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ACANTHOSIS NIGRICANS, B-CELL FUNCTION AND INSULIN RESISTANCE IN TYPE 2 DIABETIC SUBJECTS

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ABSTRACT

Objective: To study the acanthosis nigricans (AN) as marker of β-cell function and insulin resistance in type 2 diabetic subjects. **Study design:** Observational study. **Place and duration:** Department of Medicine, Liaquat University of Medical and Health Sciences Jamshoro/Hyderabad from March 2016 to September 2016. **Subjects and Methods:** A sample of 70 type 2 DM subjects was divided into 2 groups with and without AN. Random and fasting blood glucose, fasting insulin, HbA1c, blood lipids, serum creatinine and bilirubin were detected and HOMA-IR model was calculated on computer. Data was analyzed on *SPSS 22.0* (USA) software at 95% confidence interval ($P \leq 0.05$). **Results:** Type 2 diabetics with acanthosis nigricans showed association with insulin resistance. The %β-cell function and %S (insulin sensivity) showed negative correlation and HOMA-IR (insulin resistance) showed positive correlation with acanthosis nigricans. Systolic and diastolic BP, random and fasting blood glucose, fasting insulin, HbA1c, triglycerides, LDLc, HDLc, and total cholesterol showed significant derangement in type 2 diabetics with Acanthosis nigricans. **Conclusion:** The present study proposes the acanthosis nigricans is a marker of insulin resistance which may be utilized in clinical practice and the HOMA-IR can serve as a marker of insulin resistance.

KEYWORDS: Acanthosis nigricans, Insulin resistance, β-cell function, Diabetes mellitus.

INTRODUCTION

The skin is largest organ of human body. It functions as an endocrine organ. It produces various hormones and its cells bear hormone receptors. Skin manifestations of systemic disorders are of value of clinical differential diagnosis. Endocrine disorders may manifest as skin disease such as the change of pigmentation. Acanthosis nigricans (AN) is a velvety brownish skin pigment disorder which has been linked to insulin resistance (IR).[1] The IR is characterized by high insulin levels in circulation in response to glucose, occurring because of insulin resistance of target cells.[1,2] Insulin resistance is precursor of metabolic disorders such as the obesity, infertility, growth disorders, glucose intolerance, diabetes mellitus (DM) and coronary artery disease.[2]

The acanthosis nigricans (AN) is one of the established skin manifestation associated with IR. The American Diabetes Association (ADA) added AN to the list of skin markers of DM in 2000.[3] A previous study[4] reported no insulin resistance in the absence of acanthosis nigricans. The AN is frequently observed over the back of neck and axilla. Axillary and nuchal AN is commonly associated with insulin resistance.[5] Skin color may hide the AN as in Negroes. Subjects with type IV Fitzpatrick AN prototype is very common in Asian population and commonly seen over the back of neck.[6] AN looks like brown to black macular pigmentation with blurred ill defined margins with varying degrees of textural changes ranging from mild roughness to frank verrucous appearance.[7,8] Keratinocyte and melanocyte of skin bear receptors for the Insulin, IGF-1 (insulin like growth factor) and for various other hormones. Insulin and IGF-1 modulate the kertinocyte proliferation resulting in peculiar epidermal hyperplasia. Stuart et al was the first who reported association of AN and IR.[9,10]

Medical literature shows scarcity of studies correlating acanthosis nigricans and insulin resistance. The present is an observational descriptive study which was planned to evaluate and analyze the acanthosis nigricans, insulin resistance and β-cell function in type 2 DM subjects at our tertiary care hospital.

