropathic mechanisms, combination therapy such as antidepressants and/or anticonvulsants plus opioids or NSAIIs might be rational in the treatment of chronic LBP[71]. Treatment guidelines also recommend combination therapy in the treatment of neuropathic pain due to different causes as an option for patients who are unresponsive to the monotherapy[7,36]. However, combination

therapy is associated with some limitations consisting of adverse reactions and drug interactions[39,72].

In the literature, the number of clinical studies investigating the effect of combination therapy for neuropathic pain component in patients with chronic LBP is very few. Although most of the available clinical studies have investigated combinations of an opioid plus another drugs, there is only one study investigating the efficacy of celecoxib plus pregabalin combination drug therapy in a mixed population of patients including chronic LBP[71]. In this study, the authors showed that combination therapy showed significantly greater reductions in LBP, and a similar frequency of adverse reactions, compared with either celecoxib or pregabalin alone. In the literature, there were two studies investigating the benefit of an opioid plus pregabalin. In the first study, the combination of oxycodone CR plus pregabalin was compared with either oxycodone CR or pregabalin alone in 409 patients with treatment-refractory neuropathic pain (most commonly due to radiculopathy). The authors found that LBP relief was faster and more substantial in the patients with combination therapy than in those patients with pregabalin monotherapy. The patients with combination therapy showed significantly greater improvements in quality of life than patients with either oxycodone CR or pregabalin using. Combination therapy also showed a superior safety profile to both monotherapies[55]. In the second study, the authors investigated the benefit of combination of buprenorphine plus pregabalin in patients with chronic LBP. Pain reduction was found significantly greater in patients with combination therapy than in patients with buprenorphine monotherapy[73]. There were also 2 studies examining the benefit of tramadol plus paracetamol in a combination therapy for the patients with chronic LBP. In these studies, significantly greater improvements in LBP severity were determined in patients with combination therapy than in patients with placebo. Adverse reactions were found more common with the combination therapy than with placebo[74,75].

To sum up, combination therapy of pregabalin plus other analgesic drugs such as celecoxib, oxycodone CR and buprenorphine appears to be more effective in reducing neuropathic pain component whereas pregabalin monotherapy seems to be ineffective. Tramadol alone and in combination with paracetamol also appeared to be effective.

CONCLUSION

Presently, there is no available gold standard test for determining a neuropathic pain component in chronic LBP. Neurophysiological testing and screening tools have some limitations in the differentiation of a neuropathic component in chronic LBP patients. So that, bedside sensory tests is the still best available tool for assessment and diagnosis neuropathic pain among patients with chronic LBP. Due to the fact that chronic LBP consists of both nociceptive and neuropathic mechanisms, a multimodal approach to medication probably is more rational in the management of patients with chronic LBP. Therefore, combination therapy including drugs with different mechanisms of action should be given to the patients with chronic LBP. In the literature there is no clear evidence that antidepressants and opioids are effective in the management of neuropathic pain among patients with chronic LBP. In addition, there is no evidence to support the use of anti-convulsant drugs. In order to improve level of evidence in diagnosing and treating neuropathic LBP, further well-designed clinical studies investigating pharmacologic management in neuropathic pain among patients with chronic LBP are needed.

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MINIREVIEWS

Gout: A clinical overview and its association with cardiovascular diseases

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Abstract

Gout is a common disease caused by the deposition of monosodium urate (MSU) crystals in patients with hyperuricemia, and characterized by very painful recurrent acute attacks of arthritis. The gold standard for diagnosing gout is the identification of MSU crystals in synovial fluid by polarization light microscopy. Arthritis attacks can be treated with anti-inflammatory medications, such as non-steroidal anti-inflammatory drugs, colchicine, oral prednisone, or intra-articular or intramuscular glucocorticoids. To prevent gout uric acid lowering therapy with for example allopurinol can be prescribed. When gout is adequately treated, the prognosis is good. Unfortunately, the management of gout patients is often insufficient. Gout is associated with dietary factors, the use of diuretics, and several genetic factors. Comorbidities as hypertension, chronic kidney disease, cardiovascular diseases, the metabolic syndrome, diabetes, obesity, hyperlipidemia, and early menopause are associated with a higher prevalence of gout. Xanthine oxidase and chronic systemic inflammation seem to play an important role in the pathophysiology of the association between gout and cardiovascular diseases. To prevent cardiovascular diseases gout patients must be early screened for cardiovascular risk factors.

Key words: Gout; Review; Clinical; Cardiovascular diseases

Core tip: Gout is a common disease caused by the deposition of monosodium urate (MSU) crystals in patients with hyperuricemia, and characterized by very painful recurrent acute attacks of arthritis. The gold standard for diagnosing gout is the identification of MSU crystals in synovial fluid. Arthritis attacks are treated with anti-inflammatory medications, to prevent gout uric acid lowering therapy can be prescribed. When gout is adequately treated, the prognosis is good. Comorbidities as chronic kidney disease, cardiovascular diseases, and the metabolic syndrome are associated with gout. Gout patients must be early screened for cardiovascular risk factors.

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INTRODUCTION

Gout is a common disease caused by the deposition of monosodium urate (MSU) crystals in patients with hyperuricemia, and characterized by very painful recurrent acute attacks of arthritis. Gout has been recognized as a clinical entity for a long period of time. Acute gout occurring in the first metatarsophalangeal (MTP-1) joint, first identified by the Egyptians in 2640 BC, was later recognized by Hippocrates in the 5th century BC, who

referred to it as "the unwalkable disease"[1]. The first person to use the word gout (*gutta quam podagram vel artiticam vocant* - the gout that is called podagra or arthritis) was the Dominican monk Randolphus of Bocking, domestic chaplain to the Bishop of Chichester (1197-1258)[2]. Through the ages gout was known as "the king of diseases and the disease of kings", because of its association with alcohol consumption, purine-rich diet and obesity[3].

This review starts with a clinical overview on the epidemiology, pathogenesis, clinical presentation, risk factors, diagnosis, treatment, and prognosis of gout. Hereafter, the review discusses the association between gout and cardiovascular diseases.

CLINICAL OVERVIEW OF GOUT

Epidemiology

Gout is one of the most common rheumatic diseases with a prevalence of 1%-2% in the adult population in developed countries[4]. The prevalence of gout is higher in men, and rises with age[5]. Gout occurs four to ten times more often in men than in women among patients under the age of 65[5]. In the elderly, gout has a somewhat more equal sex distribution[5], possibly due to the fall of uricosuric estrogen in women after the menopause[6,7]. Accumulating evidence suggests an increase in the prevalence of gout in the last decades, which might be caused by an increased longevity and an increased prevalence of factors that promote hyperuricemia such as obesity, the metabolic syndrome, chronic kidney disease, and dietary changes[5,8-11].

Pathogenesis

Gout is caused by a disorder of the purine metabolism and results from MSU crystal deposition in and around the joints which is associated with hyperuricemia. The serum uric acid concentration is determined by the endogenous production of uric acid by synthesis and cell turnover, the exogenous supply *via* dietary intake, and renal (two-third) and intestinal (one-third) excretion[12]. Hyperuricemia is the result of uric acid overproduction, uric acid underexcretion, or a combination of the two[12]. Hyperuricemia is defined as a serum uric acid concentration that exceeds the solubility at physiologic temperature and pH (0.38-0.40 mmol/L)[3,13]. Although hyperuricemia is necessary to develop gout, it is not sufficient to cause gout. Only one cohort study from 1987 investigated the association between the level of serum uric acid and the cumulative incidence of gout. Gout occurred in just 22% of the patients with a baseline serum uric acid of more than 0.54 mmol/L over a 5-year period[14].

Necessary for the occurrence of gout arthritis is the formation of MSU crystals when hyperuricemia is present. The formation of MSU crystals depends on the solubility of uric acid in joint fluid. The solubility is influenced by factors such as temperature, pH, level of articular dehydration, concentration of cations, and the presence of nucleating agents (collagen, chondroitin sulfate, and nonaggregating proteoglycans)[12]. Variation in these factors might explain partly the preference of gout attacks in the MTP-1 joint (the relatively low temperature of this peripheral joint)[15] and in osteoarthritic joints (degeneration with decreased collagen and proteoglycans)[16], and the nocturnal onset of the attack (articular dehydration)[12,13]. However, these factors do not explain for example why gout does rarely occur in the MTP-5 joint which has probably a lower temperature than the MTP-1 joint, and gout is also rarely seen in often osteoarthritic hip joints.

MSU crystal formation leads to MSU crystal deposition in synovial fluids. MSU crystals are pro-inflammatory stimuli. MSU crystals are phagocytosed as particles by monocytes and cause an inflammatory response with the release of pro-inflammatory mediators as tumor necrosis factor (TNF)-α, interleukin (IL)-1b, and IL-6[12,13]. Mechanisms by which MSU crystals activate cells in the joint and the role of these pro-inflammatory mediators are not yet fully explained. The generally accepted hypothesis is that MSU crystals activate monocytes *via* the inflammasome leading to IL-1b production[17-21]. IL-1b can induce recruitment of other inflammatory cells within the joint to produce cytokines and chemotactic factors. This results in neutrophil influx to the joint, which is the hallmark of gouty arthritis.

