Association of Acanthosis Nigricans and Acrochordon with Insulin Resistance: A Cross-Sectional Hospital-Based Study from North India

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Abstract

Background: Insulin resistance (IR) is a pre-diabetic condition and has been reported in patients with acanthosis nigricans (AN) and acrochordon. AN and acrochordon are claimed to be cutaneous markers of IR. Aim: The purpose of this paper was to study the association of AN and acrochordon with IR. Methods: It was a cross-sectional hospital-based study. Both groups were assessed for IR by using homeostatic model assessment of insulin resistance (HOMA-IR) formula. Results: A total of 70 cases and an equal number of controls were studied. IR was observed more in cases (41.4%) compared to controls (17.1%) (P < 0.01). Mean HOMA-IR value was also significantly higher in cases (4.32 ± 4.44) compared to controls (2.27 ± 0.90) (P < 0.05). Limitations: Low number of cases and controls were taken in the study. Association with hyperlipidemia and metabolic syndrome was not elicited. Conclusions: AN and acrochordons were found to be associated with IR.

Key Words: Acanthosis nigricans, acrochordons, homeostatic model assessment of insulin resistance, insulin resistance

Introduction

Acanthosis nigricans (AN) is a dermatosis characterized by velvety, papillomatous, brownish-black, hyperkeratotic plaques, typically on the intertriginous surfaces and neck. The term AN was originally proposed by Unna, but the first case was described by Pollitzer and Janovsky in 1891. The prevalence varies from 7% to 74%, according to age, race, frequency of type, degree of obesity, and concomitant endocrinopathy. It is most common in Native Americans, followed by African Americans, Hispanics, and Caucasians. African Americans are 25 times more likely to have AN than patients of European descent. Its more common connection to obesity and insulin resistance (IR) allows for diagnosis of related disorders including type 2 diabetes, the metabolic syndrome, and polycystic ovary syndrome. Early recognition of these conditions is essential for the prevention of disease progression.

Acrochordons (skin tags) are small flesh colored to dark brown sessile or pedunculated papillomas that commonly occur on the neck, in the axillae and on the eyelids, and manifest less often on the trunk and in the groin. They have the same incidence in both sexes.

IR is a metabolic disorder in which target cells fail to respond to normal levels of circulating insulin, which results in compensatory hyperinsulinemia in an attempt to obtain an appropriate physiological response. As obesity and diabetes reach epidemic proportions in the developed world, the role of IR and its consequences are gaining prominence. At higher concentrations, however, insulin can exert more potent growth-promoting effects through binding to insulin-like growth factor 1 receptors (IGF-1Rs) that are similar in size and subunit structure to insulin receptors, but bind IGF-1 with 100- to 1000-fold greater affinity than insulin. The binding stimulates proliferation of keratinocytes and fibroblasts, leading to AN.

At present, the prevalence of diabetes is rising worldwide including our country. AN and acrochordons may be taken as a cutaneous marker of IR which is important in identifying individuals at risk for type 2 diabetes, allowing the doctor to advise a different lifestyle, thus reducing the risk of developing diabetes.

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Materials and Methods

Study design
It was a cross-sectional hospital-based study. Patients attending skin outpatient department of a tertiary health care center in north India with clinically diagnosed AN and acrochordons were enrolled in the study. Study duration was from 1st November 2016 to 30th March 2018. Age- and sex-matched equal number of controls were taken, which were cases of scabies. After taking informed consent, clinico-epidemiological data regarding the patients were noted in the case record form. Other relevant data including site, number of acrochordons, duration, and history of concomitant medications, weight, height, waist circumference were also noted. Body mass index (BMI) was calculated as weight (kg)/height² (m²). Patients were taken as obese when BMI ≥30 kg/m². Waist circumference was determined by placing a measuring tape at the level of the uppermost part of the hip bone around the abdomen (ensuring that the tape was horizontal). Patients already receiving any antidiabetic drugs, with already removed acrochordons, with pregnancy or lactation, with a known case of acne, psoriasis, polycystic ovarian syndrome were excluded from the study.

