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Original Article

Association of serum resistin with blood stasis syndrome in traditional Korean medicine for metabolic diseases: A cross-sectional multicenter observational study

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ABSTRACT

Background: Blood stasis syndrome (BSS) is considered as the cause of several chronic disease including metabolic diseases in traditional East Asian medicine. In this study, we investigated the levels of serum resistin and other proteins related to metabolic syndrome (MS) and several other diseases categories to identify the association with BSS.

Methods: This was a cross-sectional, multicenter study of patients recruited from seven traditional Korean Medicine (TKM) hospitals. To identify whether there was an association with BSS in specific disease conditions, including MS, serum protein levels were evaluated using the multiplex method.

Results: A total of 885 patients (419 patients with BSS, 376 patients without BSS, and 90 healthy controls) participated in the study, and 139 patients had MS. The resistin and insulin levels were significantly higher in patients with BSS than in patients without BSS and normal subjects ($P = 0.002$ and $P = 0.046$, respectively). Patients with BSS who had MS exhibited significantly higher resistin levels than those in patients without BSS and normal subjects ($P = 0.049$). In addition, the levels of serum resistin were significantly correlated with symptoms of the BSS, especially dark red gums, dark facial complexion, and nocturnal pain.

Conclusions: Despite several limitations, these results demonstrated that resistin levels are potentially associated with the pathogenesis of BSS in MS.

Trial registration number: Clinical Research Information Service (CRIS): KCT0000916.

1. Introduction

Blood stasis (also known as *Xueyu Zheng* in Chinese or *Oketsu* in Japanese) is an important pathophysiological concept in traditional East Asian medicine (TEAM). It is one of the most diverse physiological functions of the body and is caused by impaired blood circulation.[1–3] Consequently, blood stasis is an important underlying pathology for several disease processes in TEAM.[3–6]

In clinical practice, blood stasis syndrome (BSS) is associated with chronic and incurable diseases in various systems.[7,8] However, since the traditional medical concept of BSS is currently physiologically ambiguous, it is significantly important to develop the biological criteria for BSS from a modern perspective.

Recently, several preclinical and clinical studies on BSS have been conducted, and the correlation of BSS with diseases or physiopathology has been revealed.[9–14] Particularly, previous studies have reported that BSS is associated with metabolic syndrome (MS) and its risk factors, such as obesity, atherosclerosis, hypertension, and diabetes mellitus.[15–17] Additionally, circulating resistin levels are also correlated with risk factors for MS, including obesity, and diabetes mellitus.[18,19] Resistin is an adipocyte-specific hormone known to be related to obesity, insulin resistance, diabetes, and cardiac diseases.[20–23] In humans and murine models, resistin is mainly expressed and secreted by macrophages and related to inflammation and insulin resistance.[23–25] Some studies have suggested a relationship between serum resistin and BSS.[26–28]

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In this study, we investigated the serum levels of resistin and other proteins related to metabolic diseases and several other diseases categories to identify its association with BSS and to further understand the pathogenesis of BSS.

2. Methods

2.1. Study design

This was a cross-sectional, multicenter observational study to identify biological indices related to blood stasis as part of the project named Convergence research of the diagnostic technology for blood stasis (CoRe-Ditec-BS).[7]

2.2. Setting and participants

Patients admitted to the following seven traditional Korean medical hospitals, Kyung Hee Oriental Medical Center, Kyung Hee University Oriental Hospital at Gangdong, WonKwang Oriental Medical Hospital, Jaseng Hospital of Oriental Medicine, Cha Medical Center, Dong-guk University Oriental Medical Hospital, and Pusan National University Korean Medicine Hospital between July 2013 and December 2014. The inclusion criteria were as follows: males or females between 20 and 65 years, provision of written informed consent to participate, and conformity to the study regulations. The exclusion criteria were as follows: any psychiatric condition resulting in difficulty to communicate, critical illness, pregnancy, malignant tumors, early postpartum period without menstruation, and any condition that could influence the study assessment. Healthy individuals were free of medical diseases. The classification of diseases was recorded based on the patient's chief symptoms. To identify the disease distribution of the BSS and non-BSS groups, we utilized the ICD-10 codes of the enrolled patients.

2.3. Measurements and data collection

This study used the diagnostic criteria of MS suggested by the National Cholesterol Education Program of the United States.[29] The criteria for MS were as follows: abdominal obesity, waist circumference $\geq$ 102 cm in men (90 cm for Asian individuals) or $\geq$ 88 cm in women (85 cm for Asian individuals), triglyceride level $\geq$ 150 mg/dL, high density lipoprotein (HDL)-cholesterol level $\leq$ 40 mg/dL in men and $\leq$ 50 mg/dL in women, fasting glucose level $\geq$ 100 mg/ dL or current treatment for diabetes, and systolic blood pressure $\geq$ 130 mmHg, or diastolic blood pressure $\geq$ 85 mmHg.

