

Prevalence and risk factors for liver fibrosis detected by transient elastography or shear wave elastography in inflammatory arthritis: a systematic review

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ABSTRACT

Objective. Emerging technologies for monitoring subclinical liver fibrosis include transient elastography (TE) and shear wave elastography (SWE). A systematic review was conducted to assess the prevalence and report on predictors of liver fibrosis as detected by these technologies in inflammatory arthritis (IA) patients, including rheumatoid arthritis, spondyloarthritis and juvenile idiopathic arthritis.

Methods. MEDLINE, EMBASE and Web of Science were searched from inception to 06/27/2016 using search terms for IA or DMARDs and TE/SWE. Studies reporting on prevalence and/or risk factors for liver fibrosis as detected by TE/SWE were included. A meta-analysis was not conducted due to study heterogeneity.

Results. Seven cross-sectional and three case-control studies were included. The cut-off values to define liver fibrosis ranged from 5.3–8.6 kPa. The prevalence of liver fibrosis in RA detected by TE/SWE ranged from 3–23%, with higher prevalence found in studies using a 5.3kPa cut-off. In two studies fibrosis was reported in 16–17% of PsA patients with no JIA studies identified. Obesity was the most consistently reported independent predictor of fibrosis in three studies. Liver function tests (LFTs) were found to independently predict increased liver stiffness in one study, while cumulative dose of either methotrexate or leflunomide were predictors in two studies.

Conclusion. Methotrexate or leflunomide cumulative dose was not consistently reported as an independent predictor of liver fibrosis; whereas, obesity was more consistently identified. Of note, LFTs did not consistently predict elevated TE/SWE measures. Further

studies are needed to evaluate the prevalence and predictors of liver fibrosis and to explore the utility of using TE/SWE in IA patients.

Introduction

Inflammatory arthritis (IA) refers to a group of autoimmune conditions characterised by inflammation of the peripheral joints or spine causing pain, joint damage and disability if left untreated (1). Although treatment of IA differs depending on subtype and disease activity, the core treatment of peripheral joint synovitis are disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate, leflunomide, and sulfasalazine (2–4). In particular, methotrexate is the most commonly used DMARD and is a first-line treatment for RA (2). One potential adverse effect of many traditional DMARDs is hepatotoxicity (5), which has led rheumatology guideline groups including the American College of Rheumatology and others to recommend periodic testing of liver transaminase levels as a means of monitoring patients for hepatotoxicity (2). Some recent studies, however, have found evidence of sub-clinical liver fibrosis in IA patients treated with methotrexate, in the absence of liver enzyme abnormalities (6, 7). For this reason, additional tests and techniques may be needed to monitor IA patients for liver damage.

Non-alcoholic fatty liver disease (NAFLD) is emerging as the most common cause of liver disease in the general population, with a reported prevalence in western populations estimated between 20–30% (8, 9), due in large part to rising rates of obesity. Rates of NAFLD may be even higher in populations of patients with IA. For example, a recent systematic review

of 7 case-control studies in psoriatic arthritis (PsA) using controls without psoriasis demonstrated higher rates of NAFLD in PsA patients (Odds ratio, OR: 2.15, 95% CI 1.57–2.94) (10). The increasing prevalence of NAFLD in IA patients is an additional factor which may confound assessment while monitoring for hepatotoxicity of DMARDs, as it is also a common cause of liver enzyme abnormalities. Furthermore, monitoring guidelines for IA are largely based on studies conducted prior to the widespread recognition of NAFLD as a cause of chronic liver disease, and further algorithms using non-invasive liver testing may be necessary to better assess patient's risk of liver toxicity with DMARD use.

Transient elastography (TE) is a non-invasive technique that can be used to assess liver fibrosis in patients by measuring liver stiffness (LS) (11). In TE, low frequency elastic waves are transmitted through the liver and the velocity is used to calculate liver stiffness and quantify liver fibrosis (11). Owing to its validated diagnostic and prognostic accuracy and non-invasive nature, TE is now the recommended method for assessing liver fibrosis in patients with hepatitis C (12). To better understand the potential use of this technology in rheumatology patients with IA, we have conducted a systematic review with the aim of assessing the prevalence of sub-clinical liver fibrosis as detected by TE and to report on the predictors of sub-clinical liver fibrosis.

Materials and methods

A systematic review was conducted to identify studies that assessed the prevalence and/or risk factors for liver fibrosis in patients with IA using TE or shear wave elastography (SWE). The protocol for this study was registered with the International Prospective Register of Systematic Reviews, PROSPERO (PROSPERO 2016: CRD42016041914) (13). Reporting of this work is in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (14). As this was a systematic review it was exempt from ethics review at the University of Calgary.

