Original Research Article

Acanthosis nigricans: a clinical marker of insulin resistance

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ABSTRACT

Background: Very little information is available regarding the association of acanthosis nigricans with insulin resistance from rural areas of India. Therefore this study was carried out with the aim and objectives to study the association between acanthosis nigricans and insulin resistance and to evaluate correlation of acanthosis nigricans severity, neck severity and neck texture severity with fasting blood sugar & serum insulin especially in this rural part of central India.

Methods: In this cross sectional study with comparative group, total 162 age and sex matched subjects were divided into two groups of cases (81) with acanthosis nigricans and comparative subjects (81) without acanthosis nigricans. The severity acanthosis nigricans was assessed using the Burke's quantitative scale. Fasting blood sugar and fasting insulin levels were estimated to know the Homeostasis model assessment of insulin resistance (HOMA-IR) values. Data was analyzed by using appropriate statistical tests.

Results: The age range was 20 to 55 years with the mean of 32.82 ± 10.19 years for cases and 33.67 ± 8.09 for comparative subjects. Univariate analysis which showed significant association of acanthosis nigricans with fasting insulin and HOMA-IR with significant odds ratios and p value (p =0.0001) respectively. Fasting blood sugar showed greater risk of association in cases but it was statistically insignificant with p-value of (p =0.32). Spearman rank coefficient correlation showed weak correlation of HOMA-IR with acanthosis nigricans severity, neck severity and neck texture severity, but showed positive correlation of fasting insulin with acanthosis nigricans severity, neck severity and neck texture severity, with statistically significant P-value (p <0.05).

Conclusions: Acanthosis nigricans was strongly associated with insulin resistance with significant odds ratio and statistical significant p value (P < 0.05). Acanthosis nigricans severity, neck severity and neck texture severity showed positive correlation with fasting serum insulin with statistically significant p value (P <0.05).

Keywords: Acanthosis nigricans, Insulin resistance

INTRODUCTION

Acanthosis Nigricans (AN) is a dermatosis characterized by velvety, papillomatous, brownish-black, hyperkeratotic plaques, typically on the intertriginous surfaces and neck.[1,2] Many endocrine abnormalities are associated with acanthosis nigricans like Cushing syndrome, Addison's disease, diabetes mellitus, polycystic ovary disease, hypo and hyperthyroidism. Although several studies have found AN to be an independent predictor of hyperinsulinemia others have not.[3-7] Very little information is available in this regard from rural areas of India. Therefore this study was carried out with the aim and objectives to study the association between acanthosis nigricans, and insulin resistance and to evaluate correlation of acanthosis severity, neck severity and neck texture severity with serum insulin

especially in this rural part of central India. Early detection and intervention of this condition in patients with AN can prevent metabolic complication like diabetes mellitus.

METHODS

This cross sectional study with comparative group was conducted in the outpatient department of Dermatology, Venereology and Leprosy, Acharya Vinoba Bhave Rural Hospital attached to Jawaharlal Nehru Medical College, Sawangi (Meghe), Wardha, Maharashtra during the period Dec 2014 to Jan 2017. Age and sex matched 81 cases of acanthosis nigricans (case group) and 81 subjectes without acanthosis nigricans (comparative group) were enrolled for the study after clearance from Institutional Ethics Committee and with written informed consent. Inclusion criteria were cases and comparative subjects of age group 20 – 55 years of both the gender. Exclusion criteria were subjects on nicotinic acid, systemic glucocorticoids, topical steroids, oral contraceptive pills and protease inhibitors, cases of acanthosis nigricans with clinical features suggestive of Cushing's syndrome, addison's disease, hypo and hyperthyroidism polycystic ovary disease, underlying malignancies and syndromic (childhood onset) acnthosis nigricans. Detailed history regarding age, gender, onset and duration of skin changes was taken. History of polyuria, polyphagia and polydipsia was taken.

The patient was examined to note the clinical features of acanthosis nigricans and the overall severity of acanthosis nigricans, neck severity and neck texture severity was assessed using the Burke's quantitative scale for acanthosis nigricans (Table 1).[8]

Five anatomical sites were chosen to assess the presence and extent of AN: the neck, axilla, knuckles, elbows and knees. The neck and axilla were graded for severity on a scale from 0 to 4. The knuckles, elbows and knees were graded as AN present (1) or absent (0). A single AN score was calculated for each location. The average AN score was calculated by summing the scores of the 5 locations in each patient. The neck texture score wasn't included in the final AN score since including it would have given too much weight to one location.