Clinical presentation

Typically, a patient with a gout attack has an acute painful and swollen joint, which is often red and warm. The onset of the arthritis is abrupt. A gout attack usually affects one joint in the lower limbs. Most often, in 57% of the primary care patients[22], the MTP-1 joint was involved[23]. In 86% of primary care patients with gouty arthritis the lower leg was affected[22]. Next most frequent locations are the mid-foot, the ankle and the knee[16]. Gout attacks are self-limiting and resolve within 7-10 d. However, the arthritis attacks are often recurrent.

Recurrent gout attacks can lead to permanent joint damage and tophi depositions. Tophi can be found in or close to joints, in bursas, tendon sheaths, and in articular cartilage[24]. Clinical experience shows that in some patients later in the course of the disease the gout attacks can occur more often, and it takes more days before the attack is resolved. Then the arthritis is more frequently polyarticular and spreads to the upper limbs[16,23].

Risk factors

Many factors have been described as risk factors for the development of gout. However, the associations between these "risk" factors and gout are almost exclusively based on epidemiological studies, which of course cannot proof causal relations between these factors and gout. Epidemiological studies show that several dietary factors might increase the risk of gout, such as alcohol consumption[25,26], purine-rich meat and seafood intake[26-28], and consumption of fructose-sweetened soft drinks[26,29]. The consumption of dairy products[28], skim milk powder[30], folate, vegetables, and coffee are associated with a decreased prevalence of gout[26]. According to epidemio-

logical studies the use of thiazide and loop diuretics, but not aldosteron antagonists, are associated with the risk of gout[26,31,32]. However, these results might be confounded by cardiovascular indications[33].

Other factors can cause the development of gout. Genetics (sex[5], some genes such as *SLC2A9*, *ABCG2*, *SLC17A3*, and *SLC22A12*[3,13] and Asian descent[34,35]), age[5], and constitutional influences (body composition) are risk factors, and these cannot be influenced. Comorbidities as hypertension[36], chronic kidney disease, cardiovascular diseases[37-41], the metabolic syndrome[36,42], diabetes[42,43], obesity[36], hyperlipidemia[36], and early menopause[6] are associated with a higher prevalence of gout[26]. Nowadays, especially the association between gout and cardiovascular diseases is a large research field[37-41,44,45], but the exact mechanism of why these diseases are associated is not fully understood.

Diagnosis

The gold standard for diagnosing gout is the identification of MSU crystals in synovial fluid or in a tophus by polarization light microscopy[46]. The accuracy of the gold standard has been tested in only a few studies. The sensitivity of detection of MSU crystals was shown to be 69% with a specificity of 97%[47]. After training the sensitivity of the detection of MSU crystals can become 95% with a specificity of 97%[48]. In clinical practice most synovial fluid is aspirated from the affected joint during a gout attack. A longstanding opinion is that synovial fluid should be analyzed with a polarization microscope rapidly after aspiration, because the formation and solubility of MSU crystals might be affected by pH and temperature[49]. A recent systematic review has shown that MSU crystals can also be detected in synovial fluid which has been stored for a maximum of 8 wk[49].

Although there is a gold standard, in primary care synovial fluid analysis is often not possible or not available. Polarization light microscopes are expensive and almost only available at rheumatology departments. But approximately 90% of the gout patients are diagnosed and treated by primary care physicians[50]. Primary care physicians diagnose gout without the gold standard, based on clinical signs and symptoms, which has demonstrated to have a limited predictive value[22]. In patients with MTP-1 arthritis the diagnosis gout was right in only 77%, while primary care physicians supposed gout to be the diagnosis in 98% of the patients[51]. Even in rheumatology departments the gold standard is not always used for diagnosing gout[52,53].

Several criteria sets were developed to improve the validity of the clinical diagnosis, such as the American College of Rheumatology criteria[54], which showed a limited sensitivity (90%; 79%) and specificity (64%; 70%) in primary[55] and secondary care[56] in MSU crystal-proven gout patients, respectively. A diagnostic rule to diagnose gout without joint fluid analysis developed in a primary care population of MSU crystal-proven gout patients had better results[22], but the validity of this rule is unknown in secondary care.

Nowadays imaging techniques are increasingly used for diagnosing gout patients. Ultrasonography and dual-energy computed tomography (DECT) are promising but expensive methods for diagnosis and monitoring gout, but with yet an unknown validity in medical practice[57-62]. Compared to the gold standard of synovial fluid aspiration the main advantage of these techniques is that they are non-invasive. A disadvantage of DECT is its high exposure to radiation.

Treatment

Standard treatment consists of anti-inflammatory drugs for gout attacks, sometimes followed by long-term preventive urate lowering therapy. Acute gout attacks are treated with non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, oral prednisone, or intra-articular or intramuscular glucocorticoids. Unfortunately, there are only a few trials which compare the efficacy and safety of these therapeutics in gout patients. NSAIDs and prednisone have a comparable therapeutic effect during a gout attack[63-65]. Low-dose colchicine has the same therapeutic effect after 24 h as high-dose colchicine, but with less adverse effects[66]. Because of the lack of trials, the choice which anti-inflammatory therapy is prescribed is mainly based on comorbidity and comedications. In case of no restrictions by comorbidity and comedications, the cost of the therapy can be taken into account. In the United States, the cost of colchicine have risen after the rebranding of this therapeutic. IL-1b blockers such as canakinumab[67], anakinra[68-70], and rilonacept[71-75] are new therapeutic opportunities in patients with gouty arthritis, but their efficacy and safety should be further tested. However, these new therapeutics are expensive, and should only be prescribed in patients with frequent gout attacks who failed or have contra-indications for the traditional anti-inflammatory drugs. Trials concerning the efficacy of non-pharmacological interventions for gout attacks are even more rare, probably due to ethical and practical difficulties to set up these type of trials[76]. Only one trial was performed which shows that local ice therapy can be useful during gout attacks[77].

Preventive uric acid lowering therapy is indicated in patients with two or more gout attacks per year, tophaceous gout, or a history of uric acid urolithiasis[78,79]. The decision whether to start preventive uric acid lowering therapy or to accept frequent gout attacks and/or tophi should always be made in accordance with the patient. The aim of the uric acid lowering therapy is to decrease the frequency of gout attacks[80,81] and/or to reduce tophi[82] by sufficiently reducing the serum uric acid level. The target serum uric acid level should be at least below 0.36 mmol/L[79]. A lower target serum uric acid of 0.30 mmol/L can be aimed for in case of severe gout (for instance tophaceous gout)[78,83]. Based on evidence and experience the first choice uric acid lowering agent is the xanthine oxidase inhibitor allopurinol[78,79]. The uricosuricum benzbromarone 100-200 mg per day and allopurinol 300-600 mg per day have comparable efficacy and safety profiles[82,84]. Probenecid, an old uricosuricum, has moderate efficacy

as uric acid lowering therapeutic in patients with lack of effectiveness of or intolerance to allopurinol[85]. A trial has shown similar effects of allopurinol 200-300 mg per day and febuxostat, a new xanthine oxidase inhibitor, 80-120 mg per day[86], but in clinical practice the dose of allopurinol can be further enhanced until 600 mg. At this moment, because of high costs and little clinical experience, febuxostat should only be used when the target serum uric acid level cannot be reached by an appropriate dose of allopurinol, or when the patient is intolerant to allopurinol. In both cases benzbromarone is also a good and less expensive alternative. The uricase derivative rasburicase is now only registered for tumor lysis syndrome, but might be beneficial as uric acid lowering therapy in gout patients[87-90]. A new uricase derivative pegloticase is proven to be useful in patients who are refractory to or intolerant for conventional therapy[91-95]. Uricases should be administered intravenously with a risk of infusion reactions, and there always remains a risk for antibody formation due to the conjugation to proteins. The latter might impede the efficacy of uricases. The selective uric acid reabsorption inhibitor lesinurad might be another future treatment option[96].

Only a few studies have compared the efficacy and safety of uric acid lowering monotherapy, and solely one study looked at combination therapy of two uric acid lowering therapeutics. The combination of lesinurad and febuxostat was well tolerated, and the target serum uric acid level was achieved in all patients[97]. Based on clinical experience benzbromarone can be added to allopurinol when the target serum uric acid cannot be reached by allopurinol monotherapy. The dose of the uric acid lowering medications should be carefully increased to reduce adverse effects, and should be titrated based on serum uric acid levels[78,79]. It is generally accepted that uric acid lowering therapy should be started under several months of prophylactic anti-inflammatory medications (colchicine or NSAIDs) to prevent paradoxal gout attacks at the start, although there are no studies to prove this[78,79]. The uric acid lowering therapy should be continued lifelong.

