

RESEARCH

Open Access



Long noncoding RNA (taurine upregulated gene 1) and micro RNA-377: emerging players in the development of metabolic syndrome among psoriasis patients

Maha Alhelf^{1,2}, Laila Rashed², R. W. Doss^{3,5}, Sahar M. Mohamed^{4*} and Naglaa A. Abd Elazeem⁴

Abstract

Background Psoriasis (PsO) is an immune-mediated dermatosis and systemic inflammatory condition that can affect the skin, joints, and other organs and tissues with a range of comorbidities. The activation of proinflammatory cytokines is the primary cause of the development of skin lesions in PsO. Patients with PsO have a higher risk of developing cardiovascular metabolic comorbidities; among these is the metabolic syndrome (MetS). Particularly, MetS is characterized by abdominal obesity, hypertension, hyperglycemia, and hyperlipidemia, has been linked to PsO. The connection between PsO and MetS is believed to be caused by PsO generating systemic inflammation, which then results in elevated inflammatory adipokines, endothelial dysfunction, and insulin resistance. Micro RNA-377 and long noncoding RNA taurine upregulated 1 (TUG1) are both involved in the control of a variety of inflammatory disorders in humans and can be employed as biomarkers for the diagnosis and prognosis of psoriasis. The aim of the present study is to establish a panel of biomarkers for the early diagnosis of MetS incidence in psoriasis and thereby, reducing its lethal consequences.

Results In this study, 120 patients: 40 psoriatic patients, 40 psoriatic patients with metabolic syndrome, and 40 healthy subjects were conducted. Expressions of Long noncoding RNA Taurine Upregulated Gene-1 (TUG1), miRNA-377 and Peroxisome Proliferator-Activated Receptor- γ (PPAR- γ) were assessed in tissue lesion by real-time PCR. ELISA technique was carried out for the detection of serum levels of plasminogen activator inhibitor-1 (PAI-1) and transforming growth factor β (TGF β). Moreover, miRNA-377 expression was significantly elevated with the simultaneous down-regulation of both TUG-1 and PPAR- γ in PsO-MetS group when compared to those of PsO and control groups. Furthermore, PAI-1 and TGF β levels were higher in PsO-MetS than PsO.

Conclusions The dysregulated levels of TUG-1, miRNA-377, PPAR- γ , PAI-1, and TGF β , biomarkers may provide information about their potential role in the emergence of MetS in psoriasis patients.

Keywords Psoriasis, Metabolic syndrome, TUG-1, miRNA-377, PPAR- γ , TGF- β , PAI-1

*Correspondence:

Sahar M. Mohamed

sahr.mohamed@med.bsu.edu.eg

Full list of author information is available at the end of the article



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

1 Background

Psoriasis (PsO) is a complex and chronic inflammatory disease affecting 2–3% of the world's population [1]. Well-defined, erythematous plaques with silvery-white scales are the hallmarks of PsO and often appear in a symmetrical pattern on the scalp, elbows, knees, and trunk [2]. It is still unclear exactly how PsO pathogenesis occurs. Multiple genetic and environmental risk factors, in addition to severe immunological imbalances interact dynamically to cause PsO disease. Eventually, this can lead to a number of systemic complications [3]. Conspicuously, the Psoriasis Area and Severity Index (PASI) is the gold standard among Psoriasis evaluation tools. On a scale from 0 to 72, it evaluates and grades both the patient's responsiveness to treatment and the severity of the patient's psoriatic lesions [4].

The chronic inflammation seen in PsO is related to a higher incidence of cardiovascular risk factors such as obesity, diabetes, hyperlipidemia, and hypertension, which together make up the metabolic syndrome (MetS), a condition that is more prominent in PsO patients as compared to the general population [5]. The International Diabetes Federation states that three or more of the following characteristics define MetS: A decreased level of high-density lipoprotein cholesterol (HDL-Cholesterol) (<40 mg/dL in men and <50 mg/dL in women); and an increase in triglycerides (≥ 150 mg/dL), fasting blood glucose (≥ 100 mg/dL), and waist circumference (≥ 102 cm in men and ≥ 88 cm in women); in addition to hypertension (systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg) [6]. Therefore, inflammatory markers attributed to insulin resistance and endothelial dysfunction, show greater levels in patients with MetS, indicating higher levels of chronic inflammation [7, 8]. Pro-inflammatory cytokines that increase insulin resistance and lead to abdominal obesity include tumor necrosis factor (TNF)- α , plasminogen activator inhibitor 1 (PAI-1), transforming growth factor β (TGF β), leptin, adiponectin, and interleukin (IL)-6 [9, 10].

Notably, numerous inflammatory and cytokine-mediated pathways connect MetS and PsO. Both are a part of a fascinating system of genetic, clinical, and pathophysiological aspects. Exploration of the pathophysiological mechanisms tying MetS to PsO is important from a clinical standpoint since it may represent the possibility of novel pharmaceutical therapies. The fundamental underlying mechanisms that bind these two disorders are likely multifactorial; they typically overlap with metabolic abnormalities, which commonly coexist in psoriatic people [11].

Consistently, the maintenance of normal intracellular signaling depends on the regulation of gene expression,

and this process' disruption plays a significant role in the etiology of many diseases, including those of obesity, insulin resistance, and autoimmune disorders. About 60% of protein-coding genes are controlled by non-coding RNAs, which comprise circular RNAs (circRNAs); long chain non-coding RNAs (lncRNAs), and micro RNAs (miRNAs). These non-coding RNAs are found to be implicated in the development of many diseases, either directly or indirectly by modulating certain pathways [12]. lncRNAs play significant roles in controlling autoimmune disease and immune-mediated inflammatory diseases. Psoriasis is one of immunological disorders that has been linked to dysregulation of lncRNAs [13]. Considering this, lncRNAs are becoming recognized as important players in the development and progression of psoriasis. However, the exact lncRNA regulatory mechanisms in psoriasis are still mostly unstudied [14].

Taurine-up-regulated gene 1 (TUG1), a 7.1-kb long non-coding RNA, is implicated in the development of skin cancer and serves as competing endogenous RNA (ceRNAs) that inhibits the expression and function of miRNAs [15]. It may be hypothesized that lncRNA TUG1 functioned as an endogenous sponge of miRNA-377, reducing the levels of miRNA-377 expression [16]. According to recent studies, non-coding RNAs have a critical role in the onset and progression of psoriasis via modulating the expression of essential proteins including protein-coding genes associated with the interleukin-17 signaling pathway, the nuclear factor (NF)- κ B signaling pathway, the Jak-STAT signaling pathway and the mitogen-activated protein kinase (MAPK) signaling pathway [17, 18].

Moreover, miRNAs mediate a number of biological processes, including cellular differentiation and proliferation as well as pathological processes including neurological diseases and malignancy. For example, miRNA-377 is a key tumor suppressor in a number of human cancers and is a member of a large miRNA cluster. It has received a lot of attention recently in the context of oxidative stress and diabetic nephropathy [19].

Interestingly, there is a strong correlation between MetS and the nuclear hormone receptor superfamily member peroxisome proliferator-activated receptor gamma (PPAR- γ). PPAR- γ has been linked to improved insulin sensitivity and blood pressure control, according to previous researches [20, 21]. Consequently, PPAR- γ can affect cellular activities, such as glucose homeostasis and fat metabolism, lipid buildup, and inflammation. PPAR- γ primarily regulates gene expression through their function as ligand-activated transcription factors [21–23].

