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ORIGINAL RESEARCH

Serum Intestinal Metabolites are Raised in Patients with Psoriasis and Metabolic Syndrome

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Purpose: Psoriasis is an immune-mediated chronic inflammatory disease. Metabolic syndrome (MetS) is characterized by central obesity, hypertension, dyslipidemia, diabetes and insulin resistance (IR). Increasing evidence indicates that psoriasis is associated with MetS. This study aimed to explore some metabolite indexes which could evaluate the severity or predict the risk of psoriasis patients associated with MetS.

Patients and methods: It was a case-control study conducted in Beijing Hospital of Traditional Chinese Medicine. Sixty healthy volunteers (HC), 100 patients with psoriasis (Ps), 100 patients with MetS (MetS) and 80 patients with both psoriasis and MetS (Ps +MetS) were entered between January 2016 and December 2018. Blood samples were taken after at least 12 hours fasting and the contents of trimethylamine N-oxide (TMAO), carnitine, choline and betaine in serum were measured by Liquid Chromatography Mass Spectrometry (LC-MS/MS). Besides, the serum levels of low-density lipoprotein (LDL), high-density lipoprotein (HDL), cholesterol (CHO), triglyceride (TG), blood glucose (BG), creatinine (Cr), urea nitrogen (BUN), uric acid (UA) were determined.

Results: The non-healthy groups had different degrees of dyslipidemia, Ps-MetS> Ps >MetS. Compared with HC, the Ps had a higher level of TG; The MetS had the lowest level of HDL; The Ps+Mets had the highest level of TG and CHO. The Ps and Ps+MetS both had high level of UA, but there was no difference between the two groups. As for intestinal metabolites, the Ps had significant differences in TMAO, carnitine, and betaine in comparison with HC. The MetS had the highest level of TMAO. There was positive correlation between PASI and TMAO and betaine.

Conclusions: TMAO and betaine could serve as indexes reflecting the severity of psoriasis. TG, CHO, LDL and UA could serve as risk factors of MetS in psoriatic patients.

Keywords: psoriasis, metabolic syndrome, TMAO

Introduction

Psoriasis is a chronic immune-mediated inflammatory skin disorder characterized by hyperkeratosis or dyskeratosis of keratinocytes, dilation of dermal papillary blood vessels and inflammatory cell infiltration. The global psoriasis prevalence rate is around 2–3% of the world population.[1] At present, it is widely accepted that psoriasis is not solely a dermatological disease but a multi-system inflammatory disorder with multiple associated comorbidities, such as cardiovascular diseases,[2,3] respiratory diseases,[4,5] oral diseases,[6,7] gastrointestinal diseases,[8] chronic kidney disease, anxiety, depression, dementia, etc.[9] Among all the comorbidities, it seemed that metabolic syndrome (MetS) was more prevalent. MetS is a cluster of metabolic abnormalities including hypertension, obesity, diabetes mellitus, etc.[10–12] A meta-analysis demonstrated that psoriasis and

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MetS are intimately connected.[13] Patients with psoriasis have a significantly higher risk of developing MetS than the general population.[14] The other way around, MetS may prolong the course of psoriasis patients and make it more difficult for treatment.[15] In addition, MetS could cause cardiovascular disease, which is the primary cause leading to the death of psoriasis patients.[16–18] It seemed that there may be a shared mechanism between these two diseases and some biomarkers which could reflect the risk of MetS in psoriasis. For example, red cell distribution width (RDW) and mean platelet volume (MPV) could be employed as inexpensive, routinely obtained biomarkers in predicting myocardial infarction (MI), atrial fibrillation (AF), and chronic heart failure (CHF) in psoriasis and psoriatic arthritis.[3] In addition, resistin was reported to be a link between psoriasis and increased cardiovascular risk.[2] Therefore, it would be promising to explore such specific biomarkers.

