



Clinical Evaluation of Acanthosis Nigricans and Its Correlation with Endocrine, Metabolic and Nutritional Factors in Gujarat, India

Sohan A Patel^{1*}, Jayant B Dave², and Timir Y Mehta³

¹ Assistant Professor, Smt. S. M. Shah Pharmacy College, Amasaran, Gujarat, 387130 India.

² L. M. College of Pharmacy, Ahmedabad, Gujarat, 380009 India.

³ Samarpan Medical research organization, Modasa, Gujarat, 383315 India.

Abstract: Acanthosis nigricans (AN) refers to the velvety, black hyperpigmentation in flexures usually on the neck and axillae. AN is associated with multiple endocrinopathies and insulin resistance is reported to be a common denominator among them. The aim of the study was to identify the correlation of metabolic factors (Serum glucose, lipid profile), endocrine factors (TSH, serum insulin), and nutritional factors (vitamin B12, Ferritin) in AN patients in Aravalli district of Gujarat state. A total of Seventeen Patients (11 male and 6 female) were included in the study. History, clinical observations, physical parameters, and biochemical tests were noted in AN patients and correlation of some likely factors with AN was explored. The age was 28.41 ± 15.09 years for AN group and 35.45 ± 8.74 years for control group. The mean BMI was found to be higher in AN at 1 % level of significance ($P = 0.007$) implying that overweight/obesity is associated with AN. The mean TSH value was found to be higher in AN than control group at 5 % level of significance ($P = 0.0115$) implying that hypothyroidism (elevated TSH value) is associated with AN. The 45.45 % patients had higher blood glucose levels and some of the patients had higher level of insulin. The mean lipid profile, vitamin B12 and serum ferritin were found to be at non-significance level. All statistical tests were performed using graph pad prism software (version 5.0). Positive correlations were observed between higher fasting glucose and hyperinsulinemia with AN and others factors such as metabolic and endocrine like overweight/obesity, hypothyroidism, higher glucose and serum insulin with AN. This implies that AN can serve as a marker for detecting hyperinsulinemia and hypothyroidism. Some of the parameters like, Serum lipid profile, vitamin B12 and ferritin levels could not be correlated to AN. Thus, patients with AN can be targeted for lifestyle and behavioral modifications at an early stage to avoid the serious consequences of AN.

Key Words: Acanthosis Nigricans, Body Mass Index, TSH, Plasma Glucose, Serum Insulin

***Corresponding Author**

Sohan A Patel, Assistant Professor, Smt. S. M. Shah College of Pharmacy, Amasaran, Gujarat, 387130 India.



Received On 02 August 2021

Revised On 30 September 2021

Accepted On 04 October 2021

Published On 05 November 2021

Funding This research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors.

Citation Sohan A Patel, Jayant B Dave, and Timir Y Mehta, Clinical Evaluation of Acanthosis Nigricans and Its Correlation with Endocrine, Metabolic and Nutritional Factors in Gujarat, India. (2021). Int. J. Life Sci. Pharma Res. 11(6), L1-7
<http://dx.doi.org/10.22376/ijpbs/lpr.2021.11.6.L1-7>

This article is under the CC BY- NC-ND Licence (<https://creativecommons.org/licenses/by-nc-nd/4.0>)



Copyright © International Journal of Life Science and Pharma Research, available at www.ijlpr.com