As a well-known acute-phase reactant, PAI-1's expression is increased rapidly in response to inflammatory

cytokines (e.g., interleukin-6, interleukin-1, and tumor necrosis factor- α), transforming growth factor- β [24], hormones (e.g., insulin, glucocorticoids, adrenaline), and in response to hypoxia [25]. Because of the correlation between elevated plasma levels of (PAI-1) in psoriasis and enhanced angiogenesis, which in turn plays a significant role in the disease, it is highlighted that there is a relationship between the two [26]. In vivo, increased body mass index and signs of insulin resistance are linked with increasing plasma PAI-1 antigen and activity levels [27]. In addition, Elevated plasma PAI-1 is a common feature of patients with metabolic syndrome and diabetes [28].

TGF- β is a highly pleiotropic cytokine which plays a vital role in several crucial cellular processes. In psoriasis, TGF receptors have significantly decreased in the psoriatic epidermis [29]. Reduced TGF- β signaling is thought to boost keratinocyte hyperproliferation in the psoriasis epidermis since TGF- β 1 is a potent growth inhibitor for keratinocytes. Serum levels of inflammatory biomarkers such as C-reactive protein, tumor necrosis factor-alpha, and TGF- β have been considerably higher in hypertensive individuals with MetS than in non-MetS patients [30].

Thus, the current study aims to identify TUG-1 and miRNA377's attributes in the pathogenesis of psoriasis, as well as how their dysregulated expression affected the development of metabolic syndrome in psoriasis patients, and to investigate any potential underlying mechanisms.

2 Subjects and methods

2.1 Study population

This study included a total of 120 adults, 40 patients with PsO (26 males and 14 females), 40 patients with PsO with MetS (22 males and 18 females), and 40 healthy controls (27 males and 13 females) of the same ethnicity that matched with age and gender. Informed consent was obtained from the participants in this study after ethical committee approval from Medical Biochemistry Department, Faculty of Medicine, Cairo University. Approval code: MD-146-2019. To be enrolled in the study, patients had to be between the ages of 18 and 65 years and diagnosed as PsO patients with or without MetS. Patients under the age of 18, those suffering from autoimmune or inflammatory illnesses, or those with cancer were all excluded.

2.2 Clinical and anthropometric measurements

The evaluation of patients included a general and dermatological physical examination, the monitoring of vital signs, the assessment of laboratory results, the observation of adverse events, and the measurement of the severity of the skin disorder using the PASI score. The severity

of the disease is determined by the affected surface area, the erythema, the desquamation, and the infiltration of psoriatic plaques, which are all expressed as parts of the PASI score, which ranges from 0 to 72 [31]. A family history was obtained from each participant. Participants' height, weight, and body mass index were all measured using standardized methods. By dividing weight (in kg) by height squared, the body mass index (BMI) was determined (kg/m^2).

2.3 Sample collection and processing

From patients and controls, 5 mL of venous blood was drawn, allowed to clot, and then centrifuged at $8000\times g$ for 5 min to separate the serum, which was then kept frozen at -80°C till analysis for subsequent chemical assays. In order to analyse the results of the biochemical studies by real-time PCR, a 2 mm sample of bunch skin biopsy was taken and stored frozen at -80°C .

2.4 Biochemical assays

Blood glucose was assessed using a Colorimetric Assay kit (Catalogue No.: ab282922, Abcam, USA), and the quantitative sandwich ELISA technique using the Human Insulin Kit was used to quantify the serum insulin concentration (Catalogue No.: E0010Hu, BT LAB, China). The following formula was used to test insulin resistance using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR): HOMA-IR is calculated as follows: Fasting blood sugar (mmol/L) \times Fasting insulin ($\mu\text{IU}/\text{mL}$)/22.5. After fasting for twelve hours, serum Triglycerides and total cholesterol levels were estimated using Colorimetric Assay kits (Catalogues no.: ab65336, Abcam, USA and STA-384, Cell Biolabs, USA) respectively. LDL-Cholesterol and HDL-Cholesterol levels were quantified using enzymatic assay kits (Catalogues no.: 80069, Crystal Chem, USA and STA-394, Cell Biolabs, USA) respectively.

2.5 Enzyme-linked immunosorbent assay (ELISA)

Serum levels of TGF- β and PAI-1 were quantified by ELISA. ELISA kits: Catalogue no.: EH0287; Fine Test, Wuhan, China) and (Catalogue no.: SL1407Hu, SunLong Biotech Co., LTD, China were used, respectively, for TGF- β and PAI-1 quantification.

To quantify the TGF- β levels, according to the manufacturer's instructions, standards and samples were added into appropriate wells coated with anti-human TGF- β , and the plate was incubated for 1 h at 37°C . After washing three times with the appropriate wash solution, the HRP-Streptavidin Conjugate (SABC) working solution was added to each well at 37°C for 30 min. Subsequently, the washing step has been repeated five times and 3,3',5,5'-tetramethylbenzidine (TMB) substrate

reagent was added to each well for 30 min at 37 °C in the dark. Lastly, Stop Solution has been added, and the absorbance at 450 nm was read immediately in a stat fax 2100 plate reader.

In order to quantify PAI-1, standards and samples were added in the anti-human PAI-1 pre-coated well. After discarding the liquid in the wells, HRP-Conjugate reagent was added to each well, and the plate was incubated at 37° for 30 min. Subsequently the plate was washed three times with the specific wash buffer. According to the manufacturer's instructions, Chromogen Solution A and Chromogen Solution B were added into each well and incubated at 37° for 15 min in the dark. Lastly, Stop solution has been added, and the absorbance was read at 450 nm in a stat fax 2100 plate reader. The concentration of Human TGF-β and PAI-1 in samples were determined from the standard curve.

2.6 Gene expression analysis

The expressions of miRNA-377, TUG1 and PPAR γ genes were analyzed using real-time PCR technique. miRNA was isolated from the lesional tissue using mir-Vana kit (AM1560, USA). Total RNA was isolated using Qiagen kit (Qiagen, USA).

Primer data base with the following sequences were studied:

LncRNA-TUG1	Forward: 5'-GTCTCCGATAGTGCA CACAGC-3'; Reverse: 5'-GACCATCTCCTTCAG GACCA-3'
MiR-377	Forward:5'-AUC ACA CAA AGG CAA CUU UUG U-3'; Reverse: 5'-AAA AGUUGC CUU UGU GUG AUU U-3'
PPAR γ	Forward:5'-GCCCTTTGGTGACTT TATGGA-3'; Reverse: 5'-GCAGCAGGT TGT CTTGATG-3'
β -actin	Forward:5'-ATCACCATCTTCCAG GAGCG-3'; Reverse: 5'-CCTGCTTACCACCT TCTTG-3'

The qPCR assay with the primer sets were optimized at the annealing temperature. Relative Quantification (RQ) (relative expression): was calculated according to Applied Bio system StepOne™ software, version 3.1. The fold change results have been calculated using the threshold cycle ($2^{-\Delta\Delta CT}$) of PCR.

2.7 Statistical analysis

The IBM SPSS statistics software, version 26.0, was used to analyze and process the data (Thousand Oaks, CA, USA). The Mann–Whitney U test was used to examine the non-parametric data, and the results were presented as median with interquartile range (IQR) (1st quartile-3rd quartile). Mann–Whitney U test was used to compare the medians of the two groups. For pairwise comparisons between each of the two groups, the Post Hoc Test was performed. Medcalc statistical software, version 19.6.1, was used to produce receiver operator characteristic (ROC) curves. The multivariate analysis, correlation, and boxplots were carried out using R studio version 1.4.1103 and the R programming language software, version 4.1.3.

