Psoriasis is independently associated with nonalcoholic fatty liver disease in patients 55 years old or older: Results from a population-based study.

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ABSTRACT

Background: Recent case-control studies observed an increased prevalence of non-alcoholic fatty liver disease (NAFLD) in psoriasis patients, which is relevant in selecting optimal psoriasis treatment.

Objective: To compare the prevalence of NAFLD in people with psoriasis and those without psoriasis.

Methods: This large prospective population-based cohort study (part of the Rotterdam study) enrolled elderly participants (>65 years). NAFLD was diagnosed as fatty liver on ultrasonography in the absence of other liver diseases. Participants with psoriasis were identified using a validated algorithm. Multivariable logistic regression model was used to assess whether psoriasis was associated with NAFLD after adjusting for demographic, life-style characteristics and laboratory findings.

Results: In total, 2,292 participants were included (mean age 76.2±6.0 years; 58.7% female; mean BMI 27.4±4.2kg/m^2) of whom 118 (5.1%) had psoriasis. The prevalence of NAFLD was 46.2% in psoriasis subjects compared to 33.3% for the reference group without psoriasis (p=0.005). Psoriasis was significantly associated with NAFLD; after adjustment for alcohol consumption, pack-years and smoking status, presence of metabolic syndrome and alanine aminotransferase, psoriasis remained a significant predictor of NAFLD (adjusted OR=1.7, 95%CI 1.1-2.6).

Limitations: This was a cross-sectional study

Conclusion: Elderly participants with psoriasis are 70% more likely to have NAFLD than those without psoriasis independent of common NAFLD risk factors.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is currently the most common chronic liver disease in Western countries, and is considered the hepatic manifestation of the metabolic syndrome.[1] It was estimated that NAFLD will be the leading cause of liver transplantation by 2020.[2] The prevalence of NAFLD, diagnosed by ultrasonography, ranges from 15-34% and can be as high as 74% in obese patients.[3-6] Although the condition is mostly asymptomatic, it is the most common cause of abnormal liver enzymes in Caucasian populations.[7] NAFLD refers to a wide spectrum of liver damage, ranging from mild steatosis to non-alcoholic steatohepatitis (NASH) [8], advanced fibrosis and liver cirrhosis. The prevalence of NASH and cirrhosis due to NAFLD in the general population is estimated to be 5% and 1%, respectively. The pathophysiology of how NAFLD develops into a NASH or cirrhosis remains unclear.

Recently, three hospital-based observational studies suggested that psoriasis patients are 1.5 to 3 folds more likely to have NAFLD.[9-11] Furthermore, psoriasis patients are more likely to suffer from methotrexate-induced liver damage compared to healthy controls and patients with rheumatoid arthritis.[8] This increased risk of NAFLD and subsequent risk of liver damage was explained by an increased prevalence of NAFLD risk factors such as obesity, diabetes mellitus and alcohol consumption among psoriasis patients.[12-14] Because of the strong association of both psoriasis and NAFLD with these metabolic conditions and the potentially increased chronic systemic inflammatory status in both diseases, it is still unclear whether psoriasis is an independent risk factor for NAFLD.

In this study, we assessed whether elderly participants with psoriasis have a higher prevalence of NAFLD compared to a reference population and to what extent this association depends on other known risk factors for NAFLD.

METHODS

Participants

This study is part of the Rotterdam Study, an on-going large prospective population-based cohort study, which started in January 1990.[15] All inhabitants who were aged 55 years and older, living in Ommoord, a district in Rotterdam (The Netherlands), were invited to participate. The rationale and study design have been described previously.[15] Abdominal ultrasonography was introduced to the core protocol 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 was dispensed from automated pharmacies, where nearly all participants (98%) are registered.