In recent years, host-diet-microbiome interactions, playing a significant role in MetS, has become a hot research topic in psoriasis. Trimethylamine-N-oxide (TMAO) has attracted increasing interests among the gut-derived metabolic substances. Several dietary precursors of TMAO, including betaine, choline, phosphatidylcholine and L-carnitine,[19] can be metabolized by specific gut microbiota to trimethylamine (TMA), converted into TMAO by hepatic flavin-containing monooxygenases (FMOs), particularly FMO3, and excreted via the kidneys from the circulation.[20] TMAO has been considered as the early predictor of MetS.[20] The high serum level of TMAO not only cause hypertension, dyslipidemia, renal failure, diabetes, but aggravate the formation and deterioration of coronary atherosclerotic plaques, eventually leading to an increase in the risk of serious cardiovascular events, such as myocardial infarction, stroke and heart failure.[21]

To figure out whether the TMAO could be the early predictors of psoriasis complicated with MetS, or even serve as an efficacy predictor, a case-control study was conducted. In this study, we aimed to investigate the serum level of TMAO, betaine, carnitine and choline in healthy people, patients with psoriasis, patients with MetS, and patients with both psoriasis and MetS. In addition, we investigated the correlations of TMAO with psoriasis area and severity index (PASI) and hypothesized that TMAO could serve as a biological marker of early metabolic derangement in subjects with psoriasis.

Materials and Methods

Study Population

This is a case-control study conducted in Beijing Hospital of Traditional Chinese Medicine, Capital Medical University from January 2016 to December 2018. According to diagnostic criteria for psoriasis vulgaris[22] and MetS,[23] 60 healthy volunteers from physical examination center as healthy control (HC), 100 patients with psoriasis (Ps) and 80 patients with both psoriasis and MetS (Ps + MetS) from the department of dermatology, 100 patients with MetS (MetS) from department of ulcerative vascular surgery, including both in- and out-patients were entered the study. All subjects were interviewed by one dermatologist and underwent a thorough history and physical examination. Sociodemographic data including sex, age, educational status and marital status were recorded for each subject.

Serological Assays

A 5 ml blood sample was taken at least 12 hours fasting and then was centrifuged to separate serum, and finally stored at −80 °C for subsequent analysis. The levels of TMAO and three related metabolites (betaine, choline and carnitine) were determined by Liquid Chromatography-Electrospray Ionization-Tandem Mass Spectrometry (LC-ESI-MS/MS). Proteins were precipitated with methanol (serum: methanol, 1:4, *v/v*); samples were vortex-mixed for 2 min, centrifuged at 12,000 g for 10 min at 4 °C; then supernatants were collected and used for analysis with a 5500 Q-TRAP hybrid/triple quadrupole linear ion trap mass spectrometer (AB Sciex, Framingham, MA, USA) with electrospray ionization (ESI) in positive mode.

In addition, low-density lipoprotein (LDL), high-density lipoprotein (HDL), cholesterol (CHO), triglyceride (TG), blood glucose (BG), creatinine (Cr), urea nitrogen (BUN), and uric acid (UA) in serum were measured using an automatic biochemical analyzer (Roche P800, Switzerland).

Scoring Criteria of PASI

The PASI score was used to evaluate the severity of psoriasis-like skin lesion, which was calculated as follows:[24]

PASI (head) = 0.1 (erythema + infiltration + desquamation) × lesion area;
PASI (upper limb) = 0.2 (erythema + infiltration + desquamation) × lesion area;
PASI (trunk) = 0.3 (erythema + infiltration + desquamation) × lesion area;
PASI (lower limb) = 0.4 (erythema + infiltration + desquamation) × lesion area;
PASI total score= PASI (head) + PASI (upper limb) + PASI (lower limb) + PASI (trunk).

The severity of each symptom was assessed comparing with reference pictures. The specific scoring details are shown in Table 1.

Ethical Approval

The work has been carried out in accordance with the Code of Ethics of the World Medical Association for experiments in humans and approved by Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine, Capital Medical University (2016BL-006-01). This study was registered in Chinese Clinical Trial Registry (ChiCTR-INR -16007941). The process and purpose of the whole study were explained to participants and informed consent was obtained.

In compliance with the informed consent signed with the patient, we will share all data related to this article, and hide the patients' personal information completely.

Data Sharing Statement

No additional data are available. The data that supports the findings of this article are available by email at any time. The data is available from in the manuscript can provided by Xinwei Guo and Yeping Qin.