3 Results

3.1 Laboratory and anthropometric parameters

The clinical and anthropometric parameters of the PsO, PsO-MetS and normal groups are summarized in Table 1. There was no statistically significant difference noticed with age and sex among all study groups ($p > 0.05$). Both of PsO and PsO-MetS patients had higher BMI in comparison with the normal-weight subjects ($p = 0.04$ and $p < 0.001$, respectively), and there is a statically significance between the two groups ($p = 0.01$). PsO-MetS patients had significantly higher serum blood glucose, insulin, and HOMA-IR levels when compared to their corresponding values of both of PsO and control groups ($p < 0.001$). Conversely, PsO patients' serum insulin, blood glucose and HOMA-IR levels did not differ significantly from those of the control group.

Likewise, PsO and PsO-MetS groups had significantly higher levels of triglycerides, total cholesterol, and LDL cholesterol than the control group ($p < 0.001$). The two groups (PsO and PsO-MetS) had significantly lower HDL levels compared to the control groups ($p < 0.001$). Regarding all lipid profile values except HDL of PsO-MetS group were significantly increased compared to those of PsO group ($p = 0.04$).

3.2 Expression of TUG-1, miRNA-377 and PPAR- γ in the PsO and PsO-MetS patients

The gene expression of TUG-1, miRNA-377, and PPAR- γ in the studied groups are demonstrated in Table 2 and Fig. 1. In detail, TUG-1 gene expression was markedly lower in PsO-MetS rather than those found in PsO group ($p < 0.001$, Fig. 1a). Too, TUG-1 gene expression in PsO and PsO-MetS was significantly down-regulated as compared to those in normal group ($p < 0.001$). However,

Table 1 Clinical, anthropometric, and biochemical characteristics of the studied groups

parameters	PsO (n = 40)	PsO-MetS (n = 40)	Control (n = 40)	p
Age (years)	45.0 (28.5–54.0)	48.0 (38.5–57.3)	50.0 (41.3–53.0)	0.23
Gender (M/F), n (%)	26 (65%) / 14(35%)	22 (55%)/18 (45%)	27 (67.5%)/13 (32.5%)	0.47
PASI Score	18.3 (12.6–25.6)	4.9 (3.7–7.9)	–	< 0.001
Family history n (%)	18 (45%)	6 (15%)	–	0.007
Anthropometric parameters				
BMI (Kg/m ²)	27.31 (24.57–33.24)	32.0 (25.5–36.58)	25.82 (24.21–29.26)	0.01 ^a 0.04 ^b < 0.001 ^c
Biochemical characteristics				
Blood Glucose (mmol/L)	5.9 (4.9–7.1)	8.02 (6.35–8.88)	5.3 (5.1–5.6)	< 0.001 ^{a,c}
Insulin (μU/mL)	8.4 (6.5–9.3)	12.5 (10.3–14.9)	8.9 (8.4–10.4)	< 0.001 ^{a,c}
HOMA-IR	2.2 (1.7–2.6)	4.4 (3.5–6.0)	2.2 (1.9–2.5)	< 0.001 ^{a,c}
Triglycerides (mg/dL)	213.5 (197.5–254.8)	240 (198–277.5)	153.5 (114–177.5)	0.04 ^a < 0.001 ^{b,c}
Total cholesterol (mg/dL)	258.5 (227.5–274.8)	277 (249.3–297.5)	179 (150.5–197.8)	0.038 ^a < 0.001 ^{b,c}
LDL (mg/dL)	177.8 (170.5–184.6)	195.3 (160.7–220.4)	94.2 (79.1–115.7)	0.04 ^a < 0.001 ^{b,c}
HDL (mg/dL)	35 (29–40.5)	29.5 (19.3–37.8)	46 (41.3–53.8)	< 0.001 ^{b,c}

PsO Psoriasis, PsO-MetS Psoriasis with metabolic syndrome, PASI Score Psoriasis Area and Severity Index, BMI Body mass index, HOMA-IR Homeostatic Model Assessment for Insulin Resistance, LDL Low-density lipoprotein cholesterol, HDL High-density lipoprotein-cholesterol. All data presented as median and IQR (first quartile–third quartile) except sex presented as numbers. $p \leq 0.05$ is significant

^a Comparison between PsO and PsO-MetS

^b Comparison between PsO and Control

^c Comparison between PsO-MetS and Control

Table 2 Expression of TUG-1, miRNA-377 and PPAR-γ as well as PAI-1 and TGFβ levels in the PsO and PsO-MetS patients compared to control

	PsO (n = 40)	PsO -MetS (n = 40)	Control (n = 40)	p
TUG-1	0.48 (0.42–0.65)	0.18 (0.13–0.24)	1.01 (1.0–1.03)	< 0.001 ^{a,b,c}
miRNA-377	4.4 (2.8–5.3)	9.1 (6.4–10.2)	1.02 (1.0–1.04)	< 0.001 ^{a,b,c}
PPAR γ	0.55 (0.32–0.63)	0.29 (0.24–0.49)	1.0 (1.0–1.08)	0.001 ^a < 0.001 ^{b,c}
PAI-1(ng /mL)	24.5 (20.08–41.3)	55.8 (39.43–85.78)	13.6 (10.35–19.23)	< 0.001 ^{a,c} 0.001 ^b
TGFβ (pg/mL)	124.7 (114.2–163.7)	165.5 (145.1–194.4)	38.7 (33.7–45.1)	< 0.001 ^{a,b,c}

PsO Psoriasis, PsO-MetS Psoriasis with metabolic syndrome, TUG-1 Taurine up-regulated gene, miRNA-377 microRNA-377, PPAR γ Peroxisome Proliferator-Activated Receptor γ, PAI-1 Plasminogen activator inhibitor-1, TGFβ Transforming growth factor beta. All data presented as median and IQR (first quartile–third quartile). $p \leq 0.05$ is significant

^a Comparison between PsO and PsO-MetS

^b Comparison between PsO and Control

^c Comparison between PsO-MetS and Control

miRNA-377 expression was significantly elevated in PsO-MetS group when compared to that of PsO group ($p < 0.001$). Patients with either PsO or PsO-MetS had significant elevation in miRNA-377 gene expression compared to that of control group ($p < 0.001$, Fig. 1b).

The gene expression of PPAR-γ was analyzed as the main target gene of lipogenesis and adipogenesis in the studied individuals. Both of PSO and PSO-MetS groups had significantly decreased PPAR-γ gene expression when compared to that of the normal group, ($p < 0.001$).