1. INTRODUCTION

Acanthosis nigricans (AN) is a dermatological disorder characterized by dark, thick, velvety, black hyperkeratotic plaques, typically on the intertriginous surfaces and neck.^{1,2} AN is characterized by symmetrical hyper pigmented and hyperkeratotic plaques of the skin mainly affecting the folds of the axillae, groin, and back of the neck.³ AN is Classified into various types such as benign AN, obesity-associated AN, syndromic AN, malignant AN, acral AN, unilateral AN, medication-induced AN, and mixed-type AN.^{1,4} AN is diagnosed clinically and confirmed with a skin biopsy, blood tests, endoscopy, or x-rays may be required to eliminate diabetes or cancer. The majority of cases are associated with insulin resistance and/or obesity, screening for diabetes, and measuring glycosylated hemoglobin is also recommended. Several hormonal markers such as thyroid function tests, free testosterone, 17 (OH) progesterone, dehydroepiandrosterone sulfate (DHEAS), cortisol, gonadotropins, prolactin, immunoreactive insulin, and C-peptide levels measurements were made by radioimmunoassays.⁵ Associated with malignancy, the recognition of its more common connection to obesity and insulin resistance allows for the diagnosis of related disorders including type 2 diabetes, metabolic syndrome, and polycystic ovary syndrome.⁶ The prevalence varies, according to age, race, frequency of type, degree of obesity, and concomitant endocrinopathy.⁷ The dermatologist has an important role in identifying the subset of obese patients with acanthosis nigricans.⁸ Insulin resistance has been associated with the presence of AN.⁹ AN is associated with a variety of Endocrine imbalance, including Acromegaly, Cushing's syndrome, and polycystic ovary.¹⁰ AN is a dermatological marker of hyperinsulinemia and has been linked with metabolic syndrome in adults.^{11,12} BMI was a more sensitive screening tool than acanthosis nigricans alone, or acanthosis nigricans and BMI together for identifying children and youth with insulin resistance (IR) who are at increased risk for type 2 diabetes.¹³ Other metabolic conditions such as diabetes mellitus and impaired glucose tolerance and some other clusters of metabolic syndromes such as dyslipidemia, polycystic ovary, and arterial hypertension could also be associated.^{1,14} Investigation of AN are fasting lipoprotein profile, fasting glucose, fasting insulin, hemoglobin, and alanine aminotransferase for obesity-associated AN and radiological investigations (plain radiography, ultrasonography, magnetic resonance imaging/computerized tomography) for malignancy-associated AN.^{15,16} Acanthosis nigricans may also be idiopathic and thyroid dysfunction should be considered.^{17,18} AN occurs frequently in adolescents associated with obesity, a chronic illness that often begins in childhood and has a tremendous impact on an individual's future health.^{15,19} Patients with AN, especially childhood benign AN, are at risk for obesity, hypertension, hyper insulinemia, IR, and type 2 diabetes and AN may be used as a reliable index of IR.²⁰ The prevalence of AN in non-select populations varies from 7 to 74%, according to age, race, frequency of type, and degree of obesity and concomitance with endocrinopathy.²¹ Metabolic syndrome (MS) refers to a clustering of metabolic risk factors including central obesity, glucose intolerance, hyperinsulinemia, low high-density lipoprotein-cholesterol (HDL-C), high triglycerides (TGs), and hypertension.²² Obese adolescents at risk of type 2 diabetes were identified with a low or borderline B12 status.²³ All these studies confirmed the role of various metabolites, endocrines and nutrients factors in the

development of AN. So detailed study of these parameters in AN Patients are needed for the hour. So far, the investigation about these factors with AN in Aravalli district of Gujarat state in India has not been conducted. So, in this present study, our research group tried to identify the association and the role of metabolic factors (Serum glucose, insulin resistance, lipid profile), endocrine factors (TSH, serum insulin), and nutritional factors (vitamin B12, Ferritin) in AN patient in rural area of the Aravalli district. This study has been conducted to investigate the etiology, pathogenesis, and clinical profile in patients with AN.

2. MATERIALS AND METHODS

2.1 Participates

It was a cross-sectional hospital-based study. Seventeen patients of AN attending the dermatology OPD at Samarpan medical research organization, Modasa, Gujarat, India, and twenty-two healthy volunteers (Age from 25-50 years) were also included in this study as normal control. The Study was done from 1st November 2016 to 30th March 2018. Clinical-epidemiological data regarding the patients were noted in the case record form. Patients were included in this study after receiving informed written consent. Patients were diagnosed clinically by a dermatologist. All the patients included in the study were 10-60 years of age. Required permission for carrying out the study was obtained from Sarvajanik clinical research ethics committee, Mehsana (Ref. SCREC/2019-20/07). All participation was voluntary. The study was conducted by declaration of Helsinki.

