

# Acanthosis Nigricans and Skin Tags as Markers of Insulin Resistance in Non-Diabetic Obese Individuals

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## ABSTRACT

### BACKGROUND

Insulin resistance represents an insensitivity of peripheral tissues to the effect of insulin. Obese individuals with insulin resistance have shown increased prevalence of abnormalities of glucose metabolism. Given that insulin resistance represents an important risk factor for development of type 2 diabetes. Identification of adults with insulin resistance has been proposed as a strategy for identifying high risk adult for targeted diabetes prevention intervention.

### METHODS

We performed a cross sectional observational study on obese patients between 20 and 50 years of age attending the Outpatient Department of General Medicine at Government Vellore Medical College and Hospital for minor ailments during the period July 2017 to December 2017.

### RESULTS

Of the 100 obese individuals, acanthosis nigricans was present in about 61 individuals. There is an increase in insulin resistance with an increase in the class of acanthosis nigricans. Skin tags are present in about 60 individuals. Individuals with skin tags have significantly high HOMA-IR when compared with that of individuals without skin tags.

### CONCLUSIONS

Acanthosis nigricans and skin tags are markers of insulin resistance and insulin resistance increases quantitatively with increasing grades of acanthosis nigricans.

### KEYWORDS

Insulin Resistance, Acanthosis Nigricans, Skin Tags

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## BACKGROUND

Obesity is one of the most important, widespread, but still neglected, health issues of the public. It is significantly being associated with increase in morbidity and mortality. It is an imminent overwhelming problem seen in both well developed and in developing countries.<sup>1</sup> In India obesity is emerging as an important health various parts of the country. Almost 30-65% of the adults are either overweight or obese or have abdominal obesity.<sup>2,3</sup> India ranks 3rd only next to China and USA in the net number of obese populations.

Insulin resistance is a condition in which there is a derangement of insulin mediated glucose uptake and glucose utilisation in peripheral tissues. Obesity, especially visceral fat accumulation is mainly associated with insulin resistance (IR). Insulin resistance is considered to have a crucial role in the pathogenesis of the cardiovascular dysmetabolic syndrome, which is characterized by a constellation of factors like dyslipidaemia, hyperuricemia, hypertension and impaired glucose tolerance and is also a precursor of type 2 DM.<sup>2</sup> Insulin resistance (IR) has been proposed as a primary cause and as a sort of final common pathway for negative environmental factors, which interact with the individual genetic background to cause metabolic and hemodynamic alterations and is associated with inflammation.<sup>4,5</sup> Our study aims at identifying the prevalence of insulin resistance among obese population. The diagnosis of IR which is a pre diabetic condition will be useful to prevent the further increase in prevalence of diabetes and other morbidity.

We wanted to study acanthosis nigricans and skin tags as a marker of insulin resistance among non-diabetic obese individuals.

## METHODS

This is a cross-sectional observational study conducted among obese patients attending the outpatient department of Department of General Medicine at Government Vellore Medical College and Hospital for minor ailments, from July 2017 to December 2017. Convenient sampling technique was used. Obese individuals between 20 years and 50 years of age who attended the OPD for minor ailments were included in the study.

### Exclusion Criteria

- Patients who were known cases of diabetes and on treatment.
- Obese patients suffering from one or more disorders like coronary artery disease, cerebrovascular accident, hepatic dysfunction, renal dysfunction and endocrine abnormalities.
- Patients suffering from serious illness.
- Pregnant women.
- Patients who are on steroids or other medication which would likely to have influence on BMI.

- Patients who do not give consent to participate in the study.

A total of 100 obese patients who satisfied the above criteria was studied and analysed. Obesity is defined as BMI  $\geq 25$  according to WHO definition of obesity in Asian population. Body mass index (BMI) is a simple index of weight for height that is commonly used to classify overweight and obesity in adult population. It is defined as a person's weight in kilograms divided by square of his height in meters ( $\text{Kg}/\text{m}^2$ ). For measuring the height, patients were made to stand erect with-out slippers or shoes by facing back of their body over the wall and marking the point overhead with a pencil. The subjects are instructed to move and the distance on the wall was measured with an inch tape in 'm'. For measuring weight, the patients are instructed to stand-erect over the weighing scale without slippers and with minimal clothing and the readings were noted in kilograms. Then the BMI was calculated according to the formula and patients whose BMI was  $\geq 25$  were considered as cases.