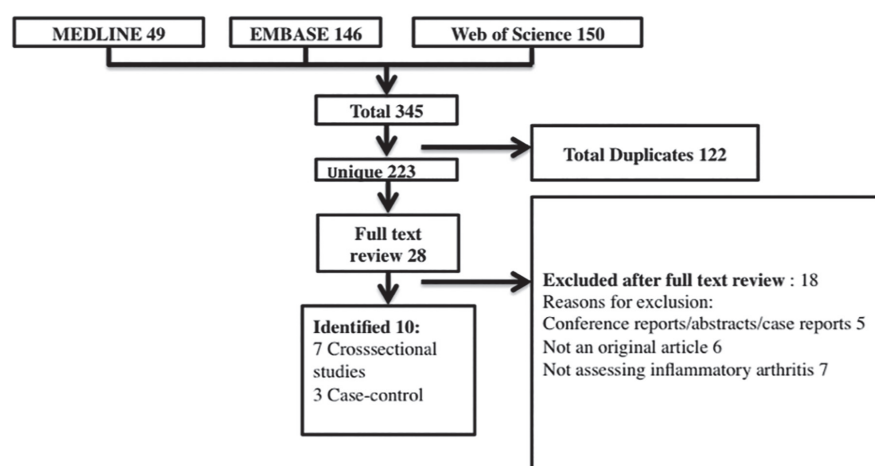


Fig 1. Selection process of included studies

Table I. Characteristics of included studies.

Study, years	Country	Study Type	Patient population	Patients (n)	Fibrosis cut-off (kPa)	% with liver fibrosis
Kim <i>et al.</i> (21), 2015	Korea	CC	RA	185	8.6	5
Laharie <i>et al.</i> (22), 2010	France	CC	RA, Psoriasis, CD	149 (RA)	7.9	5
Park <i>et al.</i> (7), 2010	Korea	CC	RA	177	7.8	3
Arena <i>et al.</i> (6), 2012	Italy	CS	RA	100	7.0	11
Barbero-Villares <i>et al.</i> (20), 2011	Spain	CS	RA, Psoriasis, IBD	17 (RA)	7.1	NR ¹
Lee <i>et al.</i> * (17), 2012	Korea	CS	RA	105	5.3	23
Park <i>et al.</i> * (18), 2014	Korea	CS	RA	101	5.3	22
Park <i>et al.</i> * (19), 2014	Korea	CS	RA	92	5.3	20
Pongpit <i>et al.</i> (24), 2016	Thailand	CS	Psoriasis, PsA	35 (PsA)	7.0	17
Seitz <i>et al.</i> (23), 2010	Switzerland	CS	RA and PsA	51 (RA) 43 (PsA)	8.0	RA=10 PsA=16

¹Study was included as risk factors for fibrosis were noted. In the entire study population (n=53) 7.5% had advanced fibrosis and one patient had cirrhosis (20). No significant difference between stiffness or fibrosis stage was noted between the subgroups (RA, psoriasis, IBD).

*These studies may have had overlapping cohorts.

CC: case control; CS: cross-sectional; CD: Crohn's disease; kPa: kilopascal; IBD: inflammatory bowel disease; NR: not reported; PsA: psoriatic arthritis; RA: rheumatoid arthritis.

Search strategy and study selection

A medical librarian assisted with developing a search strategy using a combination of Medical Subject Headings (MeSH) and non-MeSH terms for IA, DMARDs, and TE/SWE (Supplementary material). Three medical databases: MEDLINE, EMBASE and Web of Science were searched from inception to June 27, 2016 to identify relevant citations. There was no restriction based on language during the search and no suitable articles were identified that required translation. For the purpose of our study, we restricted IA to the following conditions, as they represent the most common conditions affecting adults and paediatric patients: rheu-

matoid arthritis (RA), PsA, ankylosing spondylitis (AS), and juvenile idiopathic arthritis (JIA). To be included, studies had to assess liver fibrosis by TE or SWE and report either the prevalence of fibrosis or risk factors for its development. Cross-sectional and case control studies were eligible for inclusion, whereas case series and reports were excluded.

Two reviewers (AR and CB) independently screened titles and abstracts and completed the full text review on selected studies. Disagreements were resolved through discussion to select the final number of eligible studies. Cohen's kappa was calculated as a measure of agreement between reviewers.