Diagnosis of psoriasis

Psoriasis was diagnosed either by trained physicians in Dermatology at the research center, or by records of general practitioners (GP). Participants, which were not seen at the research center, were identified using a validated algorithm based on hard copy and electronic medical records of all subjects 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. The participants seen at the research center were used as gold standard. Participants with a history of possible anti-psoriatic drug use, but without a diagnosis of psoriasis, were excluded from the analysis. The validated algorithm had a sensitivity 98%, specificity 98%, positive predictive value 62% and a negative predictive value of 99.9%. A detailed description of the psoriasis selection was described previously.[16] 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. Psoriasis severity of participants evaluated at the research center was scored using the Psoriasis Area Severity Index (PASI).[17]

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 (J.N.L.S.) with more than ten years' experience in ultrasonography. The diagnosis and grading of fatty liver was determined according to the protocol by Hamaguchi *et al* [18]. Severity of fatty liver was classified as 'no fatty liver' (score 0-1), 'mild fatty liver' (score 2-3), or 'moderate-to-severe fatty liver' (score 4-6). Participants with any of the following possible secondary causes of fatty liver were excluded from the analyses: 1) excessive alcohol consumption 2) positive HBsAg or anti-HCV, 3) use of oral pharmacological agents historically associated with fatty liver (i.e. amiodarone, corticosteroids, methotrexate, and tamoxifen). None of the psoriasis participants used methotrexate at the time of the ultrasound. Other rare causes of chronic liver disease (e.g. autoimmune liver diseases, alpha-1 antitrypsin deficiency, Wilson's disease) were not accounted for. The impact of misclassification bias is likely to be small because most of these rare diseases in a

population sample affect young patients and those treated with corticosteroids were excluded from the analysis.

Covariables

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 ultrasound examination 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), and gamma-glutamyltransferase (GGT) were analysed. 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.[19] 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.[20]

Statistical analysis

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

The association between NAFLD and psoriasis was assessed by multivariate logistic regression analysis resulting in adjusted odds ratios (OR) and 95% confidence intervals (CI). The first multivariable model adjusted for age and gender. In the fully adjusted multivariable logistic regression model, we decided *a priori* to adjust for age, gender, alcohol

consumption, smoking, the presence of the metabolic syndrome and ALT. In this model, metabolic syndrome was entered as a single covariate instead to avoid over-adjustment. The quantitative variables are handled as continue variables in the analyses.

A multivariable ordinal regression analysis was used to assess the impact of psoriasis on the severity of NAFLD (no, mild and moderate to severe), which was the dependent variable in this analysis.

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

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

The present study was reported according to the STROBE guidelines.[21]

RESULTS

Study population

Data on psoriasis diagnosis was available for all 3,205 participants who underwent an abdominal ultrasonography. After excluding cohort members with a history of possible anti-psoriatic drug use (e.g., medicated shampoos), but no diagnosis of psoriasis in their medical files or during clinical examination from the reference group, 2,617 participants remained (Figure 1). In total, 325 participants were excluded for the presence of secondary causes of fatty liver resulting in 2,292 eligible participants for the analyses.

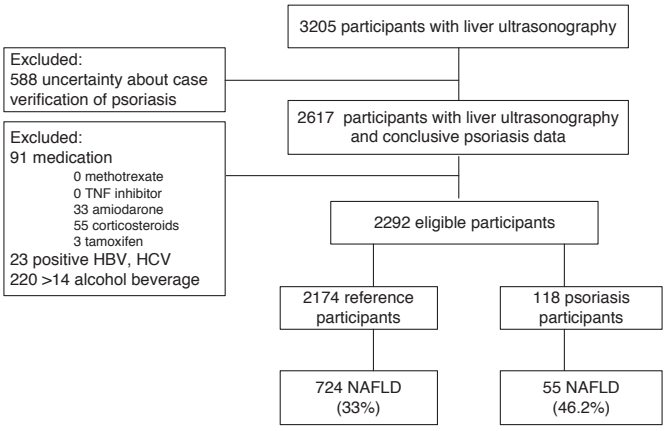

Figure 1. Flowchart of the participants of the Rotterdam study included in this study.
Abbreviations: TNF, Tumor Necrosis Factor; HBV, hepatitis B viral infection; HCV, hepatitis C viral infection; NAFLD, non alcoholic fatty liver diseases.

Psoriasis population

Of the 2,292 participants, 118 (5.1%) had psoriasis. The remaining 2,174 was defined as reference population. The average age of both populations was 76 years and 58.4% of the reference population was female compared to 62.4% of the psoriasis population (p=0.47; Table 1). Almost all participants in both groups were Caucasian.