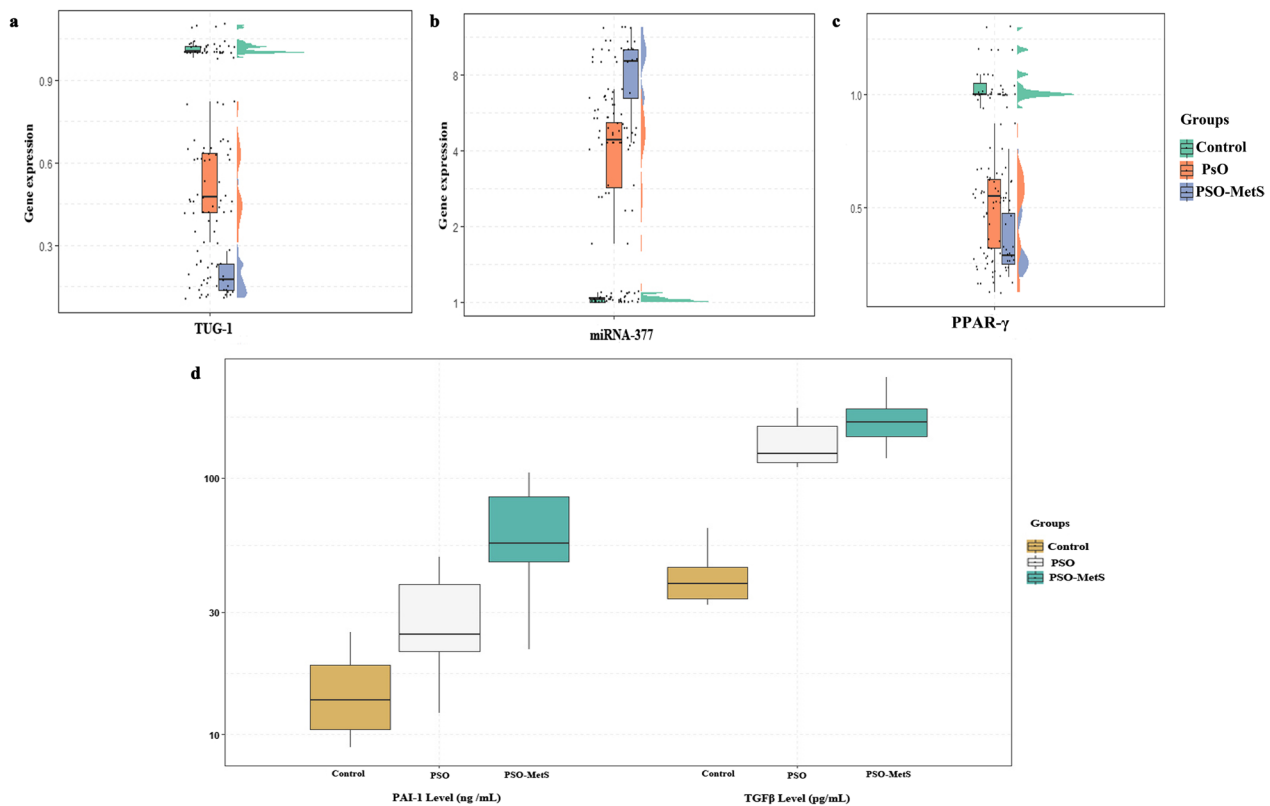


Fig. 1 Gene expression represented by raincloud plots **a** InRNA TUG1 expression. **b** miR-377 expression **c** PPAR-γ gene expression **d** Boxplots showing the levels TGFβ and PAI-1 in the studied groups

Similarly, PPAR-γ gene expression in PsO-MetS was significantly decreased as compared to PsO group ($p=0.001$) (Fig. 1c).

3.3 ELISA measurement of the plasminogen activator inhibitor (PAI-1) and transforming growth factor β (TGF-β)

According to the results of the ELISA test, the serum PAI-1 level of PsO-MetS is higher than that of the PsO or control groups ($p<0.001$). A significant increased level of PAI-1 was also detected in PsO compared to the control group ($p=0.001$). In comparison to either the PsO or control groups, there was a statistically significant increase in TGFβ levels in the PsO-MetS group ($p<0.001$). Additionally, PsO had higher levels of TGFβ than the control group ($p<0.001$) as shown in Table 2, Fig. 1d.

3.4 Multivariate analysis

Principal component analysis classified the study subjects into three main groups with a clear distinction between PsO, PsO-MetS patients, and healthy controls, according

to multivariate analysis. Arrows were used to represent the primary demographic and biochemical variables, with lengthier arrows indicating significant impact on separation. As demonstrated, miRNA-377, TGFβ, and PAI-1 levels were related to an elevated risk of metabolic syndrome in PsO patients, although TUG-1 and PPAR-γ levels were inversely correlated with that risk (Fig. 2a).

3.5 Correlation of psoriasis patients with clinical characteristics

In order to investigate the probable deregulation expression of TUG1 and miRNA-377 that might be related to the incidence of MetS among PsO patients, a correlation analysis between PsO and clinical characteristics was conducted. As shown in Fig. 2b, TUG-1 and PPAR-γ tissue gene expression were significantly correlated negatively with PASI, blood glucose, insulin, HOMA-IR, BMI, TG, Cholesterol, LDL, miRNA-377, PAI-1 and TGFβ but significantly correlated positively with HDL and with each other ($p<0.001$).

Nevertheless, the expression of miRNA-377 had significant positive correlations with blood glucose, insulin, HOMA-IR, BMI, TG, Cholesterol, LDL-cholesterol,

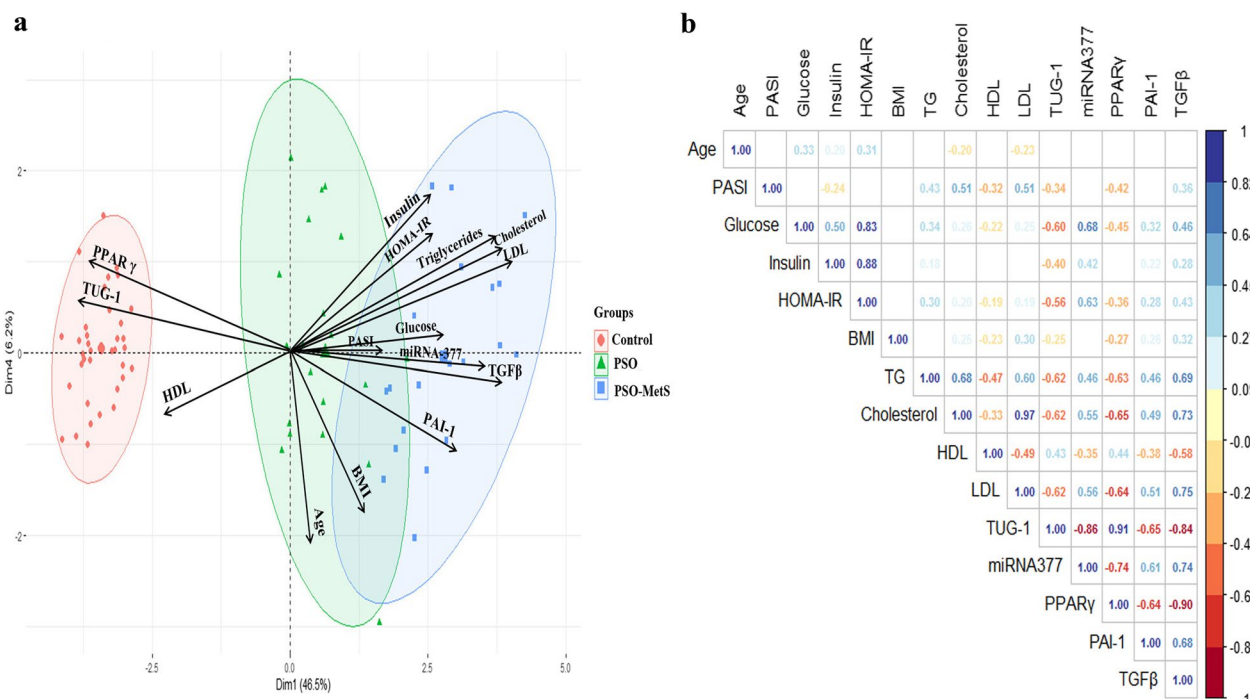


Fig. 2 a Principal component analysis for data evaluation. The multivariate analysis showed clustering of the study population into three classes as psoriasis patients with or without metabolic syndrome and healthy controls. The demographic and biochemical variables were represented as arrows; with the longer ones indicating more impact on the separation. b Correlation analysis of biochemical markers as well as metabolic components in all studied groups. Red numbers indicate significant negative correlations ($p < 0.05$), and blue numbers indicate significant positive correlations ($p < 0.05$), and the darker the color, the stronger the correlation

PAI-1, and TGF β , while it exhibited a significant negative correlation with HDL ($p < 0.001$). It has been demonstrated that serum levels of TGF β and PAI-1 significantly positively correlate with each other as well as with blood glucose, insulin, HOMA-IR, BMI, TG, total cholesterol,

and LDL-cholesterol ($p < 0.001$). Also, there was a positive significant correlation between TGF β and PASI. In contrast, there were notable negative correlations between HDL-Cholesterol, and serum levels of PAI-1 and TGF β ($p < 0.001$).