SUBJECTS AND METHODS

An observational study planned to evaluate and analyze the acanthosis nigricans, insulin resistance and β-cell function in type 2 DM subjects at our tertiary care hospital of Liaquat University of Medical and Health Sciences, Jamshoro. The study covered duration of March 2016 to September 2016. A sample of 70 type 2 DM subjects was divided into 2 groups as type 2 DM subjects without AN and type 2 DM subjects with AN. Newly diagnosed cases of type 2 DM, male gender, with and without classical AN described as brown‑to‑black macular pigmentation with blurred ill‑defined margins, in the axilla, neck and or face were included. Diabetic subjects of long duration (>5 years), chronic diabetic complications of neuropathy, nephropathy and retinopathy were excluded. Diabetics with pigmentation disorders and morbid obesity were excluded. Each subject was communicated by a medical officer. Volunteer subjects were informed about the purpose of study, benefits and losses. In-depth history of willing type 2 DM subjects was taken. They were examined for skin pigmentation. Acanthosis nigricans was diagnosed by a senior medical officer and confirmed by a Consultant Dermatologist. Clinical history and physical examination findings were noted on a pre structured proforma. Patients were requested to come on next follow up day with at least 12 hour fasting for the blood sampling. Patient biodata, body weight, age, systolic and diastolic blood pressure were noted. Blood samples of fasting and random were taken from ante cubital vein after aseptic measures. Blood samples were processed according to standard procedure. Sera were separated out for the detection of fasting blood sugar, random blood sugar, glycated HbA1 (HbA1c) and blood lipids. Signing consent form is mandatory. Blood pressure was recorded as by standards of JNC VIII.[11] DM was defined as FBG ≥ 126mg/dl or RBG ≥200 mg/dl as per ADA criteria.[12] "G*lucose oxidase*" was used for detection of blood glucose and HbA1c by assay method. Chemical analyzer Hitachi 902, Roche analyzer was used for estimation of biochemical tests.[13] Blood lipids were categorized as by ATP III; cholesterol > 200mg/dL, LDL-C >130mg/dL, HDL-C <40mg/dL, VLDL-C >30mg/dL, and triglycerides >150mg/dL. Cholesterol was estimated by enzymatic (CHOD-PAP) colorimetry method, triglycerides by enzymatic (GPO-PAP) method, HDL-Cholesterol by a precipitant method and LDL-Cholesterol by Friedewald's formula as; LDL-C = TC - HDL-C – (TG/5). Homeostasis model assessment A insulin resistance (HOMA- IR) was determined with computer generated software. HOMA-IR was used as a indicator of insulin resistance because it is sensitive, validated and specific. HOMA-IR is simple to measure from fasting insulin and fasting blood glucose by computer. HOMA-IR is best alternative of gold standard glycemic clamp test.[14] Insulin resistance (HOMA-IR) was taken as normal <2, borderline 2–2.2, moderate 2.2–3 and severe >3. Study was approved by the ethical review committee of institute. Confidentiality of patient data secured by putting proforma secret and only concerned persons were allowed to collect the data. Statistical software SPSS 22.0 (Statistical Package for Social Science SPSS, Inc. Chicago, IL, USA) was used for data analysis. Continuous variables were analyzed by student`s t-test. Pearson`s and Spearman`s correlation was performed for the continuous and categorical variable association. Data analysis at P-value of ≤0.05 was taken statistically.

RESULTS

The demography and biochemical findings of 2 groups are shown in table 1. The subjects were age and body weight matched. The systolic and diastolic BP, Random and fasting blood glucose, fasting insulin, HbA1c, triglycerides, LDLc, HDLc, and total cholesterol showed statistically significant differences between type 2 diabetics with and without Acanthosis nigricans. The %β-cell function and %S (insulin sensivity) showed negative correlation and HOMA-IR (insulin resistance) showed positive correlation with acanthosis nigricans (table 2 and 3). Insulin resistance was noted high in diabetics with acanthosis nigricans. Insulin resistance showed negative Pearson`s correlation with RBG, HbA1c, %β-cell function and %S (insulin sensivity) as shown in table 2. Spearman`s correlation revealed negative association with %β-cell function, %S (insulin sensivity) and HOMA-IR. The scatter graph 1 and 2 shows the negative association of acanthosis nigricans with insulin resistance and %β-cell function.