The overall AN severity (considering all five anatomical sites) was graded as mild, moderate and severe if the score was 1- 1.5, 1.6 to 1.9 and ≥2 respectively.

After overnight fasting of more than 8 hours, 5 ml of blood sample was drawn for the estimation of fasting blood sugar and fasting insulin levels. The Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by the formula:

– Fasting Blood Sugar (mg/dl) X Fasting Insulin (micro IU/ ml)/405.[9]

Cutoff values for fasting blood sugar was taken as ≥ 100 mg/dl, fasting insulin as > 17 µu/ml [10] and for HOMA-IR (insulin resistance) > 2.4 µu/ml.[11]

Table 1: The Burke's quantitative scale for Acanthosis Nigricans (AN).[8]

Location	Score description
Neck severity	
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 margin of the neck (usually <3 inches in breadth).
3	Moderate: extending to the lateral margins of the neck (posterior border of the sternocleidomastoid) (usually 3–6 inches), should not be visible when the participant is viewed from the front.
4	Severe: extending anteriorly (> 6 inches), visible when the participant is Viewed from the front.
Axilla	
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: localized to the central portion of the axilla, may have gone unnoticed by the participant .
3	Moderate: involving entire axillary fossa, but not visible when the arm is against the participant's side.
4	Severe: visible from front or back in the unclothed participant when the arm is against the participant's side.
Neck texture	
0	Smooth to touch: no differentiation from normal skin to palpation.
1	Rough to touch: clearly differentiated from normal skin.
2	Coarseness can be observed visually, portions of the skin clearly raised above other areas .
3	Extremely coarse: "hills and valleys" observable on visual examination.
Knuckles	Present
	Absent
Elbows	Present
	Absent
Knees	Present
	Absent

Statistical analysis

Association between the levels of variable and the disease condition was tested for statistical significance using Pearson's Chi-square test. Univariate analysis was performed wherein odds associated with each variable in favour of disease were obtained. Spearman Rank Correlation (rho) was performed to obtain the correlation of parameters of insulin resistance with acanthosis nigricans severity, neck severity and neck texture severity. All the analyses were performed using SPSS version 20.0 (IBM Corp.) software. The statistical significance was tested at 5% level.

RESULTS

The subjects were equally distributed in different age group range for case and comparative groups with no statistical difference (p= 0.14). The age range was 20 to 55 years with the mean of 32.82 ± 10.19 years for cases and 33.67 ± 8.09 for comparative subjects. The subjects were equally distributed in both the gender groups for case and comparative groups with no statistical difference

(p= 0.75). The abnormal fasting blood sugar observed in cases compared to comparative subjects was statistically insignificant (p=0.32) (Table 2). The abnormal serum insulin level observed in 29 (35.8%) cases compared to 8 (9.9%) comparative subjects was statistically significant (p=0.0002) (Table 3). The abnormal Homeostatic model assessment of insulin resistance (HOMA-IR) level observed in 45 (55.6%) cases compared to 22 (27.2%) comparative subjects was statistically highly significant (p <0.0001) (Table 4). Univariate analysis showed significant association of acanthosis nigricans with fasting insulin and HOMA-IR with significant odds ratios and p value (p = 0.0001) respectively. Fasting blood sugar showed greater risk of association in cases but it was statistically insignificant with p-value of (p=0.32) (Table 5). Out of 81 cases, 42 (51.8%) had mild, 28 (34.6%) had moderate and 11 (13.6%) had severe acanthosis nigricans (Figure 1). Spearman rank coefficient correlation showed weak correlation of HOMA-IR with acanthosis nigricans severity, neck severity and neck texture severity, but showed positive correlation of fasting insulin with acanthosis nigricans severity, neck severity and neck texture severity, with statistically significant p-value (Table 6 – 8).

Table 2: Distribution of subjects according to fasting blood sugar (FBS) levels in case and comparative groups.

Fasting Blood Sugar (mg/dl)	Case group	Comparative group	Total	χ^2 Statistic	P-value
	No. (%)	No. (%)	No. (%)		
Normal (FBS < 100)	62 (76.5)	67 (82.7)	129 (79.6)	0.9514	0.3293 (NS)
Abnormal (FBS >= 100)	19 (23.4)	14 (17.2)	33 (20.4)		
Total	81	81	162		

NS: Not significant.

Table 3: Serum insulin levels in case and comparative group with statistical significance.