Generally, MS is diagnosed if an individual meets three of the five criteria. However, in the present study, information about abdominal obesity was missing from the collected clinical data. Therefore, subjects were categorized as having MS if they met three of the four criteria.

All patient's symptoms of the BSS were collected by the case report form (CRF) for CoRe-Ditec-BS questionnaire-I.[7] Only subjects who received the same diagnoses from the two independent doctors of Korean medicine (DKMs) were included. To minimize the differences in blood stasis diagnosis between the two expert physicians, they independently evaluated the subject simultaneously. The physicians had graduated from the college of oriental medicine (6 years) and had at least 3 years of clinical experience. They received standard operating procedure training on blood stasis diagnosis and conducted the diagnosis according to standard operating procedure guidelines. A total of 1016 subjects were enrolled, and we excluded subjects who received different diagnoses from the two DKMs. Therefore, we analyzed data from 885 subjects who were diagnosed as having the same pattern by the two DKMs (Fig. 1). Each variable was graded according to the following scores: 1 = none, 2 = slight, 3 = moderate, 4 = severe, and 5 = very severe. The score for each variable for one subject was measured twice by independent DKMs, the mean score between the DKMs was utilized for statistical analysis and scores exhibiting a large difference (|score difference between two DKMs| > 3) were excluded to control the quality of the data.

2.4. Detection of blood parameters and multiplex analysis

The levels of the blood parameters for each subject, such as white blood cell (WBC) and serum lipid, were measured in Samkwang Medical Laboratories (Seoul, Korea).

Serum from each subject was collected and centrifuged at 10,000 $\times$ g to remove small particles. The supernatants were stored at –80 °C until analysis. Proteins related to diabetes in serum samples were measured using the Bio-Plex® 200 System and Bio-Plex Pro-human diabetes 10-plex assay (Bio-Rad, CA, USA). The following adipokines were detected (detection range is shown in parentheses): C-peptide (3.8 - 3265.5 pg/mL), ghrelin (8.4 - 8990.7 pg/mL), gastric inhibitory polypeptide (GIP) (17.8 - 24674.5 pg/mL), glucagon-like peptide-1 (GLP-1) (31.62 - 34096.5 pg/mL), glucagon (22.2 - 21568.5 pg/mL), insulin (11.6 - 10546.8 pg/mL), leptin (95.7 - 71542.9 pg/mL), total plasminogen activator inhibitor-1 (PAI-1) (13.1 - 3144.6 pg/mL), resistin (9.3 - 27006.8 pg/mL), and visfatin (267.7 - 264,018.4 pg/mL). The diabetes assay was performed according to the manufacturer's instructions. Samples were thawed on ice and diluted 1:4 in a sample diluent buffer.

2.5. Statistical analysis

The data were analyzed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA). The normality of continuous variables in the clinical data was tested using the Kolmogorov-Smirnov test. Significant differences between the groups were investigated using the one-way analysis of variance (ANOVA) test, and the differences between the groups were analyzed using the Bonferroni post hoc test. Categorical variables were compared using a chi-square test or Fisher's exact test. The protein level results were tested using a binary general linear model adjustment for sex, age, drinking status, body mass index (BMI) and pulse. Pearson's correlation analysis was applied to determine the association between BSS symptoms and traditional metabolic risk factors among subjects with levels of resistin and other proteins. Statistical significance was set at P-value $\leq$ 0.05.

2.6. Ethics approval

The study protocol was approved by the Institutional Review Board of the Korea Institute of Oriental Medicine (IRB No. I-1310/001-001-03) and seven participating medical centers. Informed consent was obtained from all participants.