Table 1. Demographic characteristics and biochemical findings of study subjects

	Type 2 DM	Type 2 DM+A nigricans	P-value
	Mean± SD	Mean± SD	
Age (years)	49.08±6.30	48.71±4.34	0.76
Body weight (kg)	75.29±11.50	76.00±11.90	0.79
Systolic BP (mmHg)	147.91±22.04	15.34±25.02	0.04
Diastolic BP(mmHg)	84.17±14.80	91.57±14.4	0.03
RBG (mg/dl)	237.28±71.83	268.54±56.47	0.04
FBG (mg/dl)	129.66±28.34	162.60±44.37	0.0001
Fasting Insulin (µU/L)	20.23±5.06	27.11±7.05	0.0001
HbA1c (%)	10.47±3.34	11.71±1.24	0.04
Serum Creatinine (mg/dl)	0.94±0.19	1.01±0.24	0.04
Serum Uric acid (mg/dl)	4.87±0.46	6.71±0.41	0.15

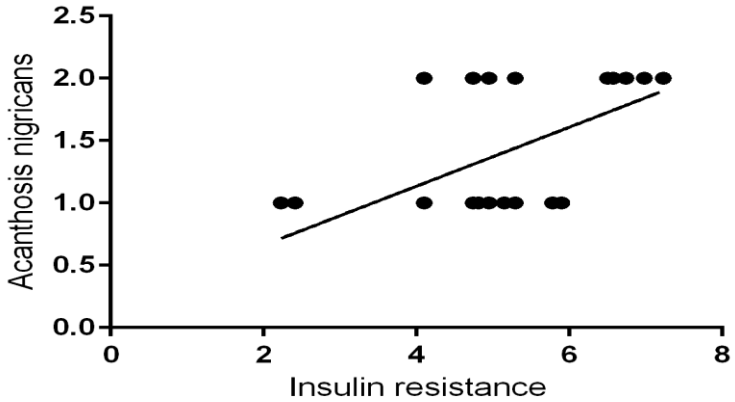
Cholesterol (mg/dl)	131.57±45.56	158.97±63.19	0.04
Triglycerides (mg/dl)	127.89±98.12	130.86±106.90	0.0001
LDL-c (mg/dl)	117.40±26.56	195.00±32.89	0.0001
HDL- c (mg/dl)	44.67±5.36	27.08±7.90	0.0001
%β-cell function	98.69±30.81	85.74±31.59	0.047
%S (insulin sensivity)	38.56±9.02	28.59±10.86	0.0001
HOMA- IR (insulin resistance)	3.85±1.21	5.12±1.11	0.0001
BP- blood pressure, RBG- random blood glucose, FBG- fasting blood glucose, HbA1c- glycated HbA1, LDL- low density lipoprotein, HDL- high density lipoprotein			

Table 2. Pearson`s correlations of Insulin resistance (IR) with different variables

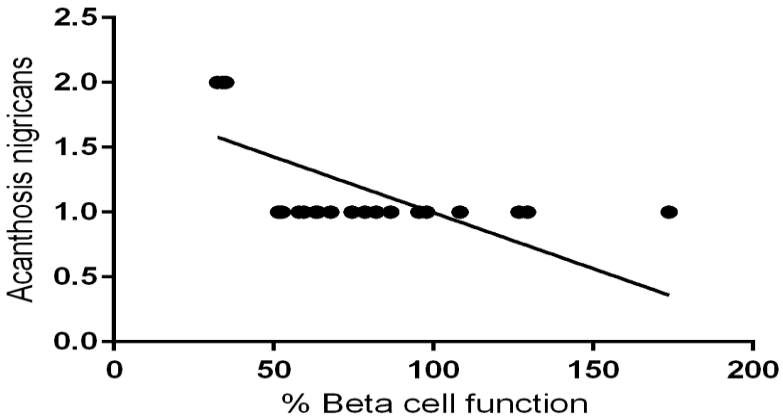
	RBG (mg/dl)	HbA1c (%)	FBG (mg/dl)	Fasting Insulin (µU/L)	%β-cell function	%S (insulin sensitivity)
r-value	-0.019	-0.042	0.199	0.224	-0.147	-0.203
P-value	0.873	0.731	0.099	0.062	0.226	0.092
(n)	70	70	70	70	70	70
**. Correlation is significant at the 0.01 level (2-tailed).						