Table II. Clinical characteristics of included cohorts.

Study	Inclusion criteria	Exclusion criteria	Mean (SD) Age (years)	% female	Mean (SD) Duration of disease (years)	Mean (SD) MTX dose (mg)/wk Mean (SD)	Cumulative MTX dose (mg) Mean (SD)	Mean (SD) Duration of MTX (years)	Mean (SD) BMI (kg/m ²)	Diabetes (%)
Arena <i>et al.</i> 2012 (6)	RA patients, minimum MTX cumulative dose 1500mg	Liver disease, LFT abnormalities, ETOH abuse >7 units/wk, other hepatotoxic drugs, pregnancy, cardiac failure (or other condition affecting LS)	64 (13)	76%	NR	10.0 (2.5)	3595.5 (1938.6)	7.1 (3.9)	25.0 (4.4)	0
Barbero-Villares <i>et al.</i> 2011 (20)	IBD, RA, psoriasis patients on MTX	Not specified aside from technical failures from TE measurement	62 (16)	70%	7 (4)	NR	2635 (1581)	5.9 (3.1)*	25.0 (4)	NR
Kim <i>et al.</i> 2015 (21)	RA patients ≥18 years of age on MTX	Hep B or C, alcohol >20g/d, other hepatotoxic drugs, technical failure of TE assessment	54 (9)	78%	NR	NR	4825 (3396)	6.3 (3.8)*	23.2 (3.0)	13.5%
Laharie <i>et al.</i> 2010 ¹ (22)	RA, psoriasis, Crohn's disease patients ≥18 years of age and on MTX	Not specified aside from technical failures from TE measurement	56 (15)	68%	NR	NR	Median 1950 (range 780, 3570)	Median 3.0 (range 1.6, 6.3)*	24.8 (4.9)	3.4%
Lee <i>et al.</i> 2012 ² (17)	RA patients on MTX >24 weeks	Viral hepatitis, liver structural abnormalities, medications for liver disease, abnormal LFTs, albumin, bilirubin, INR or platelets. Technical failure of TE assessment	Median 54 (25, 73)	81%	Median 2.7 (0.5, 14.2)*	NR	Median 2032.5 (IQR 285.0, 7800.0)	NR	Median 22.1 (18.1, 27.6)	NR
Park <i>et al.</i> 2014 (18)	RA patients on MTX + meloxicam >6 months	Abnormal lab ranges or abnormal structure of liver or kidney on US	52 (10)	84%	NR	13.4 (2.9)	2843.3 (2009.0)	3.9 (2.6)*	22.2 (2.4)	NR
Park <i>et al.</i> 2014 ⁴ (19)	RA patients on MTX + celecoxib >6 months	Abnormal lab ranges or abnormal structure of liver or kidney on US. No significant (IQR 13) liver or kidney disease or use of medications for such diseases. Use of <19,170mg cumulative dose of leflunomide.	Median 55	80%	NR	13.4 (3.2)	Median 2201.3 (IQR 3343.8)	Median 2.9 (IQR 3.8)* (IRR4.2)	Median 21.8	NR
Park <i>et al.</i> 2010 (7)	RA patients ≥18 years of age with MTX use >3 years	Liver disease, "heavy alcoholics", diabetes mellitus, chronic renal insufficiency, heart failure, BMI > 28 kg/m ² . Patients on concurrent Leflunomide.	54 (10)	95%	13 (7.7)	10.1 (1.9)	3988 (1566)	8.3 (2.8)*	21.5 (2.5)	NR
Pongpit <i>et al.</i> 2016 ³ (24)	Plaque psoriasis ≥18 years of age (included subset with PsA)	Liver disease, ETOH >20g/day, pregnancy.	49 (14)	54%	16.5 (12.1)	NR	42% had ≤1500, 24% had >1500 ^A remainder had no exposure	NR	24.8 (4.7)	18.8%
Seitz <i>et al.</i> 2010 (23)	RA and PsA with MTX >1 year ± use of anti-TNF-α for > 6 months	NR	RA: TNF- 60 (9); TNF+ 57 (13); PsA: TNF- 52 (14); TNF+ 51 (11)	RA: 65% TNF-; PsA: 30% TNF+	RA: TNF- 17.3 (10.8); TNF+ 13.0 (11.2); PsA: TNF- 9.5 (7.6); TNF+ 11.8 (11.2)	RA: TNF- 16.4 (3.8); TNF+ 16.0 (3.3); PsA: TNF- 16.1 (4.6); TNF+ 15.4 (5.4)	RA: TNF 6900 (5400); TNF+ 3800 (3200); PsA: TNF- 2700 (2300); TNF+ 3700 (3200) ^A	NR	RA: TNF- 26.0 (3.8); TNF+ 25.4 (4.4); PsA: TNF- 26.4 (3.8); TNF+ 27.0 (4.5)	RA: TNF- 7.1%; TNF+ 4.3%; PsA: TNF- 15.0%; TNF+ 13.0%

¹ The format of reporting in this study was median (range), note this was not specified as an interquartile range (IQR).