Sr. Insulin Levels	Case group	Comparative group	Total	χ^2 Statistic	P-value
	No. (%)	No. (%)	No. (%)		
Normal (<= 17)	52 (64.2)	73 (90.1)	133 (82.1)	6.2175	0.0002 (S)
Abnormal (> 17)	29 (35.8)	8 (9.9)	28 (17.3)		
Total	81	81	162		

S: Significant.

Table 4: Homeostatic model assessment for insulin resistance (HOMA-IR) levels in case and comparative group with statistical significance.

HOMA-IR Levels	Case group	Comparative group	Total	χ^2 Statistic	P-value
	No. (%)	No. (%)	No. (%)		
Normal (IR <= 2.4)	36 (44.4)	59 (72.8)	95 (58.6)	13.464	<0.0001 (HS)
Abnormal (IR > 2.4)	45 (55.6)	22 (27.2)	67 (41.4)		
Total	81	81	162		

HS: Highly Significant.

Table 2 shows that the abnormal fasting blood sugar observed in 19 (23.4%) cases compared to 14 (17.2%) comparative subjects was statistically insignificant (p= 0.3293).

Table 3 shows that the proportion of subjects with abnormal serum insulin levels were more in case compared to comparative subjects with statistically significant p value (p=0.0002). The abnormal serum

insulin levels were observed in 29 (35.8%) cases compared to 8 (9.9%) comparative subjects.

The abnormal HOMA-IR levels were observed in 45 (55.6%) cases compared to 22 (27.2%) comparative subjects.

Table 4 shows that the proportion of subjects with abnormal HOMA-IR levels were more in cases compared to comparative subjects with statistically significant p value (p <0.0001).

Table 5: Univariate analysis for the association of acanthosis nigricans with different insulin resistance parameters.

Parameters for insulin resistance	Blood Levels	Unadjusted OR [95% CI]	P-value
Fasting blood sugar (mg/dl)	Normal (FBS <100)	1.00	
	Abnormal (FBS >=100)	1.46 [0.67, 3.22]	0.3293
Fasting insulin	Normal (<=17)	1.00	
	Abnormal (>17)	4.97 [2.18, 12.61]	<0.0001
HOMA-IR	Normal (IR <=2.4)	1.00	
	Abnormal (IR >2.4)	3.35 [1.74, 6.47]	<0.0001

Table 5 depicts univariate analysis which showed significant association of acanthosis nigricans with Fasting insulin (OR 4.95, 95% CI: 2.18, 12.61, p=0.0001) and HOMA-IR (OR 3.35, 95% CI: 1.74, 6.47, p=0.0001). Fasting blood sugar (OR 1.46, 95% CI: 0.67, 3.22), showed greater risk of association in cases but it was statistically insignificant with p-value of (p=0.32).
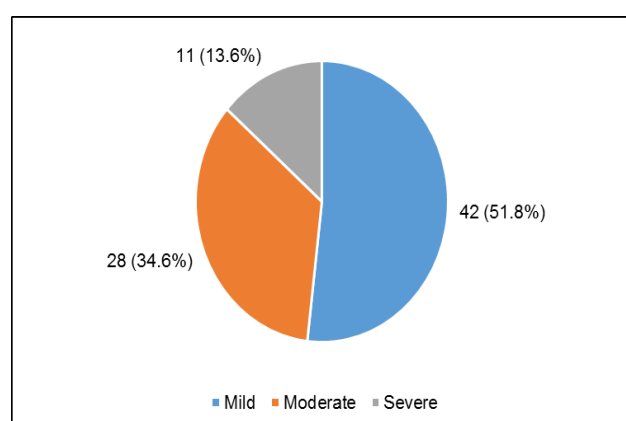

Figure 1: Distribution of patients as per acanthosis nigricans severity grading.

Figure 1 shows that out of 81 cases, 42 (51.8%) had mild, 28 (34.6%) had moderate and 11 (13.6%) had severe acanthosis nigricans.

Table 6: Spearman rank coefficient correlation between acanthosis nigricans severity and parameters for insulin resistance.

Parameters for insulin resistance	Spearman rank coefficient	P-value
HOMA-IR	0.0798	0.478
Fasting insulin	0.3415	0.002

Table 6 shows weak correlation of HOMA-IR with AN grading with coefficient of 0.0798, which was statistically insignificant with p-value of 0.478 (p >0.05). Fasting insulin, which is the deciding factor of HOMA-IR showed positive correlation with AN severity with coefficient of 0.3415, which was statistically significant with p-value of 0.002 (p <0.05).

