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Journal of Hepatology 51 (2009) 778–786

Journal of Hepatology

www.elsevier.com/locate/jhep

Prevalence, characteristics and severity of non-alcoholic fatty liver disease in patients with chronic plaque psoriasis☆

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***Background/Aims*: The association between NAFLD and psoriasis has never been explored in prospective epidemiological studies. The aim of this 2-phase study was to study the clinical features of NAFLD in patients with psoriasis.**

***Methods*: Phase 1: Investigation of prevalence and characteristics of NAFLD in an unselected cohort of 142 adult Italian outpatients with psoriasis vulgaris. Phase 2: Comparison of the psoriasis cohort subgroup with NAFLD and an age- and body mass index-matched retrospective cohort of 125 non-psoriasis patients with biopsy proven NAFLD.**

***Results*: Based on histories, laboratory tests, and ultrasound studies, 84 (59.2%) received clinical diagnosis of NAFLD; 30 had factors potentially associated with liver disease other than NAFLD (e.g., viral hepatitis, significant ethanol, methotrexate use); and 28 (19.7%) had normal livers. Comparison of the normal-liver and NAFLD subgroups revealed that NAFLD in psoriasis patients (Ps-NAFLD) was significantly correlated with metabolic syndrome ($p < 0.05$); obesity ($p = 0.043$); hypercholesterolemia ($p = 0.029$); hypertriglyceridemia ($p < 0.001$); AST/ALT ratio >1 ($p = 0.019$), and psoriatic arthritis (PsA) ($p = 0.036$). The association with PsA remained significant after logistic regression analysis (OR = 3.94 [CI, 1.07–14.46]). Compared with the retrospective non-psoriatic NAFLD cohort (controls), Ps-NAFLD patients (cases) were likely to have severe NAFLD reflected by non-invasive NAFLD Fibrosis Scores and AST/ALT >1.**

***Conclusions*: NAFLD is highly prevalent among psoriasis patients, where it is closely associated with obesity (overall and abdominal), metabolic syndrome, and PsA, and more likely to cause severe liver fibrosis (compared with nonPs-NAFLD). Routine work-up for NAFLD may be warranted in patients with psoriasis, especially when potentially hepatotoxic drug therapy is being considered.**

***Keywords*: NAFLD; Steatosis; Psoriatic arthritis; Methotrexate; Fibrosis; Liver function test**

Received 25 March 2009; received in revised form 20 May 2009; accepted 8 June 2009; available online 26 June 2009
Associate Editor: F. Negro

☆ The authors who have taken part in this study declared that they do not have anything to disclose regarding funding from industry or conflict of interest with respect to this manuscript.

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Abbreviations: PsA, Psoriatic arthritis; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; Ps-NAFLD, NAFLD associated with psoriasis; PASI, psoriasis area and severity index; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γGT, gamma glutamyl transpeptidase; HDL, high density lipoprotein; HOMA, homeostatic model assessment; NFS, NAFLD Fibrosis Score; ATPIII, Adult Treatment Panel III; SD, standard deviation; CI, confidence intervals; OR, odds ratio.

0168-8278/$36.00
doi:10.1016/j.jhep.2009.06.008

1. Introduction

Psoriasis is a chronic inflammatory skin disease that affects 1–3% of the general population. It is characterized by epidermal hyperproliferation, abnormal keratinocyte differentiation, angiogenesis with vasodilatation, and activated CD4+ and CD8+ T-cell infiltrates in the dermis and epidermis, respectively [1]. The clinical presentation is highly variable in terms of lesion localization and severity, and in nearly one-third of all cases the skin lesions are associated with an inflammatory joint disease known as psoriatic arthritis (PsA).

Recent studies have linked psoriasis to obesity and the metabolic syndrome [2–5] which are known risk factors for non-alcoholic fatty liver disease (NAFLD). The latter term refers to a broad spectrum of conditions ranging from simple fatty liver, which is relatively benign, to non-alcoholic steatohepatitis (NASH), which can give rise to fibrosis, cirrhosis, and end-stage liver disease. Anecdotal data suggest that NAFLD itself might also be associated with psoriasis [6], and an increased prevalence of this chronic liver disease might partly explain the increased risk of liver cirrhosis observed in this population [7].

Thus far, this link between NAFLD and psoriasis has never been explored in epidemiological studies. To eliminate this gap, we recently completed a two-phase study. Phase 1 consisted in a cross-sectional cohort analysis aimed at defining the prevalence and clinical features of NAFLD in psoriatic outpatients seen in a tertiary health-care center in Italy. This was followed by a non-interventional case-control study (Phase 2) conducted to compare the features of NAFLD in patients with and without psoriasis.

2. Patients and methods

2.1. Study design

This study was conducted in accordance with the *Strengthening the Reporting of Observational Studies in Epidemiology* guidelines [8] and the protocol was pre-approved by the institutional review board of the Catholic University of the Sacred Heart Medical Center in Rome, Italy. Informed consent was obtained from all study participants.