The median duration of psoriasis since first diagnosis was 10.5 years (interquartile range 13.4 years). At time of the analyses, one third of participants defined as having psoriasis received a dermatological examination at the research center and had a mean PASI of 2.9±2.8. In the past 20 years, 14% of 118 participants with psoriasis had been exposed to ultraviolet therapy (UVB and/or psoralen+UVA) and 10% had been treated with systemic therapy. None of the psoriasis participants were treated with systemic medication at time of the analyses. In only 5 out of the 118 participants with psoriasis, ultrasonography had been performed before the diagnosis of psoriasis (median duration of 2.5 month).

NAFLD prevalence

Among the psoriasis patients, 46.2% were reported to have NAFLD compared to 33.3% of the people in the reference population (p=0.005). Risk factors for NAFLD such as age, sex, ethnicity, BMI and alcohol intake did not significantly differ between participants with psoriasis and those without this skin disease. Although BMI as continuous variable was not statistically different between the two groups (p=0.07), participants with psoriasis were significantly more likely to have a BMI>30kg/m^2 and an increased waist circumference. Participants with psoriasis were also significantly more likely to be current smokers (14.9% vs 8.2%, p=0.01) and to meet the criteria for metabolic syndrome (62.2% vs 52.2%, p=0.05).

Inversely, 7.0% of participants with NAFLD had psoriasis, as did 4.2% of participants without NAFLD (p=0.007). Prevalence of the metabolic syndrome was higher in participants with NAFLD (72%) than in participants without NAFLD (42%, p<0.001). ALT, AST, GGT and HOMA-IR were significantly higher in participants with NAFLD (all p-values <0.01). No difference was seen in alcohol intake or pack-years in current smokers between participants with or without NAFLD.

Factors associated with NAFLD

Logistic regression analyses showed that psoriasis was associated with a significantly increased prevalence of having NAFLD of 70% (crude OR=1.70, 95%CI 1.17-2.46) and the risk remained increased after adjustment for age and gender (adjusted OR=1.70, 95%CI 1.17-2.47). After adjusting for alcohol consumption, pack years of smoking, smoking status, ALT and presence of the metabolic syndrome in a multivariable logistic regression model, participants with psoriasis remained 70% more likely to have NAFLD on

Table 1. General characteristics of the study population according to presence of psoriasis.

Covariables	**Total (n=2292)**	**Reference (n=2174)**	**Psoriasis (n=118)**	***P*-value***
	100%	*94.9%*	*5.1%*	
Age (years)	76.2 (±6.0)	76.2 (±6.0)	76.0 (±6.5)	0.86
Female (%)	58.6	58.4	62.4	0.47
Caucasian (%)	95.1	95.0	97.1	0.33
BMI (kg/m2)	27.4 (±4.2)	27.3 (±4.1)	28.0 (±4.8)	0.07
BMI category				0.25
Normal; BMI < 25 (%)	30.3	30.3	29.1	
Overweight; 25 ≤ BMI < 30 (%)	47.1	47.3	41.9	
Obese; BMI ≥ 30 (%)	22.7	22.3	29.1	
Alcohol intake (drinks/week)	3.8 (±3.8)	3.7 (±3.7)	4.0 (±3.8)	0.50
Smoking (Status)				0.04
Never (%)	36.7	36.8	34.2	
Former (%)	54.8	55.0	50.9	
Current (%)	8.5	8.2	14.9	
Metabolic syndrome (%)	52.7	52.2	62.2	0.05
Fasting glucose >100 mg/dL or drug treatment for elevated blood glucose	48.1	48.1	48.2	0.89
Waist circumference >88cm (♀) or >102 cm (♂)	41.5	40.8	54.7	0.004
Triglycerides >150 mg/dL or drug treatment for elevated triglycerides	43.4	43.4	44.1	0.92
HDL-C <40 mg/dL(♂) or <50 mg/dL(♀) or drug treatment for low HDL-C	41.4	41.2	45.0	0.46
BP ≥130/85 mmHg or drug treatment for elevated BP	93.7	93.8	91.5	0.30
ALT (U/L)	18 (14-23)	18 (14-23)	17 (14-22)	0.18
AST (U/L)	25 (22-29)	25 (22-29)	24 (20-27)	0.01
GGT (U/L)	22 (17-32)	22 (17-32)	23 (18-33)	0.22
HOMA-IR	2.6 (1.8-4.0)	2.6 (1.7-4.0)	2.8 (1.9-5.2)	0.09
Nonalcoholic fatty liver disease (NAFLD) (%)	34.0	33.3	46.2	0.005
Severity of NAFLD				0.01
Mild (%)	5.6	5.4	9.3	
Moderate-severe (%)	28.2	27.8	36.4	