In addition to the uric acid lowering therapy some other pharmacological measures can be helpful to reduce serum uric acid. When a gout patient is also diagnosed with hypertension, losartan could be considered as antihypertensive treatment, because of its small uric acid lowering effect[98]. Vitamin C, a safe supplement, might have a very small uric acid lowering effect[99,100], although a small randomized controlled trial in gout patients could not confirm this[101].

Additional non-pharmacological measures, like dietary advices, to reduce serum uric acid may be useful, but their uric acid lowering effects are small (10%-18%) and therapeutically insufficient (*i.e.*, no reduce of the frequency of gout flares) in most patients[26]. Observational studies showed that the intake of purine-rich meat and seafood, fructose-rich soft drinks, and alcohol should be reduced, and dairy intake and the consumption of vegetables should be encouraged[26,78,79,102]. Trials concerning the efficacy of non-pharmacological interventions to lower serum uric acid are also lacking. The only trial of dietary intervention in gout patients suggested that skim milk powder enriched with glycomacropeptide and G600 milk fat extract might reduce the frequency of gout flares[30].

Prognosis

Gout is a potentially curable disease. Unfortunately, the management of gout patients is often insufficient[5,103-107]. An important reason is the limited use of uric acid lowering therapy. Only 30%-60% of the patients are still prescribed allopurinol one year after the start of the therapy[4], and only 17% of the gout patients might be fully adherent to allopurinol therapy[108]. The poor adherence is often, unfairly, blamed on gout patients unwilling to take uric acid lowering therapy. Lack of appropriate information from their doctor is an important factor which plays a role in the poor adherence. An observational study showed that patient education, individual lifestyle advice and slow upward titration of uric acid lowering therapy according to serum uric acid levels can improve the adherence to uric acid lowering therapy[109].

Acute gout attacks and the presence of tophi account for a major component of the reported decreased health-related quality of life in gout patients, and are associated with decreased work productivity which leads to an economic burden for the society[110-112]. This emphasizes the importance of the effective management of gout. Urate lowering therapy is cost-effective when patients have two or more recurrent attacks per year[113].

THE ASSOCIATION BETWEEN GOUT AND CARDIOVASCULAR DISEASES

Nowadays, an important study field within gout research is the association between gout and cardiovascular diseases. The increasing interest in this association is probably due to its great clinical importance, because of the high prevalence of gout and cardiovascular diseases. This part of the review elaborates more on the association between gout and cardiovascular diseases.

The association of gout with cardiovascular diseases

Most studies looked at the association between hyperuricemia and cardiovascular diseases. Two systematic reviews of prospective cohort studies show that, after correction for traditional risk factors for cardiovascular diseases, patients with hyperuricemia have a significant higher risk for cardiac diseases[45], cardiac mortality[38], stroke[37], and stroke-related mortality[37]. The mean association of the risk for cardiac mortality was 12% per increase of the serum uric acid of 0.059 mmol/L[38]. In women there was a stronger association between hyperuricemia and cardiovascular diseases and mortality than in men[37,38]. Higher levels of hyperuricemia are stronger risk factors for cardiovascular diseases and mortality than lower levels of hyperuricemia[114]. Interestingly, several studies observed a J-curve relationship between serum

uric acid level and cardiovascular disease or all-cause mortality[115,116]. A low serum uric acid level might be associated with a higher mortality, because uric acid can play a protective antioxidant role[117]. It should be noticed that the definition of hyperuricemia differed between several studies and it was not always corrected for sex. Also, patients with hyperuricemia could be symptomatic (*i.e.*, gout) or asymptomatic. However, it is likely that the conclusions from studies about patients with hyperuricemia are also valid in patients with gout.

Some studies investigated the association between gout and cardiovascular diseases. Gout was shown to be associated with an increased risk for heart failure[39] and myocardial infarction[45]. Several prospective cohort studies showed that gout was also associated with cardiovascular mortality[40,41,44,118] and with overall mortality[39-41,44,118]. Gout is a stronger risk factor for cardiovascular diseases and mortality than hyperuricemia[40,41]. Tophaceous gout was a very strong risk factor for cardiovascular mortality[114]. Unfortunately, the diagnosis of gout was often not based on identification of MSU crystals, but on self-report. In MSU crystal-proven gout the association might be stronger than in gout otherwise diagnosed, and therefore the association of gout and cardiovascular diseases can be underestimated.

The pathophysiology of the association of gout with cardiovascular diseases

The pathophysiological pathways that link gout with cardiovascular diseases are not fully clear. Gout might lead to cardiovascular diseases through endothelial dysfunction caused by oxidative stress through xanthine oxidase activation. Another pathway is based on chronic systemic inflammation in patients with gout, also in asymptomatic periods, which might lead to cardiovascular diseases. Both pathways are now discussed in more detail.

Accumulating evidence shows that xanthine oxidase plays a central role in the association of hyperuricemia and gout with cardiovascular diseases. Upregulation of xanthine oxidase activity rather than decreased renal excretion of uric acid is an important factor underlying the increased serum uric acid levels in heart failure patients[119]. Endothelial dysfunction might be caused by accelerated inactivation of nitric oxide by reactive oxygen species, and xanthine oxidase is a source of reactive oxygen species production[120].

Several studies suggest that allopurinol, a xanthine oxidase inhibitor, has cardioprotective effects. Most studies looked at indicators for higher cardiovascular risk. Allopurinol improved the endothelial function[121] and resulted in an improved vasodilated capacity and peripheral blood flow in patients with heart failure[122]. Allopurinol gave a significant blood pressure reduction in patients with hyperuricemia[123-126]. In patients with chronic stable angina allopurinol increased the time to chest pain and the total exercise time[127,128]. Allopurinol inhibits the oxidation of low-density lipoprotein, which plays an important role in the development of atherosclerosis[129]. These mechanisms might contribute to a favorable effect of allopurinol on the cardiovascular risk in gout patients. The effect of allopurinol on mortality was the topic of several studies. These studies showed that allopurinol reduced the mortality in heart failure patients[130-133]. One recent study investigated the effect of allopurinol on cardiovascular outcome. Allopurinol was associated with a reduced risk of myocardial infarction[134]. On contrary, benzbromarone, an uricosuricum, did not have beneficial cardioprotective effects[129,135].

A different pathway which might link gout to cardiovascular diseases is based on chronic systemic inflammation. Low-grade chronic systemic inflammation can contribute to the development of cardiovascular diseases. Some evidence is found that in patients with hyperuricemia or gout low-grade chronic systemic inflammation is present. Serum uric acid levels were associated with C-reactive protein levels, TNF-α levels and IL-6 levels[136]. Typical gout signs seen with ultrasonography are present in asymptomatic joints of patients with hyperuricemia or gout[137]. This might imply that also in between gout attacks low-grade inflammation is present. Also in tophaceous gout, a severe form of gout with widespread urate deposition, more low-grade inflammation might be present compared to non-tophaceous gout. Tophaceous gout was shown to be stronger risk factor for cardiovascular diseases and mortality than non-tophaceous gout[114].

CONCLUSION

Gout is no longer 'the king of diseases and the disease of kings', but a very common disease which is associated with cardiovascular diseases. Not only the gout attacks should be treated, but gout patients should also be screened and treated for cardiovascular risk factors.

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MINIREVIEWS

Quantifying synovial inflammation: Emerging imaging techniques

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Abstract

Imaging techniques to assess synovial inflammation includes radiography, ultrasound, computed tomography, magnetic resonance imaging (MRI) and recently positron emission tomography. The ideal objective of imaging approaches are to quantify synovial inflammation by capturing features such as synovial hyperplasia, neo-angiogenesis and infiltration of immune cells in the synovium. This may enable clinicians to estimate response to therapy by measuring the improvement in the inflammatory signals at the level of synovium. Ultrasound can provide information regarding thickening of the synovial membrane and can reveal increased synovial blood flow using power Doppler technique. Bone marrow edema and synovial membrane thickness on MRI scan may serve as indicators for arthritis progression. Enhancement of the synovium on dynamic contrast MRI may closely mirror the inflammatory activity in the synovium. Diffusion tensor imaging is an advance MRI approach that evaluates the inflammation related to cell infiltration or aggregation in an inflamed synovium. In this review, we summarize the newer imaging techniques and their developments to evaluate synovial inflammation.

Key words: Synovitis; Imaging; Diffusion tensor imaging; Positron emission tomography; Computed tomography; Ultrasound

Core tip: Nowadays, more and more emphasis is being put on capturing the microscopic features of inflammation on non-invasive techniques of imaging. Emerging magnetic resonance imaging techniques seem to have potential to capture these molecular events and replace synovial histology in future. In this paper we have reviewed exciting recent advances in the field of imaging that pick up inflammatory signals from inflamed synovium and are likely to be available for routine clinical practice in near future.

