The Egyptian Journal of Hospital Medicine (April 2023) Vol. 91, Page 3902-3906

Serum Neprilysin Is a Significant Predictor of Metabolic Syndrome in Psoriasis Patients

Essam Mohamed Akl[1], Nehad A. Fouad[2], Marwa Bashir Amir Alamin[1], Karem Taha Khalil[*1]
Departments of [1]Dermatology, Venereology and Andrology and
[2]Medical Microbiology and Immunology, Faculty of Medicine – Benha University, Egypt
***Corresponding author:** Karem Taha Khalil, **Mobile:** (+20) 01282559828, **Email:** karem.nawar_76@yahoo.com

ABSTRACT

Background: There is a lot of disagreement on the connection between metabolic syndrome and psoriasis. A membrane-bound metallopeptidase with a wide variety of physiological uses is neprilysin (NEP). New information suggests that NEP may contribute to the aetiology of the metabolic syndrome.

Objective: To evaluate serum NEP levels and their significance in the metabolic features of psoriasis patients.

Patients and Methods: A total of fifty psoriasis patients and thirty healthy volunteers of matched age and sex participated in this case-control research. Every participant underwent clinical examination with focus on measuring the PASI score, blood pressure (systolic, SBP and diastolic, DBP), and abdominal circumference. Additionally, lipid profile, NEP, and fasting blood sugar (FBS) assays were performed.

Results: In comparison to controls, psoriasis patients had significantly higher SBP, DBP, FBS, and triglycerides (p=0.01, 0.04, 0.04, and 0.01, respectively). Median level of NEP was 225.35pg/mL with range of 45.4-540.2pg/mL in psoriasis patients compared with controls (51.65, 41.6-368.9) (p <0.001). NEP showed significant positive correlation with PASI score (r=0.462, p=0.001). NEP was found to be the only predictor of the probability of metabolic syndrome in psoriasis patients (p<0.001).

Conclusion: NEP concentrations can be used as a marker to check for metabolic syndrome in psoriasis patients.

Keywords: Psoriasis, Neprilysin, PASI, Metabolic syndrome.

INTRODUCTION

Psoriasis is considered a complex and multisystemic disease [(1)]. It is linked to the increased possibility of coronary artery disease [(2-6)]. Metabolic syndrome (MetS) includes abdominal obesity, high blood pressure, disturbed lipids, and glucose intolerance [(7)].

Neprilysin (NEP) is a plasma membrane protein that is produced by fibroblasts, endothelial, and smooth muscle cells in the mesenteric adipose tissue and pancreatic islet cells [(8)].

Endothelin, bradykinin, atrial, and brain natriuretic peptides are small vasoactive peptides, and angiotensin I and II are degraded and inhibited by NEP [(9)]. Glucagon-like peptide 1 (GLP-1) activity is destroyed by NEP, which prevents GLP-1 from binding to its receptor. Additionally, NEP inhibition improved glycemia [(10)].

Obesity and type 2 diabetes are metabolically altered conditions that increase NEP [(11)]. As a consequence, in order to assess circulating NEP levels in psoriasis patients and their clinical correlations with metabolic syndrome, the current study was carried out.

PATIENTS AND METHODS

Study population

This was a cross-sectional study at the Dermatology department, Benha University hospitals from February 2022 to August 2022. Fifty patients with psoriasis over the age of 18 years were enrolled, while control group comprised of thirty normal individuals who were of matching age and sex. Exclusion criteria for the study included those with pustular or erythrodermic psoriasis, other skin disorders, or those who had recently undergone systemic or topical psoriasis treatment.

Additionally, patients who were nursing or pregnant were not permitted to take part.

Methods

Each participant underwent a thorough general examination, including assessment of waist circumference, body mass index (BMI), and blood pressure, as well as a detailed history taking (age, sex, duration of psoriasis, and family history of psoriasis). The psoriasis severity was calculated with the aid of psoriasis area and severity index (PASI) score.

Diagnosis of MetS requires the existence of any three of the next five factors: waist circumference greater than 90 cm (males) and 80 cm (females), hypertriglyceridaemia (≥150 mg/dl); decreased HDL (<40 mg/dl) for males and (<50 mg/dl) for females; blood pressure ≥130/85 mm Hg or use of antihypertensive drugs); fasting blood sugar ≥5.6 mmol/L (100 mg/dL) [(12)].

Laboratory investigations were done for fasting blood sugar (FBS), lipid profile and serum NEP using ELISA (Baoshan District, Shanghai, China).

