Is glycogenic acanthosis a predictor of insulin resistance and metabolic syndrome?

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ABSTRACT
Background/Aims: To evaluate the incidence of insulin resistance and metabolic syndrome (MetS) in patients with glycogenic acanthosis (GA).

Materials and Methods: Thirty patients with GA, detected upon endoscopy, and 30 age- and sex-matched control patients without GA were included in this case-control study. Patients with GA were considered group 1 and control group was considered group 2. Anthropometric measurements [height, weight, and waist circumference (WC)], biochemical parameters [fasting plasma glucose (FPG), triglyceride, high-density lipoprotein (HDL), and low-density lipoprotein (LDL)], and serum fasting insulin levels were evaluated. Insulin resistance (IR) was estimated by the homeostatic model assessment of IR. MetS was diagnosed using the criteria of the National Cholesterol Education Program Adult Treatment Panel III. Odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated to evaluate associations with GA.

Results: There were no differences in terms of FPG, triglyceride, HDL, and LDL between groups (p-values 0.118, 0.114, 0.192, 0.086, respectively). WC was significantly higher in group 1 than in group 2 (103.77 vs 97.03, p=0.032). The number of patients with IR and MetS were significantly higher in group 1 than in group 2 (53.3% vs 13.3%, p=0.003 and 53.3% vs 23.3%, p=0.034). ORs [95% CI] of WC, IR, and MetS for GA were 0.68 [0.17-2.62], 7.12 [1.89-26.72], and 4.11 [1.04-16.21], respectively.

Conclusion: These findings showed that IR and MetS were significantly associated with the presence of GA.

Keywords: Esophagus, glycogenic acanthosis, metabolic syndrome, insulin resistance

INTRODUCTION
Glycogenic acanthosis (GA) is a nodular or plaque-like elevation of the esophageal squamous epithelium, with an unknown origin (1). It is incidentally detected in 3.5% of patients undergoing endoscopy (2). GA incidence is reported to be more frequent in patients with non-ulcer dyspepsia (28.3%) (3). Histopathologically, GA is seen as a benign epithelial hyperplasia containing abundant glycogen deposits (4). Although GA has been proposed to be related with disorders of glucose metabolism and the skin, including acanthosis nigricans, there is paucity of clinical studies supporting these relationships (5).

Metabolic syndrome (MetS) is a complex disease that causes endothelial dysfunction and accelerated atherosclerosis, as a result of which the risk of coronary heart disease, stroke, and peripheral arterial disease increases. Hypertension, dyslipidemia, central obesity, and impaired glucose metabolism are the main components of this syndrome. Based on modified National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III), diagnosis of MetS can be established by the presence of ≥3 of the following criteria: abdominal obesity, increased triglycerides, low high-density lipoprotein (HDL), hypertension, and impaired glucose tolerance (6). Insulin resistance (IR) is believed to be the
central event in MetS pathogenesis and is characterized by deficient biological response to insulin despite normal or even increased circulating plasma insulin levels. The effect of insulin on glucose metabolism is mostly evident on three organs or tissues, namely the liver, muscle, and fat tissue. In the liver, insulin decreases glucose production by decreasing gluconeogenesis and glycogenolysis, whereas it increases glycogen synthesis in the liver and muscle. Insulin also increases glucose uptake into the muscle and fat tissue by increasing the number of glucose transporters on cellular membrane.

Insulin resistance, which has a pivotal role in MetS, may be the cause of glycogen deposits in enlarged squamous epithelium in GA. IR may play an active role in glycogen deposition in esophageal epithelium. GA, which is commonly encountered during routine gastroenterology practice, may be a warning sign for diseases with high mortality rates such as cardiovascular diseases. We aimed to investigate the relationship of GA, a frequent yet usually ignored entity, with MetS and IR.

**MATERIALS AND METHODS**

**Study Population**

Thirty patients with GA detected during routine endoscopy between May 2014 and January 2016 in a tertiary care center and 30 age- and sex-matched controls without GA were chosen for this case-control study. Group 1 comprised patients with GA, whereas group 2 comprised control patients. Data were collected on smoking status and amount of alcohol consumption, if any. Inclusion criteria were age of 18-65 years, detection of GA on the esophagus upon endoscopy, and not using drugs affecting glucose metabolism. Exclusion criteria were type 2 diabetes, obesity due to endocrine disorders, and pregnancy.

**Anthropometric Measurements**

Anthropometric measurements such as weight, height, and waist circumference (WC) were taken for all subjects. WC was measured using a cloth tape parallel to the mid portion of the distance between the lower side of the 12th costa and spina ischiadica major. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters.