² The format of reporting in this study was median (IQR reported as 2 numbers).

³ The format of reporting in this study was median (IQR reported as a single number).

⁴ Results reported for entire cohort as separate results not available for subset with PsA.

*Values reported in weeks in these studies were converted to years for consistency in reporting and comparison between studies.

^A Converted to mg for consistency in reporting and comparison between studies.

Data abstraction and risk of bias assessment

Data abstraction was conducted in duplicate by the two reviewers using piloted data abstraction forms. For each included study, data regarding study design, characteristics of the cohort of patients including, type of IA, disease duration, and laboratory indices, such as ALT, AST and GGT levels were abstracted. Potential predictors of liver fibrosis, such as body mass index (BMI), age, sex, dose and duration of DMARD treatment were also abstracted. Data reported in different units (*e.g.* duration of disease in weeks *vs.* years) were converted to a single unit for comparison. For each study, the number of patients reported to have liver fibrosis and the cut-off value of TE measurements used to define liver fibrosis was abstracted. The proportion of the cohort with liver fibrosis was then calculated for each study. Any association found between clinical characteristics and liver stiffness in the studies was also abstracted. We contacted authors of cohort studies that included a mixed population of patients but did not report data for IA separately (*e.g.* those with only psoriasis or with inflammatory bowel disease (IBD)).

For case-control studies we used the Newcastle-Ottawa quality assessment scale to assess risk of bias (15). This scale assesses each study based on three themes including: study group selection, comparability of groups and the ascertainment of exposure. To assess the quality of cross-sectional studies, we modified a quality assessment tool that was developed by Marlais *et al.* (16). Using this tool, each cross-sectional study was assessed based on 5 questions and given a total score between 0-5. Risk of bias was assessed independently by each reviewer using the above-described tools. Where disagreements occurred, consensus was achieved by discussion.

Results

Search results and study characteristics

The search strategy identified 345 studies. After removing duplicates ($n=122$), the titles and abstracts of 223 studies

were screened and full text review was completed on 28 articles (Fig. 1). Overall, 10 observational studies ($\kappa=0.85$) met inclusion criteria, 7 of which were cross-sectional and 3 were case-control. The articles were published between 2010-2016 in Europe and Asia. Eight studies included patients with RA, one study reported on patients with PsA and one study included both RA and PsA patients. Table I summarises the characteristics of each study.

Study quality

An assessment of the quality of the cross-sectional studies is shown in supplemental Table I with ratings ranging between 2-5/5 across study design domains. Quality assessment of case-control studies is shown in supplemental Table II and total scores ranged from 6-8/10. In a majority of studies patient recruitment was often unclear, which could have led to selection bias in prevalence estimation. Specifically, it was unclear whether 3 studies (17-19) may have had overlapping cohorts, and an additional 4 studies (6, 7, 20, 21) did not describe their participant recruitment clearly enough to determine whether an unbiased prevalence estimate could be obtained. One study did not clearly report the proportion of patients with RA who had fibrosis but was still included in the review as other information on the cohort was abstracted in our evaluation of risk factors for fibrosis (20). Finally an additional 4 studies (6, 7, 22, 23) did not describe whether the person performing TE was blinded to patient diagnosis and medication status which could have also been a source of bias.

Patient characteristics

The included studies reflected a diverse group of patients with different diagnoses, such as RA, PsA, psoriasis, and IBD (Table I). The patient population was predominantly female (30 to 95%) with an average age range between 49 to 64 years (Table II). BMI was reported in all studies (Table II), although one study did not report BMI in the subset of patients with PsA. BMI ranged from 22 to 27 kg/m². The percentage of patients with diabetes was reported in 5 studies and ranged between 0 to 19%

(Table II). Disease duration was reported in 5 studies and varied between 7 to 17.3 years (Table II). In all but one study, the eligibility criteria were restricted to patients taking methotrexate. Seven studies reported a mean cumulative dose of methotrexate, which varied between 2635 to 6900 mg (Table II: those reporting only median shown in Table). Other medications that were administered concomitantly were reported in 4 studies and included leflunomide (17), non-steroidal anti-inflammatories (NSAIDs) (18, 19), and anti-tumour necrosis factor alpha (anti-TNF α) agents (23).