3. Results

3.1. General characteristics of the study subjects

A total of 885 subjects were selected in the study for data analysis. 795 patients who were diagnosed as having the same pattern by the DKMs and 90 healthy control subjects participated in the study. The non-BSS group consisted of 376 patients, and the BSS group consisted of 419 patients (Fig. 1). The general characteristics of the groups are shown in Table 1. Most patients had musculoskeletal diseases, followed by diseases of the genitourinary system and diseases of the nervous system. The proportion of patients with BSS was the highest (62.9%) in the group with genitourinary system diseases, followed by group with musculoskeletal diseases (56.1%). According to the diagnostic criteria, the MS
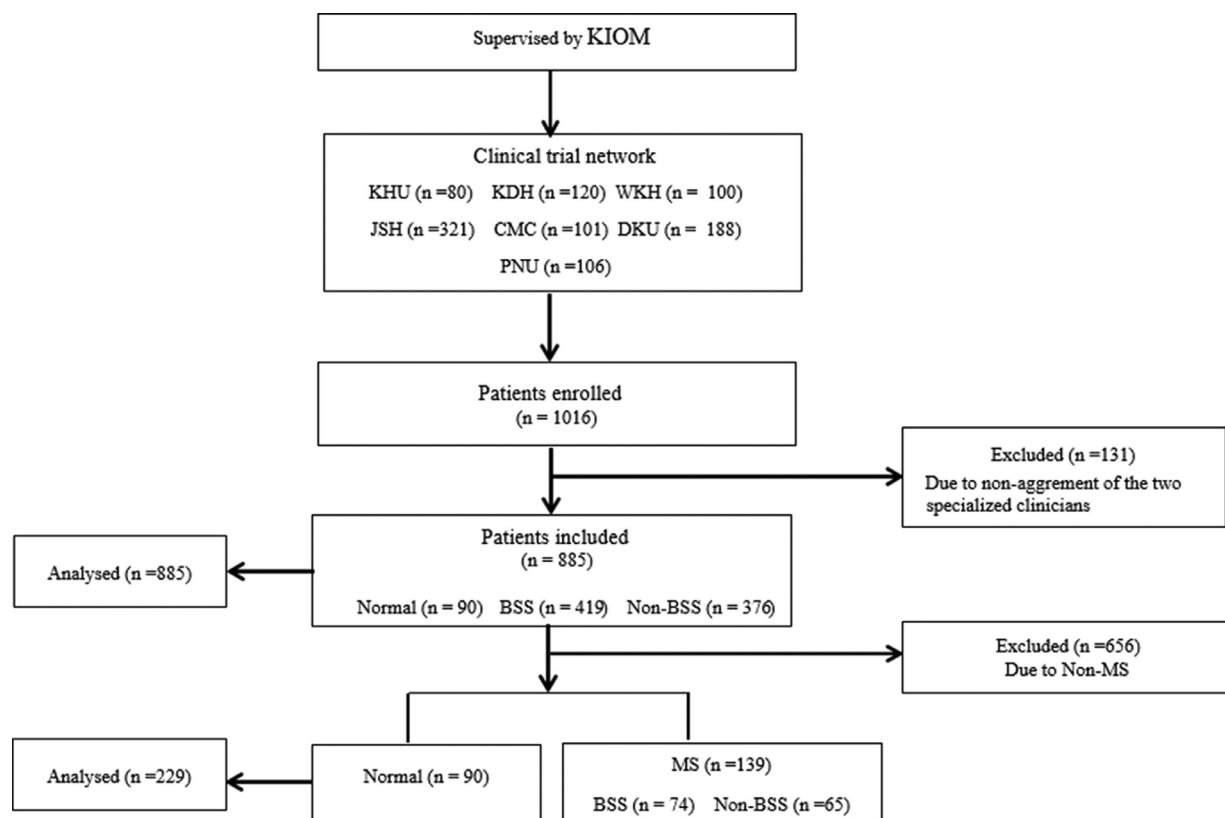
Fig. 1. Flowchart of the study. BSS, blood stasis syndrome; CMC, Cha Medical Center; DKU, Dong-guk University Oriental Medical Hospital; JSH, Jaseng Hospital of Oriental Medicine; KDH, Kyung Hee University Oriental Hospital at Gangdong; KHU, Kyung Hee Oriental Medical Center; MS, metabolic syndrome; PNU, Pusan National University Korean Medicine Hospital; WKH, WonKwang Oriental Medical Hospital.

Table 1
General characteristics of subjects.

