IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 19, Issue 1 Ser.3 (January. 2020), PP 17-24
www.iosrjournals.org

Systemic Association of Acanthosis Nigricans and Its Role as a Marker of Insulin Resistence- A Case Control Study

N Sai Pujitha, Preetham Pottipati, Madhavilatha Midde

Abstract:
Background: *Acanthosis nigricans (AN) is a dermatosis that manifests as asymptomatic and symmetrical darkening affecting the skin of intertriginous areas, in particular the axillae, groins, submammary folds and neck. It is particularly associated with obesity and insulin resistance. The association of acanthosis nigricans and hyperinsulinaemia with obesity has been of increasing interest due to modified lifestyle. Early screening for acanthosis nigricans could provide a simple and non invasive aid for identifying people who may have hyperinsulinemia and could benefit from early intervention to prevent the development of type 2 diabetes by lifestyle modifications and there by reducing the burden of diabetes and other metabolic disorders.*
Materials And Methods: *This was a case control study conducted at Department of DVL, Santhiram medical college and general hospital , Nandyal from December 2016- August 2018 . The study group includes 200 age and sex matched subjects divided into two groups of cases (100) with acanthosis nigricans and controls (100) without acanthosis nigricans. After taking informed consent , patients were evaluated in detail and findings were recorded in a pre structured proforma. Anthropometric measurements such as height , weight, BMI of both cases and controls were recorded in a standardised manner. Both cases and controls underwent investigations such as HB, Total WBC count, differential count, ESR , FBS, RBS, PPBS, HBAIC ,Fasting Serum insulin , thyroid profile , Complete urine analysis for albumin, sugar , cells , casts and liver function tests.*
Results: *In this study, majority of the cases and controls were in the age group of 30- 40 years (28%).Females out numbered males, with male to female ratio of 1:1.4. In this study neck was the most common site involved (61%), 32% of cases with acanthosis nigricans involving the neck had high fasting serum insulin levels . Seventy eight cases (78%) were either obese or overweight and number of cases with acanthosis nigricans correlated with the increase in BMI. P was highly significant (p<0.003). Out of 32% cases with high fasting serum insulin levels in this study , 19% of cases had class II obesity , 8% of cases had class III obesity, 4% of cases had obese class I and 1% of cases wereoverweight. There was a significant association of fasting serum insulin levels increase in body mass index. (p 0.001). Out of 100 cases in this study 58% cases had underlying comorbid conditions. Twenty two cases (37.9%) had Type 2 DM, six cases (10.3%) had PCOD with hirsutism ,six cases(10.3%) had metabolic syndrome, four cases(6.89%) had hypertension, Fifteen cases (25.8%) had hypothyroidism and Five cases(8.62%) had underlying malignancies. None of the controls had any comorbidities. There was significant association of acanthosis nigricans with Type 2 DM , metabolic syndrome and PCOD. P value was significant (0.003). In this study, 29 % cases had obesity associated acanthosis nigricans nigricans and there was a significant association of fasting insulin levels with increase in body mass index. (p <0.001).*

Date of Submission: 22-12-2019 Date of Acceptance: 05-01-2020

I. Introduction

Acanthosis nigricans (AN) is characterized by dark, coarse and thickened skin with a velvety texture, being symmetrically distributed on the neck, the axillae, antecubital and popliteal fossae, and groin folds, histopathologically characterized by papillomatosis and hyperkeratosis of the skin. The skin in those regions is thickened, has a velvety texture, and may be studded by skin tags. The association of acanthosis nigricans and hyperinsulinaemia, a consequence of insulin resistance associated with obesity has been of increasing interest due to modified lifestyle. 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. The pathogenesis of acanthosis nigricans in insulin resistance syndromes is due to high levels of insulin that activates the fibroblasts and keratinocytes via insulin-like growth factor receptors present on these cells. In most of cases, an important factor in diagnosing acanthosis nigricans is recognizing the presence of hyperinsulinemiawhich is a known risk factor for type 2 diabetes and the metabolic syndrome. Acanthosis nigricans is of the following types, Benign acquired acanthosis nigricans, Obesity associated acanthosis nigricans, Autoimmune acanthosis nigricans, Drug induced acanthosis nigricans, malignant acanthosis

nigricans, Acral, Nevoid, Generalised & mixed. To the best of our knowledge there are very few studies in literature showing the association of acanthosis nigricans, with insulin resistance and type 2 diabetes mellitus and its true correlation with anthropometric measurements such as body mass index. Hence this study was undertaken

II. Aims And Objectives

1. To study the clinical features of Acanthosis Nigricans and its systemic associations.
2. To study its role as a cutaneous marker of insulin resistance.