Most studies excluded patients with baseline liver enzyme or structural abnormalities (6, 17-19) or who had comorbid chronic liver disease (6, 7, 17, 19, 21, 24) or a history of high alcohol consumption (6, 7, 21, 24).

Prevalence of liver fibrosis

The prevalence of fibrosis in each study is shown in Table I. In the RA cohort, the prevalence of fibrosis in 8 included studies varied from 3 to 23%, while the prevalence of fibrosis in PsA patients in 2 included studies range between 16 to 17%. The trials were considered too heterogeneous to pool in a meta-analysis. The study design, patient populations, and inclusion criteria varied widely (Table I). The studies also used different cut-off values for TE measurements to define LS (Table I). Three Korean studies from the same centre used a cut-off value of 5.3 kPa based on a previous study that reported cut-offs for normal LS in the healthy Korean population (25). The remainder of the included studies used a cut-off between 7.0 to 8.6 kPa. The variability in cut-off thresholds for defining fibrosis is illustrated in Table I. The Korean studies included had a 2 to 4-fold increase in subclinical fibrosis compared to other RA cohorts.

Risk factors for fibrosis

Nine studies explored whether there was an association between cumulative methotrexate dose and liver fibrosis (6, 7, 17-22, 24) detected by TE or SWE, including 3 case-control studies (7, 21, 22) (Table III). In univariate

Table III. Risk factors for subclinical liver fibrosis in patients with inflammatory arthritis.

Study	Significant risk factors for fibrosis on correlation and univariate analysis	Significant risk factors for fibrosis on multivariate analysis	Other results
Arena <i>et al.</i> 2012 (6)	MTX cumulative dose ($r^2=0.64$, $p<0.0001$) MTX duration ($r^2=0.36$, $p<0.0001$) ALT ($r^2=0.05$, $p=0.025$) BMI ($r^2=NR$, $p<0.01$) GGT ($r^2=NR$, $p=0.02$) Steatosis ($r^2=NR$, $p=0.05$)	MTX Cumulative dose ($p<0.0001$)	Mean liver stiffness in patients with a cumulative MTX dose >4000 mg higher compared to those with <4000 mg ($p<0.0001$)
Barbero-Villares <i>et al.</i> 2011 (20)	No correlation between MTX cumulative dose and liver stiffness observed	No significant risk factors identified	No additional abstracted results
Kim <i>et al.</i> 2015 (21)	Age ($r=0.179$, $p=0.015$) BMI ($r=0.484$, $p<0.001$) Platelet count ($r=0.160$, $p=0.029$) AST ($r=0.162$, $p=0.028$) ALT ($r=0.222$, $p=0.002$) No correlation between MTX cumulative dose or duration of MTX treatment and liver stiffness observed	BMI (OR, 1.79; 95% CI: 1.34-2.39, $p<0.001$)	No additional abstracted results
Laharie <i>et al.</i> 2010 (22)	MTX cumulative dose: no correlation Factors associated with LS>7.9kPa High MTX cumulative dose (MTX>1500mg): no association ALT: no association Duration of MTX (>50 wks): no association Diagnosis of RA: no association Psoriasis (OR=2.47, 95% CI 1.16-5.27, $p=0.02$) BMI >28kg/m ² (OR 8.03, 95% CI: 3.66-17.58, $p<0.0001$) Alcohol >14 drinks/wk (OR 3.77, 95% CI 1.64-8.66, $p=0.002$) Metabolic syndrome (OR=4.16, 95% CI 1.76-9.82, $p=0.001$)	Factors associated with LS>7.9kPa BMI >28kg/m ² (OR=6.7, 95% CI: 2.8-16.1, $p<0.0001$) ¹ Alcohol use (OR=2.6, 95% CI: 1.1-6.3, $p=0.04$) ¹ Psoriasis: No association Metabolic syndrome: No association	No significant difference in median LS in patients with MTX 1500 mg to lower dose
Lee <i>et al.</i> * 2012 (17)	Correlation: GGT ($r=0.249$, $p<0.05$) Cumulative leflunomide ($r=0.285$, $p<0.05$) Cumulative prednisolone ($r=0.362$, $p<0.05$) Cumulative MTX dose: no correlation Factors associated with LS: GGT ($p=0.01$) Cumulative leflunomide ($p=0.04$) Cumulative prednisolone ($p<0.001$)	Cumulative dose of leflunomide (OR 1, 95% CI 1.0, 1.0, $p=0.007$).	ROC analysis: 19,170mg cumulative leflunomide predicted abnormal LS (AUROC 0.735, 95% CI 0.568, 0.903, $p=0.008$, sensitivity 60%, specificity 89.5%). Cumulative Leflunomide dose >19,170 mg OR 12.8, 95% CI 3.0, 55.1, $p<0.001$)
Park <i>et al.</i> * 2014 (18) (meloxicam study)	Correlation to LS: Mean weekly MTX dose: no correlation Factors associated with LS >5.3kPa: Duration of MTX use (OR 1.0, 95% CI 1.0, 1.0, $p=0.02$) MTX cumulative dose: no association Leflunomide cumulative dose (OR 1.0, 95% CI 1.0, 1.0, $p=0.002$)	Duration of MTX use: no association MTX cumulative dose: no association MTX mean weekly dose: no association Meloxicam cumulative dose: no association	RR of MTX weekly dose >15mg + meloxicam NS ($p=0.19$)
Park <i>et al.</i> * 2014 (19) (celecoxib study)	Inverse correlation between initial eGFR (CKD-EPI or MDRD) and high density cholesterol with LS Factors association with LS >5.3kPa: MTX cumulative dose: no association Cumulative dose of celecoxib: no association Uric acid ($p=0.02$) HDL ($p=0.006$) eGFR CKD-EPI, MDRD ($p=0.001$, $p=0.003$)	eGFR CKD-EPI ($p=0.001$) eGFR MDRD ($p=0.006$)	No additional abstracted results
Park <i>et al.</i> 2010 (7)	Correlation with TE value: AST ($r=0.184$, $p=0.014$) APRI ($r=0.187$, $p=0.013$) Platelet ($r=-0.148$, $p=0.049$) Haptoglobin ($r=-0.202$, $p=0.007$) MTX cumulative dose: no correlation	NA	No significant difference between LS between cumulative MTX > vs. <= 4000mg or healthy controls

