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The Clinical Characteristics of Obese Patients with Acanthosis Nigricans and Its Independent Risk Factors

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ABSTRACT

Objective: This study aimed to investigate the clinical characteristics and risk factors for acanthosis nigricans (AN) in obese patients.
Methods: 80 obese patients without AN (OB group) and 128 obese patients with AN (AN group) were included in this study. Clinical data for each patients were collected. Serum levels of leptin were measured by ELISA.
Results: Body mass index (BMI), uric acid (UA) levels, fasting insulin, and HOMA-IR were higher in AN than OB ($P<0.05$). The levels of leptin were significantly higher in AN than OB ($P<0.001$) after adjustment for BMI and gender. In male patients, AN showed lower serum levels of testosterone than OB ($P<0.001$). Multiple Logistic-regression analysis demonstrated that UA (OR 4.627, 95 %CI 2.443–8.762, $P<0.001$) and Leptin (OR 4.098, 95 %CI 1.237–13.581, $P=0.021$) were independent risk factors for AN. In addition, low testosterone level was an independent risk factor for AN in male obese patients (OR 39.062, 95 %CI 5.523–283.808, $P<0.001$).
Conclusions: AN is associated with more severe hyperinsulinemia and hyperuricemia in obese patients, as well as lower serum testosterone levels in male patients. UA and Leptin were independent risk factors for AN in obese patients. Low testosterone may be a valuable predictor of AN in male obese patients.

Introduction

Obesity is a global public health challenge, and it is linked to the development of multiple metabolic disorders [1]. Acanthosis nigricans (AN) is characterized by hyperpigmented and papillose thickening of the epidermis, which is mainly present on the skin folds, such as the axillae, posterior neck, umbilicus, and occasionally mucosal surfaces [2, 3]. Clinical studies have shown that AN is usually accompanied by metabolic disorders, including obesity, diabetes, hyperinsulinemia, hyperlipidemia, and insulin resistance [2]. Insulin resistance is regarded as the key mechanism that leads to the development of AN in obesity. In turn, AN is a physical marker of insulin resistance and of more profound underlying metabolic alterations in obese patients [4, 5]. However, an incomplete understanding of the mechanisms leading to AN remains a major hurdle for the development of new and effective treatment strategies.

Leptin, a hormone secreted by adipocytes and expressed in tissues such as placenta, ovaries, skeletal muscle, stomach, and liver [6], has been shown to regulate food intake and energy expenditure through a variety of neural and endocrine mechanisms [7]. Leptin and insulin are closely associated with obesity and its complications like nonalcoholic fatty liver disease (NAFLD) [8]. Leptin acts primarily on the hypothalamus to stimulate a variety of catabolic pathways [9, 10]. In addition, leptin could also promote cellular proliferation.

Uric acid (UA) is present at high levels in human plasma and has been shown to have antioxidant properties [11]. Conversely, UA also has proxidant properties, and contributes to the development of many metabolic diseases such as type 2 diabetes and cardiovascular disease [12]. UA is believed to contribute to the development of type 2 diabetes by inhibiting the bioavailability of nitric oxide and thereby inhibiting insulin secretion [13, 14]. Increased levels of serum UA have also been associated with higher risk of diabetic complications, including neuropathy [15], diabetic retinopathy [16], nephropathy [17] and microvascular complications [18, 19].

The present study aims to investigate the differences in metabolism including leptin in obese patients with or without AN. We also sought to identify biomarkers and risk factors for the development of AN in obese patients.

Patients and Methods

Patients

The present study based on data from outpatients of Shanghai Tenth People's Hospital was conducted among obese patients between August 2013 and May 2015. 80 obese patients without AN and 128 obese patients with AN aged from 18 to 36 years old were included. Obesity was defined as BMI ≥ 28 kg/m^2. Approval for the study was obtained from the Ethics Committee of the Shanghai Tenth People's Hospital. The Clinical Trials Registration Number is ChiCTR-OCS-12002381, and all the participants were asked to sign an informed consent prior to participation in the study.

Patients with medical illnesses such as clinical or laboratory evidence of cardiac, renal, liver, or severe systemic diseases (e. g., cancer and heart failure) were excluded.

Diagnostic criteria for AN

The following scale for AN was used [20]. Neck severity: 0-Absent, not detectable on close inspection; 1-Present, clearly present on close visual inspection, not visible to the casual observer, extent not measurable; 2-Mild, limited to the base of the skull, does not extend to the lateral margins of the neck (usually < 3 inches in breadth); 3-Moderate, extending to the lateral margins of the neck (posterior border of the sternocleidomastoid, usually 3–6 inches), not be visible when the participant is viewed from the front; 4-Severe, extending anteriorly (> 6 inches), visible when the participant is viewed from the front. In this study, each subject enrolled with AN had a score greater than 2.