Characteristics	Normal ($N = 90$)	Non-BSS ($N = 376$)	BSS ($N = 419$)	p
Gender (Male/Female)	26/64	198/178	134/285	**<0.001**
Age (years)	42.91±12.82[b]	46.45±12.51[a]	44.32±11.51[ab]	**0.009**
Height (cm)	162.58±7.71[b]	165.40±8.58[a]	163.96±7.35[ab]	**0.003**
Weight (kg)	59.20±10.28[c]	65.05±12.03[a]	62.96±11.25[b]	**<0.001**
BMI (kg/m^2)	22.30±2.85[b]	23.66±3.15[a]	23.34±3.42[a]	**0.002**
Drinking (yes,%)	43 (47.78)	177 (47.07)	157 (37.47)	**0.014**
Smoking (yes,%)	13 (14.44)	59 (15.69)	78 (18.62)	0.438
SBP (mmHg)	117.34±12.36	120.89±15.46	119.32±15.11	0.091
DBP (mmHg)	75.06±10.43	76.20±11.15	75.40±11.13	0.500
pulse (times/min)	78.01±12.28[a]	73.88±10.30[b]	75.39±10.26	**0.002**
Distribution of diseases (n)				
Diseases of the nervous system (VI)	–	45	37	
Diseases of the circulatory system (IX)	–	41	18	
Diseases of the respiratory system (X)	–	6	0	
Diseases of the musculoskeletal system (XIII)	–	209	267	
Diseases of the genitourinary system (XIV)	–	46	78	
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (XVIII)	–	17	8	
Diseases of the digestive system (XI)	–	12	11	
Distribution of MS				
MS	–	65	74	
Non-MS	–	311	345	

All data are presented as Mean±SD for continuous variables and as frequencies for categorical variables. [a,b,c] Significant difference between groups in which the value descends respectively by Bonferroni post hoc test. *P*-value using one-way ANOVA in continuous variables, chi-squared test in categorical variables. *P*-values with statistical significance were presented in bold (<0.05).
BMI, body mass index; BSS, blood stasis syndrome; DBP, diastolic blood pressure; MS, metabolic syndrome; SBP, systolic blood pressure.
Roman numerals by ICD-10 codes: VI, Diseases of the nervous system; IX, Diseases of the circulatory system; X, Diseases of the respiratory system; XI, Diseases of the digestive system; XIII, Diseases of the musculoskeletal system; XIV, Diseases of the genitourinary system; XVIII, Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified.

Table 2

The levels of serum proteins related to metabolic diseases.

Parameters	Total ($N = 885$)	Normal ($N = 90$)	Non-BSS ($N = 376$)	BSS ($N = 419$)	p
Resistin	4355.75±2458.69	4113.73±2305.13[ab]	4057.75±2226.42[b]	4676.51±2648.72[a]	**0.002**
Insulin	486.34±633.87	312.70±313.68[b]	496.44±566.72[a]	514.57±730.24[a]	**0.046**
Leptin	2844.46±3178.76	3055.88±3015.37	2398.75±2786.49	3202.02±3486.35	0.602
Visfatin	3296.62±1817.89	3466.46±6362.36	2587.92±5602.98	3894.44±25,679.01	0.814
C-peptide	1174.09±843.95	891.70±621.31[b]	1220.87±807.54[a]	1193.39±905.93[a]	**0.006**
Ghrelin	1453.78±1212.28	2321.48±1780.68[a]	1312.43±941.80[b]	1393.90±1205.03[b]	**<0.001**
GIP	402.81±468.78	403.44±416.49	407.67±388.95	398.26±540.83	0.735

All data are presented as Mean±SD. *P*-value using general linear model adjusted as sex, age, BMI, drinking, pulse.
[a,b,c]Significant differences between groups in which the value descends respectively by Bonferroni post hoc test.
P-values with statistical significance were presented in bold (<0.05).
BSS, blood stasis syndrome; GIP, Gastric inhibitory polypeptide.

Table 3

Changes in serum proteins associated with diabetes of the MS.

Parameters	Total ($N = 229$)	Normal ($N = 90$)	MS		p
			Non-BSS ($N = 65$)	BSS ($N = 74$)	
Resistin	4518.77±2581.65	4113.73±2305.13[b]	4337.27±2440.85[ab]	5154.96±2902.09[a]	**0.049**
Insulin	689.13±752.75	312.70±313.68[b]	907.10±753.19[a]	955.48±929.27[a]	**<0.001**
Leptin	2891.38±2991.52	3055.88±3015.37	2500.24±2847.59	3041.56±3093.71	0.301
Visfatin	2489.01±4282.85	3466.46±6362.36[a]	1934.04±1722.81[ab]	1806.61±1959.09[b]	**0.037**
C-peptide	1356.06±867.29	891.70±621.31[b]	1700.61±791.03[a]	1635.04±940.84[a]	**<0.001**
Ghrelin	1581.68±1455.38	2321.48±1780.68[a]	1055.57±658.59[b]	1144.04±1119.88[b]	**<0.001**
GIP	472.95±405.12	403.44±416.49	519.95±347.77	512.44±431.70	0.083