Table 3. Spearman`s correlations of acanthosis nigricans with insulin parameters

	%β-cell function	%S (insulin sensitivity)	IR (Insulin resistance)
r-value	- 0.310	- 0.126	0.643**
P-value	0.0498	0.298	0.0001
(n)	70	70	70
**. Correlation is significant at the 0.01 level (2-tailed)			



Graph- 1. Spearman`s correlation of acanthosis and insulin resistance (r = 0.643, P=0.0001)



Graph- 2. Spearman`s correlation of acanthosis and %β-cell function (r = -0.310, P=0.0498)

DISCUSSION

The present is the first research reporting on the β-cell function, insulin secretion and insulin resistance in type 2 Diabetic subjects with acanthosis nigricans from our tertiary care hospital. In present study, %β-cell function, %S (insulin sensivity) and HOMA- IR (insulin resistance) shows association with the acanthosis nigricans. Insulin resistance was noted in type 2 DM with Acanthosis nigricans. Insulin resistance shows inverse correlation with RBG, HbA1c, %β-cell function and %S (insulin sensivity) (table 2). The association of acanthosis nigricans with %β-cell function, %S (insulin sensivity) and HOMA- IR (insulin resistance) is in agreement with previous studies.[15-18] A previous study[15] reported high grades of AN of neck and axilla are sensitive markers of IR. In the present study, similar finding of AN as marker of IR was noted. The main disadvantage of Axillary AN is infrequent accessibility to visual screening in subjects whose dresses are highly conservative, and AN remains hidden sign. The findings of present study are supported by Burke's et al[17] who reported HOMA-IR in their research study. Similarly, Ramachandran et al[18] demonstrated a HOMA-IR of 3.3 in children of age >14 years. In present study, the HOMA-IR in type 2 DM with AN was 5.12±1.11 compared to 3.85±1.21 in those without AN (P=0.0001). Our findings are in agreement with above studies. Previous studies[15-18] substantiate our finding of HOMA-IR in diabetic subjects with acanthosis nigricans. The present study concludes the HOMA-IR and fasting insulin are excellent diagnostic tools for IR and acanthosis nigricans may be used as a clinical marker of insulin resistance. A previous study[19] reported the acanthosis nigricans is less sensitive than BMI as marker of insulin resistance. The finding substantiates the present study as AN was found associated with the Insulin resistance. Insulin resistance was negatively associated with the %β-cell function and %S (insulin sensivity (r= -0.147, r= -0.203). These findings are in agreement with previous studies.[15,20] Ventkatswami et al[15] reported association of different grades of neck AN with insulin resistance. The study reported positive correlation with increasing grades of AN, this is inconsistent to present study as grades of AN were not studied with HOMA-IR due to our study design and planned protocol. In a recent study by Verma et al[16] studied 102 subjects of facial AN and its association with body mass index, waist circumference and insulin resistance (HOMA-IR). It was reported that the facial AN was associated with an increased prevalence of obesity and insulin resistance. They proposed that the facial AN may be considered as a marker of insulin resistance. The findings corroborate with our present research work. Sharquie et al[21] studied 30 Iraqi patients with facial AN of age 16 - 58 years. They reported an increased prevalence of obesity and WC in patients with facial AN. Sharquie et al[22] reported in another study that the fasting triglyceride, total cholesterol, growth hormone, and serum leptin were significantly raised in patients with facial AN compared to controls. These findings closely corroborate the present study, as we found disturbed blood lipids, fasting glucose, fasting insulin in type 2 DM subjects with acanthosis nigricans. This further strengthens the association between acanthosis nigricans and insulin resistance. Another previous study[23] reported 50% patients had hyperglycemia and 36% had hyperinsulinism with acanthosis nigricans. The findings are in agreement with our present study observations. Our present study has several strengths as we included type 2 diabetics of acanthosis nigricans diagnosed by a consultant dermatologist. Complete patient history and blood sampling were properly handled. However, the predominantly urban population and small sample size are limitations of the present study. This may not be representative of the whole diabetic population ith acanthosis nigricans.