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INTRODUCTION

In chronic inflammatory joint diseases, synovium is the major site of inflammation. During inflammation, the phenotype of synovium is modified and it changes into thickened invasive tissue that erodes into surrounding soft tissues (cartilage, ligaments and tendons) and bone tissue. It is difficult to define the stages during the transformation of non-specific synovitis into aggressive invasive destructive synovitis[1]. Infiltration of macrophages in the synovial membrane is of pathogenic importance because macrophages generate several pro-inflammatory cytokines for example interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) activate synovial neovascularisation and cause damage to joint by various mechanisms[2]. Greater understanding about the pathogenesis of

synovial inflammation has led to development of focused biologic treatments that minimize disease progression and tissue destruction. Development of biologics such as anti-TNF-α monoclonal antibodies, antibodies against IL-6, receptor activator for nuclear factor-κ B ligand, IL-17 and CD20 (B cell) improve arthritis symptoms by reducing the synovial inflammation[3]. The full-benefits of newer treatments can only be noticed if tools are available to perfectly identify the site and severity of synovial inflammation before irreversible damage occurs. In this review, we focus on the current improvements in imaging modalities as well as how these newer imaging modalities can be applied in the monitoring of synovitis and application of these newer imaging modalities in effective control of synovial inflammation in various arthritic disorders.

RADIOGRAPHY

Virtually all patients undergo radiographs or X-rays of the joint at initial presentation to know the extent of the disease and damage to the joints. Sequential image analysis is commonly executed during the treatment to monitor synovitis progression or regression (erosion scores or joint space narrowing). It has following advantages; easy availability, extensive image acquisition of almost all the joints areas, latest digitised formats grant simple restoration and evaluation of images in future and comparatively very economical. Drawbacks include contact with ionising radiation, which is however comparatively low for one time of X-rays but can become high over a period of time during sequential X-rays[4] and, most significantly, a lack of sensitivity in detecting early synovial inflammation and early joint damage[5,6].

X-ray in synovitis progression

Plain X-rays are not beneficial in monitoring of progression of synovitis in early arthritis patients. X-rays of wrist and knee joint are abnormal in 15%-30% of patients at initial presentation who finally fulfils the diagnostic criteria of rheumatoid arthritis (RA)[7]. In early RA, radiographs reveal non-specific synovial thickening and periarticular osteopenia, neither of which is diagnostic. However, in late RA characteristic erosions and their pattern of joint involvement may suggest diagnosis of RA but by then disease is far advanced. Despite this fact, radiographs have been extensively validated in a number of clinical trials. In ATTRACT (Anti TNF Therapy in RA with Concomitant Therapy) study, examining the effectiveness of infliximab in preventing progression of joint erosions[8], the two radiologists had a high reliability with correlations varying between 0.84 at baseline to 0.92 at weeks 102 of total radiographic scores. However, radiographs provide a very little information regarding severity of inflammation and lacks quantifiable variables of inflammation in early arthritis. They are reliable indicators of damage.

ULTRASONOGRAPHY

Latest reports recommend that ultrasonography (US) may be an important imaging technique to determine the degree of synovitis in active RA joints. Furthermore, it may be more sensitive in identifying active synovial inflammation than clinical joint examination[9]. Recently, Le Boedec *et al*[10] reported that US may provide additional useful information beyond clinical joint examination in the shoulders and metatarsophalangeal joints. They further concluded that the usefulness of power Doppler and B mode ultrasound were reduced with low DAS28 score and shorter disease duration respectively[10]. US can provide information about disease activity (synovial inflammation and tenosynovitis) and joint damage (bone erosions)[11]. Hence, US not only may help in examination but may also help in monitoring outcome of treatment. Ultrasonic waves when hit the tissue interfaces, they are reflected back and these reflected waves (echo waves) are recorded to generate US images. Thickness of synovium in areas of joint capsule and tenosynovium can be detected by B mode grey scale US (GSUS)[12]. Synovial inflammation in the knee of RA patients was examined through GSUS at 5.0 MHz in a study evaluating Yttrium-90 radiation synovectomy[13]. In this study GSUS findings (suprapatellar effusion and synovial thickening) correlated well with the clinical and arthrographic findings.

US imaging approach is even more enhanced with the application of Doppler techniques[14]. Flow of red blood cells, either towards the US probe or away from it, demonstrated by Colour Doppler US is suitable for analyzing excessive flow rate in blood vessels[15]. Hypertrophy of the synovium is determined as non- displaceable, intra-articular, poorly compressible, which can be recognized by Doppler signal[16]. Thickened synovium is much less compressible therefore on probe compress fluid movement is very less while in normal synovium fluid is displaced easily on probe compression. Sometimes, normal anatomical tissues may mimic synovial inflammation due to low reflectivity of US waves, particularly with US equipment of lower resolution[17].

Power Doppler US (PDUS) is the most beneficial US technique in rheumatology. It analyses Doppler changes of the moving red blood cell, regardless of its route and rate, and is consequently well developed for the quantification of blood flow rate within the low flow synovium[18,19]. PDUS can quantify inflammatory activity in the erosions of RA by revealing increased blood flow in the synovium of these patients. Histological analysis have confirmed that changes in power Doppler signals are associated with inflammatory changes in the synovial membrane[20], however one must be cautious about artefact signals at bone synovium interface especially if gain setting of the US machine is high. Increased Doppler signal matches specifically with neutrophils recruitment and area fibrin accumulation[21], however, no exact correlation between systemic vascular endothelial growth factor expression and neo-vascularisation was demonstrated. PDUS is sensitive but also more vulnerable to false signals. The software that measures PDUS is proprietary; therefore, results from one manufacturer may not be comparable with another.

POSITRON EMISSION TOMOGRAPHY

Positron emission tomography (PET) is a sensitive image acquisition technique that depends on ion emitting isotopes of radioactive element. Positron loses energy after it collides with atoms and is exhausted after colliding with an electron, leading to the emission of two gamma rays. After collision two gamma rays travel in opposite direction. The PET sensor captures signal of these two energy packets (photons) along with their relative position. PET sensors at the same time capture signal of these energy packet from various directions. Associated computed tomography (CT) scanning offers superior structural information of the tissues and spatial localization of the PET signals. A tracer molecule fluorodeoxyglucose [(18F) FDG] has been widely used in PET research. It has homology with the sugar molecule but it contains radioactive isotope, upon accumulation in the metabolic active cells it gives the signal which is captured by PET scanning and provide information about the location of inflamed tissue. Increased uptake of this sugar analogue is directed by the various sugar transporter receptors such as GLUT1 and GLUT3 on the cell surface, both are over expressed on hyper metabolic cells. This sugar analogue is phosphorylated by the hexokinase enzyme but it is not metabolised further in the glycolytic pathway and is trapped in the cells[22].

Several attempts with the FDG PET in the estimation of synovial inflammation in arthritis demonstrated that there is enhanced uptake of 18F-FDG in the inflamed synovium[23,24]. The semi-quantitative scoring of joint involvement and quantitative uptake of 18F-FDG has been shown to correlate with markers of inflammation[25]. Another tracer molecule 11C R PK11195 has also been used in PET scanning which specifically binds to the receptors present on phagocytic cells. This group analysed joint of 11 inflammatory arthritis individuals and examine the joints with the invasive methods such as arthroscopic surgery and histology[26]. It was observed that tracer molecule accumulation was higher in inflamed joints as compared to non- inflamed joints of the same individual. The uptake of tracer molecule correlated well with expression of benzodiazepine receptor and CD68 expression on macrophages in the synovium. Being highly sensitive and ability to capture multiple joints simultaneously, PET scan may be used to pick up sub clinical synovitis. Recently, PET analysis with 18F FDG tracer molecule was conducted in 18 inflammatory arthritis patients; four of them were in disease remission status[27]. 18F FDG uptake was significantly different between patients with active RA vs patients in remission. Moreover, it has been reported that 18F FDG uptake varied with alterations in CRP and matrix metalloproteinase 3 levels in patients with RA receiving anti-TNF therapy[28,29]. However, as radiation amount of a PET-CT is high, it cannot be recommended for routine screening of RA patients in clinical practice. To overcome this problem, a new technique, PET MRI is being developed[30]. Currently, there is no data available regarding its role in evaluation of synovial inflammation. Synovial phagocytes cell were targeted with tracer molecule PK11195 in PET scanning to identify early synovial inflammation in 24 anticyclic citrullinated peptide antibody positive patients presenting with arthralgias only. PET scan was focused on hand joints only. Four patients were detected to have PET positive joints at baseline and all four developed RA within next 2 years. Amongst rest, five more developed RA but had negative PET scan at baseline. Among these five two developed arthritis of hand joints and rest three developed arthritis outside the field of view of PET scanner[31].

CT SCANNING

Compared to other imaging approaches very few CT scan based investigations are available in the context of synovial inflammation. It may assist in diagnosis of several different kinds of inflammatory arthritides. Similar to conventional X-ray, it very well demonstrates the cortical bone architecture and is considered as the gold standard for the imaging of erosions in the joints against which other imaging techniques are evaluated[32-34]. Multidetector CT generates quite excellent images which can be saved in a digital format and can be utilized to compare progression of the joint erosions during follow up. CT scan out-performed MRI in evaluating joint erosions at wrists in RA[34]. Similar data was reported by Døhn *et al*[35,36] for erosions at the metacarpophalangeal (MCP) joints during serial monitoring of patients of RA being treated with anti TNF-α therapy. CT scanning exposes to ionising rays but the influence of this is comparatively minimal as only the extremities are analysed. The major drawback of CT scanning is limited coverage of joint areas as compared to conventional X-ray imaging[37].

