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Original Article

Association between non-alcoholic fatty liver disease and chronic plaque psoriasis: Deep to the skin

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Abstract

Objective To compare the frequency of Non-Alcoholic Fatty Liver Disease (NAFLD) in psoriasis patients (cases) with. non-psoriasis patients (controls) and to stratify it with respect to various independent variables in both groups.

Methods It was a case-control study done at the Dermatology department, Lady Reading Hospital, Peshawar, with a total of 160 participants and 80 in each group. NAFDL was diagnosed with the help of abdominal ultrasound and considered relevant only after other secondary causes of NAFLD (as mentioned in exclusion criteria) were excluded.

Results The mean age in cases and controls was 36±4.77 years and 40±13.12 years respectively. The cases included 59 % male and 41% female while controls groups consisted of 51% female and 49% male patients. In Cases group, 30 patients (37.5%) had NAFLD while in Controls 16 patients (20%) patients had NAFLD disease, with p-valve =0.0144).

Conclusion Our study concludes that there is a positive association between chronic plaque psoriasis with NAFLD compared with age, gender, and body mass index (BMI)-matched non-psoriasis.

Key words
Chronic plaque psoriasis; NAFLD; BMI; PASI score.

Introduction

Affecting approximately 1-3% of the population globally, psoriasis is a chronic, multisystem immune-mediated disorder with major manifestations in the skin.[1,2] There are many different types of psoriasis, with chronic plaque psoriasis being the most prevalent subtype.[3] It accounts for around 90% of patients.[4] Erythematous plaques with white, silvery scales on top are the typical lesions.[5] Although theoretically any region of the body could be affected, the most frequently involved body areas include the scalp, extensor surfaces of upper and lower limbs, and the area around the navel. The lesion may asymptomatic or it may be accompanied by pruritus, and bleeding with minor trauma.[6] There are various tools to measure the severity of chronic plaque

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psoriasis, but the most widely accepted scoring system is PASI SCORE (psoriasis area and severity index).

Numerous systemic disorders, including diabetes mellitus, obesity, NAFLD, hypertension, metabolic syndrome, and cardiovascular mortality, have been linked to psoriasis. Overall mortality is correlated with Psoriasis's duration and PASI score.[7] NAFLD is a hepatic manifestation of metabolic syndrome, and various studies have supported this association. Simple steatosis, Non-Alcoholic Steatohepatitis (NASH), liver fibrosis, and cirrhosis are among the wide range of liver pathologies it encompasses. The severity of these conditions is correlated with disease duration and PASI score.[8] In addition to promoting epidermal hyperplasia in psoriasis, chronic inflammation, and cytokine dysregulation may also inhibit insulin signaling, change adipokine expression, and play a role in mediating insulin resistance and obesity. Considered underlying risk factors for the onset of metabolic syndrome and NAFLD include abdominal obesity and insulin resistance.[9]

We will get new information about the relationship between psoriasis and NAFLD from this study because psoriasis is a common chronic skin disease in our community and no previous study of this kind has been conducted in our setting or Pakistan.

Materials and methods

After approval of the study design from the institutional ethical review board, all Patients who presented to the dermatology unit Medical Teaching Institute (MTI), Lady Reading Hospital (LRH) Peshawar through the OPD or admitted in the ward, diagnosed as having chronic plaque psoriasis based on their medical history and clinical examination, and fulfilling the inclusion criteria were enrolled in the study through non-probability consecutive sampling, and the PASI SCORE was calculated. All other non-psoriasis patients were chosen as the controls. The patients were informed of the study's design and purpose. Those who agreed to participate in the study provided written informed consent. Basic data were collected, regarding age and sex, and Body Mass Index. Detailed history taken about all parameters mentioned in the exclusion criteria. All such patients underwent hepatic ultrasound in radiology department Medical Teaching Institution (MTI) LRH, Peshawar.