Study	Significant risk factors for fibrosis on correlation and univariate analysis	Significant risk factors for fibrosis on multivariate analysis	Other results
Pongpit <i>et al.</i> 2016 (24)	Factors association with LS >7kPa: BMI ($p<0.0001$) Waist circumference ($p<0.0001$) Diabetes ($p=0.001$) Hypertension ($p=0.003$) Dyslipidaemia ($p=0.043$) Metabolic syndrome ($p<0.0001$) PASI score ($p=0.042$) AST ($p=0.002$) ALT ($p=0.003$) Fasting glucose ($p<0.0001$) HOMA-IR ($p<0.0001$) Fatty liver by US ($p=0.019$) PsA: not associated Cumulative MTX: dose not associated	Waist circumference (OR 1.24, 95% CI:1.11, 1.38, $p=0.0002$) Diabetes (OR 12.70, 95% CI 1.84, 87.70, $p=0.010$) AST (OR 1.08, 95% CI 1.02, 1.16, $p=0.017$)	No additional abstracted results
Seitz <i>et al.</i> 2010 (23)	NA	See next column	Association of LS with anti-TNF-alpha treatment adjusted for BMI, age, gender, alcohol, diabetes, disease duration, cumulative MTX dose and folic acid dose: RA 1.73 (0.16 to 18.2) PsA 0.03 (0.001 to 1.11), $p=0.063$

and multivariate analyses only a single study found an association between elevated liver stiffness and cumulative methotrexate dose (6). In this study, by Arena *et al.* (6), patients with a cumulative dose of >4000mg of methotrexate had higher liver stiffness than patients treated with lower doses ($p<0.0001$). No case-control studies found an association between the cumulative dose of methotrexate and liver fibrosis.

While many studies excluded patients on concomitant hepatotoxic drugs, including leflunomide (Table III), one study (17) found that cumulative dose of leflunomide over 19 grams (but not cumulative methotrexate dose) was associated with increased liver stiffness (OR: 12.8, 95% CI 3.0–55.0, $p<0.001$). Seitz *et al.* (23) examined the association of liver stiffness with the use of anti-TNF α agents and in models adjusted for BMI, age, gender, alcohol, diabetes, disease duration and cumulative methotrexate dose and folic acid dose found no association with increased fibrosis in patients with RA or PsA ($p=0.063$, Table III); although, in crude and partially adjusted models there was a trend to decreased risk of fibrosis in patients with PsA treated with anti-TNF α agents. Two studies by Park *et al.* examined the combined effects of methotrexate and either celecoxib (19) or meloxicam (18) and concluded that

neither of these NSAIDs used in combination with methotrexate increased the risk of liver fibrosis.