2.2 Criteria and sites for Acanthosis nigricans

Five anatomical sites were chosen to assess the presence and extent of AN: the neck, axilla, knuckles, elbows, and knees. All these criteria were determined by a dermatologist.

2.2.1. Inclusion criteria

1. To Sign an informed consent form.
2. 10 – 60 year of old patients were included.
3. No systemic diseases
4. Both male and female patients

2.2.2. Exclusion criteria

1. Patients not willing for the study
2. Patients with acute and chronic illness
3. Participants with a history of severe systemic disease
4. Pregnant and lactating women
5. Patients on medications which can cause drug induced acanthosis nigricans (nicotinic acid, fusidic acid, stilbestrol in young males, triazinate, folic acid antagonists, antiretroviral drugs, insulin, pituitary extract, systemic corticosteroids, diethylstilbestrol, oral contraceptives, methyltestosterone and growth hormone therapy).

2.3. Study procedure

All patients (11 male and 6 female) underwent a detailed physical examination including height (in meter) and weight (in kg). From these data, body mass index (BMI) was calculated. The BMI was calculated by weight in kilograms divided by height in meters square (kg/m^2). Several researchers described AN based-on body mass index ratio (BMI). BMI was classified as per the World Health Organization criteria. (Table 1)

Table 1: Classification of Body mass index	
Classification	BMI (kg/m ²)
Underweight	< 18.5
Healthy weight	18.5 – 24.9
Overweight (pre-obesity)	25 – 29.9
Obesity, class I	30 – 34.9
Obesity, class II	35 – 39.9
Obesity, class-III	> 40

The above table reveals classification of body mass index (BMI) according to weight in kg divided height in meter square.

Other clinical markers for AN were tested from a fasting blood sample. The metabolic factors like, blood glucose and lipid profile (Total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol), Endocrine factors like thyroid stimulating hormone (TSH) and serum insulin, and nutritional factors like vitamin B12 and ferritin were estimated in Satyam laboratory, Modasa, India.

3. STATISTICAL ANALYSIS

All statistical tests were performed using GraphPad Prism 5.0 version software, and quantitative data were expressed as mean $\pm$ standard deviation ($\bar{x} \pm SD$) and count data as the number of columns (n). Students unpaired 't' test was used to establish correlation between different risk factors and AN at 1 % and 5 % significance level ($P < 0.01$ and $P < 0.05$). 't' value was also calculated using a statistical formula and

compared with the tabulated 't' value for accepting or rejecting the null hypothesis.

3. RESULTS AND DISCUSSION

The purpose of cross-section and hospital-based study was to evaluate the occurrence of acanthosis nigricans in a rural area of north Gujarat, India and its association with metabolic, endocrine and nutritional factors and their causal relationship.

3.1 Clinico Epidemiological features

3.1.1 Age and sex

Total seventeen patients with AN were included in this study that also covered 11 male (64.70 %) and 6 Females (35.30 %).

Table 2 Age wise Distribution		
AGE (In year)	NUMBER OF PATIENTS	%
0-10	00	00
11-20	08	47.05
21-30	01	5.88
31-40	04	23.52
41-50	03	17.64
>50	01	5.88
TOTAL	17	100

Their age ranged from 11-50 years with a mean $\pm$ standard deviation of 28.41 ± 15.09 years. The patients were distributed in different age groups ranging from 11 to 50 years. In this 47.05 % of patients in 11-20 years of age, 5.88 % of patients in 21-30 years of age, 23.52 % patients in 31-40 years of age, 17.64 % of patients in 41-50 years of age, and 5.88 % patients is more than 50 year of age with a mean of 28.41 ± 15.09 (Table 2). In the normal control group (17 (77.27%) Male and 5 (22.72%) female), the age ranged from 25-45 years with a mean $\pm$ standard deviation of 35.45 ± 8.744 years. Higher prevalence of AN was found in the age group of 11-20 years and this might affect the psychological status and quality of life in adults.