Micro focal CT is a better image quality strategy which enables assessment of bone mineral density. This technique has been used for the analysis of erosions in RA. In a study it was observed that small erosions in joints were seen in both controls and RA subjects, but erosions > 1.9 mm diameter were specific for RA. Using this very technique it was reported that anti interleukin 6 receptor monoclonal antibody (tocilizumab) could repair bone erosions and has favourable effect on bone remodelling in RA[38,39].

CT osteoabsorptiometry is another imaging strategy which has been utilized to evaluate periarticular osteopaenia in early inflammatory arthritis. It was observed that RA patients had significantly less mineralization at MCP joints compared to control subjects[40]. Volumetric bone mineral density evaluated with the use of a quantitative CT (high resolution-peripheral quantitative CT, HR pQCT) system confirmed the involvement of trabecular bone compartment in the peri-articular osteopenia[41]. Presently, all these newer CT scan techniques are only at research stages and are less likely to be available for routine clinical practice in near future.

MRI IN SYNOVITIS

MRI is one of the most sensitive methods available to evaluate cartilage, synovium and bone tissue changes in the joint. MRI-based quantification of synovial thickening and synovial fluid volume indicate disease activity. The signal strength related with synovial thickening is intermediate to minimal on T1 weighted image, but higher on T2 weighted image due to excessive water of synovial fluid within the synovium and reflects the degree of inflammation[42]. Synovial inflammation is further enhanced on T2 weighted image on MRI scanning. Differentiation of synovial inflammation from synovial fluid without using contrast agent is challenging; however, heavily T2 weighted images can differentiate between the two. Compared to joint effusion inflamed synovium has lower signal intensity on T2-weighted image[43]. Contrast based T1 enhancement on MR imaging with kinetic study is helpful in differentiation of effusion from inflamed synovium[44,45]. Gadolinium based contrast medium enhances inflamed synovium soon after administration however, it rapidly diffuses into synovial fluid compartment, resulting in equal signal strengths between synovium and the synovial fluid. This rate of equilibration of signals between the synovium membrane and the synovial fluid compartment may indicate the degree of leakiness of inflamed vessels in the synovium and thus intensity of inflammation[45].

Dynamic contrast enhanced MRI in synovitis progression

Dynamic contrast enhanced MRI (DCE MRI) is an imaging technique which is used for evaluation of the pharmacokinetic factors relevant to the exchange of contrast material between intravascular and extra vascular spaces and indicate the presence of new blood vessels (neo angiogenesis) in inflamed joint. T1 weighted MRI images are obtained prior to and after administration of a T1-shortening diffusible contrast agent. Post contrast time intensity curve delineating the concentration of the contrast agent in the areas of synovium reflects the intensity of inflammation in the synovium. Information obtained from the time intensity curve can be examined semi quantitatively or quantitatively with the Toft's model based software. In the semi quantitative analysis, factors that define the form of the time intensity curve, for example uptake of contrast agent, maximum enhancement and wash out ratio are calculated[46-49]. The degree of synovial inflammation is quantified by pharmacokinetic model by plotting time intensity curve which analyses diffusion of contrast agent from the vascular compartment to the extra vascular extracellular compartment[46]. The rate of exchange of contrast agent between these two compartments and amount of contrast agent in the extracellular spaces depend upon the perfusion and leakiness of the blood vessels in the synovium. DCE MRI is being progressively utilized for the recognition of synovial inflammation in early inflammatory arthritis. DCE MRI results have been correlated strongly with histological severity of inflamed knee synovium. Not only this, it was further utilized to monitor reduction in inflammation following intra articular steroid injection[50-52]. Another study reported that many RA patients display enhanced capillary leak and vascularisation of the synovium[53]. Efficacy of antiTNFα treatment in RA patients was observed by decrease in various DCE MRI parameters such as enhanced T1 relaxation time, volume transfer constant and fractional blood volume. Furthermore, volume transfer constant (kp) has been reported to be a good marker of vascularity in the synovium[49]. In other studies in RA patients, color coded DCE MRI parameters such as; micro vessels density and permeability were overlapped over anatomical MRI images, it was observed that the distribution of information produced by kps and fractional blood volume computations matches the qualitative evaluation of signal strength on post contrast T1 images[46,49]. Analyses of qualitative readings of colour coded parametric images were reliable and consistent on several image acquisitions of the same individual at different time intervals. Hence, DCE MRI represents a highly efficient technique which has potential to be non-invasive imaging biomarker for evaluation of alterations in vascularity of inflamed synovium. It can be utilized for monitoring efficacy of disease-modifying anti-rheumatic drugs (DMARD) and biologic therapies in RA and other inflammatory arthritis.

Advantages and disadvantages of various imaging techniques have been listed in Table 1.

Quantify synovial inflammation with diffusion tensor imaging

Diffusion tensor image (DTI) is a non contrast based image strategy that quantifies diffusion of fluid in vivo as well as provides details of the tissues at microscopic level[54,55]. This imaging strategy has been used in the evaluation of structure of organised tissues such as neural tissues of the brain, heart muscle tissues and intervertebral disc[56]. Because of presence of the cell membranes and other elements in *in vivo* system, diffusion of water molecules is restricted and these arrange themselves along a particular direction, along the length of tissue components rather than perpendicularly, on application of strong magnetic field. Restricted movement of water molecules in a particular direction is called as anisotropic diffusion. Anisotropy of water molecule can be utilized to obtain details about the cells organization at microscopic level[57]. Diffusion of normal fluid is isotropic and it can be analyzed with only one diffusion parameter but in biological tissue anisotropic diffusion can be described by a 3 × 3 symmetric matrix. In biological tissues, complete diffusion matrix can be computed by calculating 6 independent matrix elements. The most widely used scalar indices that are based on DTI are the fractional anisotropy (FA) and mean diffusivity (MD)[58-60]. FA is a measure of diffusion anisotropy and its minimum value "0" represents isotropic diffusion, *i.e.*, equal probability of diffusion in all directions. Whereas a maximum value of "1" represents highly restricted diffusion such as very thin fibres. MD on the other hand represents mean of

Table 1 Comparison of various non-invasive imaging techniques in assessment of synovial inflammation

Imaging technique for quantification of synovial inflammation	Advantages	Limitations
Radiography	Cost effective, Ease of access, Wide coverage of important joint regions, newer digitised formats that allow easy retrieval and comparison of images longitudinally and relative low cost	Exposure to ionising radiation, which although relatively low for one set of X-rays can cumulate over time with a potential impact on patient longevity Lack of sensitivity for detecting early joint damage and inability to image the inflammatory processes within the joint that precede damage Very little information regarding severity of inflammation Lacks quantifiable variables of inflammation in early arthritis
Ultrasonography	It is sensitive, cost effective, can be performed by the treating physician in out-patient-department basis, and can be repeated as desired for serial monitoring of inflammation	Normal anatomical structures may have low reflectivity and mimic synovitis if careful attention is not paid to technique, particularly with lower resolution equipment Operator dependent
Positron emission tomography	Sensitive, able to assess inflammation at molecular level Used for imaging sub-clinical synovitis because of their sensitivity and ability to capture many joints	Costly, Still experimental No evidences available in early synovitis. Not available at many centres and not being used in day to day clinical practices High radiation exposure
Computed tomography scanning	Cost effective Multidetector helical CT produces very high-quality images which can be stored in a digitised format and compared with later images to determine erosion progression Gold standard for imaging of bone erosions	Computed tomography scan upon whole body scanning leads to high dose radiation exposure It does provide less coverage than plain radiography as usually only one joint area is scanned
Magnetic resonance imaging	Sensitive techniques to assess soft tissue and bone changes in the joints Very sensitive for the detection of early synovial inflammation Diffusion Tensor based imaging can evaluate molecular event during synovial inflammation without contrast medium	Time consuming, Relatively costly Contrast based enhancement required for dynamic study