NAFLD was only considered relevant when all secondary causes of NAFLD, such as alcohol consumption and other factors listed in the exclusion criteria have been ruled out.[10] Its diagnosis was confirmed by hepatic ultrasound with diffused hyper echogenicity of the liver in relation to the kidneys, ultrasound beam attenuation, poor visualization of intrahepatic structures, poor visualization of the diaphragm, and absence of the typical echogenic walls of the portal veins and hepatic veins. The sensitivity and specificity of ultrasound are 90% and 95%, respectively, for the detection of mild to severe steatosis.

It was a case-control study with a sample size of 160 (80 in each group) conducted in the Department of Dermatology MTI LRH. The sample size was calculated using the WHO formula for sample size keeping NAFLD frequency in Cases and controls at 47% & 28% respectively. The power of the test was 80% and the confidence interval was 95%. By using non-probability successive sampling, patients were allocated to two groups. All patients with chronic plaque psoriasis were considered cases, whereas all patients without psoriasis were considered controls. Body Mass Index (BMI) was computed by dividing weight in kilograms

by height in meters squared (Kg/m^2). Other parameters are mentioned in the inclusion criteria**.**

Inclusion criteria Bothe genders were included in this study with all patients with chronic plaque form of psoriasis having >1 year duration as cases while non-psoriasis patients were considered as controls. All patients were in the 20-60 years range with BMI between 20-30kg/m^2.

Exclusion criteria History of alcohol intake, hepatitis B and C, malignancy, and malnutrition/ malabsorption. History of Other metabolic/ autoimmune diseases involving the liver, Drugs used that are potentially hepato-toxic/ or cause hepatic steatosis such as methotrexate, tumor necrosis factor antagonists, valproic acid, Systemic glucocorticoids, amiodarone or chemotherapeutics, etc.

Data analysis

The SPSS 22 version was used to conduct the statistical analysis. Age, disease duration, PASI score, and BMI were all continuous variables, and mean and standard deviation were calculated for each. For categorical factors like gender and NAFLD, frequencies and percentages have been determined. To determine whether the difference between the two groups was significant, the chi-square test was used, and the p-value/ odd ratio was obtained. A p-value of <0.05 was considered significant. Age, gender, disease duration, BMI, and PASI score were used to stratify NAFLD to look for effect modifiers. A chi-square post-stratification test was used. Logistic regression was used to see the impact of various variables on NAFLD in both groups. Results were summarized in the form of tables and figures.

Results

The study participants demographics and other characteristics are summarized in **Table 1**. There were 160 patients enrolled in the trial, 80 in each group. The cases had a mean age of 36±14.77 years, whereas controls had a mean age of 40±13.12 years. In both groups difference in male to female ratio was non-significant. Duration of disease was applicable to cases only. The mean duration was 7±6.83 years. 66 (83%)

Table 1 Demographic data for both cases and controls.

Variables	*Cases (n=80)*	*Controls (n=80)*	*p value*	*Odd ratio*
Age (in years)	Mean±SD (36 year±14.77)	Mean±SD (40 year±14.02)		
≤ 40	50	42	0.191	
> 40	30	38		
Gender (total160)	80	80		
Male	47	39	0.204	
Female	33	41		
Body Mass Index(BMI)	Mean±SD (24.5±3.77)	Mean±SD (23±2.60)		
≤ 25	25	66	0.015	
> 25	28	14		
PASI score	Mean±SD (12±7.53)			
≤ 14	58			
>14	22			
Duration of disease	Mean±SD (7±6.83)			
≤ 10	66			
> 10	14			
NAFLD (total160)				
Yes	30	16	0.014	2.40
No	50	64		

NAFLD=Nonalcoholic fatty liver disease, BMI=Body mass index, P value less than 0.05=significant.

Table 2 Controls stratification with respect to various variables for both cases and controls.