Assessment of insulin resistance
Assessment of IR was done by using Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) method. The calculation for IR was done by multiplying the amount of glucose (in mmol) by the amount of insulin (in μIU/mL) and dividing the result by 22.5 [HOMA-IR = glucose (mmol) × insulin (μIU/mL) ÷ 22.5]. IR was diagnosed when the result was greater than 2.71. In women, IR was considered when the result exceeded the 75th percentile (1.80).

Morning venous blood samples were collected into three vacutainer, red, grey, and purple, from all the patients after 10 to 12 hours of the fasting period. For fasting glucose, samples were sent to biochemistry laboratory. For the fasting insulin level, serum was separated from blood in red vacutainer by centrifuging the blood samples.

Estimation of fasting insulin level
The quantitative estimation of fasting insulin was done by the ELISA technique by Insulin ELISA Kit based on simultaneous binding of human insulin by two monoclonal antibodies, one immobilized on microwell plates and the other conjugates with horse radish peroxidase.

A calibration curve was then generated by plotting the absorbance versus respective insulin concentration for each calibrator. And the concentration of insulin was directly determined from that curve.

Sample size
By expecting an error of 5% and a power of 80% and with subject and control in 1:1 ratio, as per data in Sadeghian et al.[12] the required sample came out to be 140, 70 in each arm. Eligible cases aged 10-70 years with AN and/or acrochordons ≥5 who agreed to participate and themselves or their guardians signed the informed consent were enrolled. Grading of AN was done as per “The Burke’s quantitative scale for acanthosis nigricans”.[2]

Statistical analysis
The data obtained were analyzed using SPSS (statistical package for social sciences) trial version 17. The data were presented in terms of mean, standard deviation, and percentage. To assess the association between categorical variables Chi-Square test was used. Student’s t-test was used with continuous data with normal distribution and Mann-Whitney U test was used in the case of continuous data with non-normal distribution. P < 0.05 was taken as statistically significant.

Results
A total of 70 patients of AN and acrochordons and 70 patients as control were enrolled in the study. Control group consisted of patients of scabies without AN and acrochordons.

The characteristics of the cases and controls have been depicted in Table 1. In both cases and controls, the majority of the patients were of the age group of 31 to 50 years [Table 2]. Comparison of various parameters between cases and controls are given in Table 3. Various parameters including components of IR were significantly higher in cases in comparison to that in controls except for waist circumference. Difference in weight, BMI, fasting glucose, fasting insulin, and mean HOMA-IR were highly significant, while height and HbA1c were not significant.

In our study, IR was present significantly more in cases of AN and acrochordons. In cases, IR was seen in 41.4% patients while in controls it was present only in 17.1% patients (P < 0.05) with an odds ratio of 3.42. On comparing patients with AN (that is excluding the patients who had acrochordons only) to the controls, both IR and mean HOMA-IR were higher in cases, and this difference was statistically significant.

In patients with acrochordons (excluding the patients who had acanthosis nigricans only), both IR and mean HOMA-IR were higher in comparison to those of controls, and these differences were statistically significant (P < 0.05). On comparing mild grade AN to moderate to severe grade AN, difference in weight and BMI was more in a higher grade of AN, and the difference was statistically significant (P < 0.05).
Rest other parameters were also more in higher grade AN but differences were not statistically significant [Table 4]. We arbitrarily divided cases into two age groups (age <40 year and ≥40 year) and on comparing the incidence of IR were more in ≥40 year group but not statistically significant. On comparing site involvement in AN group and acrochordons group, both groups showed more frequency of IR on multiple sites involvement than single site involvement but again not statistically significant.