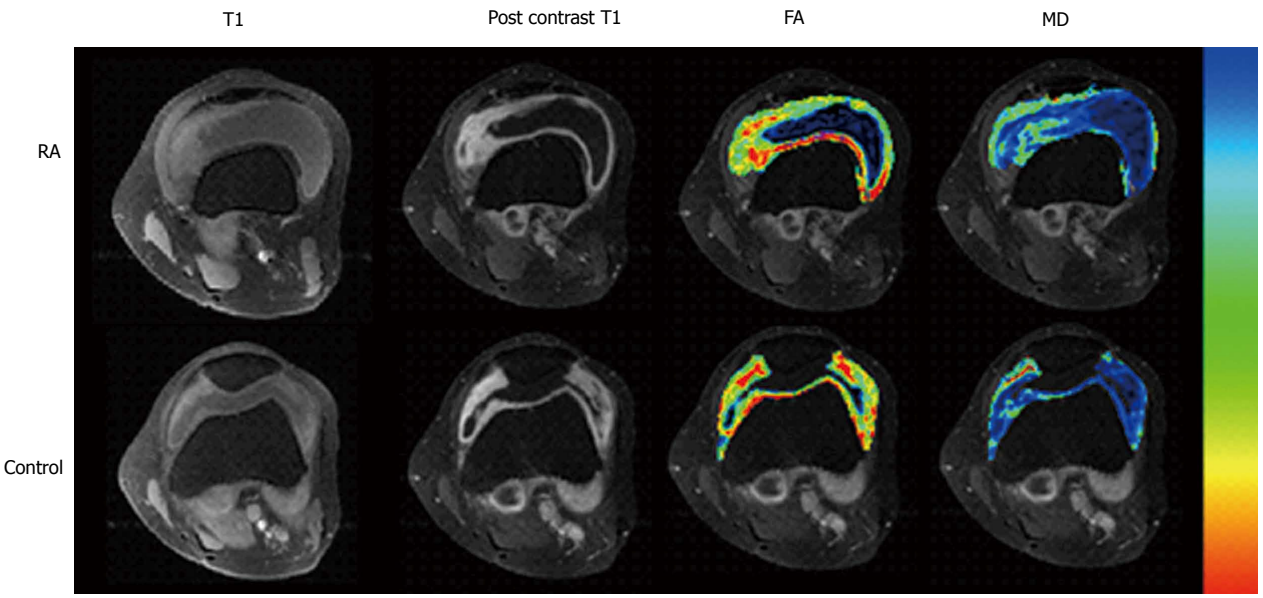

Figure 1 A 45-year-old male rheumatoid arthritis synovium shows strong enhancement on fat suppressed post-contrast T1-weighted axial image. Color coded fractional anisotropy (FA = 0.26) map from segmented region of enhanced synovial membrane overlaid on post-contrast fat-suppressed T1-weighted image show increased FA as compared to control (FA = 0.19). Mean diffusivity being inversely related to FA showed low values (1.01×10^{-3} mm^2/s). Color red denotes increased whereas blue denotes decreased values. RA: Rheumatoid arthritis; MD: Mean diffusivity; FA: Fractional anisotropy.

molecular motion independent of direction of the tissue. It depends upon the size and integrity of the cells.

We have earlier evaluated DTI parameters to assess severity of synovial inflammation in eighteen RA patients and six healthy individuals. Considerably significant high FA and reduced mean diffusivity were seen in RA individuals in comparison to controls (Figure 1). In this study we found a strong association between FA and synovial liquid IL-1β and TNF-α levels[61]. We also observed a positive correlation between cylindrical isotropy and

sICAM which suggested that the adhered inflammatory molecules on synovium represent the planar model of diffusion tensor. This led us to speculate that limited movement of water molecule in the synovium of inflammatory arthritis patients was a consequence of inflammatory cell infiltration and aggregation[62]. It has been suggested that this technique may replace synovial histology to evaluate the severity of inflammation and assess efficacy of disease modifying drug therapy[63].

CONCLUSION

Various newer imaging techniques are being utilized to explore the pathogenesis of synovial inflammation and soft tissue disruptions that occur in various inflammatory and damaging arthritides. The new emerging techniques have capability to quantify synovial inflammation and vascularity and modifications in cartilage biochemistry as well. A combination of DTI with DCE MRI may capture microscopic features of inflammation such as cellular infiltration and increased vascularity and may emerge as powerful tools to evaluate severity of inflammation at the level of synovium. These imaging strategies are important for analyzing the clinical effectiveness of DMARDs and biologics. Developments in imaging techniques, such as the miniaturization of extremity magnet for DCE and DTI MRI, and automated software programs may make these techniques available for routine clinical usage.

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Does a biological link exist between periodontitis and rheumatoid arthritis?

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Abstract

Periodontitis or Periodontal disease (PD) and Rheumatoid arthritis (RA) are two the most common chronic inflammatory diseases. Periodontitis is a biofilm associated destructive inflammatory disease of the periodontium caused by specific microorganisms. Rheumatoid arthritis is an autoimmune condition and is identified by elevated serum autoantibody titre directed against citrullinated peptides or rheumatoid factor. Periodontitis may involve some elements of autoimmunity. Recent studies have established that PD and RA show a common pathway and could be closely associated through a common dysregulation and dysfunction in inflammatory mechanism. The enzyme peptidyl arginine deiminase (PAD), expressed by *Porphyromonas gingivalis* (*P. gingivalis*) is responsible for the enzymatic deimination of arginine residuals to citrulline resulting in protein citrullination and its increased accumulation in RA. Citrullination by PAD may act as a putative biologic link between PD and RA. Association of Human leukocytic antigen-DR4 antigen has been established both with RA and PD. Several interleukins and inflammatory mediators (ILs) and Nuclear factor kappa beta ligand are linked to these common chronic inflammatory diseases. Antibodies directed against heat shock protein (hsp 70 ab) of *P. gingivalis*, *P. melanogenicus* and *P. intermedia* are raised in PD as well as RA. Both the conditions share many pathological and immunological similarities. Bacterial infection, genetic susceptibility, altered immune reaction and inflammatory mediators considered responsible for RA are also associated with PD. So it is plausible that a biological link may exist between PD and RA. Therapies aimed at modifying the expression and effect of inflammatory mediators and effector molecules such as matrix metalloproteinases, proinflammatory cytokines and autoantibodies of structural proteins may probably reduce the severity of both RA and PD.

Key words: Periodontal disease; Rheumatoid arthritis; Citrullinated peptidase; *Porphyromonas gingivalis*; Inflammatory marker; Inflammation and autoantibody

Core tip: Periodontal disease (PD) and Rheumatoid arthritis (RA) share many pathological and immunological similarities. Recent studies have established significant association between the two. Bacterial infection, genetic susceptibility, altered immune reaction and inflammatory mediators considered responsible for RA are also associated with PD. So it is plausible that a biological link may exist between PD and RA. Therapies aimed at reduction of inflammatory mediators and effector molecules can probably reduce the severity of both RA and PD.

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INTRODUCTION

Periodontal disease (PD) is an immuno inflammatory disease of the periodontium which comprises of both hard and soft tissues like gingiva, periodontal ligament, cementum and alveolar bone. It results from a complex interaction between gram negative organisms, their byproducts and the response of the host[1-4]. The resulting gingival inflammation leads to destruction of both the soft and hard tissues supporting the tooth[5]. The prevalence is said to be as high as 80% to 90%[6].

For periodontal tissues in a healthy state, a steady equilibrium exists between tissue destruction and repair. Periodontal destruction is initiated and progressed by specific periodontal microorganisms that colonize in plaque biofilm. Host microbial interaction determines the extent and severity of periodontal disease[7-9]. A large number of different species of bacteria can be identified in the dental plaque[10] but only a few of them are implicated in chronic periodontitis[11,12]. To prevent exacerbated reactions and destruction of host tissues, an appropriate tolerance mechanism is required by the host to recognize and identify nonpathogenic and pathogenic bacteria[13]. Pattern recognition receptors and microbe associated molecular patterns have a very significant role in periodontal inflammation and adaptive immune response[13,14].

The equilibrium established between anti-inflammatory and proinflammatory cytokines (IL-1α, IL-1β, TNF-α, IL-6[15], IL-7, IL-11, IL-17A, IL-17F, IFN-γ, IL-4, IL-10, IL-13, IL-16, IFN-α, TGF-β[16,17]) is responsible for the net inflammatory response. Increased levels of IL-1β, IL-12, IL-6, IL-17, TNF-α, and IFN-γ are reported in gingival tissues of chronic destructive periodontitis[18,19]. In periodontitis both Th1 (IFN-γ, IL-2, TNF-α) and Th2 (IL-4, IL-5, IL-6, IL-13) type cytokines are observed[20]. There is supporting evidence for the role of IL-17 and Th17 cells in periodontal disease[21]. IL-17 induces IL-6 and IL-8 secretion by gingival fibroblasts and also upregulates MMP - Matrix Metalloproteinases (MMP-1) and MMP-3 in these cells[22,23]. IL-17 also induces IL-1β and TNF-α secretion from macrophages and gingival epithelial cells[22,23]. Inflammatory cytokines are produced as a result of activation of toll like receptors of oral epithelial cells by the lipopolysaccharide of the gram negative periodontal pathogens[24]. Recently it has been reported that pathogenesis of many systemic diseases are associated with these inflammatory mediators. The pathways bridging periodontal infection and systemic health include transient bacteremia via metastatic infection, injury and inflammation resulting from immunological response induced by periodontal pathogens[25].

Recent studies have demonstrated that chronic periodontitis acts as a risk factor for systemic diseases like diabetes mellitus, cardiovascular disease, adverse pregnancy outcomes, rheumatoid arthritis etc[26-28].