Data are represented as mean (± standard deviation), median (25^th -75^th percentile) or percentages.
*Significance level between reference population and psoriasis. Based on T-test, Wilcoxon rank sum test or Chi-square test
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.

ultrasound examination compared to the reference population (fully adjusted OR=1.70, 95%CI 1.13-2.58; Table 2). No statistical interaction was observed between psoriasis and alcohol consumption. Moreover, restricting the regression analysis to nondrinkers, psoriasis remained significantly associated with NAFLD (p=0.03).

Ordinal regression analysis showed a significant association between psoriasis and the severity of non-alcoholic fatty liver (crude OR=1.54, 95%CI 1.11-2.15). After adjusting for alcohol consumption, pack-years of smoking, smoking status, ALT and presence of the metabolic syndrome, the presence of psoriasis increased the likelihood of having more severe NAFLD by approximately 60% (adjusted OR=1.58, 95%CI 1.06-2.38).

Table 2. Association between psoriasis and NAFLD in logistic regression analysis.

	Crude / Adjusted OR (95% CI)	*P*-value
Crude univariate model[#]		
Psoriasis	1.70 (1.17-2.46)	0.005
Age and sex adjusted		
Psoriasis	1.70 (1.17-2.47)	0.006
Multivariable adjusted*		
Age, years	0.98 (0.96-1.00)	0.01
Sex, female	1.19 (0.96-1.48)	0.10
Metabolic syndrome	3.51 (2.86-4.32)	<0.001
Smoking		0.2
Never	1	
Past	0.88 (0.67-1.15)	0.34
Current	0.99 (0.96-1.01)	0.07
Pack years	1.01 (1.01-1.02)	<0.001
Alcoholic beverages weekly	0.99 (0.96-1.01)	0.35
ALT (U/L)	1.01 (1.01-1.02)	<0.001
Psoriasis	1.70 (1.13-2.58)	0.01

[#]Nagelkerke adjusted R square=0.005; *Nagelkerke adjusted R square=0.19
Abbreviations: OR, odds ratio; CI, confidence interval; ALT, alanine aminotransferase

DISCUSSION

In this large population-based cohort study of elderly people, psoriasis was independently associated with NAFLD and increased the likelihood of having NAFLD by approximately 70%. In our study, the prevalence of NAFLD in participants with psoriasis in a general population was significantly higher than in our reference population (46% vs 33%). These prevalence estimates are comparable to results of an Italian case-control study (47%) including 130 psoriasis patients from a tertiary center (mean age 51.2, PASI>10 in 55%,) and 260 age, sex and BMI matched controls. [9] A higher prevalence

of 59% was described in another cross-sectional Italian study that enrolled consecutive out-clinic psoriasis patients in a tertiary referral center (mean age 50.1, PASI>10 in 66%).[11] An Indian hospital-based case-control study reported a prevalence of NAFLD of only 17% among 333 outpatient clinic psoriasis patients (mean age 46.3, PASI>10 in 14%) which was estimated to be twice as high as the 300 age, sex and BMI matched controls.[10] This lower prevalence in Indian patients can partly be explained by using another definition of NAFLD (liver steatosis on ultrasound combined with laboratory liver enzyme abnormalities) and/or a different distribution of other risk factors for NAFLD in this non-Western population. Furthermore, prevalence differences are likely to be explained by various clinical settings and baseline characteristics (e.g., age, disease severity, and presence of metabolic syndrome [ranging between 28%-49%] in the different studies). Compared to the other studies, the Dutch psoriasis patients were most likely to fulfil the criteria for metabolic syndrome, which may be due to the more elderly study population.