III. Materials And Methods

This was a case control study conducted at Department of DVL, Santhiram medical college and general hospital , Nandyal from December 2016- August 2018 .Only those cases were included that satisfied the following criteria:

1. Cases with Acanthosis nigricans of all age groups and both sexes
2. Control population includes – equal number of age and sex matched controls without acanthosis nigricans.
3. Patients who have understood and signed informed consent form and are willing to participate in the study

Un-cooperative patients or patients who are unable to understand the protocol & give informed consent were excluded from the study. Informed consent was obtained from each patient in our study. The study was undertaken after clearance certificate from institution ethics committee. The patient's data was recorded in a prestructured proforma that includes detailed clinical history, general and cutaneous examination. Anthropometric measurements such as height , weight, BMI of both cases and controls were recorded 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. **BMI was classified according to WHO recommendations as** [19] 18.5-24.9 – Normal, 25.0-29.9 – over weight, 30.0-34.9 -class 1 obesity,35.0-39.9- class 2obesity,>40 - class 3 obesity. Fasting blood sugar (hexo kinase method) and fasting insulin levels (automated chemiluminescence method) were done after 10-12 hours over night fast in both cases and controls. Fasting blood sugar >126mg/dl was considered as diabetes mellitus.95 Based on laboratory normal reference values, hyperinsulinaemia was defined as insulin >25 IU/dl of plasma. Collected data was analysed using SPSS (stastistical package for social sciences) software and p value was obtained using chi square test.

IV. Results

In this study, majority of the cases and controls were in the age group of 30- 40 years (28%). Mean age of the cases and controls was 37.5 years.females out numbered males, with male to female ratio of 1:1.4.out of 30 cases(30%) with diabetes mellitus and acanthosis nigricans , 12 cases(40%) had family h/o diabetes mellitus. None of the controls had diabetes mellitus or family h/o diabetes mellitus. In this study neck was the most common site involved (61%).32% of cases with acanthosis nigricans involving the neck had high fasting serum insulin levels which was stastistically significant. In this study , Seventy eight cases (78%) were either obese or overweight and number of cases with acanthosis nigricans correlated with the increase in BMI. P was highly significant ($p<0.003$). Out of 32% cases with high fasting serum insulin levels in this study , 19% of cases had class II obesity , 8% of cases had class III obesity, 4% of cases had obese class I and 1% of cases were overweight. There was a significant association of fasting serum insulin levels increase in body mass index. (p 0.001). None of the controls had high fasting serum insulin levels. Out of 100 cases in this study , 78% of cases predominantly had obesity associated acanthosis nigricans of which 29% of cases were males and 49% cases were females and it was predominantly seen in the age group of 30-40 years. obesity AN has statistically significant association with high fasting serum insulin levels ($p=0.001$). There was a positive association of fasting insulin level with increase in BMI , increase in fasting blood glucose and with obesity associated acanthosis nigricans. Out of 100 cases in this study 58% cases had underlying comorbid conditions. Twenty two cases (37.9%) had Type 2 DM, six cases (10.3%) had PCOD with hirsutism ,six cases(10.3%) had metabolic syndrome, four cases(6.89%) had hypertension, Fifteen cases (25.8%) had hypothyroidism and Five cases(8.62%) had underlying malignancies. None of the controls had any comorbidities. There was significant association of acanthosis nigricans with Type 2 DM , metabolic syndrome and PCOD. P value was significant (0.003). In this study Twenty percent (20%) of the cases had skin tags , out of which 10 cases(55.5%) had type 2 DM and obesity AN. P value was highly significant ($p=0.003$). In this study, out of 32 cases with high fasting serum insulin levels, thirty cases(93.75%) had high fasting blood glucose levels. P value is highly significant(0.001) , 29 % cases had obesity associated acanthosis nigricans nigricans and there was a significant association of fasting insulin levels increase in body mass index. ($p <0.001$).

