



Original Research Article

A case control study of association of Acanthosis nigricans, Insulin resistance and Type 2 diabetes mellitus in a tertiary care centre in South India

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ABSTRACT

Introduction: Acanthosis Nigricans is a dermatosis characterized by velvety, papillomatous, brownish black, hyperkeratotic plaques typically on the intertriginous surfaces and neck. Acanthosis Nigricans is commonly associated with disorders associated with insulin resistance, including obesity, type 2 diabetes mellitus and Polycystic ovarian syndrome. Hyperinsulinaemia is thought to play a pivotal role.

Aims: To find the association of Acanthosis Nigricans with insulin resistance and type 2 diabetes mellitus and its correlation with anthropometric measurements such as waist circumference, waist hip ratio and BMI. Settings and Design: This is a hospital based cross sectional analytical study including 30 cases with acanthosis nigricans and 30 controls.

Materials and Methods: All cases and controls underwent clinical examination, relevant anthropometric measurements, fasting sugar and fasting insulin levels.

Statistical analysis used: Collective data was analysed by frequency, percentage, mean, Standard Deviation, Karl-Pierson correlation, Chi- square test and t-test.

Results: In our study AN was significantly associated with increase in BMI, WC, WHR, skin tags, low physical activity, family history of DM, fasting glucose, and fasting insulin levels ($p=0.000$) as compared to controls. There was no significant association of AN with age, gender, comorbid conditions and blood pressure. Grade of AN, number of sites also were significantly associated with hyperinsulinemia. Therefore screening for AN would provide a simple and noninvasive method for identifying people who may have hyperinsulinemia and high risk for diabetes mellitus.

Conclusions: AN was significantly associated with increase in BMI, WC, WHR, skin tags, low physical activity, family history of DM, fasting glucose, and fasting insulin levels

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1. Introduction

The prevalence of diabetes and its adverse health effects has risen rapidly in India. The association of Acanthosis nigricans (AN) and hyperinsulinaemia, a consequence of insulin resistance associated with obesity has been of increasing interest to doctors. As most of type 2 diabetes mellitus subjects are obese, body mass index is an important confounding factor in the association of Acanthosis nigricans with type 2 diabetes mellitus.¹

AN is commonly seen over the neck, axillae, elbows, knuckles, inner surface of thighs, and popliteal fossa. Traditionally it can be subdivided into three types: (1) idiopathic form in healthy young children, (2) paraneoplastic form in association with internal malignancy, and (3) AN in obese patients with or without apparent endocrine disorders (previously known as pseudoacanthosis nigricans). The probable pathogenesis of AN in insulin resistance syndromes is attributable to high levels of insulin activating the fibroblasts (dermal cells) and keratinocytes (epidermal cells) via insulin-like growth factor receptors present on these cells.¹ With the increasing

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incidence of diabetes mellitus and obesity due to sedentary lifestyle, detection of acanthosis nigricans and other early manifestations of diabetes mellitus and its relation to hyperinsulinemia is an area of growing interest and research. The objectives of this study were:

1. To study the clinical features of Acanthosis Nigricans.
2. To determine the association between Acanthosis Nigricans, hyperinsulinaemia and obesity prone for type 2 Diabetes Mellitus.

2. Materials and Methods

We undertook a cross sectional study which included a total of thirty cases (age > 12 years) attending a hospital OPD with Acanthosis nigricans from September 2012–October 2013 and thirty age and sex matched controls. Institutional ethical clearance was obtained.

After obtaining an informed consent, a detailed history was taken including age, duration of lesion, extension of the lesion, number of sites involved, family history of DM, amount of physical activity in a week (<30 minutes of physical activity/day), any associated illnesses like diabetes mellitus, hypothyroidism, polycystic ovarian syndrome, fatty liver, hyperlipidemia. Systemic examination was done in all cases. Patients who were taking medications such as oral steroids and oral contraceptive pills were also not included in the study. Anthropometric measurements such as height, weight, BMI, WC, WHR were calculated in a standardised manner using a flexible non elastic tape by a single observer. BMI was calculated as weight in kilograms divided by height as metres square. Blood pressure was recorded in all cases. Systolic BP >130 mmHg and diastolic BP >85 mmHg was taken as high blood pressure. Waist circumference was measured using an inelastic tape with a precision of 0.1cm placed directly on the skin. Measurements were taken at the midpoint between the top edge of the iliac crest and the lateral costal margin with the patient standing with his/her arms alongside the body. Values above the 90th percentile for age and sex were considered abnormal, with cut-off points of 88cm for girls and 102cm for boys²

All cases and controls underwent a detailed cutaneous examination with respect to site of the lesion (neck, axilla, groin, knuckles, antecubital fossa, popliteal fossa, flanks, mucosa, generalised or any other). Grading of the lesion over neck was done. Patients were also examined for skin tags.