Ethics statement:

The Benha Faculty of Medicine's ethics committee for research involving human beings authorised the study (MS.5-2-2022). Everyone who took part provided their signed, informed permission. The Declaration of Helsinki for human beings, which is the international medical association's code of ethics, was followed during the conduct of this study.

Statistical analysis

Received: 09/09/2022
Accepted: 12/11/2022

The data were examined using statistical package for social sciences (SPSS) version 26. Analytical statistics like Student's t-test and Mann-Whitney U-test were utilised, as well as descriptive statistics like mean, standard deviation (±SD), number, percent, and median and range. Other tests were applied like Chi square test, Pearson correlation coefficient test, regression analysis, and ROC curve analysis, with significance at P <0.05.

RESULTS

The study comprised fifty patients with psoriasis and thirty healthy control volunteers. The patients were 25 males and 25 females, with a mean age of 47.1±12.5 and a positive family history of psoriasis in 24% (n = 12). Cases and controls were similar as regards age, sex, BMI, and waist circumference (p=0.2, 0.4, 0.1, 0.1, respectively) (Table 1).

Clinical examination data of the patients revealed, mean BMI (28.59±4.57), waist circumference (85.36±12.03), SBP (127.60±16.23), DBP (81.80±7.20) with statistical significant increase compared to control subjects regarding SBP and DBP (p=0.01, 0.04, respectively).

At the same time, laboratory measures of the patients showed, mean FBS (132.40±19.42.) and TG (143.42±63.49) with statistical significant increase compared with controls (p=0.04,0.01, respectively). While mean blood cholesterol, HDL and LDL (192.50±54.29, 38.92±5.57, 62.92±46.32, respectively) were not statistically different from controls (p= 0.4, 0.1, 0.8, respectively). The median NEP level was (225.35 pg/mL) ranging from 45.4 to 540.2 pg/mL which was significantly higher among cases when compared with controls (p=<0.001) (Table 1).

Table (1): Characteristics of the study groups

		Case (n=50)	Control (n=30)	Test of sig.	p-value
Age / years (mean ± SD)		47.1±12.5	43.2±12.6	t =1.3	0.2
Sex n, (%)	Female	25 (50%)	18 (60%)	X^2=0.8	0.4
	Male	25 (50%)	12 (40%)		
Smoking	No	31 (62%)	23 (76.7%)	X^2=1.8	0.2
	Yes	19 (38%)	7 (23.3%)		
Family history of psoriasis n, (%)	No	38 (76%)	27 (90%)	X^2=2.4	0.1
	Yes	12 (24%)	3 (10%)		
BMI (kg/m^2)		28.59±4.57	27.03±3.86	t =1.6	0.1
Waist circumference (cm)		85.36±12.03	81.03±8.9	t =1.7	0.1
SBP (mmHg)		127.60±16.23	118.00±14.95	t =2.6	0.01*
DBP (mmHg)		81.80±7.20	78.33±6.99	t =2.1	0.04*
Cholesterol (mg/dL)		192.50±46.29	188.00±45.68	t =.4	0.4
TG (mg/dL)		143.42±33.49	114.10±26.83	t =2.6	0.01*
HDL (mg/dL)		38.92±5.57	40.23±4.86	t =1.1	0.1
LDL (mg/dL)		62.92±14.32	66.10±15.72	t =0.3	0.8
Fasting blood sugar (mg/dL)		132.40±19.42	123.20±17.92	t =2.1	0.04*
NEP (pg/mL) (Median, range)		225.35 (45.4-540.2)	51.65 (41.6-368.9)	Mann-Whitney U =5.2	<0.001*

Median, range: non-parametric test.
BMI (Body Mass Index), SBP (systolic blood pressure), DBP (diastolic blood pressure), TG (Triglycerides), HDL (High Density Lipoprotein), LDL (Ligh Density Lipoprotein), NEP (Neprilysin). * Significant

The Median NEP level was significantly higher in patients with features of MetS (230.9 pg/mL) than those without (73.1 pg/mL), P=0.002 (Table 2). Statistical significant positive correlation was observed between NEP and BMI, waist circumference, SBP, DBP, FBS and PASI score (p= 0.006, 0.005, 0.024, 0.002, 0.036, 0.001, respectively) (Table 3).