Table 1: AGE DISTRIBUTION OF CASES & CONTROLS

AGE GROUP IN YEARS	GROUP		
	CASE	CONTROLS	Total
10-20	22	22	44
20-30	19	19	38
30-40	28	28	56
40-50	17	17	34
50-60	10	10	20
60-70	4	4	8
Total	100	100	200

Table 2 – SEX DISTRIBUTION

	CASE	CONTROL	TOTAL
MALE	41	41	82
FEMALE	59	59	118
TOTAL	100	100	200

Table 3 : BMI OF CASES AND CONTROLS

		GROUP		
		CASE	CONTROLS	Total
BMIWTkgHTm2	NORMAL	22	62	84
	OVER WEIGHT	22	38	60
	OBESE – I	21	0	21
	OBESE CLASS – II	26	0	26
	OBESE – III	9	0	9
Total		100	100	200

Table 4: COMORBIDITIES ASSOCIATED WITH ACANTHOSIS NIGRICANS

	CASES	CONTROLS	TOTAL
NO COMORBIDITIES	42	100	142
TYPE 2 DM	22	0	22
HYPOTHYROIDISM	15	0	15
HYPERTENSION	4	0	4
METABOLIC SYNDROME	6	0	6
PCOD	6	0	6
MALIGNANCIES	5	0	5
TOTAL	100	100	200

Table 5: SITES OF ACANTHOSIS NIGRICANS

SITE	GROUP		
	CASE	CONTROLS	Total
NO site	0	100	100
NECK	61	0	61
ACRAL	3	0	3
NECK,AXILLAE,GROIN	29	0	29
NECK, AXILLAE,CUBITAL FOSSA	7	0	7
TOTAL	100	100	200

Table 6: ASSOCIATED FEATURES WITH ACANTHOSIS NIGRICANS

	GROUP		
	CASE	CONTROLS	Total
NO ASSOCIATION	65	100	165
HYPERPIGMENTATION OF PALMS AND SOLES	4	0	4
ACHROCHORDONS	20	0	20
THYROID SWELLING	*5	0	5
ALOPECIA	3	0	3
ACNE & HIRSUTISM	3	0	3
TOTAL	100	100	200

TABLE 7 :TYPE OF ACANTHOSIS NIGRICANS

TYPE OF AN	GROUP		
	CASE	CONTROLS	Total
No AN	0	100	100
BENGIN ACQUIRED NIGRICANS	10	0	10
OBESITY AN	78	0	78
MALIGNANT AN	5	0	5
ACRAL AN	7	0	7
TOTAL	100	100	200

TABLE 8 : FASTING BLOOD SUGAR IN CASES & CONTROLS

FBS	GROUP		
	CASE	CONTROLS	Total
NORMAL	70	100	170
HIGH	30	0	30
Total	100	100	200

TABLE 9 : FASTING SERUM INSULIN LEVELS & FASTING BLOOD GLUCOSE

SERUM INSULIN	FBS HIGH	FBS NORMAL	TOTAL
HIGH	30	0	30
NORMAL	0	2	2
TOTAL	30 (93.75%)	2 (6.25%)	32(100%)

S. INSULIN	GROUP		Total
	CASE	CONTROLS	
NORMAL	68	100	168
HIGH	32	0	32
Total	100	100	200

TABLE 10 :ASSOCIATION OF S.INSULIN WITH BMI & ACANTHOSIS NIGRICANS

S.INSULIN VERSUS BMI

TABLE-23

BMI- WT(kg)/HT(m2)

		Normal	Over weight	Obese 1	Obese 2	Obese 3	Total
S.INSULIN	NORMAL	22%	21%	17%	7%	1	68%
	HIGH	0	1%	4%	19%	8%	32%
Total		22%	22%	21%	26%	9%	100%

S. INSULIN VERSUSS TYPE OF AN

TABLE-24

		TYPE OF AN				
		BAAN	OBESITY AN	MALIGNANT AN	ACRAL AN	Total
S.INSULIN	NORMAL	8%	49%	5%	6%	68%
	HIGH	2%	29%	0	1%	32%
Total		10%	78%	5%	7%	100%

PHOTOGRAPHS





V. Discussion

AN is closely associated with insulin resistance and it has been called as a clinical surrogate for laboratory determined hyperinsulinemia. Insulin resistance is a metabolic disorder in which target cells fail to respond to normal levels of circulating insulin, resulting in compensatory hyperinsulinemia. In this study, majority of the cases were in between 30- 40 years of age (28%). Mean age of the cases and controls was 37.5 years making the two group statistically comparable. In a study done by Varthakavi et al [1] the average age of cases with acanthosis nigricans 26.3+/- 1.7 years. This study showed slight female preponderance of acanthosis nigricans with a male to female ratio of 1:1.4. Other studies done by Stoddart et al [2] , Stuart et al [3] 100 and Varthakavi et al[1]. 96 have also shown female preponderance. In this study, out of 30 cases(30%) with diabetes mellitus and acanthosis nigricans , 12 cases(40%) had family h/o diabetes mellitus and none of the controls had family h/o of diabetes mellitus. Similar results were seen in a study done by Stoddart et al and Kong et al[4]. Neck was the most common site involved (61%). The second most common site of involvement was the axilla, neck , groin (29%), followed by groin, axilla and neck in 7% of cases. 32% of cases with acanthosis nigricans involving the neck had high fasting serum insulin levels. Grandhe et al[5] , Varthakavi et al [6] , Neerja Puri [7] had