All data are presented as Mean±SD. *P*-value using general linear model adjusted as sex, age, BMI, drinking, pulse.
[a,b,c]Significant differences between groups in which the value descends respectively by Bonferroni post hoc test.
P-values with statistical significance were presented in bold (<0.05).
BSS, blood stasis syndrome; GIP, Gastric inhibitory polypeptide; MS, metabolic syndrome.

group consisted of 139 patients, and the non-MS group consisted of 656 patients. In the MS group, 53.2% patients had BSS. Nearly all items related to BSS were significantly increased in the BSS group compared with those in the non BSS and normal groups (Supplemental Table 1). Among the blood parameters, platelet count, red cell distribution width (RDW), and neutrophil level were significantly increased in patients with BSS compared with those in normal subjects or patients without BSS ($P = 0.022$, $P = 0.012$, $P = 0.007$, respectively). Additionally, lymphocyte levels were decreased in patients with BSS ($P = 0.009$). Among the serum lipids, HDL-cholesterol level was shown to be significantly lower in patients with or without BSS than in the normal subjects ($P = 0.040$) (Supplemental Table 2).

3.2. Levels of serum proteins between subjects according to diseases and BSS

The average serum resistin levels were significantly higher in patients with BSS compared with those in patients without BSS and normal subjects after adjusting for age, sex, BMI, drinking status and pulse ($P = 0.002$) (Table 2). Moreover, the insulin levels were significantly higher in the patients with BSS than in normal subjects ($P = 0.046$), and the C-peptide and ghrelin levels were significantly higher and lower, respectively, in patients with BSS than in normal subjects ($P = 0.006$ and $P < 0.001$, respectively). Additionally, patient's with BSS who had MS exhibited significantly higher resistin levels than normal subjects and patients without BSS ($P = 0.049$) (Table 3). Furthermore, the insulin levels were significantly higher in the BSS group than in the normal group ($P < 0.001$). However, the visfatin and ghrelin levels were significantly lower in the BSS group than in the normal group ($P = 0.037$ and $P < 0.001$, respectively). Interestingly, patients with BSS who had musculoskeletal diseases (XIII) and symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified (XVIII), had significantly higher resistin levels than patients without BSS

Table 4

Relationship between metabolic factors and resistin levels of the subjects.

Metabolic factors			Age-adjusted	
	r[a]	p	r	p
Men ($n = 358$)				
BMI	0.016	0.765	0.018	0.731
SBP	−0.022	0.685	−0.018	0.731
DBP	−0.028	0.603	−0.026	0.621
TC	−0.010	0.857	−0.012	0.827
HDL-C	−0.073	0.173	−0.078	0.142
LDL-C[b]	−0.027	0.610	−0.029	0.589
TG	0.078	0.144	0.080	0.133
CRP	0.130	**0.014**	0.129	**0.015**
Women ($n = 527$)				
BMI	0.129	**0.003**	0.167	**<0.001**
SBP	0.055	0.215	0.081	0.062
DBP	0.041	0.355	0.061	0.164
TC	−0.030	0.496	−0.016	0.721
HDL-C	−0.037	0.403	−0.049	0.265
LDL-C	−0.020	0.648	−0.007	0.669
TG	0.010	0.815	0.034	0.436
CRP	0.196	**<0.001**	0.199	**<0.001**

BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a] *r*, Pearson correlation coefficient.
[b] LDL-C (mg/dL) = TC− HDL-C− (TG/5) by Friedewald equation.

or normal subjects ($P = 0.005$ and $P < 0.001$, respectively) (Supplemental Table 3).

Among ten serum proteins, the GLP-1, PAI-1 and glucagon were not detected because they were lower or higher than the detection range.

3.3. Relationship between resistin levels and metabolic factors

Correlation coefficients between serum resistin levels and several metabolic measures are shown in Table 4. BMI was poorly cor-

Table 5

Relationship between BSS symptoms and resistin levels of the subjects.

Symptoms/signs			Age-adjusted	
	r^a	p	r	p
Men ($n = 358$)				
Dark red gums	0.158	**0.003**	0.217	**0.001**
Dark rings around the eyes	0.125	**0.019**	0.181	**0.007**
Dark facial complexion	0.134	**0.012**	0.214	**0.001**
Abdominal mass	0.141	**0.037**	0.141	**0.037**
Rough pulse	0.184	**<0.001**	0.248	**<0.001**
Red spots on palm	−0.120	**0.024**	−0.155	**0.021**
Painful ankle, wrist, back sprain	0.144	**0.006**	0.120	0.076
Nocturnal pain	0.159	**0.003**	0.259	**<0.001**
Women ($n = 527$)				
Dark red gums	0.154	**<0.001**	0.142	**0.001**
Dark red lips	0.171	**<0.001**	0.168	**<0.001**
Dark red tongue	0.146	**0.001**	0.134	**0.002**
Ecchymosis on the tongue body	0.140	**0.001**	0.124	**0.005**
Dark facial complexion	0.119	**0.007**	0.108	**0.015**
Ecchymosis on the skin	0.086	**0.049**	0.092	**0.039**
Thick and coarse skin	−0.098	**0.026**	−0.108	**0.015**
Nocturnal pain	0.121	**0.006**	0.122	**0.006**