A number of other important risk factors for liver fibrosis were identified in the studies. The relationship between a high BMI and liver stiffness was assessed in 6 studies. Two studies identified elevated BMI as a risk factor for liver fibrosis on multivariate analysis (21, 22) and an additional study identified waist circumference as an independent risk factor for fibrosis (24).

While many studies excluded significant alcohol use (Table II), Laharie *et al.* (22) did find an independent association between alcohol use and liver stiffness >7.9 (OR 2.6, 95% CI:1.1–6.3, $p=0.04$). Park *et al.* (19) found an independent association between liver stiffness >5.3kPa and estimated glomerular filtration rate (Table III). Lastly, the study by Pongit *et al.* (24) included patients with psoriasis and although risk factors were not independently reported for the subset of patients with PsA, the presence of diabetes and abnormal AST were noted as independent risk factors for liver stiffness defined as >7kPa on TE. Importantly in this study, PsA was not a predictor of elevated liver stiffness (24).

Liver biopsy results

Liver biopsy results were reported on

patients with IA in 3 studies (6, 21, 22). In the study by Arena *et al.*, (6) 5 out of 11 patients with a liver stiffness measure of >7kPa had liver biopsy and 3 of these had no histological signs of fibrosis; whereas, 2 with values of 9.8 and 11.6kPa had mild to moderate perisinusoidal fibrosis, a common pattern of liver injury seen in low-dose methotrexate use. In addition, minimal lobular inflammation was detected in 4/5 patients. In the study by Kim *et al.* (21) 3/185 underwent liver biopsy, one had non-alcoholic fatty liver disease (NAFLD) without substantial fibrosis (liver stiffness <8.6kPa) and 2 others with liver stiffness on SWE >8.9kPa had non-alcoholic steatohepatitis (NASH) with periportal and septal fibrosis. In the study by Laharie *et al.* (22) 4/13 patients who underwent liver biopsy had a diagnosis of RA and liver stiffness values of 9.5–16.9kPa on TE. Among the 4 RA patients: 2 were not receiving methotrexate and on biopsy it was found that 1 had sinusoidal and portal fibrosis, while the other had NASH, the third had chronic hepatitis and the fourth patient had steatosis.

Discussion

This systematic review demonstrates a prevalence of fibrosis as detected by TE or SWE of between 3% to 23% in RA patients, with a higher prevalence

found in studies using a 5.3kPa cut-off. Fibrosis was reported in 16–17% of PsA patients with no JIA studies identified. Methotrexate and leflunomide are commonly used therapies to treat RA and PsA. While the risk of hepatotoxicity from these agents is low, frequent monitoring of liver enzymes is recommended while on treatment with these agents. Such frequent screening, however, may reveal elevations in liver enzymes (26), which may lead to unnecessary discontinuation of therapy. Indeed, a systematic review on the topic of risk of liver toxicity during methotrexate treatment in RA and PsA revealed a pooled cumulative incidence of elevated LFTs in 18 studies of 31% with an incidence rate of 13/100 patient-years, with highest rates during the first 2 years of use. In data available from 12/18 studies, the methotrexate dose was continued in 67% of cases, while the dose was reduced or paused in 26% of cases and in 7% of cases methotrexate treatment was discontinued (26). Findings from the same study suggest rates of LFTs abnormalities and rates of discontinuation of methotrexate therapy are higher in patients with PsA (26).

In contrast to the frequency of elevated LFTs, the rates of severe fibrosis and cirrhosis in RA are low. In the same systematic review described above, pooled data on liver biopsies from 1154 RA patients showed cirrhosis or severe fibrosis in only 0.5% and 1.3% respectively (26); while rates of mild fibrosis were found in 15.3% (26). In contrast, historical reports suggest that patients with psoriasis (and PsA) have higher rates of liver cirrhosis than the general population (27). For example, a recent systematic review revealed fibrosis in 5.7–72% of liver biopsies in 5 studies (mean $n=60$) that included psoriasis patients treated with methotrexate (28). Such findings initially led to dermatology guideline recommendations to routinely perform liver biopsies in patients treated with >1.5 g of methotrexate; however, current guidelines recommend liver biopsy after 3.5–4 g and subsequent biopsies after 1.5g in this population (29). For rheumatologists, conducting routine liver biopsies is not standard practice, even in patients

with PsA. Instead, major rheumatology guidelines recommend monitoring for liver toxicity with LFTs (2).