**Diagnosis of Hypertension**

Hypertension was defined as a systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg, according to the Seventh Report of the Joint National Committee (7). Patients with a history of hypertension or those on antihypertensive medications were considered hypertensive.

**Laboratory Assessment**

Venous blood samples for biochemical measurements were taken after an overnight fast. Fasting plasma glucose (FPG), triglyceride, HDL, and low-density lipoprotein (LDL) levels were measured using commercially available assay kits (Roche Diagnostics GmbH, Mannheim, Germany) with an autoanalyzer (cobas 501 Roche-Hitachi, Germany). Plasma insulin level was determined with the electrochemiluminescence immunoassay method using commercially available assay kits (Roche Diagnostics GmbH, Mannheim, Germany) with an autoanalyzer (cobas e601 Roche-Hitachi, Germany). IR was calculated using the homeostatic model assessment of IR (HOMA-IR) formula which was defined as fasting plasma insulin (µU/L)x fasting plasma glucose (mg/dL)/405 (8). Patients with HOMA-IR index of ≥2.5 were accepted as having IR.

**Diagnosis of Metabolic Syndrome and Insulin Resistance**

Diagnosis of MetS was put forward according to the modified NCEP ATP III criteria (9). Accordingly, patients with at least three of the following were accepted as having MetS: hyperglycemia (FPG≥100 mg/dL); hypertriglyceridemia (triglycerides≥150/mL); low HDL (<50 mg/dL) and <40 mg/dL for men and women, respectively; hypertension (blood pressure≥130/85 mmHg); and abdominal obesity (WC≥88 cm and ≥102 for men and women, respectively).

**Diagnosis of Gastroesophageal Reflux Disease**

All patients were interviewed for symptoms of gastroesophageal reflux disease (GERD) and were diagnosed with GERD according to the Montreal classification (10).

**Glycogenic Acanthosis Assessment**

Glycogenic acanthosis was diagnosed on histopathological examination of the specimen or the presence of typical endoscopic view (one or more, round/oval, whitish elevated lesions of the esophagus covered with normal mucosa and frequently <5 mm in diameter). All upper endoscopic examinations were performed with GIF-H180J, Olympus, Japan.

Written informed consent was obtained from patients who participated in this study. Approval was received for this study from the ethics committee of the Faculty of Medicine (April 16, 2014; approval number: 69).

**Statistical Analysis**

Results of analyses have been described as frequencies, means, standard error, and percentages where applicable. Categorical variables were analyzed using the chi-square test. Continuous variables were analyzed using the independent-sample t-test. Binary logistic regression was used for testing probable parameters in the development of GA. Statistical significance was defined as p<0.05 for all analyses. Statistical analysis was performed with Statistical Package for Social Sciences version 17.0 (SPSS Inc.; Chicago, IL, USA).

**RESULTS**

The study group comprised 60 patients, with 30 patients in the GA group (group 1) and 30 patients in the control group (group 2). Patient demographics, clinical data, and laboratory data were analyzed. The proportion of female patients was 46.6% in both groups. The mean age of the patients (year±standard error of mean) was 50.43±2.1 years in group 1 and 46.3±1.8 years in
Table 1. Comparison of demographic, clinical, and laboratory data of GA patients and controls

<table>
<thead>
<tr>
<th></th>
<th>GA (n=30)</th>
<th>Controls (n=30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male</td>
<td>14/16</td>
<td>18/12</td>
<td>0.438</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.43±2.1</td>
<td>46.3±1.8</td>
<td>0.140</td>
</tr>
<tr>
<td>Smoking n (%)</td>
<td>5(16.7)</td>
<td>4(13.3)</td>
<td>0.5</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>103.77±1.9</td>
<td>97.03±2.3</td>
<td>0.032*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.33±3.8</td>
<td>27.3±4.9</td>
<td>0.081</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>94.47±1.9</td>
<td>90.03±1.9</td>
<td>0.118</td>
</tr>
<tr>
<td>Fasting insulin (IU/mL)</td>
<td>16.58±2.9</td>
<td>7.77±0.6</td>
<td>0.006*</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>129.2±6.9</td>
<td>113.0±6.2</td>
<td>0.086</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>49.8±1.7</td>
<td>54.3±2.9</td>
<td>0.192</td>
</tr>
<tr>
<td>Triglyceride (mg/L)</td>
<td>142.3±10.2</td>
<td>117.2±11.9</td>
<td>0.118</td>
</tr>
<tr>
<td>Hypertension n (%)</td>
<td>10(33.3)</td>
<td>4(13.3)</td>
<td>0.127</td>
</tr>
<tr>
<td>GERD n (%)</td>
<td>11(36.7)</td>
<td>8(26.7)</td>
<td>0.574</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>4.71±1.1</td>
<td>1.68±0.1</td>
<td>0.008*</td>
</tr>
<tr>
<td>IR n (%)</td>
<td>16 (53.3)</td>
<td>4 (13.3)</td>
<td>0.003*</td>
</tr>
<tr>
<td>MetS n (%)</td>
<td>16 (53.3)</td>
<td>7 (23.3)</td>
<td>0.034*</td>
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Table 2. Multivariate analysis of risk factors for glycogenic acanthosis