Variables	*NAFLD*	*Cases*	*Controls*	*P value* *Odd ratio*
Age				
20-40 years	Yes	20	9	P value= 0.0561
	No	30	33	Odd ratio=2.444
41-60 years	Yes	10	7	P value= 0.1585
	No	20	31	Odd ratio=2.214
Gender				
Male	Yes	18	5	P value= 0.0078
	No	29	34	Odd ratio=4.221
Female	Yes	12	11	P value= 0.3783
	No	21	30	Odd ratio=1.558
BMI				
≤ 25 Kg/m^2	Yes	15	6	P value= 0.0053
	No	37	60	Odd ratio=4.857
>25 Kg/m^2	Yes	15	10	P value= 0.5757
	No	*13*	*4*	Odd ratio=0.667

Table 3 Stratification (cont.) applicable to cases only.

	NAFLD	*Frequency*	*P value* *odd ratio*
Disease duration			
≤ 10 years	Yes	24	
	No	41	P value=0.887
>10 years	Yes	5	Odds ratio=0.911
	No	9	
PASI score			
≤ 14	Yes	18	
	No	40	P value=0.0524
>14	Yes	12	Odd ratio=2.6667
	No	10	

PASI=Psoriasis Area and Severity Index, P value <0.05=significant.

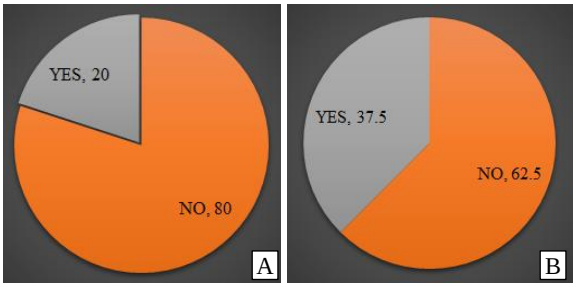

Figure 1 Percentage of NAFLD in controls (A) and cases (B).

patients had the duration of disease ≤10 years and 14 (17%) patients had duration of disease >10 years. Overall cases had greater BMI than controls. Similar to disease durations PASI score was applicable to cases only. The mean PASI Score was 12.1±7.53. In the cases, 30 patients had NAFLD while in the controls 16 patients had NAFLD. The percentage is shown in **Figure 1**. Stratification with respect to various variables in both cases and control groups is shown in **Table 2, 3**. Logistic regression analysis results are given in **Figure 2** showing BMI in controls and PASI score in cases are associated with NAFDL independent of other variables.

Discussion

Psoriasis is an immune-mediated multisystem disorder predominantly involving the skin and affecting 1-3 % population globally.[1,2] Psoriasis has numerous systemic associations, including musculoskeletal, cardiovascular, and hepatic. The most important hepatic manifestation is NAFLD.

Multiple studies have been done on associations between NAFLD and psoriasis, showing different results. To the best of our knowledge

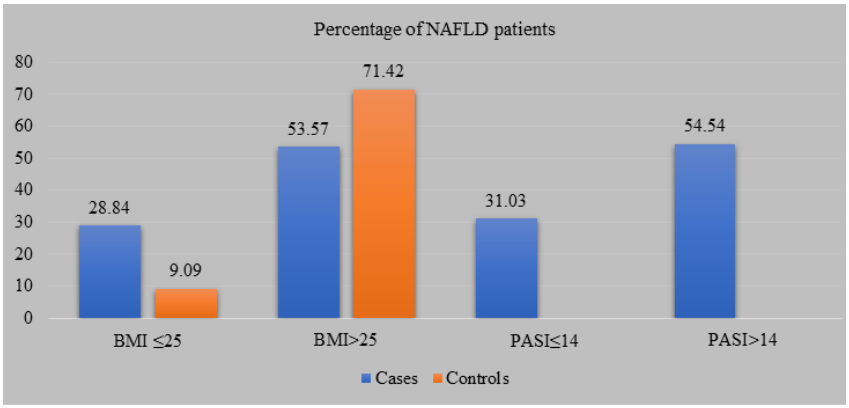

Figure 2 Impact of PASI score and BMI on prevalence of Non-Alcoholic Fatty Liver Disease.

such a study has not been done in Pakistan**,** so as our population is genetically and geographically different from other populations and has different etiological factors, that's why implementation of international literature is not possible. This study will help us to reassess whether there is an association between NAFLD with chronic plaque psoriasis or not in our population. This study also showed the impact of various variables like age, BMI, gender, duration of disease, and PASI score on NAFLD. With this study, NAFLD can be early diagnosed, frequently followed and managed accordingly.

