Clinical Evaluation of Acanthosis Nigricans and Its Correlation with Endocrine, Metabolic and Nutritional Factors in Gujarat, India

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Abstract: Acanthosis nigricans (AN) refers to the velvety, black hyperpigmentation in flexures usually on the neck and axillae. AN is associated with multiple endocrinopathies and insulin resistance is reported to be a common denominator among them. The aim of the study was to identify the correlation of metabolic factors (Serum glucose, lipid profile), endocrine factors (TSH, serum insulin), and nutritional factors (vitamin B12, Ferritin) in AN patients in Aravalli district of Gujarat state. A total of Seventeen Patients (11 male and 6 female) were included in the study History, clinical observations, physical parameters, and biochemical tests were noted in AN patients and correlation of some likely factors with AN was explored. The age was 28.41±15.09 years for AN group and 35.45±8.74 years for control group. The mean BMI was found to be higher in AN at 1 % level of significance (P = 0.007) implying that overweight/obesity is associated with AN. The mean TSH value was found to be higher in AN than control group at 5 % level of significance (P = 0.0115) implying that hypothyroidism (elevated TSH value) is associated with AN. The 45.45 % patients had higher blood glucose levels and some of the patients had higher level of insulin. The mean lipid profile, vitamin B12 and serum ferritin were found to be at non-significance level. All statistical tests were performed using graph pad prism software (version 5.0). Positive correlations were observed between higher fasting glucose and hyperinsulinemia with AN and others factors such as metabolic and endocrine like overweight/obesity, hypothyroidism, higher glucose and serum insulin with AN. This implies that AN can serve as a marker for detecting hyperinsulinemia and hypothyroidism. Some of the parameters like, Serum lipid profile, vitamin B12 and ferritin levels could not be correlated to AN. Thus, patients with AN can be targeted for lifestyle and behavioral modifications at an early stage to avoid the serious consequences of AN.

Key Words: Acanthosis Nigricans, Body Mass Index, TSH, Plasma Glucose, Serum Insulin

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INTRODUCTION

Acanthosis nigricans (AN) is a dermatological disorder characterized by dark, thick, velvety, black hyperkeratotic plaques, typically on the intertriginous surfaces and neck. AN is characterized by symmetrical hyperpigmented and hyperkeratotic plaques of the skin mainly affecting the folds of the axillae, groin, and back of the neck. AN is classified into various types such as benign AN, obesity-associated AN, syndromic AN, malignant AN, acral AN, unilateral AN, medication-induced AN, and mixed-type AN. AN is diagnosed clinically and confirmed with skin biopsy, blood tests, endoscopy, or X-rays may be required to eliminate diabetes or cancer. The majority of cases are associated with insulin resistance and/or obesity, screening for diabetes, and measuring glycosylated hemoglobin is also recommended. Several hormonal markers such as thyroid function tests, free testosterone, 17 (OH) progesterone, dehydroepiandrosterone sulfate (DHEAS), cortisol, gonadotropins, prolactin, immunoreactive insulin, and C-peptide levels measurements were made by radioimmunoassays. Associated with malignancy, the recognition of its more common connection to obesity and insulin resistance allows for the diagnosis of related disorders including type 2 diabetes, metabolic syndrome, and polycystic ovary syndrome. The prevalence varies according to age, race, frequency of type, degree of obesity, and concomitant endocrinopathy. The dermatologist has an important role in identifying the subset of obese patients with acanthosis nigricans. Insulin resistance has been associated with the presence of AN. AN is associated with a variety of Endocrine imbalance, including Acromegaly, Cushing’s syndrome, and polycystic ovary. AN is a dermatological marker of hyperinsulinemia and has been linked with metabolic syndrome in adults. BMI was a more sensitive screening tool than acanthosis nigricans alone, or acanthosis nigricans and BMI together for identifying children and youth with insulin resistance (IR) who are at increased risk for type 2 diabetes. Other metabolic conditions such as diabetes mellitus and impaired glucose tolerance and some other clusters of metabolic syndromes such as dyslipidemia, polycystic ovary, and arterial hypertension could also be associated. Investigation of AN are fasting lipoprotein profile, fasting glucose, fasting insulin, hemoglobin, and alanine aminotransferase for obesity-associated AN and radiological investigations (plain radiography, ultrasonography, magnetic resonance imaging/computerized tomography) for malignancy-associated AN. Acanthosis nigricans may also be idiopathic and thyroid dysfunction should be considered. AN occurs frequently in adolescents associated with obesity, a chronic illness that often begins in childhood and has a tremendous impact on an individual’s future health. Patients with AN, especially childhood benign AN, are at risk for obesity, hypertension, hyperinsulinemia, IR, and type 2 diabetes and AN may be used as a reliable index of IR. The prevalence of AN in non-select populations varies from 7 to 74%, according to age, race, frequency of type, and degree of obesity and comorbidity with endocrinopathy. Metabolic syndrome (MS) refers to a clustering of metabolic risk factors including central obesity, glucose intolerance, hyperinsulinemia, low high-density lipoprotein-cholesterol (HDL-C), high triglycerides (TGs), and hypertension. Obese adolescents at risk of type 2 diabetes were identified with a low or borderline B12 status. All these studies confirmed the role of various metabolites, endocrines and nutrients factors in the development of AN. So detailed study of these parameters in AN Patients are needed for the hour. So far, the investigation about these factors with AN in Aravalli district of Gujarat state in India has not been conducted. So, in this present study, our research group tried to identify the association and the role of metabolic factors (Serum glucose, insulin resistance, lipid profile), endocrine factors (TSH, serum insulin), and nutritional factors (vitamin B12, Ferritin) in AN patient in rural area of the Aravalli district. This study has been conducted to investigate the etiology, pathogenesis, and clinical profile in patients with AN.