In the present study, one third of the reference population had NAFLD, a prevalence that is comparable to previously published data in the general population of Western countries, suggesting a good internal validity of the study.[7, 22, 23 24]

Metabolic syndrome was the strongest predictor of having NAFLD followed by excessive smoking, more than doubling of upper limit of ALT and psoriasis increased the likelihood of NAFLD by approximately 70%. Even in the fully adjusted model of the most common known risk factors of NAFLD, these will explain together not even 20% (adjusted R square=0.191) and psoriasis accounted for less than 1% of the variability of developing NAFLD. This implies that the pathogenesis of NAFLD appears to be multifactorial in origin and the underlying mechanisms causing NAFLD are still largely unclear. Other risk factors of NAFLD such as genetic predisposition, lifestyle factors, drugs/toxin exposure, pro-inflammatory status and/or chronic oxidative stress that were not assessed in this and other psoriasis studies, may explain a part as well.

NAFLD is considered the hepatic manifestation of the metabolic syndrome and seems to be an independent predictor of cardiovascular disease (CVD).[1, 25, 26] The slightly elevated pro-inflammatory markers found in psoriasis, NAFLD, the metabolic syndrome and CVD, causing a "chronic inflammatory state", display considerable overlap. For example, increased levels of interleukin-6, CRP and TNFα have been demonstrated in all of these conditions. TNFα in particular is hypothesised to play a role in the development of both psoriasis and NAFLD.[4, 27, 28] Notwithstanding this considerable overlap of inflammatory markers, this does not prove any causal relationship between these different conditions.[29]

The pathogenesis of both psoriasis and NAFLD is multifactorial and complex. In both conditions environmental components and genetic factors are likely to play an important role as well. However, the exact underlying genetic mechanisms are largely unknown. In NAFLD PNPLA3 deserves most attention. PNPLA3 is associated with increased hepatic fat levels and hepatic inflammation and has been validated in a series of studies. The genes that are most likely to be affected in psoriasis are PSORS1-10, which influences the immune system and skin. As far as we know, there is no genetic overlap between psoriasis and NAFLD.[30, 31]

Although the majority of participants in this population-based study had mild psoriasis, the prevalence of NAFLD in severely affected patients from a tertiary center was comparable to that observed in a sample of patients with predominantly mild disease from the general population. This accordance we hypothesize that the association between psoriasis and NAFLD is maybe irrespective of psoriasis severity. Physicians prescribing drugs with potential liver-toxicity should be aware of the possible presence of NAFLD in both mild and severely affected psoriasis patients due to a higher risk of developing (drug-induced) advanced stage chronic liver disease.[32, 33] It could be argued that referral of psoriasis patients with a suspicion of NAFLD (e.g. due to presence of metabolic syndrome or liver enzyme abnormalities) to a hepatologist should be considered prior to starting liver-toxic medication,[34] but screening for NAFLD is not routinely advised by the "Practice guideline of NAFLD by the American Association for the Study of Liver Diseases, the American College of Gastroenterology, and the American Gastroenterological Association".[35]

Strengths and limitations

Among the strengths of this study are its population-based design, the large number of participants and the extensive availability of demographic, disease and life-style factors. In the adjusted models, we were able to include most of the known confounders that could influence the association between NAFLD and psoriasis. The study was also performed in a district of Rotterdam well-representative of the Dutch elderly general population. 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 NAFLD cannot be established. The case definition (i.e., psoriasis) was based on an algorithm with a high specificity and sensitivity (both 98%). Data on psoriasis severity was only available in a subset of patients (who were seen by a resident in dermatology) making the interpretation of the subgroup analysis hazardous. Since the population consisted of elderly participants, the results may not be generalized to younger subjects. The elderly population also explains the high prevalence of psoriasis compared to other population based studies.[36] However, NAFLD mainly affects middle-aged and

elderly people, and its prevalence increases with age.[35, 37-41] The short average duration of psoriasis with 10.5 years was not expected for this elderly population, which may suggest the existence of information bias. However, as this was not a major endpoint of this study, this is not very likely to have influenced our results. Ultrasonography is not able to differentiate between simple fatty liver and steatohepatitis. However, performing liver biopsies, the golden standard for discerning between stages of liver disease, in a population-based setting is unethical and not feasible. A final limitation concerns the self-reporting of alcohol consumption, which may imply that excessive alcoholic intake was underreported in both psoriasis and reference populations.

