Increased prevalence of advanced liver fibrosis in psoriasis patients: a cross-sectional analysis from The Rotterdam study.

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ABSTRACT

Prevalence of non-alcoholic fatty liver disease is increased in patients with psoriasis. It is unknown whether liver fibrosis relates to psoriasis. We investigated the association between psoriasis and liver fibrosis compared to participants without psoriasis within the population-based Rotterdam study. All participants were screened for liver fibrosis using transient elastrography. Liver stiffness measurement of >9.5kPa suggested advanced liver fibrosis. Psoriasis was identified using a validated algorithm. 1535 participants were included (mean age 70.5±7.9 years; 50.8% female; median BMI 26.4kg/m2(IQR 24.2-28.9) of who 74 (4.7%) had psoriasis. The prevalence of advanced liver fibrosis was 8.1% in psoriasis patients compared to 3.6% in the reference group (p=0.05). The risk of advanced liver fibrosis in psoriasis patients remained comparable after adjustment for demographics, life-style characteristics and laboratory findings (OR 2.57 (95%CI: 1.00-6.63). This study suggests that elderly with psoriasis may be twice as likely to have advanced liver fibrosis irrespective of common risk factors.

INTRODUCTION

In psoriasis patients, an increased prevalence of non-alcoholic fatty liver disease (NAFLD) has been observed.[1-4] NAFLD is currently the most common chronic liver disease in Western countries, and considered the hepatic manifestation of the metabolic syndrome.[5] The reported prevalence of NAFLD in psoriasis patients varies from 46 to 59% in Western countries independent of psoriasis severity.[1,3,4] The term NAFLD encompasses a wide spectrum of liver damage, ranging from simple fatty liver and non-alcoholic steatohepatitis (NASH), to advanced fibrosis, including liver cirrhosis and its complications (e.g. portal hypertension and hepatocellular carcinoma).[6] Although most of the patients with NAFLD have asymptomatic simple steatosis, which will not progress to more advanced stages of liver disease, a minority will develop advanced liver fibrosis. The prevalence of NASH, severe fibrosis and cirrhosis due to NAFLD in the general population is estimated to be 6%, 4.2% and 1.1%, respectively.[6,7]

No data are available on the prevalence of advanced liver fibrosis in patients with psoriasis. Based on an increased prevalence of NAFLD in psoriasis patients, an increased prevalence of advanced liver fibrosis may be expected. A non-invasive and reproducible method for assessing liver fibrosis is by transient elastrography (TE; Fibroscan®).[8] TE has a high diagnostic accuracy, independent of the underlying liver disease, in predicting advanced liver fibrosis.[8] Up to now three small studies have evaluated TE in patients with psoriasis using high dose methotrexate (MTX).[9-11] It has been observed that psoriasis patients are more likely to develop MTX induced liver toxicity compared to patients with rheumatoid arthritis and Crohn's disease using this drug; however, it is unknown if this is due to psoriasis and/or their different profile of risk factors for liver toxicity.[12,13]

For our study, we used data from the Rotterdam Study: an on-going large prospective population-based cohort study in middle-aged and elderly participants. The specific design of the Rotterdam Study provides the opportunity to systematically evaluate liver disease in all participants with the use of the Fibroscan. The main objective of our study is to investigate if participants with psoriasis have a higher risk of advanced liver fibrosis as measured by TE compared to participants without psoriasis in the population-based Rotterdam Study [14] and how this association is affected by known risk factors for liver fibrosis. In addition, we performed subgroup analyses for participants with NAFLD.

METHODS

Study population

This study has been conducted within The Rotterdam Study, which started in January 1990. [14] All inhabitants, aged 55 years and older, living in Ommoord, a district in Rotterdam (The Netherlands), were invited to participate. The rationale is to study factors that determine the occurrence of chronic diseases in elderly people. The study design has been described previously. [14] TE was introduced to the core protocol in January 2011 and ultrasound at the fifth survey of the Rotterdam Study (February 2009 - February 2012), which constitutes the baseline survey for the present study. Clinical skin examinations for the screening of dermatological conditions started in September 2010. In addition, each participant completed an extensive interview, fasting blood was collected and anthropometric measurements were conducted. Detailed information on drug prescriptions were derived from automated pharmacies, where nearly all participants (98%) are registered.