Methods

Blood samples were obtained between 07:00 AM and 10:00 AM after 10 h of fasting. Serum was separated and stored at − 80 °C until further analysis. Total cholesterol (TC), triglycerides (TG), free fatty acids (FFA), uric acid (UA) and oral glucose tolerance test (OGTT) were measured. In addition, free testosterone was measured in males only. The homeostasis model of assessment for insulin resistance (HOMA-IR) was calculated on the basis of fasting values of plasma glucose and insulin according to the HOMA model formula: HOMA-IR = fasting insulin × fasting glucose, divided by 22.5 [21]. Serum leptin levels were measured after an overnight fasting by ELISA (R&D)

Statistical analysis

All statistical analysis was performed with IBM SPSS version 18.0 for Windows (IBM Corporation, Armonk, NY). Quantitative data were presented as mean ± standard deviation (SD) and the count data as the number of columns (n). Independent samples Student's t tests were used for statistical comparisons. Pearson or Spearman methods were used for correlation analysis to assess the correlation between leptin and other variables. Analysis of covariance (ANCOVA) was applied to determine the difference in serum leptin between the 2 groups after adjusting BMI and gender. Logistic-regression analysis was performed to determine the risk factors for AN. A P-value of less than 0.05 was considered statistically significant.

Results

The general characteristics and demographics of the patients are displayed in ▶ **Table 1**. There was no statistically significant difference in age, FFA, TC, TG, and blood glucose between the 2 groups. Compared with the OB group, the AN group had increased UA ($P < 0.001$), CRP ($P = 0.016$), plasma insulin levels (at 0 min, 30 min, 60 min, ($P < 0.001$), and 120 min ($P = 0.001$)), C-peptide at each point ($P \leq 0.001$), and HOMA-IR ($P = 0.008$).

AN patients had higher serum levels (34.74 ± 2.95 ng/ml) of leptin than the OB group (26.25 ± 2.74 ng/ml) ($P < 0.001$) after adjusting for BMI and gender (▶ **Table 2**).

In male patients, the AN group had lower serum of testosterone than OB group (7.89 ± 3.35 nmol/l vs 12.72 ± 3.57 nmol/l, respectively) ($P < 0.001$). The two groups showed no significant difference in E2 and progesterone levels ($P = 0.239$, and 0.177 respectively) (▶ **Table 3**).

Serum level of leptin was correlated with BMI ($P < 0.001$), plasma insulin 0 min, 30 min, 60 min, 120 min, 180 min ($P = 0.005$, 0.001, 0.003, < 0.001, < 0.001) and C-peptide 30 min ($P = 0.003$), 60 min ($P < 0.001$), 120 min ($P = 0.004$), 180 min ($P = 0.038$) (▶ **Table 4**).

Furthermore, logistic regression analysis was performed to identify the risk factors for AN in obese patients, including FFA, BMI, age, TSH, UA, Leptin, TG, TC, Testosterone. Results demonstrated that increased UA ($P < 0.001$) and increased Leptin ($P = 0.021$) were independently correlated with AN. Testosterone was another independent risk factor in males only ($P < 0.001$). In females, UA was the only independent risk factor ($P = 0.014$) (▶ **Table 5**).

Discussion

Obesity has become a worldwide public health problem. However, few studies have focused on the differences between obese patients with and without AN. In this study, we demonstrated that compared with OB, AN patients had more severe degrees of hyperinsulinemia, hyperuricemia, hyperleptindemia, and hypoandrogenisim in male patients. The data presented herein also provide the first evidence that UA and leptin were risk factors for the development of AN. We also provide evidence that low serum levels of testosterone may differentiate obese patients with AN from those without AN.

Previous study has demonstrated that AN is closely associated with insulin resistance [22], we presented that AN patients had high serum levels of fasting insulin, and hyperinsulinemia demonstrating high degrees of insulin resistance. Compared with OB, AN patients had higher serum levels of leptin. Our result is supported by Atwa's study [5], which also reported higher serum leptin in obese AN patients. Study showed that leptin could stimulate the production of important growth factors [23] which may lead to induce proliferation of oral keratinocytes. Therefore, Elevated leptin levels may play a pathological role in the development of skin hyperpigmentation in AN. Stallmeyer [24] demonstrated that in leptin-deficient ob/ob mice, supplement leptin could improve re-epithelialization. They observed that the leptin receptor subtype ob/Rb

▶ **Table 1** Baseline characteristics and blood test results (n = 208).