Patients underwent skin examination which was aimed to identify the presence and degree of acanthosis nigricans (AN) in axilla and other regions and presence and number of skin tags. Patients with  $> 5$  skin tags are considered as positive. Acanthosis was graded based on standard scale of 0-4 as described by Burke et al. Neck grading 0: Not visible, grade 1 Present: clearly present on close visual inspection, not visible to the casual observer, extent not measurable. Grade 2, Mild: limited to the base of the skull, does not extend to the lateral margin of the neck (usually, 3 inches in breadth), grade 3: extending to the lateral margins, not visible from the front, and grade 4: extending anteriorly. Acanthosis axilla grading 0: Absent, grade 1: Present on close visual examination, grade 2: Localized to the central portion of axilla, grade 3: involving the entire axilla, grade 4: extending beyond axilla.

Around 5 ml of venous blood was collected after overnight fasting for 12 hours duration. Fasting plasma glucose was measured using glucose oxidase - peroxidase method. Serum insulin was measured by using ELISA (Monobind Inc USA). HOMA-IR (Homeostasis Assessment Model) for insulin resistance is calculated by using the formula

$$\text{HOMA-IR} = \frac{\text{fasting insulin (U/l)} \times \text{fasting glucose (mg/dl)}}{405}$$

A cut off value of 2.5 was taken to classify the patients into groups. Patients having HOMA-IR  $\geq 2.5$  were considered to have insulin resistance and those with HOMA-IR value less  $< 2.5$  were considered as not having insulin resistance.

### Statistical Analysis

The prevalence of Insulin resistance in obese patients was calculated in percentage using HOMA-IR  $> 2.5$  as a cut-off. To study the influence of Acanthosis nigricans (positive vs. negative), the mean HOMA-IR of the positive group and

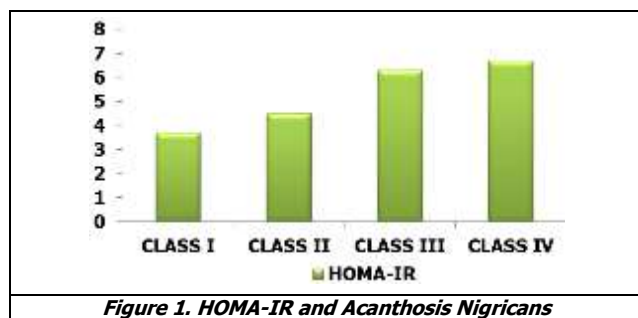
negative group are compared for statistical significance using unpaired students t - test. To analyse the association between severity of acanthosis nigricans and insulin resistance the mean HOMA IR of individuals with the 4 grades of acanthosis nigricans are calculated separately and are compared for statistical significance using ANOVA test. All the statistical analyses were done using the Statistical Package for Social sciences software version 17.

**RESULTS**

Of the 100 obese individuals, acanthosis nigricans was present in about 61 individuals. The acanthosis nigricans present in the neck or axilla is graded into four classes based on Burk et al criteria. The highest of the grade (Neck AN or Axillary AN) was taken and the individuals were grouped into 4 classes. The mean HOMA-IR of each group was calculated and was compared for statistical significance by ANOVA. There is an increase in insulin resistance with an increase in the class of acanthosis nigricans. The mean HOMA-IR of those without acanthosis nigricans was also compared with that of those with acanthosis nigricans.