3.1.2. Sites

In this study, the neck was the most common site involved, followed by the axilla, face, and groin. Other sites such as the antecubital fossa, knuckles, and sub mammary areas were also involved (Figure 1).

3.1.3. Body mass index (BMI)

The mean BMI was found to be 27.54 ± 3.74 kg/m² in AN.

Table 3 Body mass index of AN and control group				
ACANTHOSIS NIGRICANS		CONTROL		P
BMI (kg/m ²)	(N=17)	%	(N=22)	%
< 18.5	00	00	01	4.54 %
18.5-24.9	05	29.41 %	13	59.09 %
25-29.9	08	47.05 %	07	31.81 %
30-34.9	02	11.76 %	02	9.09 %
MORE THAN 35	02	11.76 %	00	00
TOTAL	17	100 %	22	100 %
Mean ± SD	27.54 ± 3.748		23.78 ± 4.303	

The values are Mean ± SD of BMI ($P < 0.05$), * = less significant, *** = Highly significance, ** = Moderate significance,

The values are Mean ± SD of BMI ($P < 0.05$), *** = Highly significance, ** = Moderate significance, * = less significance

The mean values are significantly different from the control group 23.78 ± 4.30 at 1 % level of significance ($P = 0.007$). This is also indicated by rejection of the null hypothesis where calculated 't' value (2.7912) is higher than tabulated 't' value (2.234) ($t_c > t_T$). This implies that overweight/obesity is associated with AN. Out of the AN group, 70.57% were

found to be overweight/obese as against 40% seen in the control group (Table 3). The positive correlation between obesity & AN observed in the study is in agreement with published data. The prevalence of overweight is a greater risk factor for the development of AN.²⁴ Pankaj et al.²⁵ has also reported the presence of obesity induced AN or pseudo-AN in 70%, syndromic AN in 23.4%, and malignant AN in 6.6% of Indian patients.

3.1.4. Lipid profile

Table 4 Lipid profile of AN and control group			
LIPID PROFILE	ACANTHOSIS NIGRICANS (N=17)	CONTROL (N=22)	P
TOTAL CHOLESTEROL (mg/dl)	150±29.86	158.2±27.30	0.4098 ^{ns}
TRIGLYCERIDES (mg/dl)	112.1±39.77	121.3±48.72	0.4601 ^{ns}
HDL CHOLESTEROL (mg/dl)	46.98±13.77	43.38±3.50	0.2460 ^{ns}
LDL (mg/dl)	82.04±24.21	90.51±26.92	0.4269 ^{ns}
VLDL (mg/dl)	21.91±8.973	24.26±9.743	0.4539 ^{ns}
LDL/HDL	2.043 ± 0.506	2.109 ± 0.659	0.7395 ^{ns}
TOTAL/HDL	38.27 ± 139	36.84 ± 0.746	0.6728 ^{ns}
TOTAL LIPIDS	563.0 ± 169.0	614.4 ± 86.60	0.0929 ^{ns}

The values are Mean ± SD ($P < 0.05$), ns – non-significant

The mean lipid profile was not found to be different in control and AN group at 5 % significance level. It was unexpectedly a bit lower than the control group except HDL. The P value of total lipid 0.929 and higher values for individual lipids (Table 4). This implies that lipid profile was not elevated in AN group. The results are not in agreements with published literature. The previous study has also shown

that TSH levels are slightly increased in obesity and are associated with BMI²⁶.