Table 7 shows weak correlation of HOMA-IR with neck severity with coefficient of -0.0172, which was statistically insignificant with p-value of 0.878. Fasting insulin, which is the deciding factor of HOMA-IR showed positive correlation with neck severity with coefficient of 0.2259, which was statistically significant with p-value of 0.042 (p <0.05).

Table 7: Spearman rank coefficient correlation between neck severity and parameters for insulin resistance.

Parameters for insulin resistance	Spearman rank coefficient	P-value
HOMA-IR	-0.0172	0.878
Fasting insulin	0.2259	0.042

Table 8: Spearman rank correlation between neck texture and parameters for insulin resistance.

Parameters for insulin resistance	Spearman rank coefficient	P-Value
HOMA-IR	0.0892	0.428
Fasting insulin	0.2843	0.010

Table 8 shows weak correlation of HOMA-IR with neck texture with coefficient of 0.0892, which was statistically insignificant with p-value of 0.428 (p >0.05). Fasting insulin, which is the deciding factor of HOMA-IR showed positive correlation with neck texture with coefficient of 0.2843, which was statistically significant with p-value of 0.010 (p <0.05).

DISCUSSION

In present study table 2 shows that the abnormal fasting blood sugar observed in 19(23.4%) cases compared to 14 (17.2%) comparative subjects was statistically insignificant (p= 0.32). Table 3 shows that the abnormal serum insulin levels observed in 29 (35.8%) cases compared to 8 (9.9%) comparative subjects was statistically significant (p= 0.0002). Table 4 shows that the abnormal HOMA-IR levels observed in 45 (55.6%) cases compared to 22 (27.2%) comparative subjects was statistically significant (p <0.0001). Ayaz et al in their study showed significant association of acanthosis nigricans cases with fasting insulin (p=0.0001) and HOMA-IR (p=0.0001) but no association with fasting blood sugar (p=0.13) as compared to subjects without acanthosis nigricans.[12] Venkatswami et al in their cross sectional study observed significant association of acanthosis nigricans with fasting insulin (p=0.04) and HOMA-IR (p=0.005) but no association with fasting blood sugar (p=0.62).[13] Kamel et al in their case control study showed significant association of acanthosis nigricans with fasting insulin (p=0.000) and no association with fasting blood sugar (p=0.10) as compared to subjects without acanthosis nigricans.[14] HOMA-IR has not been done in their study. Patidar et al in their study observed statistically significant correlation with fasting glucose, fasting insulin and HOMA-IR (p <0.05).[15]

Findings regarding fasting insulin and HOMA-IR of present study are in accordance with above mentioned studies. But abnormal fasting blood sugar was not found to be associated with acanthosis nigricans and this could be explained by the fact that hyperinsulinemia observed in cases is often able to maintain glucose homeostasis in the presence of insulin resistance in the initial stages; thus the blood glucose in these patients is generally in the normal range and this indicates a prediabetic condition.

Results of univariate analysis depicted in table 5 showed significant association of acanthosis nigricans with fasting insulin (OR 4.95, 95% CI: 2.18, 12.61, p=0.0001) and HOMA-IR (OR 3.35, 95% CI: 1.74, 6.47, p=0.0001). Fasting blood sugar (OR 1.46, 95% CI: 0.67, 3.22), showed greater risk of association in cases but it was statistically insignificant with p-value of (p=0.32). Acharya et al in their case – control study, on univariate analysis showed a statistically significant association of fasting blood sugar (OR=3.98; CI=95;P=0.01).[16] They have not done univariate analysis of insulin, HOMA-IR.

Table 6 shows week correlation of HOMA-IR with acanthosis nigricans severity with coefficient of 0.0798, which was statistically insignificant with P-value of 0.478 (P > 0.05). Fasting insulin, which is the deciding factor of HOMA-IR showed positive correlation with AN grading with coefficient of 0.3415, which was statistically significant with P-value of 0.002 (P < 0.05). Studies with individual neck and axillary severity grading and its