	OB	AN	
Variables	**N = 80**	**N = 128**	**P-value**
Male (%)	30 (37.5)	69 (53.9)	0.021
Age (year)	28.22 ± 7.81	26.44 ± 8.27	0.102
BMI	36.43 ± 4.56	37.15 ± 5.71	0.112
FFA (mmol/l)	0.55 ± 0.21	0.60 ± 0.20	0.143
CRP (mg/l)	4.17 ± 4.91	9.22 ± 22.52	0.016
UA (umol/l)			
Male	397.03 ± 74.48	501.60 ± 103.71	< 0.001
Female	352.21 ± 68.58	414.55 ± 77.89	< 0.001
TC (mmol/l)	4.96 ± 1.17	4.84 ± 0.90	0.412
TG (mmol/l)	1.84 ± 1.13	1.82 ± 0.95	0.865
TSH (mU/l)	2.35 ± 1.39	2.74 ± 1.55	0.072
OGTT glucose			
0 min	5.98 ± 2.43	5.69 ± 1.81	0.360
30 min	9.83 ± 3.14	9.77 ± 2.38	0.888
60 min	10.70 ± 4.53	10.54 ± 3.53	0.768
120 min	9.19 ± 5.11	8.71 ± 3.56	0.464
180 min	6.98 ± 4.99	6.23 ± 3.16	0.226
Plasma insulin			
0 min	23.46 ± 15.81	34.27 ± 17.27	< 0.001
30 min	114.42 ± 119.22	178.70 ± 126.64	< 0.001
60 min	132.38 ± 127.88	205.42 ± 123.04	< 0.001
120 min	116.59 ± 144.70	182.24 ± 127.02	0.001
180 min	61.13 ± 112.37	85.59 ± 91.29	0.087
C-peptide			
0 min	3.63 ± 1.67	4.62 ± 1.41	< 0.001
30 min	8.81 ± 4.94	11.23 ± 4.53	< 0.001
60 min	10.34 ± 5.43	13.28 ± 4.51	< 0.001
120 min	10.33 ± 5.41	12.76 ± 4.40	< 0.001
180 min	6.69 ± 3.33	8.54 ± 4.11	0.001
HOMA-IR	6.45 ± 7.03	8.65 ± 4.82	0.008

OB: obese patients without acanthosis nigricans. AN: obese patients with acanthosis nigricans. BMI: Body Mass Index. M/F: Male/Female. FFA: Free fatty acid. CRP: C reactive protein. UA: Uric Acid. TC: total cholesterol. TG: triglyceride. OGTT: oral glucose tolerance test. HOMA-IR: homeostasis model of assessment for insulin resistance. Results are presented as mean ± SD

▶ **Table 2** Serum levels of leptin of the 2 groups after adjusting BMI and gender analysis by ANCOVA (n = 208).

Variables	OB	AN	P-value
Leptin (ng/ml)	26.25 ± 2.74	34.74 ± 2.95	< 0.001

▶ **Table 3** Hormone levels in male patients (n = 99).

	OB	AN	
Variables	**N = 30**	**N = 69**	**P-value**
Leptin (ng/ml)	13.77 ± 5.83	38.43 ± 32.82	< 0.001
E2 (pmol/l)	154.54 ± 37.27	139.38 ± 65.52	0.239
Testosterone (nmol/l)	12.72 ± 3.57	7.89 ± 3.35	< 0.001
Progesterone (nmol/l)	2.26 ± 2.15	1.84 ± 0.94	0.177

OB: obese patients with acanthosis nigricans. AN: obese patients with acanthosis nigricans

▶ **Table 4** Correlation coefficient of serum leptin with different variables in AN patients and OB patients.

Variables	Correlation index	P-value
BMI	0.321	< 0.001
FFA	− 0.016	0.823
CRP	0.005	0.948
TC	0.008	0.904
TG	− 0.084	0.226
OGTT glucose		
0 min	− 0.032	0.646
30 min	− 0.800	0.250
60 min	− 0.047	0.500
120 min	− 0.004	0.958
180 min	− 0.022	0.751
Plasma insulin		
0 min	0.194	0.005
30 min	0.227	0.001
60 min	0.204	0.003
120 min	0.256	< 0.001
180 min	0.244	< 0.001
C-peptide		
0 min	0.158	0.220
30 min	0.207	0.003
60 min	0.185	< 0.001
120 min	0.197	0.004
180 min	0.144	0.038
HOMA-IR	0.123	0.076

BMI: Body Mass Index. M/F: Male/Female; FFA: Free fatty acid. CRP: C reactive protein. UA: Uric Acid. TC: total cholesterol. TG: triglyceride. OGTT: oral glucose tolerance test. HOMA-IR: homeostasis model of assessment for insulin resistance

was constitutively expressed in non-wounded skin while leptin was persist present at the wound site during healing. Takahashi [25] reported that leptin could promote cell proliferation and induce THF-α production by blood monocytes, also. In addition, leptin receptor was found in normal human keratinocyte (NHK) cell and Hut 102 cells in protein and mRNA. So leptin could combine with its receptor and promote cell proliferation which may lead to AN. The analysis of our study revealed leptin was positively correlated with insulin and C peptide, suggesting serum levels of leptin might be a key feature of hyperinsulinemia and insulin resistance. Leptin is an independent risk factor for AN, and high serum levels of leptin as symbol of AN in obese patients.