Statistical Analysis

All the results were performed by IBM SPSS version 22.0 for Windows (SPSS, Inc., Chicago, IL, USA). Data were presented in the form of means (M) ± standard deviations (SD). Non-parametric tests were applied for further analysis for the data doesn't have a normal distribution. Differences across groups were evaluated by one-factor analysis of variance (ANOVA) and differences between two means were examined using the *Mann–Whitney U* test (*Mann–Whitney* test). *Pearson's* correlation coefficient (*Pearson's* r) was calculated to examine the linear correlation between PASI scores and intestinal metabolites (TMAO, betaine, choline, carnitine). A P-value of < 0.05 was considered statistically significant.

Results

Clinical Characteristics of the Study Population

The general data of study subjects in four groups are summarized in Table 2. The mean age of four groups was 47 ± 14.75, 41.33 ± 12.51, 61.19 ± 12.51 and 43.65 ± 14.52 separately. Except for the MetS, no significant difference was observed for age. Most of the patients with MetS were from department ulcerative vascular surgery and had a history of

Table 1 Scoring Criteria of PASI

Symptoms	0	1	2	3	4
Erythema	None	Slightly reddish	Red, not deep	Markedly reddened	Extremely reddened
Scales	None	Very fine scales covering<50%	Fine scales covering>50%	Coarse scales covering>50%	Very coarse scales covering>50%
Thickness	None	Mild 0.25 mm	Moderate 0.5 mm	Severe 1 mm	Very severe 1.25 mm
Area	0=None	1=1%-9%	2=10%-29%	3=30–49%	
		4=50–69%	5=70–89%	6=90–100%	

Note: PASI adapted from: Fredriksson T, Pettersson U. Severe psoriasis – oral therapy with a new retinoid. *Dermatologica*. 1978;157(4):238-244.[46]
Abbreviation: PASI, Psoriasis Area and Severity Index.

Table 2 Clinical Characteristics of the Study Population

Characteristics	HC n=60	Ps n=100	MetS n=100	Ps+MetS n=80
Gender				
Male (%)	31(51.7)	68(68)	67(67)	58(72.6)
Female (%)	29(48.3)	32(32)	33(33)	22(27.4)
Age (M ± SD)	47 ± 14.75	41.33 ± 12.51	61.19 ± 12.51	43.65 ± 14.52
Biochemical index (M ± SD)				
LDL (mmol/L)	2.45 ± 0.66	2.73 ± 0.73	2.53 ± 0.89	2.89 ± 1.23*
HDL (mmol/L)	1.25 ± 0.30	1.17 ± 0.30	1.11 ± 0.28**	1.17 ± 0.31
CHO (mmol/L)	4.23 ± 0.81	4.45 ± 0.93	4.21 ± 1.10	4.69 ± 0.99*
TG (mmol/L)	1.18 ± 0.47	1.60 ± 1.10**	1.51 ± 0.97	2.25 ± 1.48***$^{\#\#\#}$
BG (mmol/L)	4.94 ± 0.75	5.05 ± 0.79	7.05 ± 2.27***$^{\#\#\#}$	5.57 ± 1.89*
Cr (μmol/L)	61.35±13.67	65.32 ± 15.81	78.56 ± 25.6***$^{\#\#\#}$	65.11 ± 13.75
UA (μmol/L)	324.85±99.314.00	391.76±102.63***	349.98±114.98$^{\#\#}$	387.42±125.43**
BUN(mmol/L)	± 1.09	4.51 ± 1.43	6.96 ± 2.37***$^{\#\#\#}$	4.04 ± 1.31

Notes: *P< 0.05, **P< 0.01, ***P< 0.01, compared to HC. $^{\#\#}P$< 0.01, $^{\#\#\#}P$< 0.01, compared to Ps.
Abbreviations: HC, healthy volunteers; Ps, psoriasis; MetS, metabolic syndrome; Ps+MetS, psoriasis with metabolic syndrome.

type 2 diabetes mellitus (T2DM), because abnormal lipid metabolism and abnormal glucose metabolism are present in type 2 diabetes mellitus (T2DM).