^{a} r, Pearson correlation coefficient. BSS, blood stasis syndrome.

related with serum resistin level in men ($r = 0.016$, $P = 0.765$) and relatively correlated in women ($r = 0.129$, $P = 0.003$). A moderate correlation in both sexes was noted between resistin and C-reactive protein (CRP) as an inflammatory marker, which remained positive even after adjustment for age ($P < 0.001$).

3.4. Relationship between resistin levels and blood stasis symptoms

The results of the relationship between resistin levels and symptoms of the BSS are shown in Table 5. Resistin levels in men were significantly correlated with dark red gums, dark rings around the eyes, dark facial complexion, abdominal mass, rough pulse, red spots on the palm, painful ankle/ wrist/ back sprain and nocturnal pain ($P < 0.05$). And Resistin levels in women were significantly correlated with dark red gums, dark red lips, dark red tongue, ecchymosis on the tongue body, dark facial complexion, ecchymosis on the skin, thick and coarse skin, and nocturnal pain.

4. Discussion

In this study, we elucidated that serum resistin levels are involved in metabolic diseases in patients with several disorders, including MS with or without BSS, and in normal subjects. Among the serum proteins, the resistin level was significantly higher in patients with BSS than in patients without BSS. Patients with BSS who had MS exhibited significantly higher resistin levels than normal subjects.

In addition, resistin was significantly correlated with dark red gums, dark facial complexion, and nocturnal pain in BSS in both sexes. Moreover, resistin was significantly correlated with CRP as an inflammatory marker in both sexes.

Resistin is an adipokine and known to be related to metabolic diseases.[18–25] Qi et al. reported that serum resistin was significantly associated with IL6, CRP, and insulin resistance in Chinese population.[24] Fargnoli et al. also reported an association between resistin, and, IL6, and TNF-α.[25] This indicates that the increase in serum resistin level might affect multiple cell types to promote inflammation, insulin resistance, and cardiac pathology. Additionally, several studies have suggested the possibility of a relationship between serum resistin level and BSS. Mao et al. reported that patients with BSS with coronary heart disease had an observed lower insulin sensitivity index and higher serum insulin level than control patients and patients with other syndromes.[26] Recently, it

was found that Tongqiaohuoxue decoction, which is widely used in BSS treatment, improved insulin resistance in high-fat diet-induced obese mice.[28] A functional single nucleotide polymorphism in the promoter region of resistin was significantly associated with a decrease in serum insulin level and homeostasis model assessment insulin resistance in obese subjects.[30] Additionally, an increase in circulating resistin level is associated with an increase in insulin resistance, oxidative stress, and platelet activation in type 2 diabetes mellitus.[31] The abovementioned results show that BSS and resistin could be connected through insulin resistance. According to our results, patients with BSS who had MS exhibited significantly higher resistin levels than normal subjects. And the resistin level was significantly higher in patients with BSS than in patients without BSS.

Some studies reported that serum resistin was significantly associated with CRP in patients.[32–33] In this study, resistin was significantly correlated with CRP in both sexes. A previous study showed that CRP level was significantly higher in the BSS group with high serum amyloid P component (SAP) level.[34]

Our results may suggest that resistin levels are potentially associated with the pathogenesis of BSS in TKM for metabolic diseases. The increase in resistin levels might be a useful indicator of BSS in various diseases, including MS.

One limitation of our study is the fact that this was a cross-sectional, observational study. This study does not demonstrate changes in resistin levels following treatment or elucidate the mechanisms of BSS. Further studies are needed to determine the functional properties of resistin in BSS. Additionally, the group sizes were not balanced for different disease systems. Lastly, all patients were allocated into two experts among fourteen DKMs in each site for blood stasis diagnosis. While the large number of DKMs who participated in this study increased the generalizability of the results, it is possible that the variety of experiences offered by these DKMs was another limitation to the study regardless of the standard operating procedure training on blood stasis diagnosis.