**Discussion**

AN and acrochordons are the cutaneous signs suggestive of IR. IR is one of the mechanisms involved in the pathogenesis of diabetes mellitus type-2 (DM Type-2) and DM Type-2 is causatively associated with hyperinsulinemia.
India has one of the highest prevalence of DM Type-2 in the world. The number is expected to be about 57.2 million by the year 2025. Recent studies in India show an increasing trend in DM Type-2 in adolescents and children. The percentage of adult urban subjects affected with diabetes has more than doubled from 1984 (5.2%) to 2000 (13.9%). In our study, the majority of patients of AN and acrochordon were from urban habitat (77.14%) and they also had more IR (46.3%) (P < 0.05).

There is a paucity of studies from India on the prevalence of IR in a patient with AN and acrochordons, especially in north Indian population. There is one study from north India in which only 30 patients with AN were studied without controls and hyperinsulinemia were detected in 40% of patients. In our study, we observed a higher prevalence of IR in AN and acrochordon patients (41.4%) compared to controls (17.1%) (OR = 3.42) (P < 0.05).

Kerala with children aged between 10 and 17 years and showed that the most sensitive physical marker of IR was AN (90%) and the most specific was BMI (91%). In a study by Verma et al., 102 patients with facial AN were taken in which 79% patients had IR. In Venkatswami et al. study, among 300 patients of AN aged 18-55 years, 94 (31.3%) had IR.

Similarly, Stoddart et al. and Kong et al. recognized AN as an independent risk factor associated with hyperinsulinemia, with the development of DM. Stoddart et al. showed that children with a family history of type 2 diabetes presented AN more often and that acanthosis was more frequent in patients with hypertension and high BMI. Sadeghian et al. investigated the presence of IR in obese women with and without AN, and the skin lesions proved to be a marker for IR. They studied 32 patients with AN and 34 patients without AN had IR in 15.6% and 0%, respectively (P < 0.05). The mean value of HOMA-IR was 3.5 ± 1.9 and 2.6 ± 0.9 µmol/ml in patients with and without AN, respectively (P < 0.05).

In this study also, on comparing patients with AN (that is excluding the patients who had acrochordon only) to controls both IR and mean HOMA-IR were higher in cases, and this difference was statistically significant (P < 0.05).

### Table 3: Different parameters in cases and controls

| Parameter               | Cases     | Controls   | Remarks, t, P  |
|-------------------------|-----------|------------|----------------|
| Weight (kg)             | 71.74±11.20 | 63.85±10.44 | t=4.307, P<0.001 |
| Height (meter)          | 1.61±0.08 | 1.58±0.07 | t=−2.242, P<0.027 |
| BMI (kg/m²)             | 27.36±3.79 | 25.27±3.55 | t=−3.368, P<0.001 |
| Waist Circumference (cm)| 96.48±7.09 | 94.17±6.79 | t=−1.967, P=0.051 |
| HbA1c                   | 5.78±0.71 | 5.55±0.32 | t=−2.497, P<0.014 |
| Fasting Glucose (mg/dl) | 97.47±23.76 | 87.20±9.41 | t=3.362, P<0.001 |
| Fasting Insulin (µIU/mL)| 15.97±10.10 | 10.38±3.18 | Z=2.472*, P<0.001 |
| HOMA-IR                 | 4.32±4.44 | 2.27±0.90 | Z=−2.507*, P<0.012 |
| Fasting Glucose (mmol)  | 5.40±1.33 | 4.84±0.52 | t=3.267, P<0.001 |