3.1.5. Thyroid stimulating hormones (TSH)

The mean TSH was found to be 2.99 ± 2.42 miu/l in AN.

Table 5 TSH level of AN group and control group			
	ACANTHOSIS NIGRICANS (n= 15)	CONTROL (n=22)	P Value
TSH (miu/l)	2.99 ± 2.424	1.515 ± 0.1750	0.0115*

The values are Mean ± SD of TSH ($P < 0.05$), * = less significant

The mean values were significantly higher than control group 1.54 ± 0.17 at 5 % level of significance ($P = 0.0115$). This implies that hypothyroidism (elevated TSH value) is associated with AN (Table 5). The positive correlation between hypothyroidism along with obesity has also been

reported in literature. AN is associated with multiple endocrinopathies and insulin resistance is reported to be a common denominator among them. The mechanism of insulin resistance has been reported to be a post receptor binding defect or structure abnormality in circulating insulin.

Hyperinsulinemia is a regular correlate of skin disorders. It has also been reported that Hypothyroidism may be associated with AN and that treatment of hypothyroidism does not resolve hyperinsulinemia or AN.²⁷ Literature also reports that obese women are more prone to AN than men. Higher TSH value has been proposed to be protective

factors in obese women that improve fat distribution in obesity.²⁸

3.1.6. Fasting blood glucose and insulin

The mean fasting blood glucose was found to be 93.33 ± 11.83 mg/dl.

Table 6 Blood glucose level	
Fasting Blood glucose	Number of Patients
Normal Blood glucose level (< 99 mg/dl)	06 (54.54 %)
Higher Blood glucose level (> 99 mg/ml)	05 (45.45 %)
Total	11 (100%)
Mean $\pm$ SD (mg/dl)	93.33 ± 11.83

Table 6, reveal number of patients had fasting blood glucose within normal range and higher level

Table 7: Data of insulin in AN patient	
Patients	Level of insulin (miu/l)
1	32.59
2	52
3	89
4	213.49

The table reveal level fasting insulin in AN patients

In 6 out of 11 cases, the FPG values were normal (less than 100 mg/dl) and in 5 out of 11 cases, FPG values were above normal (Table 6). Out of 5 patients with elevated FPG, 4 were tested for fasting levels of insulin and 4 out of 4 showed hyperinsulinemia (Table 7). The positive correlation between fasting glucose/hyperinsulinemia and AN group observed in the study are in agreements with published data. A directly proportional relationship between serum insulin levels and AN severity has been documented^{11,29}. Native Americans were reported to have higher BMI and fasting insulin levels, and lower HDL-Cholesterol in cases with

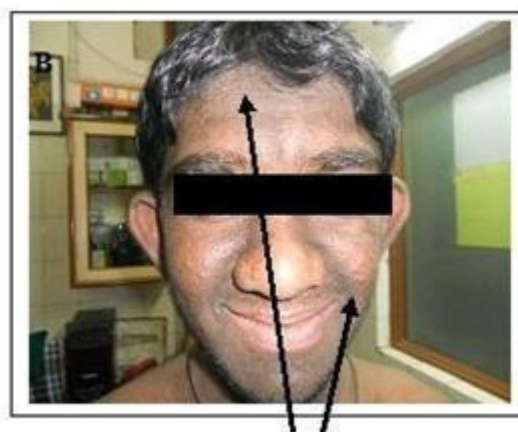
those with less severe AN^{30,31}.

3.1.7. Serum vitamin B12 and ferritin

The serum vitamin B12 level was observed in four patients of AN (Mean $\pm$ SD, 421 ± 131.6 pg/ml). All values are in normal range (211-911 pg/ml). The serum ferritin level observed in two patients of AN (Mean $\pm$ SD, 41.25 ± 2.33 ng/ml). Both values are in normal range (30-450 ng/ml). No correlation was observed between vitamin B12 or ferritin levels with AN.