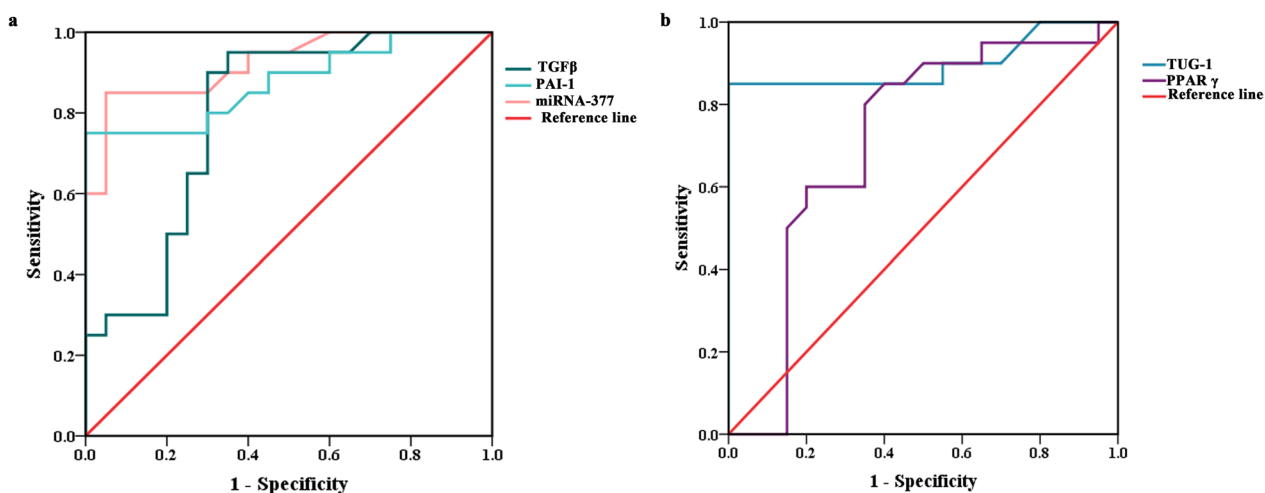


Fig. 3 Comparison of ROC curves for prediction of psoriasis with metabolic syndrome a ROC curve of TGF β , PAI-1 and miRNA-377 levels b ROC curve of TUG-1, and PPAR- γ gene expression

Table 3 Area under curve, 95% confidence interval, cut-offs and sensitivity- specificity obtained from ROC curve analysis

	TUG-1	miRNA-377	PPAR γ	PAI-1 (ng /mL)	TGF β (pg/mL)
AUC	0.898	0.924	0.714	0.876	0.794
Sensitivity %	85	85	80	75	95
Specificity %	100	95	65	100	65
Accuracy	0.85	0.8	0.45	0.75	0.6
Cut-off level	≤ 0.28	> 5.8	≤ 0.49	> 49.3	> 128.4
95% CI	0.809–0.954	0.842–0.971	0.602–0.809	0.784–0.939	0.689–0.876
<i>p</i> -Value	< 0.0001	< 0.0001	0.0006	< 0.0001	< 0.0001
PPV %	100	94.4	69.6	100	73.1
NPV %	87	86.4	76.5	80	92.9

Confidence interval CI; PPV Positive predictive value, NPV Negative predictive value

3.6 Receiver-operating characteristic curve analysis

In order to evaluate the diagnostic efficiency of TUG-1, miRNA-377 and PPAR γ and other potential markers including serum levels of TGF β and PAI-1, AUC (Area Under Curve) was measured for each. the results illustrated that the highest AUC for miRNA-377 as [(0.924, 95% CI 0.842–0.971, *p*-value < 0.001)] followed by TUG-1 [(0.898, 95% CI 0.809–0.954, *p*-value < 0.001)], PAI-1 [(0.876, 95% CI 0.784–0.939, *p*-value < 0.001)], TGF β [(0.794, 95% CI 0.689–0.876, *p*-value < 0.001), and, PPAR γ [(0.714, 95% CI 0.602–0.809, *p*-value = 0.0006)] (Fig. 3a,b and Table 3).

4 Discussion

As previously mentioned, cytokines are released during psoriasis, triggering an immune-mediated response in the skin that causes excessive epidermal proliferation and chronic skin inflammation [32]. Obviously, PsO and the MetS have similar pathophysiology and outcomes as well as a number of cardiovascular risk factors. Unfortunately, for PsO-MetS, clinical care takes longer, costs more, and has a greater death rate [33]. Given this, if particular metabolic risks could be identified in their early stages, it would open up a window for positive outcome [34]. Subsequently, this study was carried out to determine the role of TUG-1 and miRNA377 in the pathogenesis of PsO, as well as how their dysregulated expressions affected the development of MetS in PsO patients.

The non-coding RNAs have recently been discovered to be key participants in PsO through affecting keratinocyte activities and the dysregulation of inflammatory responses in the damaged skin [35]. Correspondingly, microRNAs have a significant role in the regulation of gene expression and transcription, contributing to a variety of cellular metabolic processes as well as the onset and progression of various skin diseases [36]. LncRNAs play a role in the skin via controlling a variety of targets. TUG1 and its target miRNA-377 are examples of

lncRNA-miRNA axes interaction. In the current work, the expressions of LncRNA TUG1 and its associated target miRNAs in PsO patients were investigated.

In the present study, the expression of TUG1 was down-regulated in PsO and PsO-MetS patients compared to the normal controls. TUG1 expression and PASI were also found to be significantly negatively correlated. This finding is in accordance with a study performed by He et al., who reported that abnormal expression of LncRNAs has been associated with psoriasis [37]. TUG1 was also found to be significantly downregulated in the PsO-MetS group compared to the PsO group. Its significant negative correlation with MetS components such blood glucose, insulin, HOMA-IR, BMI, TG, Cholesterol, and LDL and positive correlation with HDL may assist in understanding why it is more downregulated in patients with MetS. As expected, it is possible to deduce a connection between metabolic disorders and TUG1 down-regulation. Similar conclusions, including decreased insulin synthesis and secretion, were confirmed by other researchers who hypothesized that TUG1 may be involved in the regulation of islet cell and visceral and subcutaneous adipose tissues activities [38–40].

Moreover, in this study's PsO and PsO-MetS patients, miRNA-377 was significantly up-regulated in comparison to healthy controls. Our findings supported a study by Abdelghaffar et al., who indicated that patients with diabetic nephropathy had a statistically significant higher percentage of miRNA-377 up-regulation than the control group [41]. In this study, PsO-MetS patients had miRNA-377 levels that were higher than those in the PsO group. The prior finding was validated by miRNA377 expression's significant positive correlations with blood glucose, insulin, HOMA-IR, BMI, TG, cholesterol, and LDL-cholesterol, whereas it showed a significant negative correlation with HDL. These results could confirm those published by Wang et al. and Abdelghaffar et al., who established that overexpression

of miRNA-377 induces oxidative stress and has a significant positive correlation with LDL cholesterol, which has been associated to vascular complications in diabetics [41, 42]. This shed light into miRNA-377's role in psoriasis pathogenesis by induction of oxidative stress and its dysregulation linked to MetS. It is worth noting that, this is the first study that documents an up-regulation of miRNA377 in Egyptian patients with PsO.