In our study, the mean age in cases and controls was 36±14.77 years (comparable to local study results)[11] and 40±14.02 years respectively. Males and females were 59% and 41% in cases and 49% and 51% in controls respectively. In cases, 37.5% of patients had NAFLD while in controls 20% of patients had NAFLD as shown in **Figure 1**. On Logistic regression, PASI score in cases and BMI in controls were strongly associated with NAFLD as shown in **Figure 2**.

Similar results were found in a study by Gisondi P *et al.* which showed a greater frequency of NAFLD in psoriasis patients vs. controls (47% vs. 28%; p=0.0001). Patients with psoriasis and NAFLD (n=61) had higher blood C-reactive protein concentrations, greater psoriasis severity as PASI score (p=0.01), and were more likely to have metabolic syndrome than patients with psoriasis alone (n=69). Such patients also had greater BMI, age, and disease duration. In our study, age and disease duration had no significant effect on NAFLD, which could be explained by the fact that we had fewer patients in higher age and disease duration categories. On Regression analysis, the PASI score was strongly associated with NAFLD independent of other variables. In comparison, the lower prevalence in our study could be attributed to a different lifestyle, rural populations, and manual labor in our region.[12]

NAFLD was more common in patients with psoriasis in a different study by Awosika O *et al.* with a percentage of 21.2% vs. 7.8% respectively in cases and controls, (p=0.04), but when age, sex, and body mass index (BMI) were controlled for, psoriasis was not linked to NAFLD (p=0.25).[13] Another study conducted on military patients also showed non-significant NAFLD prevalence in those with and without psoriasis (OR: 1.03, 95 % CI: 0.59-1.78), but overall increased risk of NASH was observed in psoriasis patients. Patients with psoriasis who also had NAFLD were more likely to be obese (p=0.01) than those without NAFLD. Such patients exhibited hyperglycemia, hyperinsulinemia, and hyperlipidemia during investigations. PASI score was not significantly associated with NAFLD.[14]

An Indian study, found the prevalence of NAFLD as 17.4% and 7.9% in psoriasis patients and controls, respectively, who were matched for age, sex, and BMI. Patients with NAFLD exhibited longer disease durations, higher PASI scores, and more obesity. The adoption of different diagnostic criteria for NAFLD (i.e., evidence of steatosis on liver ultrasound and elevation of liver enzymes and triglycerides) and ethnic differences in risk variables may help to explain the lower prevalence of NAFLD in this Indian population. Rural lifestyle may be responsible for a lower percentage of NAFDL in controls.[15]

Three case-control studies on Italian and Dutch populations showed a greater prevalence of NAFLD (46%-59%).[12,16,17] This disparity is most likely due to the use of various hepatotoxic drugs including nifedipine and estrogen, that are not excluded by history. The underreporting of alcohol usage may be another significant factor. As NAFLD increases with aging.[16,18] This study population had greater means for age, 72.2 and 52 for Dutch and Italians respectively leading to greater NAFLD prevalence. This age-related phenomenon could be explained by the fact that with aging liver's ability to detoxify various chemicals decreases, leading to cumulative damage and steatosis.[20] In our study, the lower frequency of NAFDL could be explained by lower mean BMI and mean ages in psoriasis patients.