Despite these limitations, this study may help to provide information regarding resistin levels in patients with BSS in the clinical setting.

Author contributions

Conceptualization: MMK and JJY. Methodology: MMK and MHC. Formal analysis: MMK. Writing – Original Draft: MMK. Writing – Review & Editing: MMK, MHC and JJY. Supervision: MHC and JJY.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Ethical statement

This research was reviewed and approved by the institutional review board of the Korea Institute of Oriental Medicine and seven participating medical centers (No. I-1310/001-001-03). Informed consent was obtained from all participants.

Data availability

The data that support the findings of this study of this study are available from the corresponding author upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.imr.2021.100719.

References

1. Gunter RN. *Blood Stasis–China'S Classical Concept in Modern Medicine*. New York: Elsevier; 2007.
2. *. WHO International Standard Terminologies on Traditional Medicine in the Western Pacific Region*. Geneva: WHO; 2007.
3. Terasawa K, Shinoda H, Imadaya A, Tosa H, Bandoh M, Satoh N. The presentation of diagnostic criteria for Oketsu syndrome. *Int J Orient Med*. 1983;34:1–17. doi:10.3937/kampomed.34.1.
4. Choi TY, Jun JH, Park BK, et al. Concept of blood stasis in Chinese medical textbooks: a systematic review. *Eur J Integr Med*. 2016;8(3):158–164. doi:10.1016/j.eujim.2015.09.137.
5. Bensky D, Gamble A. *Chinese Herbal Medicine Materia Medica*. Seattle: Eastland Press; 1986.
6. Park B, Yun KJ, Jung J, et al. Conceptualization and utilization of blood stasis syndrome among doctors of Korean medicine: results of a web-based survey. *Am J Transl Res*. 2014;6(6):857–868.
7. Lee JA, Kang BK, Park TY, et al. CORE-DITEC-BS (COnvergence REsearch of the DIagnostic TEChnology for Blood Stasis): study protocol. *Eur J Integr Med*. 2015;7(4):417–422. doi:10.1016/j.eujim.2014.10.009.
8. Park B, You S, Jung J, Lee JA, Yun K, Lee MS. Korean studies on blood stasis: an overview. Evid Based. *Compl Alternat Med*. 2015;2015. doi:10.1155/2015/316872.
9. Du JP, Shi DZ, Li TC, Xu H, Chen H. Correlation between blood stasis syndrome and pathological characteristics of coronary artery in patients with coronary heart disease. *J Chin Integr Med*. 2010;8(9):848–852. doi:10.3736/jcim20100908.
10. Liu P, Duan JA, Bai G, Su SL. Network pharmacology study on major active compounds of siwu decoction analogous formulae for treating primary dysmenorrhea of gynecology blood stasis syndrome. *Zhongguo Zhong Yao Za Zhi*. 2014;39(1):113–120.
11. Goto H. Blood stasis syndrome in Japan and its molecular biological analysis. *Chin J Integr Med*. 2014;20(7):490–495. doi:10.1007/s11655-014-1882-7.
12. Huang Y, Wang JS, Yin HJ, Chen KJ. The expression of CD14+CD16+ monocyte subpopulation in coronary heart disease patients with blood stasis syndrome. Evid Based. *Complement Alternat Med*. 2013;2013. doi:10.1155/2013/416932.
13. Wang J, Yu G. A systems biology approach to characterize biomarkers for blood stasis syndrome of unstable angina patients by integrating MicroRNA and messenger RNA expression profiling. *Evid Based Complement Alternat Med*. 2013;2013. doi:10.1155/2013/510208.
14. Yuan ZK, Wang LP, Huang XP. The screening and the functional pathway analysis of differential genes correlated with coronary heart disease of blood stasis syndrome. *Zhongguo Zhong Xi Yi Jie He Za Zhi*. 2012;32(10):1313–1318.
15. Zhou XQ, Liang H, Sun X, Zhou HT. Correlation between TCM blood stasis pattern of coronary heart disease and coronary angiography result: a meta-analysis. *Chin. J Evid Based Med*. 2012;12(12):1470–1477.
16. Liu X, Guo C, Ma X, Tian R, Zhang Y, Yin H. Relationship between serum estrogen levels and blood stasis syndrome in postmenopausal women with coronary heart disease. *Pak J Med Sci*. 2015;31(1):25–30.