In conclusion, psoriasis seems to be independently associated with NAFLD in this cross-sectional population-based study of elderly Dutch individuals. The increased prevalence of NAFLD in participants with psoriasis should alert physicians to consider possible chronic hepatic involvement prior to administering therapies with potentially liver toxicity.

REFERENCES

1. Hamaguchi M, Kojima T, Takeda N, Nakagawa T, Taniguchi H, Fujii K et al. The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. *Ann Intern Med* 2005;143:722-8.
2. Musso G, Gambino R, Cassader M , Pagano G. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. *Ann Med* 2011;43:617-49.
3. Ioannou GN, Boyko EJ , Lee SP. The prevalence and predictors of elevated serum aminotransferase activity in the United States in 1999-2002. Am J Gastroenterol 2006;101:76-82.
4. Wenk KS, Arrington KC , Ehrlich A. Psoriasis and non-alcoholic fatty liver disease. J Eur Acad Dermatol Venereol 2011;25:383-91.
5. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med 2002;346:1221-31.
6. Bellentani S, Saccoccio G, Masutti F, Croce LS, Brandi G, Sasso F et al. Prevalence of and risk factors for hepatic steatosis in Northern Italy. Ann Intern Med 2000;132:112-7.
7. Adams LA, Angulo P , Lindor KD. Nonalcoholic fatty liver disease. CMAJ 2005;172:899-905.
8. Taylor WJ, Korendowych E, Nash P, Helliwell PS, Choy E, Krueger GG et al. Drug use and toxicity in psoriatic disease: focus on methotrexate. J Rheumatol 2008;35:1454-7.
9. Gisondi P, Targher G, Zoppini G , Girolomoni G. Non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. J Hepatol 2009;51:758-64.
10. Madanagobalane S , Anandan S. The increased prevalence of non-alcoholic fatty liver disease in psoriatic patients: A study from South India. Australas J Dermatol 2012.
11. Miele L, Vallone S, Cefalo C, La Torre G, Di Stasi C, Vecchio FM et al. Prevalence, characteristics and severity of non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. J Hepatol 2009;51:778-86.
12. Boehncke WH. Epidemiology and potential pathomechanisms of cardiovascular comorbidities in psoriasis: a report from the GRAPPA 2010 annual meeting. J Rheumatol 2012;39:441-4.
13. Davidovici BB, Sattar N, Prinz JC, Puig L, Emery P, Barker JN et al. Psoriasis and systemic inflammatory diseases: potential mechanistic links between skin disease and co-morbid conditions. J Invest Dermatol 2010;130:1785-96.
14. Kimball AB, Guerin A, Latremouille-Viau D, Yu AP, Gupta S, Bao Y et al. Coronary heart disease and stroke risk in patients with psoriasis: retrospective analysis. Am J Med 2010;123:350-7.
15. Hofman A, van Duijn CM, Franco OH, Ikram MA, Janssen HL, Klaver CC et al. The Rotterdam Study: 2012 objectives and design update. Eur J Epidemiol 2011;26:657-86.
16. Dowlatshahi EA, Kavousi M, Nijsten T, Ikram MA, Hofman A, Franco OH et al. Psoriasis is not associated with atherosclerosis and incident cardiovascular events: the Rotterdam Study. J Invest Dermatol 2013.
17. Langley RG , Ellis CN. Evaluating psoriasis with Psoriasis Area and Severity Index, Psoriasis Global Assessment, and Lattice System Physician's Global Assessment. Journal of the American Academy of Dermatology 2004;51:563-9.
18. Hamaguchi M, Kojima T, Itoh Y, Harano Y, Fujii K, Nakajima T et al. The severity of ultrasonographic findings in nonalcoholic fatty liver disease reflects the metabolic syndrome and visceral fat accumulation. Am J Gastroenterol 2007;102:2708-15.
19. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA et al. Diagnosis and management of the metabolic syndrome - An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735-52.