AN at the neck



AN at Face

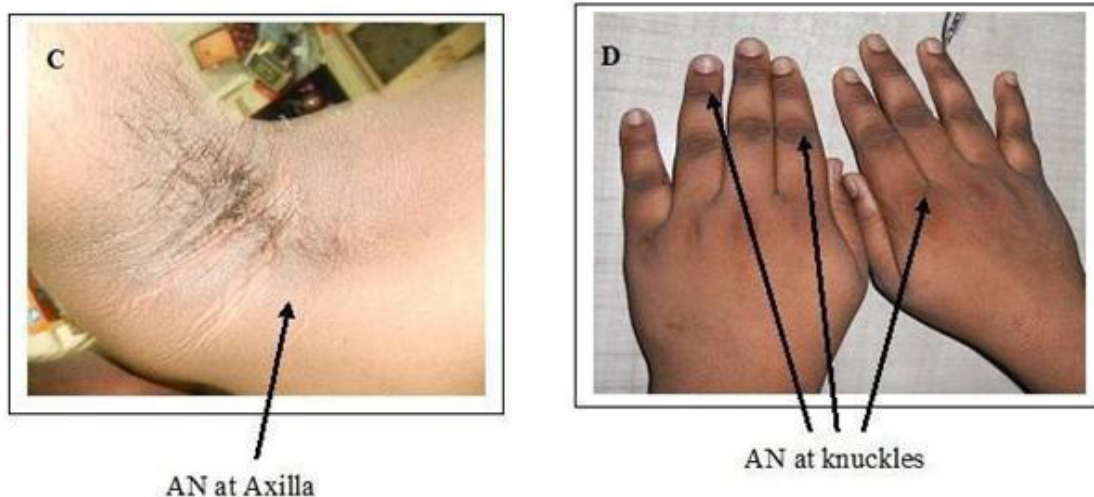


Fig 1: A: AN at Neck; B: AN at Face; C: AN at Axilla; D: AN at knuckles

4. CONCLUSION

Positive correlations were found between several metabolic and endocrine factors like overweight/obesity, hypothyroidism (elevated TSH value), higher serum glucose and serum insulin and AN. This implies that AN can serve as a marker for detecting hyperinsulinemia, hypothyroidism and related conditions. No correlation was found between lipid profile, vitamin B12 and ferritin with AN. It is important to identify persons at high risk of early detection, regular screening and management can help to decrease the risk of AN. The present study has showed poor awareness of AN in rural population. Thus, patients with AN can be targeted for lifestyle and behavioral modifications at an early stage to avoid the serious consequences of AN.

5. Limitation of study

The number of the patients for the study is very small and therefore it is not possible to get a solid conclusion but

contributes to the objective of our study and helps further research for better AN therapy.

6. AUTHORS CONTRIBUTION STATEMENT

Dr. Timir Y. Mehta, consultant to patients and diagnosed Acanthosis nigricans patients. Dr. J. B. Dave and Mr. Sohan A. Patel collected and analyzed patient's data and necessary inputs were given towards the designing of the manuscript. All authors discussed the methodology and results and contributed to the final manuscript.

7. ACKNOWLEDGEMENTS

The authors thanked the patients for the cooperation in our study.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