Importantly, the inflammatory response is controlled by PPARs, which are ligand-dependent transcription factors that are activated by fatty acids and their derivatives. Psoriasis has altered PPAR- γ expression, which affects lipid and glucose metabolism as well as the disease's systemic inflammation [43]. Regarding PPAR- γ gene expression, the present research found a significant down-regulation in both PsO and PsO-MetS groups compared to healthy controls. Besides, we detected a significant negative correlation between the PPAR- γ expression and PASI score which suggests that PPAR- γ plays a role in the severity of psoriasis. The previous results may agree with those of Westergaard et al. and Mittal et al., who identified that PPAR- γ expression was diminished in psoriatic plaques, indicating that irregular activation of PPAR- γ driven intra-cellular pathway can contribute to skin-damaging immune-inflammatory response seen in this disorder. Therefore, the symptoms of psoriatic patients who received PPAR- γ agonists were improved [44, 45].

In this study, there was a significant downregulation in PPAR- γ gene expression in PsO-MetS compared to PsO group. In agreement with SAYED and HALIM, who stated that PPAR- γ levels showed significantly lower levels among PsO-MetS patients when compared to PsO patients [46]. The down-regulation of PPAR- γ in psoriasis patients with MetS could be explained due to inflammatory cytokines, such as TNF- α , which are highly raised in the skin and blood of psoriatic patients, play a crucial role in the activation of T cells, encourage angiogenesis, and cause epidermal hyperproliferation [47]. TNF- α is also linked to the persistent inflammation that is present in obesity and has a role in the insulin resistance that is present in MetS [48]. Psoriasis is an example of a Th-1 inflammatory disorder, and chronic Th-1 inflammation has a role in the pathogenesis of obesity, MetS, diabetes, atherosclerosis, and myocardial infarction [49]. The anti-inflammatory characteristics of PPAR- γ allow it to regulate inflammatory responses by blocking nuclear factor-kB and activating protein, as well as by inhibiting the generation of interleukin-2 and TNF α —by T cells [50]. There is a link between the downregulation of PPAR- γ and the immunological contexts involved in the development of both disorders since PPAR- γ overexpression requires the existence of a T-helper (Th)-2 cytokine profile and downregulation of (Th)-1 response [51]. This

indicates an additional effect of PPAR- γ downregulation on the pathogenesis of both diseases by inducing uncontrolled inflammation.

One perspective of this finding is that lncRNA TUG1 regulated the expression of miRNA-377, which in turn controlled the expression of PPAR- γ . For that reason, it can be assumed that down-regulation of TUG-1 associated with both of up-regulation of miRNA-377 and down-regulation PPAR- γ may contribute to the inflammatory cascade responses and chronicity that characterize psoriasis. The present study showed that dysregulation of MetS components were correlated with the dysregulation of these parameters expression, indicating a related connection between psoriasis and MetS. As a result one can suggest that TUG-1, miRNA-377 and PPAR- γ should be included among the factors suspected of being connected to pathophysiology of PsO-MetS.

The MetS is characterized by an increased level of particular inflammatory mediators such as PAI-1, which are similar to the mediators produced by the chronic systemic Th1 lymphocyte-mediated inflammation that is diagnostic of PsO [52]. The current study revealed that PsO-MetS has significantly higher serum levels of PAI-1 than PsO provides, and that both PsO and PsO-MetS patients have elevated serum levels of PAI-1 when compared to controls. This was in line with the results of Teixeira et al., who noticed a significant correlation between MetS and PAI-1, which was higher in MetS patients [53]. The elevation in PAI-1 levels in the blood is expected among PsO-MetS patients since PsO may further induce insulin resistance, glucose and lipid metabolism abnormalities, and vascular dysfunction, resulting in the corresponding effects [54]. For that reason, TNF- α increases the levels of PAI-1, which prevents tissue-type plasminogen activator from activating, leading to impaired fibrinolysis and uncontrolled clotting [55]. Remarkably, significant and positive correlations between MetS components and PAI-1 had also been reported in this study. These correlations could confirm the previous results. Higher levels of PAI-1 may work in concert with other factors to increase the immune inflammatory response in psoriasis and/or the presence of MetS [56].

Transforming growth factor- β (TGF- β) secretion and function dysregulation has been associated with a variety of skin diseases, including psoriasis, complications with wound healing, the formation of hypertrophic scars, and skin cancer [57]. The data revealed that PsO-MetS group has a significant enrichment in TGF- β level of skin lesions compared to those of PsO and control due to proinflammatory cytokines activation. Similar observation were reported by Meki et al. who illustrated that

TGF- β serum content in patients with PsO was significantly higher compared to that in controls [58]. It has been demonstrated that serum TGF- β levels significantly correspond with the metabolic components during the development of psoriasis.

5 Conclusion

Taken together, our study results firstly reveal the critical impact of the interaction between lncRNA TUG1 and miRNA-377 on the PsO-MetS group. Previous study postulated that lncRNA TUG1 functioned as an endogenous sponge of miRNA-377, lowering its expression levels [16]. This study demonstrates a possibly novel regulatory mechanism of TUG-1 down-regulation in PsO-MetS patients that increased miRNA-377 expression; where miRNA-377 inhibit its target gene PPAR- γ and thereby raise TGF- β and PAI-1 levels highlighting their critical contribution to the immunological imbalance and skin lesions caused by proinflammatory and metabolic factors in psoriasis (Additional file 1). In addition, our ROC curve analysis also indicated that dysregulation of TUG-1, miRNA-377, PPAR- γ , TGF- β and PAI-1 could predict MetS with a relatively high sensitivity and specificity. As a conclusion, it is possible to recommend that the desregulated parameters TUG-1 and miRNA-377 have a role in the pathogenesis of PsO disease and this could increase the risk of developing MetS in psoriasis patients via acting on PPAR γ , TGF β and PAI-1.

Abbreviations

PsO	Psoriasis
MetS	Metabolic syndrome
TUG1	Taurine-up-regulated gene 1
PASI	Psoriasis Area and Severity Index
TNF α	Tumor necrosis factor- α
PAI-1	Plasminogen activator inhibitor 1
TGF β	Transforming growth factor β
PPAR- γ	Peroxisome proliferator-activated receptor gamma
BMI	Body mass index
miRNA-377	Micro RNA-377

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s43088-023-00404-6>.

Additional file 1.

Acknowledgements

Not applicable

Author contributions

MA was responsible for supervising the research, helped in writing and reviewing of the paper. LR was responsible for designing the study protocol, supervising the research, and reviewing of the paper. RW Doss performed the interpretation of the results and reviewing of the paper. SMM designated and performed the practical work, analysis, writing, reviewing, and editing of the paper. NAAE performed the data analysis. All authors read and approved the final version of the manuscript submitted for publication.

Funding

The study was not funded by any supporting organization.

Availability of data and materials

All necessary data analyzed during this study are included in this published article. Any additional data could be available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate

All participants signed informed written consents with the declaration of data confidentiality. Ethical committee approval was obtained from Medical Biochemistry Department, Faculty of Medicine, Cairo University. Approval code: MD-146-2019.

Consent for publication

All co-authors have contributed significantly to the current work and agreed with the content of the manuscript.

Competing of interest

The authors have no relevant financial or non-financial interests to disclose.

Author details

¹Biotechnology School, Nile University, Giza, Egypt. ²Medical Biochemistry and Molecular Biology Department, Faculty of Medicine, Cairo University, Giza, Egypt. ³Dermatology Department, Faculty of Medicine, Beni-suef University, Beni Suef, Egypt. ⁴Medical Biochemistry and Molecular Biology Department, Faculty of Medicine, Beni-suef University, Beni Suef, Egypt. ⁵Dermatology Department, Faculty of Medicine, Cairo University, Giza, Egypt.