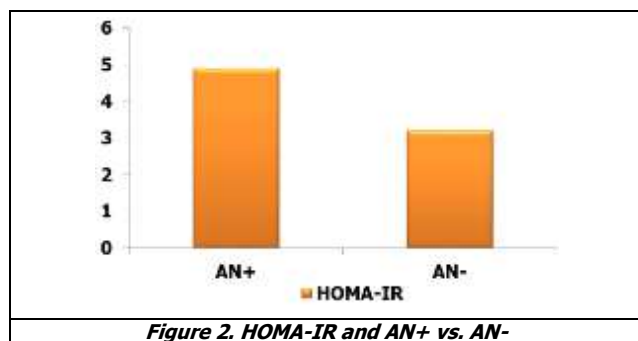
| AN Class  | N  | Mean HOMA-IR  | p-value |
|-----------|----|---------------|---------|
| Grade I   | 21 | 3.706 ± 2.09  | 0.0008  |
| Grade II  | 18 | 4.453 ± 0.498 |         |
| Grade III | 16 | 6.308 ± 3.06  |         |
| Grade IV  | 6  | 6.682 ± 3.80  |         |

**Table 1. Mean HOMA-IR and acanthosis nigricans**



|              | AN+ (n=61)  | AN- (n=39)  | p-value |
|--------------|-------------|-------------|---------|
| Mean HOMA-IR | 4.91 ± 2.52 | 3.15 ± 1.44 | <0.0001 |

**Table 2. HOMA-IR of AN vs. NON-AN**

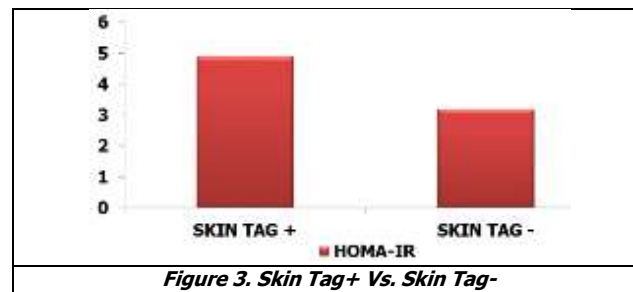


Skin tags are present in about 60 individuals. The mean HOMA-IR of the individuals with skin tags was compared

with those without skin tags. Individuals with skin tags has significant high HOMA-IR when compared with that of individuals without skin tags.

|              | SKIN Tags + N=60 | SKIN Tags - N=40 | p-value |
|--------------|------------------|------------------|---------|
| Mean HOMA-IR | 4.928 ± 2.541    | 3.162 ± 1.439    | <0.0001 |

**Table 3. HOMA-IR and Skin Tag**



**DISCUSSION**

**Acanthosis Nigricans**

Of the 100 obese individuals, acanthosis nigricans was present in about 61 individuals. The acanthosis nigricans present in the neck or axilla is graded into four classes based on Burk et al criteria.

**Neck Grading**

- Grade I- Visible only on close inspection.
- Grade II -Confined to the base of the skull.
- Grade III- Extending laterally up to the posterior border of the sternocleidomastoid.
- Grade IV- Visible (encircling the neck).

**Axilla Grading**

- Grade I- Present on close visual examination.
- Grade II- Localized to the central portion of axilla.
- Grade III- involving the entire axilla.
- Grade IV- extending beyond axilla.

The mean HOMA IR of grade I - IV were 3.706 ± 2.09, 4.453 ± 0.498, 6.308 ± 3.06, 6.682 ± 3.80 when analysed by ANOVA showed a significant increase in the insulin resistance. (p= 0.008). In a study by Venkataswamy et al<sup>6</sup> showed an increased insulin resistance was associated with both neck and axillary acanthosis nigricans. The prevalence of Acanthosis nigricans in general populations in a study by Stuart et al<sup>7,8</sup> varies from 7% to 74%. It varies according to age of the individual, race, obesity degree and associated endocrinopathy. Stoddart and Kong<sup>9,10</sup> showed Acanthosis nigricans is an independent risk for with insulin resistance and for hyperinsulinemia, with the development of diabetes.