9. REFERENCES

1. Venkatswami S, Anandam S. Acanthosis nigricans: a flag for insulin resistance. *J Endocrinol Metab Diabetes S Afr.* 2014 Jan 1;19(2):68-74. doi: 10.1080/16089677.2014.11073603.
2. Fasunla JA, Ijaluola GT. Acanthosis nigricans in the head and neck region. *Ann Ibadan Postgrad Med.* 2008;6(1):53-6. doi: 10.4314/aipm.v6i1.64043, PMID 25161446.
3. Shah NG, Khatu SS, Gokhale NR, More YE, Khismatrao D. Acanthosis nigricans: A cutaneous marker for metabolic syndrome. *Med J DY Patil Vidyapeeth.* 2019 Jan 1;12(1):16.
4. Barbato MT, Criado PR, Silva AK, Averbeck E, Guerine MB, Sá NB. Association of acanthosis nigricans and skin tags with insulin resistance. *Anais brasileiros de dermatologia.* 2012 Feb;87(1):97-104.
5. Puri N. A study of pathogenesis of acanthosis nigricans and its clinical implications. *Indian J Dermatol.* 2011 Nov;56(6):678-83. doi: 10.4103/0019-5154.91828, PMID 22345770.
6. Singh SK, Agrawal NK, Vishwakarma AK. Association of acanthosis nigricans and acrochordon with insulin resistance: A cross-sectional hospital-based study from North India. *Indian J Dermatol.* 2020 Mar;65(2):112-7. doi: 10.4103/ijd.IJD_646_18, PMID 32180596.
7. Katz AS, Goff DC, Feldman SR. Acanthosis nigricans in obese patients: presentations and implications for prevention of atherosclerotic vascular disease. *Dermatol Online J.* 2000 Sep;6(1):1. PMID 11328611.
8. Barbato MT, Criado PR, Silva AK, Averbeck E, Guerine MB, Sá NB. Association of acanthosis nigricans and skin tags with insulin resistance. *An bras dermatol.* 2012 Feb;87(1):97-104. doi: 10.1590/s0365-05962012000100012, PMID 22481657.
9. Sreedevi C, Car N, Pavlic-Renar I. Dermatologic lesions in diabetes mellitus. *Diabetol Croat.* 2002;31(3):147-59.
10. Corina D, Monica M, Adela CE, Teodora C, Camelia D, Sabău I, Ioana M. The role of acanthosis nigricans in identifying clinical and metabolic features of the