Received: 3 February 2023 Accepted: 29 June 2023

Published online: 19 July 2023

References

- Loganathan A, Kamalaraj N, El-Haddad C, Pile K (2021) Systematic review and meta-analysis on prevalence of metabolic syndrome in psoriatic arthritis, rheumatoid arthritis and psoriasis. *Int J Rheum Dis* 24(9):1112–1120
- Korman N (2020) Management of psoriasis as a systemic disease: what is the evidence? *Br J Dermatol* 182(4):840–848
- Yamanaka K, Yamamoto O, Honda T (2021) Pathophysiology of psoriasis: a review. *J Dermatol* 48(6):722–731
- Harari M, Shani J, Hristakieva E, Stanimirovic A, Seidl W, Burdo A (2000) Clinical evaluation of a more rapid and sensitive Psoriasis Assessment Severity Score (PASS), and its comparison with the classic method of Psoriasis Area and Severity Index (PASI), before and after climatotherapy at the Dead-Sea. *Int J Dermatol* 39(12):913–918
- Teklu M, Zhou W, Kapoor P, Patel N, Dey AK, Sorokin AV, Manyak GA, Teague HL, Erb-Alvarez JA, Sajja A (2021) Metabolic syndrome and its factors are associated with noncalcified coronary burden in psoriasis: an observational cohort study. *J Am Acad Dermatol* 84(5):1329–1338
- Moore JX, Chaudhary N, Akinyemiju T (2017) Peer reviewed: Metabolic syndrome prevalence by race/ethnicity and sex in the United States, National Health and Nutrition Examination Survey, 1988–2012. *Preventing chronic disease* 14
- Liu Y-S, Wu Q-J, Xia Y, Zhang J-Y, Jiang Y-T, Chang Q, Zhao Y-H (2019) Carbohydrate intake and risk of metabolic syndrome: a dose–response meta-analysis of observational studies. *Nutr Metab Cardiovasc Dis* 29(12):1288–1298
- Silveira Rossi JL, Barbalho SM, Reverete de Araujo R, Bechara MD, Sloan KP, Sloan LA (2022) Metabolic syndrome and cardiovascular diseases: going beyond traditional risk factors. *Diabetes Metab Res Rev* 38(3):e3502
- Reddy P, Lent-Schochet D, Ramakrishnan N, McLaughlin M, Jialal I (2019) Metabolic syndrome is an inflammatory disorder: a conspiracy between adipose tissue and phagocytes. *Clin Chim Acta* 496:35–44
- Vykoukal D, Davies MG (2011) Vascular biology of metabolic syndrome. *J Vasc Surg* 54(3):819–831