Table (2): Comparison between patients with and without metabolic syndrome regarding neprilysin

	Absent		Present		Mann-Whitney U	p-value
	Median	Range	Median	Range		
NEP (pg/mL)	73.1	41.6-395.1	230.9	45.3-540.2	3.1	0.002*

Median, range: non-parametric test. *Significant

Table (3): Correlations between neprilysin and general characteristics

	R	p-value
Age (years)	0.053	0.642
Disease duration (year)	0.105	0.466
PASI	0.462	0.001*
BMI (kg/m2)	0.385	0.006*
Waist circumference (cm)	0.31	0.005*
SBP (mmHg)	0.319	0.024*
DBP (mmHg)	0.429	0.002*
Fasting blood sugar (mg/dL)	0.298	0.036*
Cholesterol (mg/dl)	-0.014	0.904
Triglycerides (mg/dL)	0.138	0.223
HDL (mg/dL)	-0.034	0.762
LDL (mg/dL)	0.039	0.733

*significant

ROC curve revealed that cut-off point of NEP (192.9 pg/mL) could be excellent predictive test of MetS in psoriasis patients with 90% sensitivity and 80% specificity (AUC, 0.93 and 95% CI, 0.86-0.99) (Table 4, Figure 1).

Table (4): Receiver Operating Characteristic (ROC) curve analysis of the cut-off values of neprilysin for prediction of metabolic syndrome in psoriasis patients

Variable	Cut-off value	AUC	95% CI	Sensitivity	Specificity
NEP(pg/mL)	>192.9	0.93	0.86-0.99	90	80

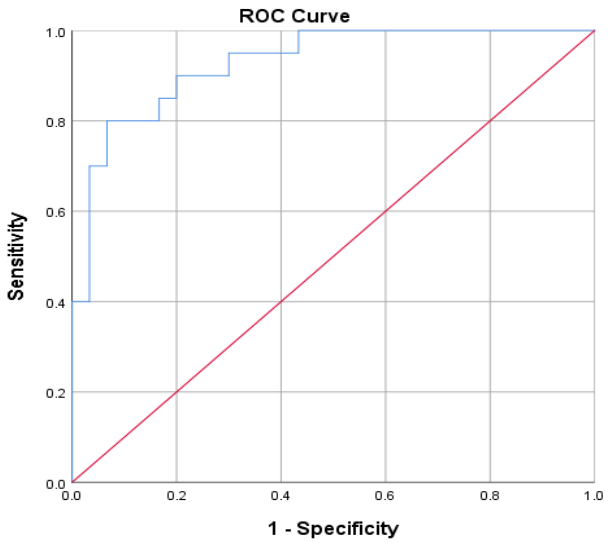

Figure (1): Receiver Operating Characteristic (ROC) curve analysis of the cut-off values of NEP for prediction of metabolic syndrome in psoriasis patients.

Univariate logistic regression analysis showed that BMI and NEP level were significant predictors for MetS in psoriasis patients (p=.0.018, <0.001, respectively), while on multivariate logistic regression analysis, NEP level was the only significant predictor for metabolic syndrome in psoriasis patients (p<0.001) (Table 5).

Table (5): Univariate and multivariate logistic regression analyses of various variables for prediction of metabolic syndrome in psoriasis patients

	Univariate analysis				Multivariate analysis			
	p-value	OR	95%CI		p-value	OR	95%CI	
Age	0.061	1.048	0.998	1.101				
Sex	0.251	1.962	0.621	6.193				
BMI	0.018*	1.192	1.031	1.378	0.146	1.157	0.951	1.407
Waist circumference	0.345	0.977	0.930	1.026				
Family history	0.590	1.455	0.373	5.679				
Smoking	0.344	1.784	0.538	5.914				
PASI score	0.375	0.961	0.879	1.050				
NEP	<0.001*	1.017	1.009	1.026	<0.001*	1.017	1.008	1.026

*Significant

DISCUSSION

Psoriasis is a systemic inflammatory condition that is linked to a diversity of comorbidities, including cardiovascular disease, diabetes, and MetS, in addition to being a dermatological disorder [13]. In the present work, we have demonstrated that psoriasis patients exhibit more MetS traits than do controls. That is in line with a lot of research carried out in other countries [14-20].

However, contrary research has found no discernible change in MetS characteristics in psoriasis cases [21, 22]. These contradicting results could be the result of varied MetS assessment criteria, various racial/ethnic and genetic backgrounds, and various lifestyles in various countries.

The most common features of MetS in our patients with psoriasis were high blood pressure (SBP & DBP), FBS, and TG, and their prevalence varied significantly between study groups. However, there were no substantial variations in Cholesterol, HDL, or LDL levels.

The mechanism of this association between psoriasis and MetS is uncertain whether one of the two disorders precedes or encourages the other [23]. Both entities have common causal chronic inflammatory status [24], similar cytokines [25, 26], and both share some genetic loci [27].