Comparisons of biochemical indices including lipid metabolic index, blood glucose metabolism index and kidney function index among groups were presented in Table 2. In terms of lipid metabolism, several relevant biochemical indicators, including TG, CHO, HDL, and LDL were measured. Compared with HC, the Ps had higher level of TG (P< 0.01); The MetS showed lower level of HDL (P< 0.01); And the Ps+MetS presented higher level of TG (P< 0.001), CHO (P< 0.05) and LDL (P< 0.01). Pairwise comparisons revealed that statistical differences across three non-healthy groups. The TG (P< 0.001), LDL (P< 0.05) and CHO (P< 0.01) showed highest level in Ps+MetS. Although the means of four lipid metabolism indexes in Ps were higher than MetS, no differences were observed between them. As for glycemic metabolism, the MetS had the highest BG level (P< 0.001), and significant difference was also observed between HC and Ps+MetS (P< 0.05). Beyond the above-mentioned, several parameters, including Cr, BUN, UA about kidney function were also determined. Compared with HC, the Ps and Ps+MetS both had higher level of UA (P< 0.01); The MetS showed higher level of BUN (P< 0.001) and Cr (P< 0.001). Among the three non-healthy groups, the MetS presented the highest level of Cr and BUN (P< 0.001). While for the UA, the Ps had a higher level than MetS. And there were no statistical differences between Ps and Ps+MetS.

The Levels of Serum Metabolites and Correlation Between the Metabolites and PASI Score

The statistical comparisons of intestine metabolites in the four groups were also carried out in Table 3. Compared with healthy controls, TMAO levels were significantly higher in Ps (P< 0.001) and MetS (P< 0.001); Although there was a little increasing tendency in Ps+MetS, no difference was observed. For the other three related metabolites, pairwise

Table 3 Intestinal Metabolites of the Study Population

Metabolites (ng/ml)	HC (M ± SD)	Ps (M ± SD)	MetS (M ± SD)	Ps + MetS (M ± SD)
TMAO	1.98 ± 0.91	6.27 ± 2.92***	10.25 ± 5.49$^{\#\#\#}$	3.10 ± 1.83$^{\#\#\#}$
Carnitine	50.18 ± 11.32	44.20 ± 7.93***	42.52 ± 11.46	51.32 ± 9.45$^{\#\#\#}$
Betaine	16.27 ± 6.78	55.94 ± 15.83***	40.64 ± 15.10$^{\#\#\#}$	32.34 ± 7.50$^{\#\#\#}$
Choline	8.99 ± 2.27	10.25 ± 2.14	13.20 ± 4.74$^{\#\#\#}$	8.50 ± 2.79$^{\#\#\#}$

Notes: ***P< 0.01, compared to HC. $^{\#\#\#}P$< 0.01, compared to Ps.
Abbreviation: TMAO, trimethylamine N-oxide.

group comparisons revealed significant findings. In comparison with healthy, the lower carnitine level ($P < 0.001$) and higher betaine level ($P< 0.001$) were measured in Ps. Compared with psoriatic patients, the Ps+MetS presented higher level of carnitine ($P< 0.001$), lower level of betaine ($P< 0.001$) and choline ($P< 0.001$), and the MetS had lower level of betaine ($P< 0.001$). Besides, noticeable statistical differences were observed between MetS and Ps+MetS in levels of these three metabolites, namely carnitine ($P< 0.001$), betaine ($P< 0.001$), and choline ($P< 0.001$).

Further, the correlation between intestine metabolites and PASI score was analyzed in Figure 1. Based on the statistical results, it was found that TMAO ($P< 0.0001$), betaine ($P< 0.01$) and choline ($P < 0.05$) were positively correlated with PASI score. Moreover, there was no correlation between carnitine and PASI score ($P> 0.05$).

Discussion

A strong relationship between psoriasis and MetS has been reported in the literature.[25,26] Naturally, diets that have direct relationships with MetS became one of the hot topics. It was reported specific nutrients in food had an influence on inflammatory cell signaling transcriptional factors by affecting endogenous miRNA synthesis.[27] Furthermore, it has been proved that intermittent fasting has beneficial effects on psoriatic arthritis, regardless of the implicated drug therapy.[28,29] Meanwhile, different dietary structures do have impacts on psoriasis patients undergoing phototherapy.[30] Therefore, reasonable diet planning is of great hope to controlling psoriasis and MetS.