11. Gisondi P, Fostini AC, Fossà I, Girolomoni G, Targher G (2018) Psoriasis and the metabolic syndrome. *Clin Dermatol* 36(1):21–28
12. Dandare A, Rabia G, Khan MJ (2021) In silico analysis of non-coding RNAs and putative target genes implicated in metabolic syndrome. *Comput Biol Med* 130:104229
13. Yan J, Song J, Qiao M, Zhao X, Li R, Jiao J, Sun Q (2019) Long noncoding RNA expression profile and functional analysis in psoriasis. *Mol Med Rep* 19(5):3421–3430
14. Song J-K, Yin S-Y, Li W, Li X-D, Luo Y, Luo Y, Xing M, Li B, Kuai L (2021) An update on the role of long non-coding RNAs in psoriasis. *Chin Med J* 134(04):379–389
15. Khan AQ, Ahmad F, Raza SS, Zarif L, Siveen KS, Sher G, Agha MV, Rashid K, Kulinski M, Buddenkotte J (2022) Role of non-coding RNAs in the progression and resistance of cutaneous malignancies and autoimmune diseases. *Seminars in Cancer Biology*. Elsevier, pp 208–226
16. Duan L-J, Ding M, Hou L-J, Cui Y-T, Li C-J, Yu D-M (2017) Long non-coding RNA TUG1 alleviates extracellular matrix accumulation via mediating microRNA-377 targeting of PPAR γ in diabetic nephropathy. *Biochem Biophys Res Commun* 484(3):598–604
17. Sonkoly E, Bata-Csorgo Z, Pivarcsi A, Polyanka H, Kenderessy-Szabo A, Molnar G, Szentpali K, Bari L, Megyeri K, Mandi Y (2005) Identification and characterization of a novel, psoriasis susceptibility-related noncoding RNA gene. *PRINS J Biol Chem* 280(25):24159–24167
18. Wang Y, Zhu J, Xu J, Du J, Lu X (2021) The long non-coding RNA and mRNA expression profiles in keratinocytes from patients with psoriasis vulgaris. *Ann Palliat Med* 10(8):9206–9214
19. Alhelf M, Rashed LA, Ragab N, Elmasry MF (2022) Association between long noncoding RNA taurine-upregulated gene 1 and microRNA-377 in vitiligo. *Wiley Online Library*
20. Ekun OA, Oyekunle AO, Igbadumhe CO (2021) Evaluation of peroxisome proliferator-activated receptor-gamma (Ppar- γ) and metabolic dysfunction among hypertensive Nigerians. *Endocr Metab Sci* 5:100108
21. Nair AR, Agbor LN, Mukohda M, Liu X, Hu C, Wu J, Sigmund CD (2018) Interference with endothelial PPAR γ causes accelerated cerebral vascular dysfunction in response to endogenous renin-angiotensin system activation. *Hypertension (Dallas, Tex:1979)* 72(5):1227
22. Dieperink E, Hauser P, Dockter K, Miranda J, Evenson M, Thuras P (2021) Reduced alcohol use in patients prescribed pioglitazone. *Am J Addict* 30(6):570–577
23. Matheson J, Le Foll B (2020) Therapeutic potential of peroxisome proliferator-activated receptor (PPAR) agonists in substance use disorders: a synthesis of preclinical and human evidence. *Cells* 9(5):1196
24. Dennler S, Itoh S, Vivien D, ten Dijke P, Huet S, Gauthier J-M (1998) Direct binding of Smad3 and Smad4 to critical TGF β -inducible elements in the promoter of human plasminogen activator inhibitor-type 1 gene. *EMBO J* 17(11):3091–3100
25. Liao H, Hyman MC, Lawrence DA, Pinsky DJ (2007) Molecular regulation of the PAI-1 gene by hypoxia: contributions of Egr-1, HIF-1 α , and C/EBP α . *FASEB J* 21(3):935–949
26. Davidovici BB, Sattar N, Jörg PC, Puig L, Emery P, Barker JN, Van De Kerckhof P, Stähle M, Nestle FO, Girolomoni G (2010) Psoriasis and systemic inflammatory diseases: potential mechanistic links between skin disease and co-morbid conditions. *J Invest Dermatol* 130(7):1785–1796
27. Alessi M-C, Poggi M, Juhan-Vague I (2007) Plasminogen activator inhibitor-1, adipose tissue and insulin resistance. *Curr Opin Lipidol* 18(3):240–245
28. Grant P (2007) Diabetes mellitus as a prothrombotic condition. *J Intern Med* 262(2):157–172
29. Doi H, Shibata M-A, Kiyokane K, Otsuki Y (2003) Downregulation of TGF β isoforms and their receptors contributes to keratinocyte hyperproliferation in psoriasis vulgaris. *J Dermatol Sci* 33(1):7–16
30. Sciarretta S, Ferrucci A, Ciavarella GM, De Paolis P, Venturelli V, Tocci G, De Biase L, Rubattu S, Volpe M (2007) Markers of inflammation and fibrosis are related to cardiovascular damage in hypertensive patients with metabolic syndrome. *Am J Hypertens* 20(7):784–791
31. Fredriksson T, Pettersson U (1978) Severe psoriasis—oral therapy with a new retinoid. *Dermatology* 157(4):238–244
32. Abidi A, Rizvi DA, Saxena K, Chaudhary S, Ahmad A (2020) The evaluation of efficacy and safety of methotrexate and pioglitazone in psoriasis patients: a randomized, open-labeled, active-controlled clinical trial. *Indian J Pharmacol* 52(1):16
33. Gui XY, Yu XL, Jin HZ, Zuo YG, Wu C (2018) Prevalence of metabolic syndrome in Chinese psoriasis patients: A hospital-based cross-sectional study. *Journal of Diabetes Investigation* 9(1):39–43
34. Sun L, Guo X, Qin Y, Li P, Yu C, Gao X, Xie X, Xu X (2022) Serum intestinal metabolites are raised in patients with psoriasis and metabolic syndrome. *Clin Cosmet Investig Dermatol* 15:879
35. Abdallah HY, Tawfik NZ, Soliman NH, Eldeen LA (2022) The lncRNA PRINS-miRNA-mRNA axis gene expression profile as a circulating biomarker panel in psoriasis. *Mol Diagn Ther* 26(4):451–465
36. Radhakrishna U, Uppala R, Jhala DD, Vadsaria N, Patel M, Uppala LV, Vishweswariah S, Vedangi A, Saiyed N, Damiani G (2022) Methylated miRNAs may serve as potential biomarkers and therapeutic targets for hidradenitis suppurativa. *J Eur Acad Dermatol Venereol* 36(2022):2199–2213
37. He X, Ou C, Xiao Y, Han Q, Li H, Zhou S (2017) LncRNAs: key players and novel insights into diabetes mellitus. *Oncotarget* 8(41):71325
38. Alipoor B, Nikouei S, Rezaeinejad F, Malakooti-Dehkordi S, Sabati Z, Ghasemi H (2021) Long non-coding RNAs in metabolic disorders: pathogenic relevance and potential biomarkers and therapeutic targets. *J Endocrinol Invest* 44(10):2015–2041
39. Zhang P, Li Y, Tu S, Cheng X (2021) SP1-induced lncRNA TUG1 regulates proliferation and apoptosis in islet cells of type 2 diabetes mellitus via the miR-188-3p/FGF5 axis. *Eur Rev Med Pharmacol Sci* 25(4):1959–1966
40. Ebrahimi R, Toolabi K, Jannat Ali Pour N, Mohassel Azadi S, Bahiraei A, Zamani-Garmsiri F, Emamgholipour S (2020) Adipose tissue gene expression of long non-coding RNAs; MALAT1, TUG1 in obesity: is it associated with metabolic profile and lipid homeostasis-related genes expression? *Diabetol Metab Syndr* 12(1):1–13
41. Abdelghaffar S, Shora H, Abdelatty S, Elmougy F, El Sayed R, Abdelrahman H, Soliman H, Algebaly H, Ahmed S, Alfay P (2020) MicroRNAs and risk factors for diabetic nephropathy in Egyptian children and adolescents with type 1 diabetes. *Diabetes Metab Syndr Obes Targets Ther* 13:2485
42. Wang W, Ding X-Q, Gu T-T, Song L, Li J-M, Xue Q-C, Kong L-D (2015) Pterostilbene and allopurinol reduce fructose-induced podocyte oxidative stress and inflammation via microRNA-377. *Free Radic Biol Med* 83:214–226
43. Lima EdA, Lima MMDdA, Marques CDL, Duarte ALBP, Pita IdR, Pita MGdR (2013) Peroxisome proliferator-activated receptor agonists (PPARs): a promising prospect in the treatment of psoriasis and psoriatic arthritis. *An Bras Dermatol* 88:1029–1035
44. Westergaard M, Henningsen J, Rasmussen S, Kristiansen K, Johansen C, Svendsen ML, Jensen UB, Schrader HD, Staels B, Iversen L (2003) Expression and localization of peroxisome proliferator-activated receptors and nuclear factor κ B in normal and lesional psoriatic skin. *J Invest Dermatol* 121(5):1104–1117
45. Mittal R, Malhotra S, Pandhi P, Kaur I, Dogra S (2009) Efficacy and safety of combination Acitretin and Pioglitazone therapy in patients with moderate to severe chronic plaque-type psoriasis: a randomized, double-blind, placebo-controlled clinical trial. *Arch Dermatol* 145(4):387–393
46. Sayed SS, Halim DAA (2012) Psoriasis and metabolic syndrome: Is peroxisome proliferator-activated receptor-part of the missing link? *Eur J Dermatol* 22(5):622–628
47. Setty AR, Curhan G, Choi HK (2007) Obesity, waist circumference, weight change, and the risk of psoriasis in women: Nurses' Health Study II. *Arch Intern Med* 167(15):1670–1675
48. Gustafson B, Hammarstedt A, Andersson CX, Smith U (2007) Inflamed adipose tissue: a culprit underlying the metabolic syndrome and atherosclerosis. *Arterioscler Thromb Vasc Biol* 27(11):2276–2283
49. Azfar RS, Gelfand JM (2008) Psoriasis and metabolic disease: epidemiology and pathophysiology. *Curr Opin Rheumatol* 20(4):416
50. Tanaka T, Masuzaki H, Hosoda K, Nakao K (2010) Critical roles of PPAR-gamma in every aspect of the metabolic syndrome. *Nihon Rinsho Jpn J Clin Med* 68(2):203–209
51. Jo S-H, Yang C, Miao Q, Marzec M, Wasik MA, Lu P, Wang YL (2006) Peroxisome proliferator-activated receptor γ promotes lymphocyte survival through its actions on cellular metabolic activities. *J Immunol* 177(6):3737–3745
52. Al-Mutairi N, Al-Farag S, Al-Mutairi A, Al-Shiltawy M (2010) Comorbidities associated with psoriasis: an experience from the Middle East. *J Dermatol* 37(2):146–155

53. Teixeira GG, Mari NL, de Paula JCC, Cataldi de Alcantara C, Flauzino T, Lozovoy MAB, Martin LMM, Reiche EMV, Maes M, Dichi I (2020) Cell adhesion molecules, plasminogen activator inhibitor type 1, and metabolic syndrome in patients with psoriasis. *Clin Exp Med* 20(1):39–48
54. Dimitrov B, Ilieva K, Gospodinov D, Komsa-Penkova R (2019) Impact of carriage of 4G/5G PAI-1 and Glycoprotein IIb/IIIa polymorphism on development of Chronic Obstructive Pulmonary Disease in a patient with psoriasis vulgaris. *Clin Case J IMAB Ann Proc Sci Papers* 25(2):2537–2543
55. Rotter V, Nagaev I, Smith U (2003) Interleukin-6 (IL-6) induces insulin resistance in 3T3-L1 adipocytes and is, like IL-8 and tumor necrosis factor- α , overexpressed in human fat cells from insulin-resistant subjects. *J Biol Chem* 278(46):45777–45784
56. Dowlatshahi E, Van Der Voort E, Arends L, Nijsten T (2013) Markers of systemic inflammation in psoriasis: a systematic review and meta-analysis. *Br J Dermatol* 169(2):266–282
57. Liu X-x, Feng A-p, He Y-m, Li Y, Wu Y, Lian X, Hu F, Li J-w, Tu Y-t, Chen S-j (2016) Association of down-regulation of CD109 expression with up-expression of Smad7 in pathogenesis of psoriasis. *J Huazhong Univ Sci Technol [Med Sci]* 36(1):132–136
58. Meki ARM, Al-Shobaili H (2014) Serum vascular endothelial growth factor, transforming growth factor β 1, and nitric oxide levels in patients with psoriasis vulgaris: their correlation to disease severity. *J Clin Lab Anal* 28(6):496–501

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.