20. Wallace TM, Levy JC , Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004;27:1487-95.
21. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007;335:806-8.
22. Marchesini G, Marzocchi R, Agostini F , Bugianesi E. Nonalcoholic fatty liver disease and the metabolic syndrome. Curr Opin Lipidol 2005;16:421-7.
23. Kotronen A , Yki-Jarvinen H. Fatty liver: a novel component of the metabolic syndrome. Arterioscler Thromb Vasc Biol 2008;28:27-38.
24. Koehler EM, Schouten JN, Hansen BE, van Rooij FJ, Hofman A, Stricker BH et al. Prevalence and risk factors of non-alcoholic fatty liver disease in the elderly: Results from the Rotterdam study. J Hepatol 2012;57:1305-11.
25. Loria P, Lonardo A, Bellentani S, Day CP, Marchesini G , Carulli N. Non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease: an open question. Nutr Metab Cardiovasc Dis 2007;17:684-98.
26. Targher G, Marra F , Marchesini G. Increased risk of cardiovascular disease in non-alcoholic fatty liver disease: causal effect or epiphenomenon? Diabetologia 2008;51:1947-53.
27. Uysal KT, Wiesbrock SM, Marino MW , Hotamisligil GS. Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. Nature 1997;389:610-4.
28. Dowlatshahi EA, van der Voort EA, Arends LR , Nijsten T. Markers of systemic inflammation in psoriasis: a systematic review and meta-analysis. Br J Dermatol 2013.
29. Nijsten T , Wakkee M. Complexity of the association between psoriasis and comorbidities. J Invest Dermatol 2009;129:1601-3.
30. Li YY. Genetic and epigenetic variants influencing the development of nonalcoholic fatty liver disease. World J Gastroenterol 2012;18:6546-51.
31. Perera GK, Di Meglio P , Nestle FO. Psoriasis. Annu Rev Pathol 2012;7:385-422.
32. Langman G, Hall PM , Todd G. Role of non-alcoholic steatohepatitis in methotrexate-induced liver injury. J Gastroenterol Hepatol 2001;16:1395-401.
33. Rosenberg P, Urwitz H, Johannesson A, Ros AM, Lindholm J, Kinnman N et al. Psoriasis patients with diabetes type 2 are at high risk of developing liver fibrosis during methotrexate treatment. J Hepatol 2007;46:1111-8.
34. Rivera R , Vanaclocha F. [Nonalcoholic fatty liver disease and psoriasis] Higado graso no alcoholico y psoriasis. Actas Dermosifiliogr 2010;101:657-8.
35. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K et al. The Diagnosis and Management of Non-alcoholic Fatty Liver Disease: Practice Guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology 2012;142:1592-609.
36. Stern RS, Nijsten T, Feldman SR, Margolis DJ , Rolstad T. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. J Investig Dermatol Symp Proc 2004;9:136-9.
37. Amarapurkar D, Kamani P, Patel N, Gupte P, Kumar P, Agal S et al. Prevalence of non-alcoholic fatty liver disease: population based study. Ann Hepatol 2007;6:161-3.
38. Chen CH, Huang MH, Yang JC, Nien CK, Yang CC, Yeh YH et al. Prevalence and etiology of elevated serum alanine aminotransferase level in an adult population in Taiwan. J Gastroenterol Hepatol 2007;22:1482-9.

39. Frith J, Day CP, Henderson E, Burt AD , Newton JL. Non-alcoholic fatty liver disease in older people. Gerontology 2009;55:607-13.
40. Li H, Wang YJ, Tan K, Zeng L, Liu L, Liu FJ et al. Prevalence and risk factors of fatty liver disease in Chengdu, Southwest China. Hepatobiliary Pancreat Dis Int 2009;8:377-82.
41. Park SH, Jeon WK, Kim SH, Kim HJ, Park DI, Cho YK et al. Prevalence and risk factors of non-alcoholic fatty liver disease among Korean adults. J Gastroenterol Hepatol 2006;21:138-43.