similar results in which Nape of neck was the most frequently affected site. In a study done by Luby et al fasting plasma insulin concentration was directly proportional to severity of the acanthosis nigricans involving the neck.[8] In this study there were Twenty two cases (22%) with normal BMI. Seventy eight cases (78%) were either obese or overweight. Most of the cases belonged to obese category (56%). Number of cases with acanthosis nigricans correlated with the increase in BMI. P was highly significant ($p<0.003$). In a study done by Venkataswamy s and Anandam mean BMI was 32.36 kg/m2 and they also found that BMI was significantly higher in patients with acanthosis nigricans.[9] 112 In this study , out of 32% cases with high fasting serum insulin levels, 19% of cases had class II obesity , 8% of cases had class III obesity, 4% of cases had obese class I and 1% of cases were overweight. There was a significant association of fasting insulin levels increase in body mass index. (p 0.001) Burke et al found that severity of acanthosis nigricans was associated with elevated fasting insulin and increased Body Mass Index. He also reported prevalence of acanthosis nigricans to be 41.1% in diabetic patients and 31.6% in healthy individuals.[10] In a case control study done by Venkataswamy s and Anandam using fasting serum insulin as the diagnostic test it was found that patients with acanthosis nigricans were significantly more insulin resistant than the controls without acanthosis nigricans. The same results were obtained even when HOMA used as diagnostic test.[11] Out of 100 cases in this study , 78% of cases predominantly had obesity associated acanthosis nigricans of which 29% of cases were males and 49% cases were females and it was predominantly seen in the age group of 30-40 years. obesity AN has statistically significant association with high fasting serum insulin levels ($p=0.001$). There was a positive association of fasting insulin level with increase in BMI , increase in fasting blood glucose and with obesity associated acanthosis nigricans. In a Study done by Martha L. Stoddart, Kathleen S. Blevins and Wenyu Wang et al, Higher insulin levels were observed in female subjects, overweight/obese individuals, those with type 2 diabetes, and those with family history of type 2 diabetes. Obesity AN wassignificantly associated with hyperinsulinemia ($P = 0.0001$) in multivariate analysis.[12] Out of 100 cases in this study 58% cases had underlying comorbid conditions. Twenty two cases (37.9%) had Type 2 DM, six cases (10.3%) had PCOD with hirsutism ,six cases(10.3%) had metabolic syndrome, four cases(6.89%) had hypertension, Fifteen cases (25.8%) had hypothyroidism and Five cases(8.62%) had underlying malignancies. None of the controls had any comorbidities. There was significant association of acanthosis nigricans with Type 2 DM , metabolic syndrome and PCOD. P value was significant (0.003). It correlated with various studies done by Robert et al [13] , Scott [14] 110 & Charnvises et al.[15] In this study Twenty percent (20%) of the cases had skin tags , out of which 10 cases(55.5%) had type 2 DM and obesity AN. P value was highly significant ($p=0.003$). In a Case-Control Study of Achrochordons as a Cutaneous Sign of Metabolic Syndrome by R Shah, A Jindal, and NM Patel A total of 110 patients having two or more achrochordons and age- and gender matched 110 controls were included in the study. A total of 58 patients and 12 controls with achrochordons were diagnosed with overt diabetes mellitus (DM) and it was statistically significant.[16] In this study, out of 32 cases with high fasting serum insulin levels, thirty cases (93.75%) had high fasting blood glucose levels. P value is highly significant (0.001) , 29 % cases had obesity associated acanthosis nigricans nigricans and there was a significant association of fasting insulin levels increase in body mass index. ($p <0.001$). Similar results were seen in studies done by Grandhe et al (62.6%), Stoddart et al (15%), Neerja Puri [17] , (hyperinsulinaemia in 40%, diabetes in 30%), Mukhtar et al [18] (39.4%).

VI. Conclusion

Acanthosis nigricans is found to have female preponderance in this study with mean age of onset between 30-40 years. The most common site of involvement was neck and second most common was axilla. The most common type of acanthosis nigricans in this was obesity associated acanthosis nigricans. Body mass index, was significantly higher in cases with obesity compared to controls and there was also increase in fasting insulin levels in cases compared to controls increasing their risk for diabetes mellitus in the future. Therefore we conclude that acanthosis nigricans is independently associated with hyperinsulinemia and therefore may be useful as an early indicator for type 2 diabetes mellitus. So, early screening for acanthosis nigricans can serve as a diagnostic aid in identifying population at risk of developing metabolic diseases.