Unfortunately, there is conflicting data on the relationship between abnormal LFTs and abnormal liver biopsy results as shown in a systematic review by Visser and van der Heijde (26) that identified 6 studies with an association between abnormal LFTs and liver biopsy abnormalities and 6 studies without. The reasons for this discrepancy are unclear and not explained by the authors but could relate to differences patient-level factors (including underlying pre-existing liver damage, concurrent alcohol or other medication use) or in study design. With respect to study design, of potential importance is how “abnormal LFTs” were defined in the studies, as some looked at the total number of abnormal tests, others at the percentage of abnormal tests, and some at the mean enzyme levels over time. A more recent systematic review of non-invasive tests for detecting liver fibrosis in patients with psoriasis on methotrexate revealed a pooled sensitivity in 6 studies of only 38% (30). This discordance between LFT abnormalities and underlying liver fibrosis is disconcerting; however, a number of non-invasive biochemical and imaging modalities have been proposed to bridge the gap and improve screening for occult liver disease.

In this study we present the first systematic review on the use of TE and SWE in IA cohorts. While in this study we originally intended to report a pooled prevalence estimate of subclinical fibrosis as detected by TE and SWE, there were numerous methodologic concerns with the included studies which prevented pooling of the data for meta-analysis. Nonetheless, the review reveals relatively low rates of fibrosis detected by TE in the majority of studies, with the exception of the Korean studies (17–19), which used a lower threshold for fibrosis of 5.3kPa and reported rates of subclinical fibrosis between 2–4 fold higher than other cohorts. This suggests that further studies may need to be conducted to determine appropriate cut-offs for determination of fibrosis based on ethnicity.

Unfortunately, measures of diagnostic accuracy of TE were not available for these studies, as the gold standard test (liver biopsy) was not systematically performed in any of the studies. However, a systematic review of patients with psoriasis on methotrexate (excluding patients with PsA) (30) recently reviewed non-invasive tests for liver fibrosis, using liver biopsy as the reference standard and 2 studies were found that evaluated TE ($n=34$). The pooled sensitivity and specificity for TE was 0.6 (0.15–0.95) and 0.80 (0.59–0.93) respectively for detecting fibrosis (30). We also examined risk factors for fibrosis detected by TE and the findings highlight an ongoing controversy. While the majority of studies found no association between fibrosis and methotrexate therapy, a single study (6) did find a significant and independent association between methotrexate cumulative dose and liver fibrosis in RA patients. The study reports higher mean stiffness in patients receiving a cumulative dose of methotrexate >4000 mg (6). Of note, the mean duration of methotrexate use appeared slightly longer in this study compared to others; however, other study characteristics were similar. There was a paucity of data on other medications as a majority of studies excluded other potentially hepatotoxic medications; however, cumulative dose of leflunomide was an independent predictor in a single study (17).

Other independent risk factors associated with fibrosis identified in our study included elevated BMI and waist circumference, alcohol use, renal impairment, diabetes and elevated AST. Interestingly, the only independent predictor of elevated liver stiffness that was confirmed in more than one study was elevated BMI. This is important as obesity rates worldwide are rising and consequently the rates of many obesity-related disorders including diabetes, heart disease and the metabolic syndrome have increased. Indeed in populations with RA, up to 50% of patients worldwide are overweight or obese according to a recent international study (31). It should therefore be noted that the BMI's reported in many of the studies were lower than North American co-

horts, including at our centre (32) and that this may have influenced results. Our review has a number of limitations. First, it is possible that studies were missed and not included if they were not listed in the databases searched. There were also no studies found on children with JIA or on patients with other types of spondyloarthritis. Most importantly, our review is limited by the heterogeneity of the methods used to conduct the studies and we were unable to conduct a meta-analysis. Finally, there were a limited number of biopsies conducted in the reported studies, therefore the clinical significance of the TE/SWE result was not always apparent. In conclusion, subclinical fibrosis can be measured by non-invasive TE or SWE in patients with IA. However, the prevalence of subclinical fibrosis remains unclear and further study is warranted. As these technologies become more readily available, including in North America, further algorithmic application to the screening for subclinical liver disease in patients with IA is anticipated. Use of these technologies may be especially important as the rates of obesity are rising and the rates of comorbid liver disease may also consequently increase.

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