correlation with various metabolic parameters and insulin resistance are available. So far no studies have been done in the past, to know the correlation of AN severity which all together includes neck severity, axillary severity, involvement of knuckles, knees and elbow. Table 7 shows weak correlation of HOMA-IR with neck severity with coefficient of -0.0172, which was statistically insignificant with P-value of 0.878. fasting insulin, which is the deciding factor of HOMA-IR showed positive correlation with neck severity with coefficient of 0.2259, which was statistically significant with p-value of 0.042 (p <0.05). Patidar et al in their study observed statistically significant correlation with fasting insulin (p <0.05) and concluded that acanthosis nigricans neck severity grading correlates well with insulin resistance and can be used as a clinical surrogate for assessment of severity of insulin resistance.[15] Abeer M. Kamel et al in their case control study showed positive significant correlation between the neck severity and fasting insulin (p=0.000).[14] Venkatswami et al in their cross sectional study observed that grade III and IV neck severity were more predictive of raised serum insulin (p=0.042) and IR.[13] They concluded that acanthosis nigricans grading is an inexpensive and non-invasive way of identifying pre-diabetes. Ayaz et al in their study showed significant positive correlation between AN and fasting insulin (p=0.0001).[12] Table 8 shows weak correlation of HOMA-IR with neck texture with coefficient of 0.0892, which was statistically insignificant with P-value of 0.428 (P > 0.05). Fasting insulin, which is the deciding factor of HOMA-IR showed positive correlation with neck texture with coefficient of 0.2843, which was statistically significant with P-value of 0.010 (p <0.05). There is only one study available to review the findings regarding neck texture. Venkatswami et al in their cross sectional study observed that neck texture II and III were more predictive of raised serum insulin (p=0.004) and IR.[13]

Findings of present study regarding positive correlation between acanthosis nigricans severity grading, neck severity grading, neck texture severity gradings and insulin level were in accordance with the findings of above mentioned studies.

Acanthosis nigricans neck severity, neck texture depends upon the fasting insulin level. Hyperinsulinemia is one of the import factors deciding the acanthosis nigricans severity, neck severity and neck texture severity which is also reflected in present study by positive correlation of acanthosis nigricans severity grading, neck severity grading, and neck texture grading with abnormal fasting insulin levels.

Keratinocytes and fibroblasts exhibit insulin-like growth factor 1 receptors (IGF-1Rs) on their surface. At low concentrations, insulin regulates carbohydrate, lipid and protein metabolism and can weakly promote growth by binding to "classic" insulin receptors. 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 insulin-like growth factor 1 (IGF-1) with 100- to 1000-fold greater affinity than insulin. The binding stimulates proliferation of keratinocytes and fibroblasts, leading to acanthosis nigricans. Hyperinsulinemia not only causes acanthosis nigricans by exerting a direct toxic effect, but indirectly by increasing free IGF-1 levels in circulation by decreasing IGFBP-1 and IGFBP-2 levels.

Schematic diagram depicts the relation between acanthosis nigricans and insulin resistance (Figure 2).
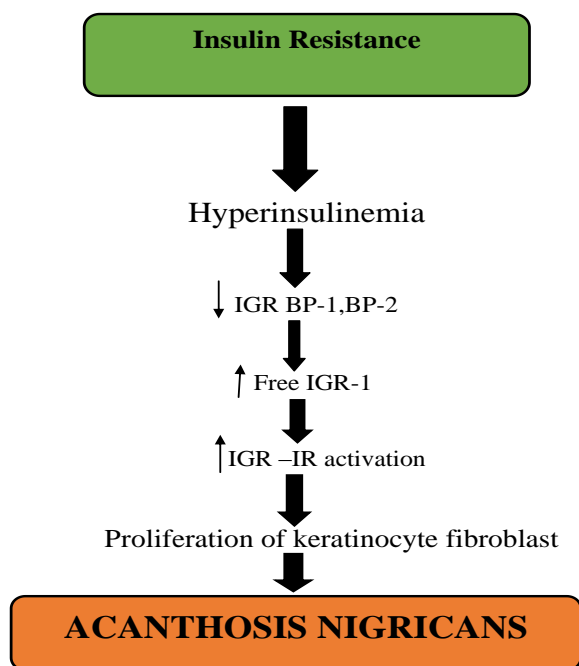

Figure 2: Schematic diagram depicts the relation between acanthosis nigricans and insulin resistance.

CONCLUSION

In this cross sectional study with comparative group acanthosis nigricans was found to be strongly associated with insulin resistance with significant odds ratio and statistical significant p value (P < 0.05). Acanthosis nigricans severity grading, neck severity and neck texture showed positive correlation with fasting serum insulin with statistically significant p value (P < 0.05).

ACKNOWLWDGEMENTS

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