References

[1]. Varthakavi PK, Waingankar A, Patel KL, Wadhwa SL, Khopkar U, Sengupta RA et al. Acanthosis Nigricans : A dermatologic marker of metabolic disease. Indian J of Dermatol Venereol Leprol.2002;68(2):67-72.
[2]. Stoddart ML, Blevins KS, Lee ET, Wang W, Blackett PR. Association of acanthosis nigricans with hyperinsulinemia compared with other selected risk factors for type 2 diabetes in Cherokee Indians: the
[3]. Cherokee Diabetes Study.Diabetes Care. 2002; 25: 1009-14.
[4]. Stuart CA, Gilkison CR, Keenan BS, Nagamani M.Hyperinsulinemia and acanthosis nigricans in African Americans. J Natl Med Assoc. 1997 Aug;89(8):523-7.

[5]. Kong AS, Williams RL, Rhyne R, Urias-Sandoval V, Cardinali G,Weller NF et l. Acanthosis Nigricans: high Prevalence and Association with Diabetes in a Practice-based Research Network Consortium—A Primary care Multi-Ethnic Network (PRIME Net) Study. PRIME Net Clinicians J Am Board Fam Med. 2010;23(4):476–485.
[6]. 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- 4.
[7]. Varthakavi PK, Waingankar A, Patel KL, Wadhwa SL, Khopkar U, Sengupta RA et al. Acanthosis Nigricans : A dermatologic marker of metabolic disease. Indian J of Dermatol Venereol Leprol.2002;68(2):67-72.
[8]. Puri N. A Study of pathogenesis of Acanthosis Nigricans and its clinical implications. Indian J of Dermatol. 2011;56(6):678-83.
[9]. Kathleen King, Luby Garza, Jan Marie Ozias.The US Surgeon General's, TDH Diabetes Program/Texas Diabetes Council. 2002; 62:2.
[10]. Venkatswami S and Anandam Acanthosis nigricans: a flag for insulin resistance, Journal of Endocrinology, Metabolism and Diabetes of South Africa, (2014) 19:2, 68-74.
[11]. Burke JP, Hale DE , Hazuda HP, Stern MP. A quantitative scale of acanthosis nigricans. Diabetes care 1999;22(10):1655-9.
[12]. Venkatswami S and Anandam Acanthosis nigricans: a flag for insulin resistance, Journal of Endocrinology, Metabolism and Diabetes of South Africa, (2014) 19:2, 68-74.
[13]. Stoddart ML, Blevins KS, Lee ET, Wang W, Blackett PR. Association of acanthosis nigricans with hyperinsulinemia compared with other selected risk factors for type 2 diabetes in Cherokee Indians: the Cherokee Diabetes Study.Diabetes Care. 2002; 25: 1009-14.
[14]. Henry RR. Insulin Resistance: from predisposing factor to therapeutic target in type 2 diabetes .Clinical therapeutics.2003;25(3):b47-63.
[15]. Scott AT, Metzig AM, Hames RK, Schwarzenberg SJ, Dengel DR, Biltz GR et al. Acanthosis nigricans and oral glucose tolerance in obese children. Clin Pediatr. 2010;49(1):69-71.
[16]. Charnvises K, Weerakiet S, Tingthanatikul Y, Wansumrith S, Chanprasertyothin S, Rojanasakul A. Acanthosis nigricans: clinical predictor of abnormal glucose tolerance in Asian women with polycystic ovary syndrome. Gynecol Endocrinol. 2005;21(3):161-4.
[17]. R Shah, A Jindal, NM Patel Acrochordons as a Cutaneous Sign of Metabolic Syndrome: A Case-Control Study 2014 Mar-Apr; 4(2): 202–205.
[18]. Puri N. A Study of pathogenesis of Acanthosis Nigricans and its clinical implications. Indian J of Dermatol. 2011;56(6):678-83.
[19]. 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): 372-6.
[20]. Appropriate body mass index for asian populations and its implications for policy and intervention strategies. WHO Expert consultation. Lancet.2004;363 (9403):157-63.

Source of Support: None Declared
Conflict of Interest: None Declared

N Sai Pujitha.et.al. "Systemic Association of Acanthosis Nigricans and Its Role as a Marker of Insulin Resistence- A Case Control Study."*IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 19(1), 2020, pp. 17-24.