17. JI W, Zhou J, Wang S, Ji Z. Logistic regression analysis of relevance between different blood stasis syndromes and related factors in angina pectoris patients. *Chin Arch Tradit Chin Med*. 2013;7(40):1591–1592.
18. Savage DB, Sewter CP, Klenk ES, et al. Resistin/Fizz3 expression in relation to obesity and peroxisome proliferator–activated receptor-γ action in humans. *Diabetes*. 2001;50(10):2199–2202.
19. Senolt L, Housa D, Vernerova Z, et al. Resistin in rheumatoid arthritis synovial tissue, synovial fluid and serum. *Ann Rheum Dis*. 2007;66(4):458–463.
20. Schwartz DR, Lazar MA. Human resistin: found in translation from mouse to man. *Trends Endocrinol Metab*. 2011;22(7):259–265. doi:10.1016/j.tem.2011.03.005.
21. Devanoorkar A, Kathariya R, Guttiganur N, Gopalakrishnan D, Bagchi P. Resistin: a potential biomarker for periodontitis influenced diabetes mellitus and diabetes induced periodontitis. *Dis Markers*. 2014;2014. doi:10.1155/2014/930206.
22. Jamaluddin MS, Weakley SM, Yao Q, Chen C. Resistin: functional roles and therapeutic considerations for cardiovascular disease. *Br J Pharmacol*. 2012;165(3):622–632. doi:10.1111/j.1476-5381.2011.01369.x.
23. Al-Suhaimi EA, Leptin Shehzad A. resistin and visfatin: the missing link between endocrine metabolic disorders and immunity. *Eur J Med Res*. 2013;18(1):12. doi:10.1186/2047-783X-18-12.
24. Qi Q, Wang J, Li H, et al. Associations of resistin with inflammatory and fibrinolytic markers, insulin resistance, and metabolic syndrome in middle-aged and older Chinese. *Eur J Endocrinol*. 2008;159(5):585–593. doi:10.1530/EJE-08-0427.
25. Fargnoli JL, Sun Q, Olenczuk D, et al. Resistin is associatedis associated with biomarkers of inflammation while total and high-molecular weight adiponectin are associated with biomarkers of inflammation, insulin resistance, and endothelial function. *Eur J Endocrinol*. 2010;162(2):281–288. doi:10.1530/EJE-09-0555.
26. Mao W, Ye W, Liu Q, Huang Z, Chen S, Qin N. Preliminary study on relationship between tcm syndrome-type and insulin resistance in coronary heart disease. *Chin J Integr Med*. 2001;7:292. doi:10.1007/BF02934375.
27. Shim EH, Lee HY, Lee MS, You SS. Anti-adipogenic effects of the traditional herbal formula Dohongsamul-tang in 3T3-L1 adipocytes. *BMC Complement Altern Med*. 2017;17:542. doi:10.1186/s12906-017-2038-z.
28. Kim SH, Park HS, Hong MJ, et al. Tongqiaohuoxue decoction ameliorates obesity-induced inflammation and the prothrombotic state by regulating adiponectin and plasminogen activator inhibitor-1. *J Ethnopharmacol*. 2016;192:201–209. doi:10.1016/j.jep.2016.07.023.
29. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation*. 2005;112(17):2735–2752.
30. De Luis DA, Aller R, Izaola O, Primo D, Romero E. Association of the rs9939609 gene variant in FTO with insulin resistance, cardiovascular risk factor and serum adipokine levels in obese patients. *Nutr Hosp*. 2016;33(5):573. doi:10.20960/nh.573.
31. Santilli F, Liani R, Di Fulvio P, et al. Increased circulating resistin is associated with insulin resistance, oxidative stress and platelet activation in type 2 diabetes mellitus. *Thromb Haemost*. 2016;116(6):1089–1099. doi:10.1160/TH16-06-0471.
32. Al-Daghri N, Chetty R, McTernan PG, et al. Serum resistin is associated with C-reactive protein & LDL cholesterol in type 2 diabetes and coronary artery disease in a Saudi population. *Cardiovasc Diabetol*. 2005;4:10. doi:10.1186/1475-2840-4-10.
33. McTernan PG, Fisher FM, Valsamakis G, et al. Resistin and type 2 diabetes: regulation of resistin expression by insulin and rosiglitazone and the effects of recombinant resistin on lipid and glucose metabolism in human differentiated adipocytes. *J Clin Endocrinol Metab*. 2013;88(12):6098–6106. doi:10.1210/jc.2003-030898.
34. Jung J, Cha MH, Lee HY, et al. The association of C-reactive protein and serum amyloid P with blood stasis syndrome in Traditional Korean Medicine for general disease conditions: a cross-sectional, observational study. *Eur J Integr Med*. 2016;8(4):432–437. doi:10.1016/j.eujim.2016.02.010.