Assessment of psoriasis

Psoriasis was diagnosed either by trained physicians in dermatology at the research center, or by records of general practitioners (GP). Among participants who were seen at the research center a Psoriasis Area and Severity Index (PASI) was conducted to estimate disease severity. Hard copy and electronic medical records of all participants using anti-psoriatic drugs or who had a diagnostic code for psoriasis were screened for the diagnosis of psoriasis in the GP notes, medical specialist reports and hospital discharge letters. Participants with a history of possible anti-psoriatic drug use, but without a diagnosis of psoriasis, were excluded from the analysis. A more detailed description of this selection process was described previously.[15] Participants without psoriasis were defined as the reference cohort.

The date of onset of psoriasis was the date of the first diagnosis of psoriasis in the medical records, first anti-psoriatic medication available in the pharmacy database or the self-reported date of onset, whichever came first.

Diagnosis of liver fibrosis

Measurement of liver stiffness was performed using TE (Fibroscan, EchoSens, Paris, France) by a single, certified and experienced operator. The right lobe of the liver was assessed through the intercostal space in patients lying on their back with the right arm in maximal abduction. The examination lasted about 5-10 minutes. If the distance from the skin to the liver was more than 2,5 cm an XL-probe was used instead of the normal M-probe. The liver stiffness measurement (LSM) was expressed in kilopascals (kPa). TE was considered reliable if ≥10 validated measurements were recorded with at least 60%

success rate and the interquartile range (IQR) was less than 30% of the median LSM. LSM >9.5 kPa was used as a cut-off for the presence of advanced liver fibrosis and >13 kPa was used for cirrhosis. This cut-off level was deliberately chosen, for it yields high positive predictive value for presence of advanced fibrosis in various liver diseases, including (N)AFLD. [8,16-18]

Diagnosis of NAFLD

Abdominal ultrasonography was performed by certified and experienced technicians on Hitachi HI VISION 900 in all study participants. Images were re-evaluated by a hepatologist (JNLS) with more than ten years' experience in ultrasonography. The diagnosis of fatty liver was made based on specific ultrasound criteria according to the protocol by Hamaguchi *et al.*[19] Participants with any of the following possible secondary causes of fatty liver were excluded from the NAFLD analyses: 1) excessive alcohol consumption 2) positive HBsAg or anti-HCV, and 3) use of oral pharmacological agents historically associated with fatty liver (i.e. amiodarone (n=13), corticosteroids (n=28), methotrexate (n=0), and tamoxifen (n=2)).

Co-variables

Participants were interviewed at home using a standardized questionnaire to obtain data concerning demographics, medical history, comorbid conditions, smoking behaviour, alcohol intake, and (prior) drug use. Data from the first interview prior to TE were used. Excessive alcohol consumption was defined as more than 14 drinks weekly for men and women. Pack-years of smoking were calculated as years of smoking (excluding years of non-smoking) multiplied by the average number of packs (containing 20 cigarettes) smoked per day.

Anthropometric measurements were performed by well-trained nurses. Body Mass Index (BMI) was calculated as weight(kg)/ length(m^2). Waist and hip circumference were measured in centimeters. The average of two blood pressure measurements, obtained at a single visit in sitting position after a minimum of 5 minutes rest, was used for analysis.

Fasting blood samples were collected on the morning of ultrasound examination. Blood lipids, glucose and alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), and platelets were analysed using automatic enzymatic procedures and insulin, HBsAg and anti-HCV antibodies were measured by automatic immunoassay (Roche Diagnostics GmbH, Mannheim, DE).