MATERIALS AND METHODS

1. Participates

It was a cross-sectional hospital-based study. Seventeen patients of AN attending the dermatology OPD at Samarpan medical research organization, Modasa, Gujarat, India, and twenty-two healthy volunteers (Age from 25-50 years) were also included in this study as normal control. The Study was done from 1st November 2016 to 30th March 2018. Clinical-epidemiological data regarding the patients were noted in the case record form. Patients were included in this study after receiving informed written consent. Patients were diagnosed clinically by a dermatologist. All the patients included in this study were 10-60 years of age. Required permission for carrying out the study was obtained from Sarvajanik clinical research ethics committee, Mehsana (Ref. SCREC/2019-20/07). All participation was voluntary. The study was conducted by declaration of Helsinki.

2. Criteria and sites for Acanthosis nigricans

Five anatomical sites were chosen to assess the presence and extent of AN: the neck, axilla, knuckles, elbows, and knees. All these criteria were determined by a dermatologist.

2.1. Inclusion criteria

1. To Sign an informed consent form.
2. 10 – 60 year of old patients were included.
3. No systemic diseases
4. Both male and female patients

2.2. Exclusion criteria

1. Patients not willing for the study
2. Patients with acute and chronic illness
3. Participants with a history of severe systemic disease
4. Pregnant and lactating women
5. Patients on medications which can cause drug induced acanthosis nigricans (nicotinic acid, fusidic acid, stilbestrol in young males, triazinate, folic acid antagonists, antituboviral drugs, insulin, pituitary extract, systemic corticosteroids, diethylstilbestrol, oral contraceptives, methyltestosterone and growth hormone therapy).

2.3. Study procedure

All patients (11 male and 6 female) underwent a detailed physical examination including height (in meter) and weight (in kg). From these data, body mass index (BMI) was calculated. The BMI was calculated by weight in kilograms divided by height in meters square (kg/m²). Several researchers described AN based-on body mass index ratio (BMI). BMI was classified as per the World Health Organization criteria. (Table I)
Other clinical markers for AN were tested from a fasting blood sample. The metabolic factors like, blood glucose and lipid profile (Total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol), Endocrine factors like thyroid stimulating hormone (TSH) and serum insulin, and nutritional factors like vitamin B12 and ferritin were estimated in Satyam laboratory, Modasa, India.

### 3. STATISTICAL ANALYSIS

All statistical tests were performed using GraphPad Prism 5.0 version software, and quantitative data were expressed as mean ± standard deviation (± SD) and count data as the number of columns (n). Students unpaired ‘t’ test was used to establish correlation between different risk factors and AN at 1 % and 5 % significance level (P<0.01 and P < 0.05). ‘t’ value was also calculated using a statistical formula and compared with the tabulated ‘t’ value for accepting or rejecting the null hypothesis.

### 3. RESULTS AND DISCUSSION

The purpose of cross-section and hospital-based study was to evaluate the occurrence of acanthosis nigricans in a rural area of north Gujarat, India and its association with metabolic, endocrine and nutritional factors and their causal relationship.

#### 3.1 Clinico Epidemiological features

#### 3.1.1 Age and sex

Total seventeen patients with AN were included in this study that also covered 11 male (64.70 %) and 6 Females (35.30 %).