2.2. Study population

To determine the prevalence and characteristics of NAFLD associated with psoriasis (Ps-NAFLD), we recruited a cohort of patients from the Dermatology Outpatient Clinic over a 2-year period (January 1, 2006–December 31, 2007). The only eligibility criteria were age $\geqslant$18 years and a clinical diagnosis of chronic plaque psoriasis.

Each participant was examined by 2 dermatologists (C. De S. and P.A.), who classified the psoriasis in accordance with the *International Classification of Diseases, Tenth Revision*, determined whether the patient had PsA (based on the criteria recommended by Moll and Wright) [9] and recorded all systemic psoriasis medications used by the patient within the 12 months prior to enrolment. Each dermatologist also independently calculated the patient's Psoriasis Area and Severity Index (PASI), a composite score ranging from 0 to 72 that reflects the erythema, induration, and scaliness of the lesions in 4 body areas (head, trunk, arms, legs) [10]. The average of the 2 scores was used for analysis. Complete medical histories were taken by a trained physician, who also reviewed the patients' medical charts and recorded their height (m), weight (kg), body mass index (BMI), and waist circumference (measured in centimeters midway between the lower border of the rib cage and the iliac crest).

After a drug wash-out period of 4 weeks (for patients on systemic treatment at the time of enrolment), each participant had a panel of blood tests, which included serum levels of alanine and aspartate aminotransferase [ALT and AST, respectively], total bilirubin, albumin, alkaline phosphatase, and gamma glutamyl transpeptidase [γGT]; fasting transferrin saturation; alpha 1 antitrypsin and ceruloplasmin levels, serology for hepatitis B and C viral infections; serum antinuclear, liver/kidney microsomal, mitochondrial, smooth-muscle, and/or neutrophil cytoplasmic antibody titers; C-reactive protein levels; complete blood count; platelet count; total and high density lipoprotein [HDL] cholesterol; total triglycerides; fasting glucose; and fasting insulin levels. The insulin resistance index was determined by homeostatic model assessment (HOMA) using the following formula: (fasting plasma insulin $\times$ fasting plasma glucose)/22.5 [11]. Percutaneous fine-needle liver biopsies were proposed (but not obligatory) for all patients with significant hypertransaminasemia (see *Definitions*) lasting more than 6 months and/or clinical diagnosis of NAFLD associated with obesity, age >50 years, and/or hyperglycemia >110 mg/dL. Specimens (at least 2.5 cm long and 5 μm thick) were stained with hematoxylin/eosin, Masson's trichrome, and PAS and examined under blinded conditions by a single experienced pathologist.

In Phase 2, the psoriasis patients found to have NAFLD in Phase 1 (Ps-NAFLD cases) were compared with an age-, sex-, and BMI-matched set of retrospective nonPs-NAFLD controls randomly selected from the database of our Outpatient Liver Disease Clinic. The following inclusion criteria were used for the control group: biopsy-confirmed diagnosis of NAFLD; no evidence of psoriasis; observation during the 2-year recruitment period used in Phase I; availability of complete laboratory data sets from our medical center's centralized laboratory; complete clinical records, including liver biopsy data; and informed consent to the use of clinical data for the purposes of this study. We used 2 different surrogate markers for severity of NAFLD: AST/ALT >1 and the NAFLD Fibrosis Score (NFS) [12].

2.3. Definitions and diagnostic criteria

For the purposes of this study, Adult Treatment Panel III (ATP III) definitions were adopted [13]. Patients were considered to have *diabetes* if their fasting glucose was $\geqslant$126 mg/dl or they were taking specific treatment for this disorder [14]. Other definitions included *significant ethanol intake*, >20 g/day for either sex (self-reported and confirmed by at least 1 close relative); *transaminase elevation*, AST or ALT >45 U/L (the upper normal limit at our hospital); and *significant hypertransaminasemia*, AST or ALT level >90 U/L (at least two times the upper normal limit).

Sonographic diagnosis of fatty liver was based on the presence of the bright liver pattern (Toshiba Aplio xV scanner and PVT-375BT abdominal transducer; Toshiba Corporation, Japan), as recommended by the American Gastroenterology Association [15]. *Clinical diagnoses of NAFLD* were made in the presence of sonographic features of hepatic steatosis and the absence of *all* the following factors: significant ethanol intake; history of cancer and/or chemotherapy within the last 5 years; drug-induced liver disease within the last 5 years; autoimmune liver disease (manifested by positive serum antinuclear, liver/kidney microsomal, mitochondrial, smooth-muscle, and/or neutrophil cytoplasmic antibody titers); seropositivity for hepatitis B (HBs-Ag) or C infection and autoantibodies (anti-HCV IgG); fasting transferrin saturation >45%; low serum alpha1-antitrypsin levels; ceruloplasmin levels indicative of Wilson's disease; and previous use of methotrexate (which is reportedly associated with histological findings similar to those of NASH) [16]. *Histological diagnoses of NAFLD and NASH* were based on the Brunt criteria and NAFLD Activity Scores [17].