Although the exact underlying mechanism of MetS in psoriasis has not been fully explained, it was suggested that overlap in the pathological mechanism between Ps and MetS. For instance, the psoriasis-associated inflammatory factors (IL-1β, IL6, TNF-α) could alter the lipoprotein composition, enhance adhesion molecule expression and aggravate cholesterol crystallization formation, finally leading to atherosclerosis.[31] In return, a large number of adipokines produced by adipose tissue in MetS have a contributive role in the initiation and maintenance of psoriatic inflammatory. In clinical treatment, the psoriatic patients with MetS have a longer duration, increased costs and higher mortality rate.[32] Therefore, if some metabolic risks could be detected in the early stages, it would provide an opportunity window for effective intervention.

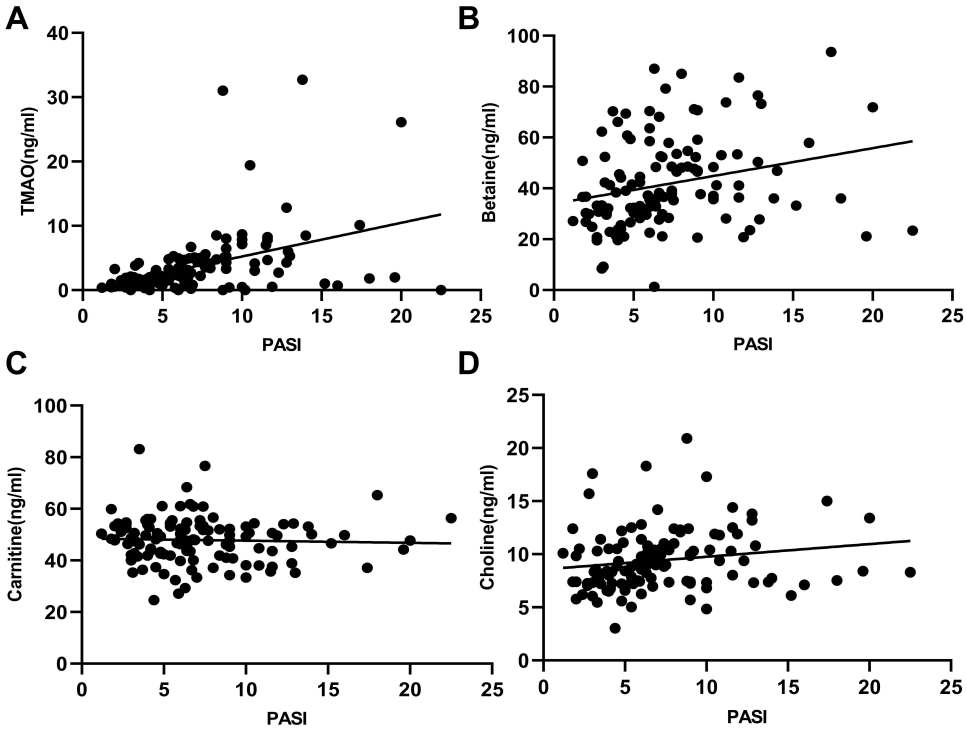

Figure 1 Correlation between several intestinal metabolites and PASI score. (**A**) TMAO had a positive correlation with PASI score (r = 0.4237, P < 0.001); (**B**) Betaine had a positive correlation with PASI score (r = 0.2533, P = 0.0049); (**C**) Carnitine had no correlation with PASI score (r = −0.3852, P = 0.6736); (**D**) Choline had a negative correlation with PASI score (r = −0.1799, P = 0.0473).

According to the previous study, we chose several metabolic indicators, such as blood glucose, TG, HDL, LDL and CHO, considered as MetS risk factors.[33] Meanwhile, there is evidence that MetS has a close association with kidney malfunctions.[34] So, we also detected the serum level of UA, Cr and BUN. Besides the mentioned above, TMAO and three of its precursors, intestinal metabolites, were chosen, for TMAO is the early predictor of MetS.[20] This study was performed to find out the association between psoriasis and MetS risk factors and figure out some early predictors of psoriasis with concomitant MetS, or even serve as an efficacy predictor.