The findings of the current study demonstrated that PASI score has no predictive function in metabolic risk with psoriasis. Likewise, several other studies failed to discover any connection between MetS and psoriasis severity [17, 22, 28]. Contrarily, a number of investigators discovered a correlation between MetS and the severity of psoriasis, ranging from mild to severe psoriasis [29, 30].

NEP levels were noticeably greater in psoriasis sufferers compared to controls. Additionally, NEP revealed a statistically significant distinction between patients with MetS and those without it. NEP was the sole significant predictor of MetS in psoriasis patients on multivariate longitudinal regression analysis. In line with our results, **Standeven *et al.* [9] and Gul *et al.* [31]** who also found an independent relationship between NEP and MetS.

Adipocytes secrete NEP, which may play a role in controlling adipocyte function [32]. GLP-1 is degraded and rendered inactive by NEP [10], as well as inhibition of NEP raises GLP-1 levels in the bloodstream. This finding implies that in diabetic and obese conditions, NEP may have an impact on insulin secretion and sensitivity, and glucose tolerance [33]. On the other hand, an enhanced breakdown of vasoactive peptides like bradykinin or the natriuretic peptides, which results in endothelial dysfunction, reduced vaso-relaxation, and raised blood pressure, could provide a mechanism connecting higher NEP activity in plasma to hypertension [9].

The fact that we have found, a positive correlation between NEP and PASI score, recommends that NEP may have a part in the pathogenesis of psoriasis. The increased levels of NEP, which have a positive correlation with SBP, DBP, and FBS, may account for the relationship between MetS and psoriasis. Likewise, **Rice *et al.* [34] and Ramanathan and Padmanabhan [35]** reported significant correlations between circulating NEP and the MetS components.

LIMITATIONS

The current study is thought to have weaknesses due to its small patient population and single-center design.

CONCLUSION

NEP is a useful biomarker for psoriasis and its related comorbidities. It not only aids in enhancing the prognosis of primary illnesses but also guards against negative consequences like coronary heart disease and stroke.

Supporting and sponsoring financially: Nil.
Competing interests: Nil.

REFERENCES

1. **Kim N, Thrash B, Menter A (2010):** Comorbidities in Psoriasis patients. Semin Cutan Med Surg., 29:10-5.
2. **Ryan C, Kirby B (2015):** Psoriasis is a systemic disease with multiple cardiovascular and metabolic comorbidities. Dermatol Clin., 33: 41-55.
3. **Baeta I, Bittencourt F, Gontijo B *et al.* (2014):** Comorbidities and cardiovascular risk factors in patients with psoriasis. An Bras Dermatol., 89: 735-44.
4. **Gelfand J, Neimann A, Shin D *et al.* (2006):** Risk of myocardial infarction in patients with psoriasis. JAMA., 296: 1735-41.
5. **Gelfand J, Troxel A, Lewis J *et al.* (2007):** The risk of mortality in patients with psoriasis: results from a population-based study. Arch Dermatol., 143:1493-9.
6. **Gelfand J, Dommasch E, Shin D *et al.* (2009):** The risk of stroke in patients with psoriasis. J Invest Dermatol., 129: 2411-8.
7. **National Cholesterol Education Program (NCEP) (2002):** Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult TreatmentPanel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation, 106: 3143-421.
8. **Zraika S, Koh D, Barrow B *et al.* (2013):** Neprilysin deficiency protects against fat-induced insulin secretory dysfunction by maintaining calcium influx. Diabetes, 62: 1593-1601.
9. **Standeven K, Hess K, carter A *et al.* (2011):** Neprilysin, obesity and the metabolic syndrome. Int J Obes., 35(8): 1031-1040.
10. **Wand C, Leung N, Lapointe N *et al.* (2003):** Vasopeptidase inhibitör omapatrilat induces profound insulin sensitization and increases myocardial glucose uptake in Zucker fatty rats: studies comparing a vasopeptidase inhibitör, angiotensin-converting enzyme inhibitor and angiotensin II type I receptor blocker. Circulation, 107(14): 1923-1929.