The metabolic syndrome was defined, according to Adult Treatment Panel III criteria, as the presence of at least three of the following five traits: 1) abdominal obesity, defined as a waist circumference in men >102cm and in women >88cm, 2) serum triglycerides ≥1.7 mmol/L or drug treatment for elevated triglycerides, 3) serum HDL cholesterol <1.0mmol/L in men and <1.3mmol/L in women or drug treatment for low HDL-C, 4)

blood pressure ≥130/85mmHg or drug treatment for elevated blood pressure, 5) fasting plasma glucose ≥5.6 mmol/L or drug treatment for elevated blood glucose.[20] Insulin resistance index was calculated using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR): fasting glucose(mmol/L) x fasting insulin(mU/L)/22.5. [21]

Statistical analysis

Chi-square tests, Student's t-tests or Wilcoxon rank sum tests were used to test for statistical significance of differences in distribution of categorical data and continuous data between participants with and without psoriasis.

The association between liver fibrosis and psoriasis was investigated by logistic regression, where LSM >9.5 kPa by TE suggested presence of advanced liver fibrosis. Two multivariable models were used: one adjusted for age and gender and in the second model we *a priori* decided to adjust for age, gender, alcohol consumption, presence of the metabolic syndrome, steatosis and ALT (all risk factors of liver fibrosis). Metabolic syndrome was included as a single co-variable instead of the five cardiovascular risk factors as mentioned previously to avoid over-adjustment. As a sensitivity analysis a linear regression model was used to investigate the association between the presence of psoriasis and LSM (log-transformed) as a continuous variable. Furthermore, since an increased prevalence of NAFLD was previously reported in psoriasis patients,[1-4] all analyses were also repeated among participants with NAFLD separately.

P-values were two-sided and values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS 20.0 (IBM, UK).

The study was approved by the Medical Ethics Committee of the Erasmus Medical Center in Rotterdam. Written informed consent was obtained from all participants.

RESULTS

Study population

TE and conclusive psoriasis data were available for 2466 participants of the Rotterdam Study (Figure 1). From this population 1535 participants had a reliable TE (62.2%), which was similar between the psoriasis and reference population. Participants with a pacemaker (1.4%), an unreliable TE (27.9%) or failure of the TE (9.8%) were excluded. The proportion of overweight and obese participants was significantly higher among those with a failure (88.7%, p<0.001) or unreliable (74.9% p<0.001) TE compared to those with a reliable TE (64.8%). Regarding reliability of TE, no differences were observed between the psoriasis and reference population.

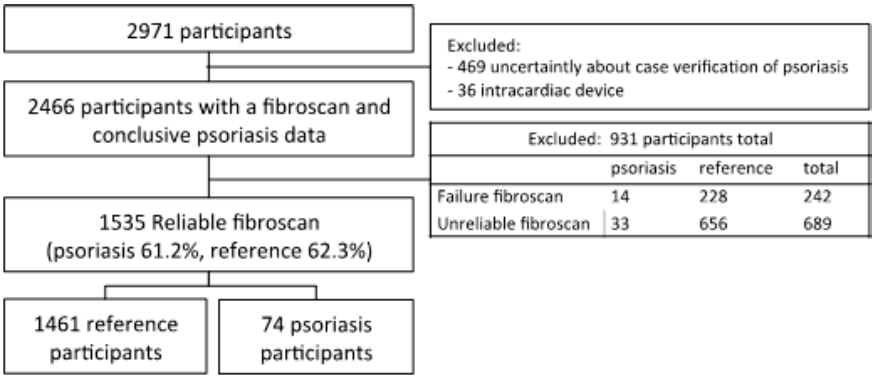

Figure 1. Flowchart of the participants of the Rotterdam study included in this study.