All patients underwent fasting blood sugar (hexokinase method) and fasting insulin levels (chemiluminescence method) after about 10-12 hours overnight fast. Fasting blood sugar >100mg/dl was considered as elevated blood sugar according to the International Diabetes Federation criteria. Fasting insulin levels of >25 was considered as elevated insulin levels (laboratory reference value).

2.1. Statistical Analysis

Collective data was analysed by frequency, percentage, mean, Standard Deviation, Karl-Pierson correlation, Chi-square test and t-test.

3. Results

This study showed that patients with acanthosis nigricans were more in the younger age group ($p=0.029$), equal preponderance in both the sexes with a male to female ratio of 1:1 ($p=0.796$). Neck was the most common site involved (100% of the cases) followed by axilla (86.6%) and groin (73.3%). Less common sites involved were antecubital fossa, popliteal fossa, flanks and knuckles (Figure 1). Grade 4 involvement was seen in 46.7%, grade 3 in 30%, grade 2 in 13.3% and grade 1 involvement in 10% (Figure 2). Six cases (20%) had a positive family history of DM ($p=0.012$). Majority of the cases (24 cases, 80%) had lower physical activity as compared to controls ($p<0.001$). Three cases (10%) had history of other comorbid conditions/systemic involvement (hirsutism with PCOD, fatty liver disease with hypercholesterolaemia, hypothyroidism with fatty liver, $p=0.019$). Majority of the cases (93.3%) were either obese or overweight ($p<0.001$). Of these 43.3% belonged to overweight category. Waist circumference of more than 88cm in females and 102cm in males was considered as high risk. 'High risk' waist circumference was seen in 76% of the cases

($p<0.001$). Waist hip ratio >1 in males and >0.85 in females was considered to be high risk. 20 cases (66.7%) belonged to 'high risk group' among cases ($p<0.001$).

Most of the cases (66.7%) had skin tags ($p=0.001$). Presence of skin tags correlated positively with fasting insulin ($p=0.00$).

Most of the cases (90%) had normal blood pressure only 10% had pre hypertension ($p=0.119$). Six cases (20%) had elevated fasting glucose and 24 cases (80%) had normal plasma glucose levels ($p=0.044$).

Majority of the cases (19 cases, 63.3%) had elevated fasting plasma insulin levels. None of the controls had elevated fasting plasma insulin levels ($p<0.001$).

4. Discussion

With the country having the highest number of diabetic patients in the world, diabetes is posing an enormous health problem to our country today. The forerunner of diabetes mellitus, hyperinsulinaemia is associated with cutaneous and physical signs like acanthosis nigricans and obesity. As most of type 2 diabetes mellitus subjects are obese, body mass index is an important confounding factor in the association of Acanthosis Nigricans with type 2 diabetes mellitus, which is why it is said that "Acanthosis nigricans is not a skin disease per se but a cutaneous sign of an underlying condition or disease".³



Fig. 1: Acanthosisnigricans involving axilla, groin, cubital fossa and knuckles

In states of insulin resistance, acanthosis nigricans may result from excess insulin binding to IGF-1 receptors on keratinocytes and fibroblasts.

4.1. Grading of acanthosis nigricans⁴

Neck severity is graded as

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 less than 3 inches in breadth)

3 – Moderate: extending to the lateral margins of the neck (posterior border of sternocleidomastoid) (usually 3-6 inches), should not be visible when the participant is viewed from front.

4 – severe : extending anteriorly (>6 inches), visible when the participant is viewed from the front.

Our study showed a significant association between hyperinsulinemia, BMI and acanthosis nigricans. In a study done by Neerja Puri, hyperinsulinaemia was seen in 40% of patients and diabetes in 30%. The commonest age group was 11-20 years with 33.3% patients. Neck was commonest site of involvement in 93.3% of patients. Females outnumbered males with a ratio of 3:2 in this study.⁵

Grandhe et al observed significant association between Acanthosis Nigricans with body mass index and other anthropometric measurements in their study. He found a higher prevalence of Acanthosis Nigricans among diabetics (62.6%) when compared to healthy subjects (40%).¹

Stuart et al⁶ in his study showed that when simultaneously controlling for other variables, only AN, obesity, and physical activity were statistically significant predictors

of hyperinsulinemia. AN and obesity were positively associated with hyperinsulinemia, whereas physical activity was significantly protective against hyperinsulinemia.