Rheumatoid arthritis (RA) is a chronic inflammatory disease of articular joint with unknown etiology marked by a symmetric, peripheral polyarthritis and often results in joint damage and physical disability. The pathogenic hallmark of RA is synovial inflammation and proliferation, focal bone erosion and thinning of articular cartilage. Articular cartilage is an avascular tissue composed of a specialized matrix of collagen, proteoglycans and other proteins. Chondrocytes contribute to the unique cellular component. Cartilage is a highly responsive tissue that reacts to inflammatory mediators and mechanical factors, which in turn alters the balance between cartilage anabolism and catabolism. The structural damage to the mineralized cartilage and subchondral bone is mediated by osteoclasts[29].

Worldwide prevalence of RA, an autoimmune condition is approximately 1%[30]. It is diagnosed as chronic inflammatory polyarthritis when five or more joints are affected[29]. On close observation, a number of similarities seem to exist between the supporting periodontal structures and articular joint (Table 1).

SIMILARITIES BETWEEN RA AND PD

Periodontitis is a destructive chronic inflammatory disease of the periodontium caused by biofilm associated specific microorganisms[31-33]. Rheumatoid arthritis is an autoimmune condition and is characterized by elevated serum autoantibody titre directed against citrullinated peptides or rheumatoid factor (RF)[34,35]. Autoantibodies such as RF and anti-citrullinated protein/peptide antibody (ACPA) may be found in the sera of RA patients long before clinical onset of disease[27]. Periodontitis may also involve some elements of autoimmunity[36]. Autoantibodies and specific T cells against host molecules, such as type 1 collagen, have been detected in periodontal disease[23]. Recent studies have established statistically significant association between PD and RA[37-41]. The likelihood of PD among patients with RA is high. Also a higher prevalence of RA has been reported among patients with moderate to severe PD[41]. Joseph R. reported more periodontal destruction in RA group, pointing to a positive association between these diseases[42]. When comparing patients with RA and those with PD, many similarities have been reported in terms of serum cytokine and gene expression profiles, increased levels of serum matrix metalloproteinases, reactive oxygen species, lipid mediators, and neutrophil associated enzymes[5,43-46]. It has further been proposed that polymorphisms relating to genes encoding inflammatory cytokines might confer susceptibility to RA and PD[47-49]. Table 2 depicts some similarities observed in the pathogenesis of RA and PD.

Role of Porphyromonas gingivalis and immune response

Periodontal pathogens like *Porphyromonas gingivalis* (*P. gingivalis*) can invade the blood vessels and endothelial cells and lead to persistent bacteremia. It has the ability to in-

Table 1 Similarities between periodontal structures and articular joint

Supporting periodontal structures	Articular joint
Periodontal structures comprise of cementum, alveolar bone, periodontal ligament, gingival crevicular fluid and gingiva	Articular joints comprise of articular cartilage, bone, ligaments, synovial cavity, synovial fluid, and synovial capsule
Cementum is an avascular tissue	Articular cartilage is an avascular tissue
Periodontal ligament is a thin connective tissue that surrounds the root connecting it to the alveolar bone	Synovial tissue is a thin layer of connective tissue. It consists primarily of two cell types-type A synoviocytes (macrophage derived) and type B synoviocyte (fibroblast derived)
Periodontal ligament is collagenous and consists of epithelial rests of malassez, fibroblasts, osteoblasts and ground substances (hyaluronic acid and proteoglycans-fibronectin and laminin)	Synovial fibroblasts are the most abundant and produce the structural components of the joints including collagen, fibronectin and laminin
Gingival crevicular fluid is an infiltrate of blood	Synovial fluid is an infiltrate of blood

Table 2 Similarities in pathogenesis periodontal disease and rheumatoid arthritis

PD	RA
Chronic immunoinflammatory disease	Chronic immunoinflammatory disease
Periodontal pathogen is the main etiological agent with some element of autoimmunity	Bacteria/peptide as an adjunct antigen in autoantibody production
HLA-DR antigen association	HLA-DR antigen association
Inflammatory infiltrate mainly consists of B cells, plasma cells, PMN, T cell, dendritic cell, and macrophages	Inflammatory infiltrate consists of T cell, B cell, plasma cell, dendritic cell, mast cell, macrophages, and few granulocytes
Increases level of IL-1, TNF-α, PGE2, MMPs, NF-κB, RANK/RANKL/OPG, osteoclast activation	Increases level of IL-1, TNF-α, PGE2, MMPs NF-κβ, RANK/RANKL/OPG, osteoclast activation
Th1, ↑ ed Th2 and Th 17	Th1 = Th2 and Th 17
Role of nitric oxide	Role of nitric oxide
Genetic and environmental influences	Genetic and environmental influences
Bacterial DNA of anaerobes and high antibody titres against heat shock protein of *P.gingivalis*, *P. Melanogenicus* and *P. Intermedia*[95]	Bacterial DNA of anaerobes and high antibody titres against heat shock protein of *P. gingivalis*, *P. Melanogenicus* and *P. Intermedia*[95]

PD: Periodontal disease; RA: Rheumatoid arthritis; IL: Inflammatory mediator; MMPs: Matrix metalloproteinases; HLA: Human leukocytic antigen; HLA-DR: Human leucocyte antigen- D related; RANK: Receptor activator of nuclear factor kappa-β; RANKL: Receptor activator of nuclear factor kappa-β ligand; OPG: Osteoprotegerin; *P. gingivalis*: *Porphyromonas Gingivalis*; *P. intermedia*: *Prevotella intermedia*; *P. melaninogenicus*: *Prevotella melaninogenicus*; TNF: Tumor necrosis factor; NF-κB: Nuclear factor - kappa β; IL: Interleukin; PGE2: Prostaglandin E2.

vade primary chondrocytes of knee joints. As a result, cell cycle progression gets delayed, ultimately leading to accelerated apoptosis of these chondrocytes[50]. The virulence of *P. gingivalis* is mainly associated with its trypsin like proteolytic activity and ability to produce arginine and lysine -specific cysteine endopeptidase like gingipain R and gingipain K respectively[51]. Gingipain aids in evasion of host defense, tissue destruction and infection[52,53]. It leads to activation of MMPs (1, 3 and 9) and degradation of host proteins (laminin, fibronectin and collagen)[54]. Being the only identified bacterium with expression of peptidyl arginine deiminase (PAD), *P. gingivalis* and PAD represent a notable pathogenic element of RA[55-58]. PAD catalyses the deimination of arginine residuals to citrulline, a form of post-translational protein modification[59] which leads to an irreversible translation of arginine to citrulline[56,59]. However one important difference is that PAD expressed by *P. gingivalis* and human PAD are not exactly homologous[56,59]. It has been reported that in RA there is an increased citrullination of structure proteins[60]. This probably accounts for the fact that *P. gingivalis* titre significantly correlates with ACPA titre in RA patients[56,61-65].

GENETIC PROFILE IN PD AND RA

The most potent disease risk gene in RA and PD is the genome on the human leukocytic antigen (HLA) region[66]. HLA-DR4 antigen is associated with both RA and PD. This genetic association between these chronic inflammatory conditions also points to the biologic link between them[65,67-69]. Hitchon and colleagues have reported an association between *P. gingivalis* and the presence of ACPA in a population with predominant RA-predisposing HLA-DRB1 alleles. This gene-environment interaction may contribute to the breaking up of self-tolerance to citrullinated proteins. It could also amplify autoimmune reactions which could predispose to RA[70].

MARKERS OF INFLAMMATION IN PD AND RA

The synovial fluid of RA patients is rich in proinflammatory cytokines and many interleukins, (IL-1, IL-6, IL-8, IL-15, and IL-17) as well as NF-κB ligand (RANKL) which can be linked with RA[71,72]. Similar profile of inflammatory mediators has been identified in chronic periodontitis[35,73,74]. Elevated serum levels of TNF-α is associated with both these chronic inflammatory diseases[74,75]. Lipopolysaccharides and other bacterial byproducts stimulate the release of TNF-α and it upregulates the release of prostaglandin E2 (PGE2) and MMPs that stimulate osteoclast activation. These inflammatory processes ultimately lead to bone resorption in both RA and PD[76].