Of 1535 participants, 74 (4.8%) had psoriasis; the remaining 1461 participants were defined as the reference population. The distribution of age and gender was comparable between both groups, and the majority were Caucasian. Metabolic syndrome and obesity (BMI and waist circumference) were not significantly different between the participants with psoriasis and the reference population although metabolic syndrome was slightly more present in the participants with psoriasis. (Table 1) At the time of the analyses the median disease duration of psoriasis was 11.2 years (IQR15.8 years) and no participant was using systemic anti-psoriatic drugs. Furthermore, by then almost half of the psoriasis participants had received a dermatological examination at the research center, and had a median PASI score of 2.0 (IQR 3.2), representing a predominately mild psoriasis population.

Liver fibrosis evaluation

The risk factors for liver fibrosis were generally comparable between participants with and without psoriasis (Table 1). However, the prevalence of steatosis, diagnosed by ultrasonography was greater in participants with psoriasis versus the reference population (44.3% versus 34.0%, respectively, p=0.02). (Figure 2) The prevalence of advanced fibrosis, defined as a LSM>9.5kPa, was 8.1% in the psoriasis participants and 3.6% in the reference participants, which is an almost two-and-a-half times higher risk of advanced fibrosis for psoriasis participants (crude OR 2.39; 95%CI 0.99-5.76). The characteristics of participants with psoriasis with advanced fibrosis are summarized in table 2.

After adjustment for age and gender, psoriasis remained significantly associated with advanced liver fibrosis (LSM >9.5kPa) (adjusted OR 2.36, 95%CI 0.95-5.85). The odds ratio increased slightly to 2.57 (95%CI 1.00-6.63) after additional adjustment for age, gender, alcohol consumption, ALT, presence of the metabolic syndrome and steatosis in a multivariable logistic regression model. (Table 3)

Table 1. General characteristics of the study population stratified by psoriasis and NAFLD

	All participants			*Participants with NAFLD*		
	Reference (n=1461)	**Psoriasis (n=74)**	***P*[a]-value**	**Reference (n=375)**	**Psoriasis (n=20)**	***P*[a]-value**
Co-variables	*95.3%*	*4.7%*		94.9%	5.1%	
Age (years)	70.5±8.0	71.2 ±6.5	0.34	69.6±7.6	73.6±6.5	0.02
Female (%)	51.1	44.6	0.27	50.4	60.0	0.40
Caucasian (%)	95.4	98.6	0.21	94.5	94.7	0.72
BMI (kg/m2)	26.4 (24.2-28.9)	26.6 (24.1-28.5)	0.47	29.0 (26.9-31.2)	28.5 (26.7-32.5)	0.74
Alcohol intake (drinks/week)	5.0 (0.6-7.5)	7.5 (0.9-7.5)	0.07	2.63 (0.56-7.5)	4.97 (0.23-7.5)	0.75
Alcoholic more than 14 weekly (%)	13.2	17.8	0.26	n/a	n/a	n/a
Viral hepatitis (%)	0.8	1.4	0.57	n/a	n/a	n/a
Hepatotoxic medication (%)	2.8	2.7	0.96	n/a	n/a	n/a
Smoking (Status)			0.45			0.63
Never (%)	34.6	27.4		33.3	25.0	
Former (%)	53.9	60.3		59.7	70.0	
Current (%)	11.5	12.3		6.9	5.0	
Metabolic syndrome (%)[b]	46.5	52.1	0.36	68.5	83.3	0.18
Fasting glucose >100 mg/dL or drug treatment for elevated blood glucose	47.0	41.4	0.40	66.3	60.0	0.62
Waist circumference >88cm (♀) or >102 cm (♂)	34.2	45.8	0.07	61.6	81.2	0.12
Triglycerides >150 mg/dL or drug treatment for elevated triglycerides	41.7	41.1	0.93	52.5	64.3	0.39
HDL-C <40 mg/dL(♂) or <50 mg/dL(♀) or drug treatment for low HDL-C	37.3	37.5	0.97	47.4	42.9	0.74
BP ≥130/85 mmHg or drug treatment for elevated BP	91.7	88.1	0.34	96.0	93.8	0.66

Table 1. General characteristics of the study population stratified by psoriasis and NAFLD (continued)