11. **Willard J, Barrow B, Zraika S (2017):** Improved glycaemia in high-fat fed neprilysin deficient mice is associated with reduced DPP-4 activity and increased active GLP-1 levels. Diabetologia, 60(4): 701-708.
12. **Grundy S, Cleeman J, Daniels S *et al.* (2005):** Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation, 112: 2735-2752.
13. **Chat V, Uppal S, Kearns D *et al.* (2021):** Translating the 2020 AAD-NPF guidelines of care for the management of psoriasis with systemic nonbiologics to clinical practice. Cutis, 107: 99–103.
14. **Love T, Qureshi A, Karlson E *et al.* (2011):** Prevalence of the Metabolic Syndrome in psoriasis: Results from the National Health and Nutrition Examination Survey, 2003-2006. Arch Dermatol., 147:419-24.
15. **Langan S, Seminara N, Shin D *et al.* (2012):** Prevalence of metabolic syndrome in patients with psoriasis: A population-based study in the United Kingdom. J Invest Dermatol., 132:556-62.
16. **Miller I, Ellervik C, Zarchi K *et al.* (2015):** The association of metabolic syndrome and psoriasis: a population- and hospitalbase cross-sectional study. J Eur Acad Dermatol Venereol., 29: 490-7.
17. **Gisondi P, Tessari G, Conti A *et al.* (2007):** Prevalence of metabolic syndrome in patients with psoriasis: a hospital based case-control study. Br J Dermatol., 157:68-73.
18. **Madanagobalane S, Anandan S (2012):** Prevalence of metabolic syndrome in south Indian patients with psoriasis vulgaris and the relation between disease severity and metabolic syndrome: A hospital-based case control study. Indian J Dermatol., 57: 353-7.
19. **Takahashi H, Iizuka H (2012):** Psoriasis and metabolic syndrome. J Dermatol., 39: 212-218.
20. **Puig L, Kirby B, Mallbris L *et al.* (2014):** Psoriasis beyond the skin: a review of the literature on cardiometabolic and psychological comorbidities of psoriasis. Eur J Dermatol., 24: 305-311.
21. **Takahashi H, Takahashi I, Honma M *et al.* (2010):** Prevalence of metabolic syndrome in Japanese psoriasis patients. J Dermatol Sci., 57:143-4.
22. **Kim G, Park H, Kim H *et al.* (2012):** Analysis of cardiovascular risk factors and metabolic syndrome in korean patients with psoriasis. Ann Dermatol., 24:11-5.
23. **Snekvik I, Nilsen T, Romundstad P *et al.* (2019):** Metabolic syndrome and risk of incident psoriasis: Prospective data from the HUNT Study, Norway. Br J Dermatol., 180: 94–99.
24. **Davidovici B, Sattar N, Prinz *et al.* (2010):** Psoriasis and systemic inflammatory diseases: Potential mechanistic links between skin disease and comorbid conditions. J Invest Dermatol., 130: 1785–1796.
25. **Armstrong E, Krueger J (2016):** Lipoprotein metabolism and inflammation in patients with psoriasis. Am J Cardiol., 118: 603–609.
26. **Ferretti G, Bacchetti T, Campanati A *et al.* (2012):** Correlation between lipoprotein(a) and lipid peroxidation in psoriasis: Role of the enzyme paraoxonase-1. Br J Dermatol., 166: 204–207.
27. **Lu Y, Chen H, Nikamo P *et al.* (2013):** Association of cardiovascular and metabolic disease genes with psoriasis. J Invest Dermatol., 133: 836–839.
28. **Nisa N, Qazi M (2010):** Prevalence of metabolic syndrome in patients with psoriasis. Indian J Dermatol Venereol Leprol., 76: 662-65.
29. **Neimann A, Shin D, Wang X *et al.* (2006):** Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol., 55: 829-35.
30. **Choi W, Park E, Kwon I *et al.* (2010):** Association between psoriasis and cardiovascular risk factors in Korean patients. Ann Dermatol., 22: 300-6.
31. **Gul O, Sisman P, Cander S *et al.* (2022):** Plasma neprilysin levels in patients with polycystic ovary syndrome. Acta Endocrinol (Buchar), 18(1):35-39.
32. **Schling P, Schafer T (2002):** Human adipose tissue cells keep tight control on the angiotensin II levels in their vicinity. J Biol Chem., 277(50):48066–48075.
33. **Jordan J, Stinkens R, Jax T *et al.* (2017):** Improved insulin sensitivity with angiotensin receptor neprilysin inhibition in individuals with obesity and hypertension. Clin Pharmacol Ther., 101: 254–263.
34. **Rice G, Jones A, Grant P *et al.* (2006):** Circulating activities of angiotensin-converting enzyme, its homolog, angiotensin-converting enzyme 2, and neprilysin in a family study. Hypertension, 48(5):914–920.
35. **Ramanathan K, Padmanabhan G (2020):** Soluble neprilysin: A versatile biomarker for heart failure, cardiovascular diseases and diabetic complications—A systematic review. Indian Heart J., 72(1): 14–19.