- metabolic syndrome in obese children. *Acta Med Marisiensis*. 2011 Oct 1;57(5).
11. Stoddart ML, Blevins KS, Lee ET, Wang W, Blackett PR, Cherokee Diabetes Study. 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 Jun 1;25(6):1009-14.
12. Nsiah-Kumi PA, Beals J, Lasley S, Whiting M, Brushbreaker C, Erickson J, Qiu F, Yu F, Canaris G, Larsen JL. Body mass index percentile more sensitive than acanthosis nigricans for screening Native American children for diabetes risk. *J Natl Med Assoc*. 2010 Oct 1;102(10):944-9. doi: 10.1016/s0027-9684(15)30714-8, PMID 21053710.
13. Araújo LM, Porto MV, Netto EM, Ursich MJ. Association of acanthosis nigricans with race and metabolic disturbances in obese women. *Braz J Med Biol Res*. 2002 Jan;35(1):59-64. doi:10.1590/s0100-879x2002000100008.
14. Guevara-Gutiérrez E, Tlacuilo-Parra A, Gutiérrez-Fajardo P, Sánchez-Tenorio T, Barba-Gómez F, Miranda-Díaz A. A study of the association of acanthosis nigricans with subclinical atherosclerosis. *Indian journal of dermatology, venereology and leprology*. 2017 Mar 1;83(2).
15. Phiske MM. An approach to acanthosis nigricans. *Indian Dermatol Online J*. 2014 Jul;5(3):239-49. doi: 10.4103/2229-5178.137765, PMID 25165638.
16. Bhati N, Sashindran VK, Philip S. Acanthosis nigricans in patients with HIV infection and its relation to metabolic syndrome. *Int J HIV Aids Res*. 2019; Feb;2(1).
17. Verdich J. Acanthosis nigricans associated with adenocarcinoma of the thyroid gland. *Dermatologica*. 1980;161(5):355-60. doi: 10.1159/000250388, PMID 7439484.
18. Ng HY. Acanthosis nigricans in obese adolescents: prevalence, impact, and management challenges. *Adolesc Health Med Ther*. 2017;8:1-10. doi: 10.2147/AHMT.S103396, PMID 28031729.
19. Das A, Misra P, Panda S. Childhood acanthosis nigricans. *Indian Journal of Paediatric Dermatology*. 2019 Jul 1;20(3):199.
20. Araújo LMB, Viveiros AMCd, Lopes RC, Viana AdC, Fukui RT, Ursich MJM. Acanthosis nigricans in obese women in a mixed-race population: a marker of metabolic disturbances. *An Bras Dermatol*. 2002 Oct;77(5):537-43. doi: 10.1590/S0365-05962002000500003.
21. Shah NG, Khatu SS, Gokhale NR, More YE, Khismatrao D. Acanthosis nigricans: A cutaneous marker for metabolic syndrome. *Med J DY Patil Vidyapeeth*. 2019 Jan 1;12(1):16. doi: 10.4103/mjdrdypu.mjdrdypu_44_18.
22. Varthakavi PK, Waingankar A, Patel KL, Wadhwa SL, Khopkar U, Sengupta RA, Merchant PC, Mehtalia SD, Nihalani KD. Acanthosis nigricans: A dermatologic marker of metabolic disease. *Indian J Dermatol Venereol Leprol*. 2002 Mar 1;68(2):67-72.
23. Ho M, Halim JH, Gow ML, El-Haddad N, Marzulli T, Baur LA, Cowell CT, Garnett SP. Vitamin B12 in obese adolescents with clinical features of insulin resistance. *Nutrients*. 2014 Dec;6(12):5611-8. doi: 10.3390/nu6125611, PMID 25486369.
24. Kong AS, Williams RL, Smith M, Sussman AL, Skipper B, Hsi AC, Rhyne RL, RIOS Net Clinicians. Acanthosis nigricans and diabetes risk factors: prevalence in young persons seen in southwestern US primary care practices. *Ann Fam Med*. 2007 May 1;5(3):202-8. doi: 10.1370/afm.678, PMID 17548847.
25. Verma R, Jorwal P, Keshwani P. Association of acanthosis nigricans with anthropometric and biochemical parameters in young Indian males. *Ann Niger Med*. 2014 Jul 1;8(2):65. doi: 10.4103/0331-3131.153354.
26. Verma S, Vasani R, Joshi R, Phiske M, Punjabi P, Toprani T. A descriptive study of facial acanthosis nigricans and its association with body mass index, waist circumference and insulin resistance using HOMA2 IR. *Indian Dermatol Online J*. 2016 Nov;7(6):498-503. doi: 10.4103/2229-5178.193898, PMID 27990384.
27. Matsuoka LY, Wortsman J, Gavin III JR, Kupchella CE, Dietrich JG. Acanthosis nigricans, hypothyroidism, and insulin resistance. *Am J Med*. 1986 Jul 1;81(1):58-62. doi: 10.1016/0002-9343(86)90182-8, PMID 3728554.
28. Chen Y, Ma B, Sheng C, Yang P, Qu S. Thyroid hormone associated with Acanthosis nigricans and fat distribution in obese patients.
29. Bhagyanathan M, Dhayanithy D, Parambath VA, Bijayraj R. Acanthosis nigricans: A screening test for insulin resistance—An important risk factor for diabetes mellitus type-2. *Journal of family medicine and primary care*. 2017 Jan;6(1):43.
30. Hermanns-Lê T, Scheen A, Piérard GE. Acanthosis nigricans associated with insulin resistance: pathophysiology and management. *Am J Clin Dermatol*. 2004 Jun 1;5(3):199-203. doi: 10.2165/00128071-200405030-00008, PMID 15186199.
31. Copeland K, Pankratz K, Cathey V, Immohotichey P, Maddox J, Felton B, McIntosh R, Parker D, Burgin C, Blackett P. Acanthosis nigricans, insulin resistance (HOMA) and dyslipidemia among Native American children. *J Okla State Med Assoc*. 2006 Jan 1;99(1):19-24. PMID 16499154.