	All participants			***Participants with NAFLD***		
	Reference (n=1461)	**Psoriasis (n=74)**	***P*[a]-value**	**Reference (n=375)**	**Psoriasis (n=20)**	***P*[a]-value**
Co-variables	*95.3%*	*4.7%*		94.9%	5.1%	
ALT (U/L)	18 (14-24)	18 (14-24)	0.89	22 (16-28)	22 (17-25)	0.94
AST (U/L)	25 (22-29)	24 (21-31)	0.67	25 (22-29)	25 (21-30)	0.63
GGT (U/L)	23 (17-34)	25 (19-37)	0.20	26 (19-37)	26 (21-40)	0.55
Bilirubin	8 (6-11)	9 (6-12)	0.52	8.0 (6.0-11.0)	6.5 (5.8-11.0)	0.24
Platelet count (G/L)	258 (217-301)	271 (231-332)	0.008	255 (211-311)	271 (186-323)	0.98
HOMA-IR	2.5 (1.6-3.7)	2.5 (1.8-3.7)	0.66	3.9 (2.6-5.9)	4.2 (2.9-5.4)	0.90
Steatosis on ultrasound (%)	34.0	44.3	0.016	n/a	n/a	n/a
Cirrosis on Fibroscan (%)	1.1	3.4	0.13	1.6	8.6	0.005
Advanced liver fibrosis on Fibroscan (%)	3.6	8.1	0.045	4.0	15.0	0.022
Fibroscan stiffness (kPa)	4.9 (4.1-6.2)	5.4 (4.4-6.6)	0.10	5.3 (4.4-6.7)	6.3 (4.9-7.3)	0.066

Data are represented as mean (± standard deviation), median (interquartile range) or percentages.
Abbreviations: BMI, Body Mass Index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; N/A, not applicable.
[a]Significance level between reference population and psoriasis. Based on T-test, Wilcoxon rank sum test or Chi-square test. [b]Metabolic syndrome was defined as the presence of at least three of the five traits.

Linear regression analysis also showed that psoriasis is a predictor for the severity of fibrosis measured as log-LSM (crude **β** 0.04, standard error (SE) 0.02 P=0.03). After adjusting for age, gender, alcohol consumption, ALT and presence of the metabolic syndrome and steatosis this correlation remained the same (adjusted **β** 0.04, SE 0.02 P=0.04).

NAFLD population

A subgroup analysis was performed for participants with NAFLD. Of 2502 participants, 400 were excluded because of the presence of secondary causes for liver steatosis. A third of the remaining 2102 participants had NAFLD (n=704), and of these 39 (5.5%) had psoriasis. In this subgroup analysis 395 participants had reliable TE data (56%). The psoriasis participants were significantly older (74 vs 70 years p=0.02) than the reference participants, but the distribution of the other co-variables such as, gender, BMI, metabolic syndrome and liver enzyme tests were comparable. Using TE, a significantly greater prevalence of advanced fibrosis was demonstrated in participants with psoriasis versus the reference population (15% vs 4% p=0.02). Moreover, more participants with

Table 2. Characteristics of 6 psoriasis patients with advanced fibrosis and psoriasis

Participants[a]	Gender	Age (years)	BMI (kg/m^2)	MS	Alcoholic drinks weekly	MTX use	NAFLD	Liver stiffness (kPa)	ALT	PASI
1	M	87	23.1	Yes	18	no	n/a	11.7	12	0.4
2	F	66	24.1	Yes	18	no	n/a	25.4	32	3.0
3	M	81	28.5	Yes	0	no	yes	15.5	12	capitis
4	M	76	28.1	Yes	5	no	no	10.2	19	-
5	F	75	23.5	Yes	8	no	yes	46.4	19	3.3
6	M	80	33.9	Yes	5	no	yes	9.6	16	-