*Mann Whitney U-test; P values in bold means significant

### Table 4: Comparison of parameters in different grades of Acanthosis nigricans

| Parameter               | Mild (n=20) | Moderate to Severe (n=37) | Remarks |
|-------------------------|-------------|---------------------------|---------|
| Weight (kg)             | 67.15±9.33  | 74.37±12.57               | t=1.253, P=0.028 |
| Height (meter)          | 1.61±0.07   | 1.61±0.08                 | t=−0.226, P=0.822 |
| BMI (kg/m²)             | 25.77±3.16  | 28.28±3.87                | t=−2.489, P<0.016 |
| HbA1c                   | 5.58±0.35   | 5.87±0.80                 | t=−1.511, P=0.136 |
| Fasting Glucose (mg/dl) | 90.10±10.92 | 100.11±26.45              | t=1.614, P=0.112 |
| Fasting Insulin (µIU/mL)| 13.00±7.46  | 17.96±11.49               | t=1.737, P=0.088 |
| HOMA-IR                 | 3.00±2.03   | 5.07±5.40                 | t=−1.645, P=0.106 |
| Fasting glucose (mmol)  | 5.00±0.60   | 5.53±1.48                 | t=−1.527, P=0.133 |
| Waist Circumference (cm)| 94.02±7.66  | 97.54±6.85                | t=−1.776, P=0.081 |
| Insulin resistance*     | 6 (30%)     | 18 (62.16%)               | χ²=1.852, P=0.174 |

*Percentage
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Tamega et al.\cite{24} studied for the association of acrochordons with IR and found IR in 31.1% in cases while only 2.8% in controls which was significant ($P < 0.05$). Jowker et al.\cite{35} found a higher mean insulin level in cases of acrochordons 18.3 ± 11.2 compared to controls 9.7 ± 3.4 ($P < 0.05$). In this study also, we found that patients with acrochordons (that is excluding the patients who had AN only) compared to controls, both IR and mean HOMA-IR were higher in cases and this difference was statistically significant. In this study, those patients who had both AN and acrochordons also had higher IR and mean HOMA-IR, and the differences were statistically significant.

Some studies had not found a significant association between AN and IR. Caceres et al. studied the relationship between IR and AN among Bolivian children and adolescents with obesity aged from 4 to 18 years and observed IR in 70.8% in cases of AN and 54% in controls with no significant difference between them ($P = 0.14$).\cite{26} Similarly, Hirschler et al. studied 74 obese children with AN (41) and without AN (33) and found mean HOMA-IR was 6.6 in cases in comparison to 4.9 in controls ($P = 0.19$).\cite{27}

In our study, the most common site of AN was neck (94.7%) followed by axilla (40.3%). In 35% of the cases, it involved both neck and axilla. These findings are almost similar to the findings in studies performed on Indian\cite{28} and Mexican American populations\cite{2}. It is also supported by Hoffmann et al. in which most common site for AN was the neck (94%; $n = 109$), followed by the axillae (45%; $n = 52$), with 39% ($n = 45$) of these having AN in both the neck and axillae.\cite{29}

We observed a higher level of fasting insulin, fasting glucose, HOMA-IR, BMI, and waist circumference in cases than in controls, in which except waist circumference (96.48 ± 7.09 in cases to 94.17 ± 6.79 in controls, $P = 0.051$) all were statistically significant. Higher BMI level in our study had also been supported by various studies. Phyllis et al. study showed that prevalence of AN increased with BMI percentile group, particularly those with BMI at or above the 95th percentile, where 58% of youth had AN.\cite{30} Hirschler et al. studied 1250 young Hispanic subjects in Argentina, and found a positive correlation between AN with BMI.\cite{31} Jorwal et al. studied 120 patients (40 cases of AN and 80 controls); they also found acanthosis nigricans to be associated with high fasting blood sugar and BMI values.\cite{32} Severity of AN found to be proportional to weight. In person with more weight AN was more severe.

In our study, the results showed IR positivity of higher percentage in the subjects of age ≥40 year, male gender, and having multiple site involvement of AN and acrochordons but not statistically significant. This may be due to smaller sample size. For generalization of the result, this study may be conducted with a larger sample size.

On the basis of our study, we may conclude that AN and acrochordons may be taken as a cutaneous marker for IR in the northern part of India. By early diagnosis, we may prevent its consequences by doing early treatment, health education, and life style modifications.

**Limitations**

A low number of cases and controls were taken in the study. Association with hyperlipidemia and metabolic syndrome was not studied.

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**Conflicts of interest**

There are no conflicts of interest.

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