Another Indian population-based study conducted on non-psoriasis patients showed miscellaneous results.[18] The mean age and BMI in this study were 39.1±12.3 years, and 26.6±5.1 respectively, with 49% of male patients, and NAFLD frequency was 16.6%. All these parameters are comparable to our control group (non-psoriasis patients). NAFDL risk factors include raised BMI, old age, and male gender. Except for BMI no other risk factor is comparable to our study. In this study, NAFDL frequency increased with age until 70 years and then decreased. The gender-related issue could be explained by the fact that in our study there were more female patients in the higher BMI group and BMI is an independent risk factor for NAFLD.[19]

A systemic review by Alessandro Mantovani *et al.* concluded that NAFLD may affect up to 50% of psoriasis patients. Such patients tend to have higher PASI scores, high BMI, and metabolic syndrome, comparable to our study results on logistic regression analysis. NAFDL may further progress along the spectrum and up to 1/4 may develop NASH.[21]

A systemic review based on seven case-control studies found a higher prevalence of NAFLD in psoriasis than controls. The risk of NAFLD was correlated with psoriatic arthritis (two studies; 51 930 patients; (OR: 2.07, 95%CI: 1.59-2.71) and psoriasis severity (two studies; n = 505 patients; (OR: 2.25, 95%CI: 1.37-3.71). There was an increased prevalence of obesity, hypertension, and diabetes in psoriasis patients with NAFLD. The Gender and BMI associations with NAFLD were also comparable with our study.[22]

Limitations of our study

First of all, it was an observational study with no prospective follow-up, so the impact of various topical and systemic therapies and disease duration in long term on NAFLD severity and progression cannot be established.

Second, to estimate the true spectrum (simple steatosis, non-alcoholic steatohepatitis, liver fibrosis, and cirrhosis) and severity of NAFLD, a liver biopsy is needed, which is an invasive procedure, has many complications, especially in patients with cardiovascular morbidities and

most patients are not ready to give consent for it.

Conclusion

Our study concludes that there is a positive association of chronic plaque psoriasis with NAFLD when compared with non-psoriasis patients of the same age, gender, and body mass index.

Recommendations

Based on the findings of our study, abdominal ultrasound can be recommended for all chronic plaque psoriasis patients, to early diagnose NAFLD and to slow its progression to NASH and cirrhosis through lifestyle modifications [23]