We found that three non-healthy groups had different degrees of dyslipidemia based on the statistical results The severity of dyslipidemia seemed to meet a gradually increasing trend, namely Ps+ MetS> Ps >MetS. CHO, TG, LDL and HDL are common indexes of blood lipid in the clinic. The increase of CHO, TG, LDL and the decrease of HDL component is a reflection of a lipid metabolism disturbance. Specifically, in comparison with the HC, the Ps had only one abnormal index, which was consistent with the study of Farshchian et al,[35] while the Ps+MetS had three abnormal indexes (TG, LDL and CHO); Generally speaking, diabetic dyslipidemia is typically featured by high TG and low HDL levels.[36] The MetS only had low HDL in the study due to TG is closely related to diet. Because the MetS patients we included strictly abide by the hospitalized diet. Therefore, we have observed dyslipidemia in patients with psoriasis, which is consistent with previous reports.[37]

As for the sugar metabolism, the MetS and Ps-MetS had abnormal BG levels. It was no doubt that the MetS had the highest level for the majority of the MetS were diagnosed with T2DM. The Ps-MetS had a relatively higher BG level in comparison with HC. However no significant difference was found between Ps and HC, the mean BG of Ps had an increasing trend.

As far as kidney function, although the high UA level of Ps and Ps-MetS indicated abnormalities in purine metabolism, there was no difference between Ps and Ps-MetS. While in the study of Yilmaz et al,[38] they determined that UA levels were higher in patients with Ps and MetS than in patients with Ps alone. It is possible that the different results were due to the severity of psoriasis, because Zhang Ying's meta-analysis presented that moderate to severe psoriasis were more likely to have high level UA.[39]

On the question of intestinal metabolites, the results indicated that Ps and Ps+MetS both had a significantly high level of metabolites except carnitine compared with HC, and the serum metabolites concentrations in Ps were higher than that in Ps+MetS. Meanwhile, the severity of psoriasis had a positive correlation with intestinal metabolites, namely TMAO, choline and betaine. It has been reported that TMAO is the early predictor of MetS, particularly in cardiovascular disease. Betaine and choline are the dietary precursors of TMAO. On the one hand, TMAO caused vascular aging and vascular cell senescence and through oxidative stress;[40] On the other hand, TMAO increased thrombosis risk through multiple mechanisms, including changing lipid and hormone homeostasis, promoting platelet hyperreactivity, regulating cholesterol and sterol metabolism, and inducing endothelial dysfunction by activating NLRP3 inflammatory bodies.[41,42] The treatment of MetS in psoriasis can improve the condition of psoriasis, and it has been proved that weight loss interventions were effective in reducing the psoriatic arthritis severity and improving skin lesions.[43] Decreasing the TMAO level has become an effective means to prevent or treat atherosclerosis by adjusting dietary substrate, regulating microbial metabolism and inhibiting FMOs.[44,45] Meanwhile, psoriatic patients are at higher risk of cardiovascular disease. Our study reveals that TMAO and its related dietary precursors had positive correlations with psoriasis. It suggests that TMAO could be used as a marker to prevent the occurrence of metabolic syndrome or worsening cardiovascular disease in psoriatic patients.

According to this study's findings, lipid metabolism indexes were abnormal in psoriatic patients, and the higher levels of the lipoprotein, the higher the risk of accompanying MetS. The same applies to UA. In addition, TMAO, betaine and choline could serve as indexes reflecting the severity of psoriasis.

Conclusion

The intestinal metabolites (TMAO and betaine) in the patient's serum are positively correlated with psoriasis, suggesting that psoriasis and metabolic syndrome have a common pathological mechanism, which can predict the risk of MetS in psoriasis. However, due to lack of sufficient human resources and good invest, our research sample was relatively small

and the sampling range was narrow, so a large-scale clinical study may be performed. In addition, more efforts should be made to verify this conclusion by performing in vitro and vivo experiments.

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Disclosure

The authors declare that they have no conflicts for this work.

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