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>WC</td>
<td>0.68 (0.17-2.62)</td>
<td>0.582</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>7.12 (1.89-26.72)</td>
<td>0.004*</td>
</tr>
<tr>
<td>MetS</td>
<td>4.11 (1.04-16.21)</td>
<td>0.043*</td>
</tr>
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Glycogenic acanthosis is a benign, plaque-like elevation of the esophageal mucosa that is rich in glycogen (2). It is regarded as a degenerative process, considering the fact that it is frequently encountered in the fifth and sixth decade and there are increments in the number and size of acanthotic nodules with advancing age (11). Similarly, Tsai et al. (12) found median age of GA patients to be approximately 50 years. In our study, even though our GA patients were older than the control group, the difference was not statistically significant. This finding suggests that there may be other factors effective in the development of GA.

Glycogenic acanthosis has been reported to be more commonly encountered in the upper esophagus than in the lower esophagus, suggesting they might be related with GERD. However, lesions do not usually regress with antireflux treatment putting the proposed relationship in question (4). We did not detect any significant difference in terms of GERD between GA and control groups.

Glycerogen is the storage form of glucose and is mainly deposited in the liver and muscle. It can be synthesized either through direct or indirect pathway. Glycerogen synthesis occurs via the elevation of blood glucose and insulin levels in the postprandial state or decrements of glycogen deposits after exercise (13). Insulin increases glucose influx into the muscle tissue through glucose transporters. It also plays an active role in the activation and dephosphorylation of glycogen synthetase. Insulin exerts mitogenic activity on normal and neoplastic epithelial cells either directly or through insulin-like growth factor pathway (14). The cause of abundant glycogen in hypertrophic squamous epithelium in case of GA might be hyperinsulinemia. The fact that our GA patients had higher fasting insulin and more IR supports our hypothesis.

Insulin resistance is closely related to continuous hyperinsulinemia. Malnutrition and lack of physical exercise play a role in the development of peripheral IR. Peripheral IR is the major determinant of MetS and type 2 diabetes development. IR can be defined as impaired insulin-derived glucose transport in insulin-sensitive tissues, but it causes atherosclerosis and
endothelial dysfunction (15). IR can be found in people with normal plasma glucose level and acts in the development of atherosclerosis and cardiovascular events, independently from other risk factors (16).

Metabolic syndrome is an important risk factor in the development of multiple diseases, mainly type 2 diabetes and coronary heart disease. Multiple groups defined various criteria for MetS definition (17). We preferred the frequently cited NCEP ATP III criteria for MetS definition (9). The proportion of patients with MetS was significantly higher in patients with GA than in controls. IR plays a pivotal role in MetS etiopathogenesis (18). These findings support the hypothesis that IR might be an important factor in GA pathogenesis.

Groups were analyzed in terms of parameters comprising NCEP ATP III criteria of MetS. Among these criteria, WC was significantly higher in GA patients, whereas no significant differences could be detected between the groups regarding other criteria. WC is a significant predictor of IR that can be measured in a simple, non-invasive manner (19). Despite the fact that WC was significantly higher in patients with GA, odds ratio was small. Although WC is among MetS criteria, there is no consensus on the cut-off value (20). If criteria with lower WC values had been accepted, the risk of development of GA could be significantly higher.

There are several limitations of our study (1). Our study group had limited number of patients (2). Although the study showed the close relation of IR with GA, it is insufficient in clearly identifying the cause. Further studies examining the effect of insulin on the esophageal muscle can be helpful in enlightening this issue (3). Proportion of the patients with MetS was significantly higher in GA group, although analyses of parameters comprising MetS criteria did not reach this statistical significance. Further studies evaluating criteria other than NCEP ATP III in patients with GA might shed light on these controversial findings.

In conclusion, we found that there was a significant association between IR, MetS, and the presence of GA. These novel findings require further research, and we believe they may be important enough to change our routine clinical practice.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Yıldırım Beyazıt University School of Medicine (Decision Date: 16.04.2014/Decision No: 69).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.


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