[a] None of these participants have a viral hepatitis or used hepatotoxic mediation.
Abbreviations: BMI, Body Mass Index; ALT, alanine aminotransferase; MS, metabolic syndrome; n/a, not applicable

psoriasis had a LSM>13kPa, suggesting liver cirrhosis, than the reference population (8.6% vs 1.6% p=0.005). (Table 1)

Logistic regression analyses in this NAFLD population showed that psoriasis participants had a four times greater risk for advanced liver fibrosis compared to the reference population (crude OR 4.2, 95%CI 1.1-16.0). This risk remained four times increased after adjustment for age, gender, alcohol consumption, ALT and presence of the metabolic syndrome in a multivariable logistic regression model (fully adjusted OR=4.1, 95%CI 1.01-17.0).

Table 3. Univariate and multivariate adjusted model assessing the association between psoriasis and advanced liver fibrosis[a]

	Normal liver vs. fibrosis	
	OR (95% CI)	***P*-value**
Crude univariate model[b]		
Psoriasis	2.39 (0.99-5.76)	0.052
Age and sex adjusted		
Psoriasis	2.36 (0.95-5.85)	0.06
Multivariable adjusted[c]		
Age, years	1.13 (1.08-1.17)	<0.001
Sex, female	1.90 (1.03-3.49)	0.04
Metabolic syndrome	1.63 (0.89-3.02)	0.12
Alcoholic beverages weekly	0.99 (0.95-1.03)	0.75
ALT (U/L)	1.03 (1.02-1.05)	<0.001
steatosis	1.51 (0.81-2.80)	0.19
Psoriasis	2.57 (1.00-6.63)	0.051

[a]Advanced liver fibrosis defined as LSM >9.5
[b]Nagelkerke R square=0.007; [c]Nagelkerke R square=0.164.
Abbreviations: OR, odds ratio; CI, confidence interval; ALT, alanine aminotransferase

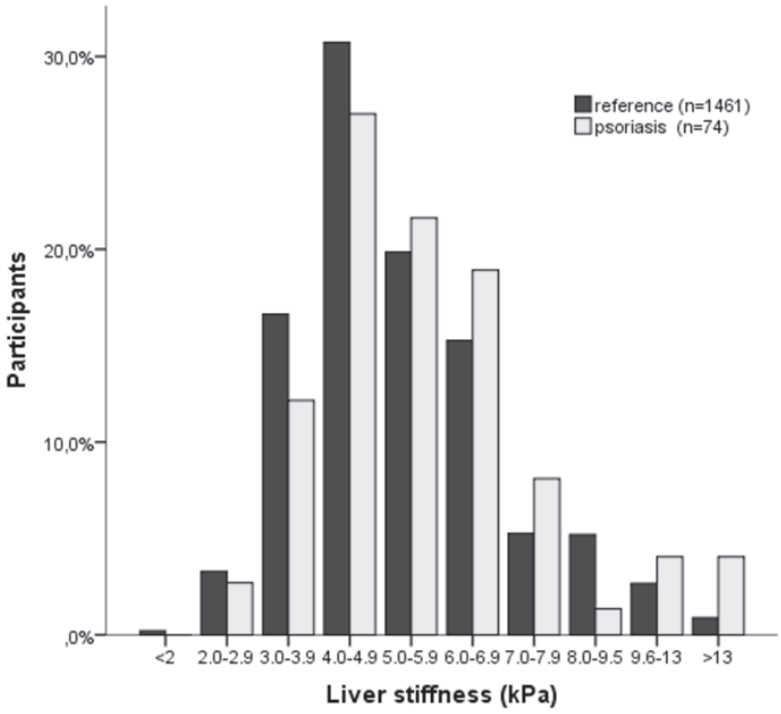

Figure 2. Distribution of reliable liver stiffness measurements in psoriasis and reference participants. Transient elastrography was used to measure the liver stiffness measurements. P=0.08

Furthermore, in a linear regression analysis, the association between psoriasis and liver fibrosis (continuous LSM) was confirmed as well (crude and fully adjusted **β** 0.07, SE 0.04 P=0.04).