<table>
<thead>
<tr>
<th>AGE (In year)</th>
<th>NUMBER OF PATIENTS</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>00</td>
<td>00</td>
</tr>
<tr>
<td>11-20</td>
<td>08</td>
<td>47.05</td>
</tr>
<tr>
<td>21-30</td>
<td>01</td>
<td>5.88</td>
</tr>
<tr>
<td>31-40</td>
<td>04</td>
<td>23.52</td>
</tr>
<tr>
<td>41-50</td>
<td>03</td>
<td>17.64</td>
</tr>
<tr>
<td>&gt;50</td>
<td>01</td>
<td>5.88</td>
</tr>
<tr>
<td>TOTAL</td>
<td>17</td>
<td>100</td>
</tr>
</tbody>
</table>

Their age ranged from 11-50 years with a mean ± standard deviation of 28.41±15.09 years. The patients were distributed in different age groups ranging from 11 to 50 years. In this 47.05 % of patients in 11-20 years of age, 5.88 % of patients in 21-30 years of age, 23.52 % patients in 31-40 years of age, 17.64 % of patients in 41-50 years of age, and 5.88 % patients is more than 50 year of age with a mean of 28.41±15.09 (Table 2). In the normal control group (17 (77.27%) Male and 5 (22.72%) female), the age ranged from 25-45 years with a mean ± standard deviation of 35.45±8.744 years. Higher prevalence of AN was found in the age group of 11-20 years and this might affect the psychological status and quality of life in adults.

#### 3.1.2 Sites

In this study, the neck was the most common site involved, followed by the axilla, face, and groin. Other sites such as the antecubital fossa, knuckles, and sub mammary areas were also involved (Figure 1).

#### 3.1.3. Body mass index (BMI)

The mean BMI was found to be 27.54 ± 3.74 kg/m² in AN.
Table 3: Body mass index of AN and control group

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>ACANTHOSIS NIGRICANS (N=17)</th>
<th>CONTROL (N=22)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 18.5</td>
<td>00 % 00</td>
<td>01 % 4.54  %</td>
<td>0.0070**</td>
</tr>
<tr>
<td>18.5-24.9</td>
<td>05 29.41 %</td>
<td>13 59.09 %</td>
<td></td>
</tr>
<tr>
<td>25-29.9</td>
<td>08 47.05 %</td>
<td>07 31.81 %</td>
<td></td>
</tr>
<tr>
<td>30-34.9</td>
<td>02 11.76 %</td>
<td>02 9.09 %</td>
<td></td>
</tr>
<tr>
<td>MORE THAN 35</td>
<td>02 11.76 %</td>
<td>00 00</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>17 100 %</td>
<td>22 100 %</td>
<td></td>
</tr>
</tbody>
</table>

The values are Mean ± SD of BMI (P < 0.05), * = less significant, *** = Highly significance, ** = Moderate significance. The mean values are significantly different from the control group 23.78 ± 4.30 at 1 % level of significance (P = 0.007). This is also indicated by rejection of the null hypothesis where calculated 't' value (2.7912) is higher than tabulated 't' value (2.234) (tC > tT). This implies that overweight/obesity is associated with AN. Out of the AN group, 70.57% were found to be overweight/obese as against 40% seen in the control group (Table 3). The positive correlation between obesity & AN observed in the study is in agreement with published data. The prevalence of overweight is a greater risk factor for the development of AN.24 Pankaj et al.25 has also reported the presence of obesity induced AN or pseudo-AN in 70%, syndromic AN in 23.4%, and malignant AN in 6.6% of Indian patients.

3.1.4. Lipid profile

Table 4: Lipid profile of AN and control group

<table>
<thead>
<tr>
<th>LIPID PROFILE</th>
<th>ACANTHOSIS NIGRICANS (N=17)</th>
<th>CONTROL (N=22)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL CHOLESTEROL (mg/dl)</td>
<td>150±29.86</td>
<td>158.2±27.30</td>
<td>0.4098 ns</td>
</tr>
<tr>
<td>TRIGLYCERIDES (mg/dl)</td>
<td>112.1±39.77</td>
<td>121.3±48.72</td>
<td>0.4601 ns</td>
</tr>
<tr>
<td>HDL CHOLESTEROL (mg/dl)</td>
<td>46.98±13.77</td>
<td>43.38±3.50</td>
<td>0.2460 ns</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>82.04±24.21</td>
<td>90.51±26.92</td>
<td>0.4269 ns</td>
</tr>
<tr>
<td>VLDL (mg/dl)</td>
<td>21.91±8.973</td>
<td>24.26±9.743</td>
<td>0.4539 ns</td>
</tr>
<tr>
<td>LDL/HDL</td>
<td>2.043 ± 0.506</td>
<td>2.109 ± 0.659</td>
<td>0.7395 ns</td>
</tr>
<tr>
<td>TOTAL/HDL</td>
<td>38.27 ± 139</td>
<td>36.84 ± 0.746</td>
<td>0.6728 ns</td>
</tr>
<tr>
<td>TOTAL LIPIDS</td>
<td>563.0 ± 169.0</td>
<td>614.4 ± 86.60</td>
<td>0.0929 ns</td>
</tr>
</tbody>
</table>

The values are Mean ± SD (P < 0.05), ns – non-significant. The mean lipid profile was not found to be different in control and AN group at 5 % significance level. It was unexpectedly a bit lower than the control group except HDL. The P value of total lipid 0.929 and higher values for individual lipids (Table 4). This implies that lipid profile was not elevated in AN group. The results are not in agreements with published literature. The previous study has also shown that TSH levels are slightly increased in obesity and are associated with BMI26.