References

1. Jiang S, Hinchliffe TE, Wu T. Biomarkers of an autoimmune skin disease—psoriasis. Genomics, proteomics & bioinformatics. 2015 Aug 1;13(4):224-33.
2. Campanati A, Marani A, Martina E, Diotallevi F, Radi G, Offidani A. Psoriasis as an immune-mediated and inflammatory systemic disease: From pathophysiology to novel therapeutic approaches. Biomedicines. 2021 Oct 21;9(11):1511.
3. Singh RK, Lee KM, Ucmak D, Brodsky M, Atanelov Z, Farahnik B, Abrouk M, Nakamura M, Zhu TH, Liao W. Erythrodermic psoriasis: pathophysiology and current treatment perspectives. Psoriasis: Targets and Therapy. 2016 Jul 20:93-104.
4. Mahajan R, Handa S. Pathophysiology of psoriasis. Indian Journal of Dermatology, Venereology and Leprology. 2013 Jul 1;79:1.
5. Gisondi P, Bellinato F, Girolomoni G. Topographic differential diagnosis of chronic plaque psoriasis: challenges and tricks. Journal of Clinical Medicine. 2020 Nov 8;9(11):3594.
6. Boehncke WH, Boehncke S, Schön MP. Managing comorbid disease in patients with psoriasis. Bmj. 2010 Jan 15;340.
7. Horreau C, Pouplard C, Brenaut E, Barnetche T, Misery L, Cribier B, Jullien D, Aractingi S, Aubin F, Joly P, Le Maître M. Cardiovascular morbidity and mortality in psoriasis and psoriatic arthritis: a systematic literature review. Journal of the European Academy of Dermatology and Venereology. 2013 Aug;27:12-29.
8. Solomon G. The role of weight loss in the treatment of psoriasis: evidence that psoriasis is a systemic inflammatory disorder linked to metabolic syndrome. British Journal of Dermatology. 2014 Mar 1;170(3):492-3.
9. Rattanakaemakorn P, Fleischer AB. Psoriasis or obesity is a risk factor for nonalcoholic fatty liver disease. Journal of the American Academy of Dermatology. 2014 Sep 1;71(3):588.
10. Gisondi P, Barba E, Girolomoni G. Non-alcoholic fatty liver disease fibrosis score in patients with psoriasis. Journal of the European Academy of Dermatology and Venereology. 2016 Feb;30(2):282-7.
11. Sohail SU, Iqbal N, Kumar A, Fatimee S, Khan A, Nangrejo R. Prevalence of Psoriasis Vulgaris and Its Associated Risk Factors in Pakistan. JPRI [Internet]. 14Sep.2021 [cited 27Aug.2022];33(43B):390-5.
12. Gisondi P, Targher G, Zoppini G, Girolomoni G. Non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. Journal of hepatology. 2009 Oct 1;51(4):758-64.
13. Awosika O, Eleryan MG, Rengifo-Pardo M, Doherty L, Martin LW, Ehrlich A. A case-control study to evaluate the prevalence of nonalcoholic fatty liver disease among patients with moderate-to-severe psoriasis. The Journal of Clinical and Aesthetic Dermatology. 2018 Jun;11(6):33.
14. Roberts KK, Cochet AE, Lamb PB, Brown PJ, Battafarano DF, Brunt EM, Harrison SA. The prevalence of NAFLD and NASH among patients with psoriasis in a tertiary care dermatology and rheumatology clinic. Alimentary pharmacology & therapeutics. 2015 Feb;41(3):293-300.
15. Madanagobalane S, Anandan S. The increased prevalence of non-alcoholic fatty liver disease in psoriatic patients: a study from South India. Australasian journal of dermatology. 2012 Aug;53(3):190-7.
16. van der Voort EA, Koehler EM, Dowlatshahi EA, Hofman A, Stricker BH, Janssen HL, Schouten JN, Nijsten T. Psoriasis is independently associated with

nonalcoholic fatty liver disease in patients 55 years old or older: results from a population-based study. Journal of the American Academy of Dermatology. 2014 Mar 1;70(3):517-24.

17. Miele L, Vallone S, Cefalo C, La Torre G, Di Stasi C, Vecchio FM, D'Agostino M, Gabrieli ML, Vero V, Biolato M, Pompili M. Prevalence, characteristics and severity of non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. Journal of hepatology. 2009 Oct 1;51(4):778-86.
18. Amarapurkar D, Kamani P, Patel N, Gupte P, Kumar P, Agal S, Baijal R, Lala S, Chaudhary D, Deshpande A. Prevalence of non-alcoholic fatty liver disease: population-based study. Annals of hepatology. 2007 Jul 1;6(3):161-3.
19. Wang L, Guo J, Lu J. Risk factor compositions of nonalcoholic fatty liver disease change with body mass index in males and females. Oncotarget. 2016 Jun 6;7(24):35632.
20. Kim H, Kisseleva T, Brenner DA. Aging and liver disease. Current opinion in gastroenterology. 2015 May;31(3):184.
21. Mantovani A, Gisondi P, Lonardo A, Targher G. Relationship between non-alcoholic fatty liver disease and psoriasis: a novel hepato-dermal axis?. International journal of molecular sciences. 2016 Feb 5;17(2):217.
22. Candia R, Ruiz A, Torres-Robles R, Chávez-Tapia N, Méndez-Sánchez N, Arrese M. Risk of non-alcoholic fatty liver disease in patients with psoriasis: a systematic review and meta-analysis. Journal of the European Academy of Dermatology and Venereology. 2015 Apr;29(4):656-62.
23. Kwak MS, Kim D. Non-alcoholic fatty liver disease and lifestyle modifications, focusing on physical activity. The Korean journal of internal medicine. 2018 Jan;33(1):64.