Many studies like Yamazaki et al<sup>11</sup> demonstrated the association between acanthosis nigricans and insulin resistance. The researchers found a positive association between Acanthosis nigricans and insulin resistance in Japanese children. Stuart et al studied 89 African Americans with Acanthosis nigricans and observed 21.3% prevalence of type 2 diabetes among them. A study of Burke et al<sup>12</sup> also

observed that increased levels of fasting insulin and high insulin resistance in patients with Acanthosis nigricans. Sadeghian et al, in his study in obese women with acanthosis nigricans and without Acanthosis nigricans for the presence of insulin resistance, and the Acanthosis nigricans is a marker for insulin resistance. The mean HOMA-IR was  $3.5 \pm 1.9$  for those with Acanthosis nigricans and  $2.6 \pm 0.9$  for patients without acanthosis nigricans, (p value is  $<0.05$ ).

Copeland et al.<sup>13</sup> studied the association between acanthosis nigricans and insulin resistance in children and found that the severity of acanthosis nigricans correlated with the HOMA IR values. He also observed that acanthosis nigricans showed to be an independent risk factor for insulin resistance. Wiegand et al.<sup>14</sup> observed obese children and adolescents to conclude that the presence of acanthosis nigricans is a risk for high HOMA-IR values. The mechanism by which insulin resistance causes acanthosis nigricans is by its mitogenic effects. The compensatory hyperinsulinemia caused by insulin resistance causes insulin to act on with insulin like growth factor receptors (IGF-1). This triggers the proliferation of keratinocytes and fibroblasts. Acanthosis nigricans is caused by the factors which stimulate epidermal keratinocyte growth and proliferation of dermal fibroblast. The epidermal growth factor is an important mediator of proliferation of keratinocyte. EGF receptor and Epidermal Growth Factor are found in excessive amounts in the epidermis which is hyperproliferative. EGF act on insulin-like growth factor receptor when present in high doses and causes keratinocyte proliferation. The IGF-1 receptor present in the basal layer of the epidermis, suggests that there is a role of IGF-1 and EGF in the regulation of growth of epidermis and their role in the pathogenesis of acanthosis nigricans in IR individuals.

### Skin Tags

Skin tags pedunculated tumours, they are soft in consistency.<sup>15-17</sup> they usually affect middle aged individuals and elderly individuals. They are usually located in the neck, groin and the armpits. They are skin coloured and vary in size from 1 mm to 1 cm in diameter.<sup>18</sup> histologically, they have lost collagen fibers and blood capillaries which are dilated.<sup>19</sup> The frequency increases in general population above 40 years of age. In the general population about 20 to 25% persons may have skin tags.<sup>20</sup> The mean HOMA IR in patients with skin tags in our study is  $4.928 \pm 2.541$  and without skin tags is  $3.162 \pm 1.439$  showing a significant difference ( $p < 0.0001$ ) Banik states, though skin tags are present in 46% of the general population only 14% have more than eight lesions in the body. The fibroblasts proliferation of that occurs due to hyperinsulinemia, causes skin tags. This is due to of the insulin-like growth factor receptors activation. Skin tags are related to serum fasting insulin levels. Many studies relate insulin resistance, serum IGF - 1 levels and skin tags. In a study by Jowkar et al., serum insulin levels in patients with skin tags are significantly higher than in control individuals. This suggests the importance of insulin resistance in the pathogenesis of skin tags. As in acanthosis nigricans, insulin is not the only

one mediator in the pathogenesis of skin tags, but it is the most important factor of these.<sup>21</sup> Rasi et al. showed that patients with more than 30 skin tags in the body are at 52% risk of developing DM.<sup>22</sup> there was no correlation found between the location of skin tags and IR. One exception for this is the skin tags in the infra-mammary region in women. This is associated with IR.<sup>21</sup> Multiple ( $>8$  lesions) skin tags are more sensitive than Acanthosis nigricans when finding insulin resistance, but the specificity is lesser. Tamega et al. found an independent association between skin tags and insulin resistance. Presence of  $>5$  skin tags showed an increase of 1.4 units in the HOMA-IR. The association of skin tags with Body mass index and increased triglyceride found in this study further strengthens the association between skin tags and insulin resistance.<sup>23</sup>

## CONCLUSIONS

Acanthosis nigricans and skin tags are markers of insulin resistance and insulin resistance increases quantitatively with increasing grades of acanthosis nigricans.

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