3.1.5. Thyroid stimulating hormones (TSH)

The mean TSH was found to be 2.99 ± 2.42 miu/l in AN.

Table 5: TSH level of AN group and control group

<table>
<thead>
<tr>
<th>TSH (miu/l)</th>
<th>ACANTHOSIS NIGRICANS (n=15)</th>
<th>CONTROL (n=22)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>2.99 ± 2.424</td>
<td>1.515 ± 0.1750</td>
<td>0.0115*</td>
</tr>
</tbody>
</table>

The values are Mean ± SD of TSH (P < 0.05), * = less significant. The mean values were significantly higher than control group 1.54 ± 0.17 at 5 % level of significance (P = 0.0115). This implies that hypothyroidism (elevated TSH value) is associated with AN (Table 5). The positive correlation between hypothyroidism along with obesity has also been reported in literature. AN is associated with multiple endocrinopathies and insulin resistance is reported to be a common denominator among them. The mechanism of insulin resistance has been reported to be a post receptor binding defect or structure abnormality in circulating insulin.
Hyperinsulinemia is a regular correlate of skin disorders. It has also been reported that Hypothyroidism may be associated with AN and that treatment of hypothyroidism does not resolve hyperinsulinemia or AN. Literature also reports that obese women are more prone to AN than men. Higher TSH value has been proposed to be protective factors in obese women that improve fat distribution in obesity.

### 3.1.6. Fasting blood glucose and insulin

The mean fasting blood glucose was found to be $93.33 \pm 11.83$ mg/dl.

<table>
<thead>
<tr>
<th>Fasting Blood glucose</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Blood glucose level (&lt; 99 mg/dl)</td>
<td>06 (54.54 %)</td>
</tr>
<tr>
<td>Higher Blood glucose level (&gt; 99 mg/ml)</td>
<td>05 (45.45 %)</td>
</tr>
<tr>
<td>Total</td>
<td>11 (100%)</td>
</tr>
</tbody>
</table>

**Table 6** Blood glucose level

In 6 out of 11 cases, the FPG values were normal (less than 100 mg/dl) and in 5 out of 11 cases, FPG values were above normal (Table 6). Out of 5 patients with elevated FPG, 4 were tested for fasting levels of insulin and 4 out of 4 showed hyperinsulinemia (Table 7). The positive correlation between fasting glucose/hyperinsulinemia and AN group observed in the study are in agreements with published data. A directly proportional relationship between serum insulin levels and AN severity has been documented.

Native Americans were reported to have higher BMI and fasting insulin levels, and lower HDL-Cholesterol in cases with those with less severe AN.

### 3.1.7. Serum vitamin B12 and ferritin

The serum vitamin B12 level was observed in four patients of AN (Mean ± SD, 421± 131.6 pg/ml). All values are in normal range (211-911 pg/ml). The serum ferritin level observed in two patients of AN (Mean ± SD, 41.25 ± 2.33 ng/ml). Both values are in normal range (30-450 ng/ml). No correlation was observed between vitamin B12 or ferritin levels with AN.
4. **CONCLUSION**

Positive correlations were found between several metabolic and endocrine factors like overweight/obesity, hypothyroidism (elevated TSH value), higher serum glucose and serum insulin and AN. This implies that AN can serve as a marker for detecting hyperinsulinemia, hypothyroidism and related conditions. No correlation was found between lipid profile, vitamin B12 and ferritin with AN. It is important to identify persons at high risk of early detection, regular screening and management can help to decrease the risk of AN. The present study has showed poor awareness of AN in rural population. Thus, patients with AN can be targeted for lifestyle and behavioral modifications at an early stage to avoid the serious consequences of AN.

5. **Limitation of study**

The number of the patients for the study is very small and therefore it is not possible to get a solid conclusion but contributes to the objective of our study and helps further research for better AN therapy.

6. **AUTHORS CONTRIBUTION STATEMENT**

Dr. Timir Y. Mehta, consultant to patients and diagnosed Acanthosis nigricans patients. Dr. J. B. Dave and Mr. Sohan A. Patel collected and analyzed patient’s data and necessary inputs were given towards the designing of the manuscript. All authors discussed the methodology and results and contributed to the final manuscript.

7. **ACKNOWLEDGEMENTS**

The authors thanked the patients for the cooperation in our study.

8. **CONFLICT OF INTEREST**

Conflict of interest declared none.

9. **REFERENCES**


10. Corina D, Monica M, Adela CE, Teodora C, Camelia D, Sabău I, Ioana M. The role of acanthosis nigricans in identifying clinical and metabolic features of the