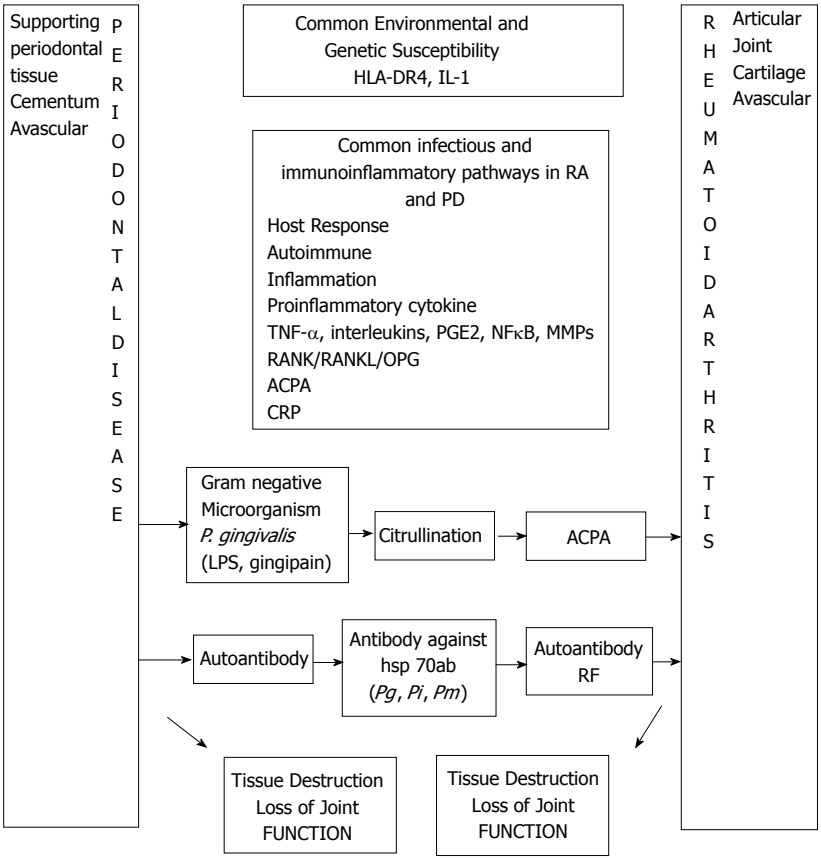

Figure 1 Hypothetical model of biological link between rheumatoid arthritis and periodontal disease. ACPA: Anti-citrullinated protein/peptide antibody; CRP: C reative protein; HLA: Human leukocyte antigen; hsp: Heat shock protein; LPS: Lipopolysaccharide, MMPs: Matrix metalloprotienases; NFκB: Nuclear factor kappa β; OPG: Osteoprotegerin; PD: Periodontal disease; PGE2: Prostaglandin E2; RANK: Receptor activator of nuclear factor kappa β; RANKL: Receptor activator of nuclear factor kappa β ligand; RA: Rheumatoid arthritis; RF: Rheumatoid factor; TNF-α: Tumor necrosis factor alpha; ACPA: Anti-citrullinated protein; RF: Rheumatoid factor; *P. gingivalis*: *Porphyromonas gingivalis*; IL: Interleukin.

EFFECTS OF THERAPY FOR RHEUMATOID ARTHRITIS ON PERIODONTAL DISEASE AND THERAPY FOR PERIODONTAL DISEASE ON RHEUMATOID ARTHRITIS

It has been suggested that treatment of periodontitis in patient with RA improved their response to RA therapy[77-80]. Treatment of RA with disease modifying antirheumatic drugs (DMARDS) improves their periodontal condition due to its host modulatory effect, thus masking the gingival inflammation and actual periodontal destruction[81-83]. Similarly, reduction in the systemic inflammation by the additional effect of periodontal therapy may also have been masked by DMARDs[35]. Al-Katma *et al*[84] assessed the role of scaling and root planning (SRP) on RA and demonstrated that there was an improvement in RA scores in the test group as compared to the control group. Advances in treatment of RA have identified novel therapeutic targets such as anticytokine therapy. Anti-TNF-α therapy used to control RA may also be beneficial in the management of periodontitis[85-88]. Ortiz *et al*[77] assessed the additional effect of non-surgical periodontal therapy (NSPT) in RA patients under anti-TNF-α therapy and reported that regardless of the medications, supportive periodontal therapy had a positive result on the clinical features of RA. In the absence of periodontal treatment anti-TNF-α therapy alone had no relevant outcome on the periodontal condition[77].

DOES A BIOLOGIC LINK EXIST BETWEEN PERIODONTAL DISEASE AND RHEUMATOID ARTHRITIS?

First of all, PD and RA share many pathological and immunological similarities. A cyclic nature of disease activity is seen in both RA and PD. There is evidence to suggest that PD could act as a potential risk factor for RA[24,89,90]. Similarly, RA subjects have significantly increased clinical attachment loss (CAL)[19-21]. Increased levels of antibodies to periodontopathic bacteria are reported to have been identified in sera and synovial tissues of patients with RA[63,70,81,91]. Correlation of serum level IgG antibodies to *P. gingivalis* with anticyclic citrullinated peptide indicates that serum protein citrullination via peptidyl arginine deiminase of *P. gingivalis* drives RA responses[63,70]. Citrullination by PAD may act as a biologically plausible mechanistic link between PD and RA. Furthermore the presence of RA might predispose individuals to PD[92,93]. Clinical trials suggest that treatment of PD has a significant effect on RA severity and vice versa[84,94].

Second, it is suspected that *IL-1* gene polymorphism affects the cytokine protein in RA and PD. HLA DR4 antigen is associated with both the conditions which points to the biological link between the two[67].

Third, it is reported that antibodies against heat shock protein (hsp 70 ab) of *P. gingivalis, P. melanogenicus and P. intermedia* are elevated not only in supporting periodontal tissues but also in synovial tissue of articular joints of RA patients[91,95].

Fourth point, Both RA and PD have shown raised titres of IL-10, IL-1α , IL-1β, MMPs, TNF-α ,LT-α and low titres of IL-1α and IL-6[45]. A common inflammatory marker dysfunction seems to be associated with both the articular joint and supporting periodontal tissue.

Bacterial infection, genetic susceptibility, altered immune reaction and inflammatory mediators considered responsible for RA are also associated with PD. So it is plausible that a biological link may exist between PD and RA (Figure 1).

EVIDENCES LINKING PD AND RA

Several studies have revealed that the prevalence of PD was high in patients with RA[40,42] and that PD severity was greater in RA patients[45]. Mercado *et al*[39] (2001) demonstrated a relation between RA and severity of periodontitis in a case control clinical study. Pischon *et al*[40] (2009) in a cross sectional clinical study showed significantly more CAL in RA subjects as compared to non-RA subjects. They have concluded that oral hygiene may account for this association to some extent. Kobayashi *et al*[49] (2007) reported that IL-1 and FCγR gene polymorphism have potential risk for RA and periodontitis.

Martinez-Martinez *et al*[96] (2009) in a case series clinical study on subjects with refractory RA and periodontitis found that *P. intermedia, P. gingivalis,* and *T. denticola* were the most predominant gram negative bacteria identified in synovial fluid, which substantiates the concept of anti-CCP and citrullinated structure protein. Dissick *et al*[41] (2010) in a case control study demonstrated that RA+ patients have more moderate to severe periodontitis. They have reported that females and smokers are at more risk in the RA+/periodontitis complex

Okada *et al*[81] (2011) demonstrated that corticosteroids, anti-rheumatic drugs, NSAIDs and TNF-α antagonists therapy improved the clinical features of periodontitis in RA patients. Presence of anti-PG IgG antibodies in RA+ patients may influence the serum RF level and periodontal health status[81]. Mayer *et al*[83] (2009) in a case control study concluded that TNF-α levels correlated with overall CAL and that inhibition of proinflammatory cytokines may account for the reduction of periodontal parameters. In another case control study, Ribeiro *et al*[94] (2005) evaluated the role of NSPT on RA status and found that RF decreased after periodontal intervention. The effects of NSPT in subjects with and without RA was studied by Pinho Mde *et al*[97] (2009) and they stated that that the relation between RA and periodontal disease activity is unclear. The effect of NSPT on RA patients under anti-TNF-α was studied by Ortiz *et al*[77] (2009) who inferred that NSPT had a positive effect on the clinical parameters of RA. Okada *et al*[98] in (2013) suggested that periodontal treatment decreases the levels of antibodies to *P. gingivalis* and citrulline in patients with RA and Periodontitis. They concluded that these observations may reflect the role of *P. gingivalis* in the protein citrullination which is related to the pathogenesis of RA[98]. Kaur *et al*[78] (2014) in a systematic review and meta analysis reported that non surgical periodontal therapy could lead to improvement in clinical and biochemical disease activity in RA.

Quirke *et al*[99] in 2013 reported that *P. gingivalis* is seemingly distinctive among periodontal pathogens in having PPAD (*P. gingivalis* peptidylarginine deiminase) with potential to evoke autoimmune response. They opined that the peptidyl citrulline specific immune response to PPAD might break tolerance in RA and could be a target for therapy[99]. Agnihotri *et al*[100] in (2014) reviewed the link between RA and PD in the elderly and inferred that thorough understanding of the link between the two chronic inflammatory diseases might be beneficial in rendering better health care protection and betterment of the life style of aged individuals.

CONCLUSION

The relationship between RA and PD can be attributed to common dysfunction and dysregulation in inflammatory mechanisms. Apparently, the common factors are bacterial lipopolysaccharides and inflammatory mediators. Development of specific autoantibodies by citrullination of protein by *P. gingivalis* may be the connecting link between RA and PD. Therapies aimed at suppression of inflammatory mediators and effector molecules such as MMP, proinflammatory cytokines and autoantibodies of structural proteins may probably reduce the severity of both RA and PD.

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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