DISCUSSION

This is the first large population-based cohort study of middle-aged and elderly people which demonstrates that participants with psoriasis have a two-fold higher risk of advanced liver fibrosis than participants without this skin disease. This risk increases up to four times among the subgroup of participants with NAFLD and is independent of systemic anti-psoriatic drugs and other known risk factors associated with liver fibrosis, such as alcohol consumption and BMI, that may have been more prevalent in psoriasis patients. Previous studies focused on liver fibrosis in the context of MTX induced hepatotoxicity, but these studies have limited sample sizes and were restricted to patients with severe psoriasis eligible for liver biopsy in tertiary centers.[22-25] In contrast to the 8.1% of

psoriasis patients with advanced liver fibrosis using TE in this study, the prevalence of advanced liver fibrosis in the highly selected patients treated with methotrexate ranged from 6.9% to 69.5%.[25] The prevalence of liver fibrosis in our non-psoriatic reference population (3.6%) is similar to that observed in other population based studies confirming the validity of the ascertainment of liver fibrosis using TE.[26,27]

In patients with inflammatory diseases like ulcerative colitis, Crohn's disease and psoriasis, TE is mainly used to monitor MTX-induced hepatotoxicity.[9,10,13,28,29] In a recent small study of Bray et al, TE was compared to liver biopsy in 21 patients (median age 59 years, 43% female), of whom 48% had a reliable examination. They concluded that a combination of TE and procollagen III N-terminal propeptide could be used for monitoring drug safety.[10] Another diagnostic study among 24 psoriasis patients suggested that the combined use of Fibrotest and TE may be beneficial in establishing the grade of liver fibrosis in MTX-induced liver fibrosis in psoriasis patients.[9] Two studies in Crohn's disease patients demonstrated that severe liver fibrosis is rare in patients who receive high dose methotrexate regimens,[13,29] nevertheless both studies recommend TE in the follow-up of these patients.

ALT is often used in daily practice as a diagnostic marker to detect liver damage, but its accuracy remains controversial. In this study, in both the logistic and the linear analyses continuous ALT level was significantly associated with LSM>9.5kPa, suggesting the presence of advanced liver fibrosis with greater liver stiffness (as continuous measurement). However, this ALT increment was in almost all of the participants within the normal range of ALT level. Furthermore, median ALT levels were normal in the total study population as well as in the NAFLD population. Neither did any of the six patients with psoriasis and advanced fibrosis show elevated ALT levels. Our findings are comparable to a previous study with participants from the Rotterdam Study[7] and a recently published systematic review.[25] Altogether, ALT seems to be a poor diagnostic marker for NAFLD and liver fibrosis and therefore may be limited to monitor acute liver toxicity (i.e. drug induced hepatitis), but not for the development of liver fibrosis in psoriasis patients. Other diagnostic tests including TE, Fibrotest, PIIINP, and the Enhanced Liver Fibrosis (ELF™) test are more accurate in detecting liver fibrosis and seem more appropriate to monitor drug-induced effects in the follow-up of psoriasis patients if indicated.

In clinical practice it could therefore be considered that patients with psoriasis and an increased hepatic risk profile at baseline may be referred to a hepatologist for a TE before commencing potentially hepatotoxic medication. During systemic therapy TE may be repeated at a regular interval, also depending on the baseline TE, to monitor for signs of liver fibrosis A liver biopsy should be considered in patients with a LSM of >

9.5kPa depending on the patients' clinical background and is strongly recommended in patients with a LSM of > 13kPa.[26,27]