In a study by Mukhtar et al of the students with AN, 39.4% had hyperinsulinemia compared with 8.6% of students without AN. Thirty-four percent (34%) of students with obesity had hyperinsulinemia compared with 4.8% without. Students who were obese and had AN were 19.7 times more likely to have hyperinsulinemia than those who did not have AN and were not obese.⁷

The Acanthosis Nigricans Screening Tool is a noninvasive, reliable, and easy to use tool that allows for a quick assessment of insulin resistance.⁸

In a study by Valeria et al⁹ waist circumference is a predictor of insulin resistance syndrome in children and adolescents and could be included in clinical practice as a simple tool to help identify children at risk. The study demonstrated that a family history of diabetes together with features of the dysmetabolic syndrome conferred a very high risk of subsequent diabetes. In our study there was a positive association of fasting insulin level with waist circumference, waist hip ratio and increase in body mass index. Among the cases with at risk waist circumference, fasting insulin was elevated in 82.6% of the patients.(p<0.001)

In our study cases with 3 or >3 sites involvement were twice more susceptible to have elevated fasting insulin. Increase in grade of AN was positively associated with increase in body mass index, waist circumference and waist hip ratio. Cases with grade 3 and grade 4 involvement were five to six times more likely to have elevated fasting insulin levels. Among cases with 'at risk' waist hip ratio, 90% had elevated fasting insulin levels. (p<0.001)

Because it is now well documented that modification of lifestyle habits can delay or possibly prevent the onset of the disease, early risk detection using simple and noninvasive methodology may reduce the heavy burden of diabetes (and its many serious complications) at both the individual and community level.¹⁰

In our study low physical activity was seen in 80% of the patients as compared to 16% of the controls.

The landmark Diabetes Prevention Program study demonstrated that lifestyle interventions can prevent or delay the onset of type 2 diabetes mellitus (T2DM) by as much as 58%, making identification of high risk patients a priority in primary care.¹¹

5. Conclusion

AN is independently associated with hyperinsulinemia and therefore may be useful as an early indicator of high risk for diabetes. Early screening for AN would provide a relatively simple and noninvasive method for identifying people who may have hyperinsulinemia and could benefit from early intervention to prevent the development of type 2 diabetes

by lifestyle modifications that may reduce the heavy burden of diabetes in the community.

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None.

7. Conflict of Interest

None.

References

1. Grandhe NP, Bhansali A, Dogra S, Kumar B. Acanthosis Nigricans: relation with type 2 diabetes mellitus, anthropometric variables, and body mass in Indians. *Postgrad Med J*. 2005;81:541–544.
2. Appropriate body mass index for Asian populations and its implications for policy and intervention strategies. WHO expert consultation. *Lancet*. 2004;33(9403):1573.
3. Valia RG, Valia AR. IADVL Textbook of Dermatology 3rd ed. Bhalani publishing house Mumbai ; 2008,.
4. Burke JP, Hale DE, Hazuda HP, Stern MP. A quantitative scale of acanthosis nigricans. *Diabetes Care*. 1999;22(10):1655–1659.
5. Puri N. A Study of pathogenesis of Acanthosis Nigricans and its clinical implications. *Indian J Dermatol*. 2011;56(6):678–683.
6. Stuart CA, Gilkison CR, Keenan BS, Nagamani M. Hyperinsulinemia and acanthosis nigricans in African Americans. *J Natl Med Assoc*. 1997;89(8):523–527.
7. Mukhtar Q, Cleverly G, Voorhees R, McGrath J. Prevalence of acanthosis nigricans and its association with hyperinsulinemia in New Mexico adolescents. *J Adolesc Health*. 2001;28(5):372–376.
8. Scott LK, Hall LM. Reliability and Validity of the acanthosis nigricans screening tool for use in elementary school-age children by School Nurses. *J Sch Nurs*. 2012;28(6):442–447.
9. Hirschler V, Aranda C, Calcagno ML, Maccalini G, Jadzinsky M. Can waist circumference identify children with the metabolic syndrome? *Arch Pediatr Adolesc Med*. 2005;159(8):740–744.
10. Kalus AA, Chien AJ, Olerud JE. Diabetes Mellitus and other endocrine diseases. vol. 2 of Fitzpatrick's dermatology in general medicine. New york(USA) ; 2008,. p. 1462–1465. The McGraw-Hill.
11. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6):393–403.

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