Many researches have already confirmed that hyperuricemia is closely associated with metabolic syndrome [26, 27], cardiovascular disease [28], and has regulatory effects on the metabolism of liver, adipose tissue and skeletal muscle [29]. In type 2 diabetes, effective control of uric acid could increase glomerular filtration rate (GFR) and protect kidney function [30]. However, no research has already focused on the relationship between UA and obesity

▶ **Table 5** Risk factors for acanthosis nigricans in obese patients by logistic regression analysis.

	Total N = 208			Males (N = 99)			Females (N = 109)		
	OR	**95 % CI**	**P**	**OR**	**95 % CI**	**P**	**OR**	**95 % CI**	**P**
UA	4.627	2.443–8.762	< 0.001	3.975	0.910–17.359	0.067	2.830	1.234–6.490	0.014
Leptin	4.098	1.237–13.581	0.021	13.730	2.059–91.569	0.007	1.415	0.346–5.792	0.629
T	–	–	–	39.062	5.523–283.808	< 0.001	–	–	–

UA: Uric acid, T: Testosterone

related AN. In our study, compared with the OB group, AN patients showed higher degrees of hyperuricemia. Kleikamp [31] reported that an obese male patient had a history of hyperuricemia with thickening, coarseness and hyperpigmentation in the intertriginous areas of skin. This study showed that in most patients with diabetes, UA levels above normal were due to insulin resistance and hyperinsulinemia [32]. The process of AN is also related to insulin resistance. The present study showed that compared with OB patients, AN patients had higher levels of serum insulin at 0, 30, 60, and 120 min. It is possible that high levels of UA indicate the presence of AN due to insulin resistance. Multiple logistic-regression analysis demonstrated UA was an independent risk factor in both males and females for AN. This may have indications for treatment. For instance, obese patients with elevated UA may be at increased risk for developing AN and subsequently more severe insulin resistance. This group of patients likely warrants more aggressive and earlier initiation of treatment. Further studies are still needed to identify the underlying mechanism whereby UA leads to AN.

To our knowledge, no previous study has studied testosterone levels in AN patients. In the subgroup analysis for male patients, we found that AN patients had significantly lower serum levels of total testosterone than OB patients, and multiple logistic-regression analysis showed that lower serum testosterone were an independent risk factor of AN in male patients. However, the 2 groups showed no significant differences in other hormones including E2 and P indicating the specificity of testosterone. Studies showed that excess body weight in men is a factor associated with lower total testosterone levels [33] and lower total testosterone was an independent predictor of metabolic syndrome [34]. In type 2 diabetes patients with hypogonadotropic hypogonadism (HH), testosterone treatment could increased insulin sensitivity [35]. In obese young adults, it was demonstrated that free testosterone plasma levels were negatively associated with the intima-media thickness of the common carotid artery [36]. However, total testosterone includes free testosterone and sex hormone binding globulin (SHBG). Studies have shown that obesity was associated with lowered SHBG and may involve suppression of hepatic SHBG synthesis by elevated concentrations of insulin, but the mechanism has yet to be fully elucidated [37, 38]. Our study did not assess the individual contributions of free testosterone and SHBG, therefore further work will be needed to determine the effects of each in the development of AN.

There are several limitations to this study. Primarily, while we provide some data regarding the metabolic features of AN and the potential role of leptin, additional work will be needed to elucidate the underling mechanisms. Secondly, this study was limited because of the small number of patients. Therefore, we cannot infer causality from our results. Finally, our results might not be applied to other racial or age groups because the subjects enrolled in this study were Chinese adults.

Conclusions

Our study demonstrated that patient with AN have significantly higher levels of leptin compared with obese patients without AN. We also demonstrated that both UA and leptin levels are independently correlated with AN. In males, a low testosterone level was found to be a risk factor for AN. Our work provides a useful model for prediction of AN and for the selection of obese patients who need early radical intervention. Large, multicenter, randomized, double blind control studies are needed to confirm these findings and additional work is needed to understand the underlying mechanisms and signaling pathways involved.

Authors' Contribution

Yueye Huang conceived of the study and wrote the manuscript. Jiaqi Chen, Xingchun Wang, Yan Li and Shezhen Yang participated the design of the study. Shen Qu organized the paper and approved the final version. All authors read and approved the final version.

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Conflict of interest

The authors declare that they have no conflict of interest.

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