A direct causal relationship between psoriasis and advanced liver fibrosis cannot be established in this cross sectional study because we lack the longitudinal component. The logistic and linear adjusted regression models suggest an association and a possible correlation between psoriasis and advanced liver fibrosis, even in this study population that consisted of participants with mild psoriasis who did not use systemic anti-psoriatic medication. There have been studies that evaluated pre-treatment liver biopsies in rheumatoid arthritis and described liver abnormalities in nearly all patients suggesting that underlying pathophysiological mechanisms of the disease may play a role as well.[13,30,31] Conventional explanations for the association of NAFLD and advanced liver fibrosis and psoriasis are the increased presence of components of the metabolic syndrome, increased alcohol intake and the use of hepatotoxic medication, but the distribution of these factors was comparable between the psoriasis patients and the reference population. The low-grade chronic inflammatory state, seen both in psoriasis and NAFLD may play a role in the development of advanced fibrosis, but this needs to be studied in more detail before it proves to be the missing link in the relationship between these diseases.[32-34] Also, the inflammation does not explain the fact that methotrexate toxicity is seen more often in psoriasis patients than rheumatic patients or Crohn's disease, [12,13] two inflammatory diseases known to have a higher inflammatory state than psoriasis.[35,36] Other hypotheses that explain the observed increased prevalence of advanced liver fibrosis in psoriasis are possible genetic similarities, life style factors such as nutrition that were not included in the analyses or another still unknown common pathway for psoriasis and liver fibrosis.

Strengths and limitations

The strengths of this study are its population-based design, the large number of participants and the extensive availability of demographic, pharmacological, disease and life-style factors and serological markers of liver damage. In the adjusted models, we were able to include most of the known confounders that could influence the association between both advanced liver fibrosis and NAFLD with psoriasis. The study was also performed in a district of Rotterdam well representative of the Dutch elderly general population. Notwithstanding the large number of participants, the available cases with psoriasis and liver fibrosis remain small explaining the borderline significance often found in this study and the wider range of the confidence interval in the NAFLD subpopulation. However, the different analytic approaches and subgroup analysis all show the same trend suggesting the validity of the findings. An intrinsic limitation of the cross-sectional study design is that the temporal relationship remains unclear and that a direct causal relationship between psoriasis and advanced liver fibrosis cannot be

established. The case definition (i.e., psoriasis) is based on an algorithm, which included a clinical examination by a trained physician, with a high specificity and sensitivity (both 98%).[15] Since the population consisted of elderly participants, the results may not be generalized to younger subjects with psoriasis. The elderly population also explains the high prevalence of psoriasis compared to other population-based studies.[37]

At present, liver biopsy is still the golden standard for the assessment of liver fibrosis. However, performing liver biopsies in a population-based setting is unethical and not feasible. Furthermore this invasive method is associated with patient discomfort and, in rare cases, with serious complications in 1% or more of patients.[38] In addition, accuracy of liver biopsy is limited due to sampling error and intra- and interobserver variability.[39] Therefore, different non-invasive methods have been evaluated in recent years, including routine biochemical and haematological tests, surrogate serum fibrosis markers and TE.[40,41] TE can be learned easily and has an excellent reproducibility, with an intraobserver and interobserver agreement of 98%.[42] A recent meta-analysis concluded that a higher stage of liver fibrosis (a higher cut-off value) improves test accuracy.[8] We used a cut-off value of 9.6 kPa (≤ F3) which is the highest value to detect liver fibroses next to liver cirrhosis (>13 kPa; F4). Another shortcoming in our study is the failure rate or unreliable TE in one-third of the participants. This mostly affected the overweight and obese patients irrespective of using an XL probe. This may have led to a selection bias and may have led to an underestimation of the prevalence of advanced liver fibrosis in our study. However, the failure rate of the TE was equally distributed amongst participants with and without psoriasis suggesting a nondifferential misclassification bias.

Conclusion

This study suggests that middle-aged and elderly people with predominately mild psoriasis and without any systemic psoriasis medication, have an increased risk of advanced liver fibrosis independently of other known risk factors, especially in participants with pre-existing NAFLD. The clinical implications of the study findings are that it questions the usefulness of ALT in monitoring the development of liver fibroses and stimulates the use of other diagnostic approaches such as the TE, especially in psoriasis patients with (components of) metabolic syndrome that are being screened prior to and during potentially hepatotoxic therapies.

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