CONCLUSION

The present study concludes the acanthosis nigricans is a marker of insulin resistance which may be utilized in clinical practice and the homeostasis model assessment-insulin resistance (HOMA-IR) may be used as a reliable marker of insulin resistance. Future studies with large sample size are recommended to be conducted in the indigenous diabetic population.

REFERENCES

1. Bahadursingh S, Mugalsingh C, Seemungal T, Teelucksingh S. Acanthosis nigricans in type 2 diabetes: prevalence, correlates and potential as a simple clinical screening tool - a cross-sectional study in the Caribbean. Diabetol Metab Syndrome 2014; 6: 77.
2. Guevara-Gutierrez 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 J Dermatol Venerol Leprol 2017; 83(2): 190-4.
3. Freedman D, Khan L, Serdula M, et al. Inter-relationships among childhood BMI, childhood height, and adult obesity: the Bogalusa Heart Study. Int J Obes Metab Discord 2004; 28(1): 10-16.
4. Koh YK, Lee JH, Kim EY, Moon KR. Acanthosis Nigricans as a Clinical Predictor of Insulin Resistance in Obese Children. Pediatr Gastroenterol Hepatol Nutr 2016; 19(4): 251–8.
5. Sadeghian G, Ziaie H, Amini M, Ali Nilfroushzadeh M. Evaluation of insulin resistance in obese women with and without acanthosis nigricans. J Dermatol. 2009; 36(4): 209-212.
6. Noviarti D, Rini EA, Oenzil F. Association of resistin level with acanthosis nigricans in obese adolescents. Paediatr Indones 2016; 56: 32–36.
7. Kong AS, Williams RL, Rhyne R, Urias-Sandoval V, Cardinali G, Weller NF, et al. Acanthosis nigricans: high prevalence and association with diabetes in a practice-based research network consortium-a PRImary care Multi-Ethnic network

(PRIME Net) study. J Am Board Fam Med 2010; 23: 476–485.
8. Baden LR. Acanthosis Nigricans and Insulin Resistance. New England J Med 2016; June 16: e31.
9. Puri N. A study of pathogenesis of acanthosis nigricans and its clinical implications. Indian J Dermatol 2011; 56: 678‑83.
10. Krishnakanth, Anandan S, Gayathri R, Adikrishnan S, Murugan S, Sudha R, Mahalakshmi V. Clinico Pathological Study of Acanthosis Nigricans and its Correlation with Obesity and Insulin Resistance. J Evolution Med Dent Sci 2015; 4(90): 15566-77.
11. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. Evidence-Based Guideline for the Management of High Blood Pressure in Adults Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). J Am Med Assoc 2014; 311(5): 507-520.
12. American Diabetes Association (ADA). Standards of medical care in Diabetes. Diabetes Care 2016; 35(1): 11–63.
13. Razi F, Nasli E, Farzami MR, Tootee A, Qorban M, Ebrahimi SA, et al. Effect of the different assays of HbA1c on diabetic patients monitoring. J Diabetes Metab Disord 2015; 14: 65.
14. Schwartz B, Jacobs D, Moran A, Steinberger J, Hong C, Sinaiko A. Measurement of Insulin Sensitivity in Children: Comparison between the euglycemic‑hyperinsulinemic clamp and surrogate measures. Diab Care 2008; 31: 783‑8.
15. Venkatswami S, Anandam S. Acanthosis nigricans: a flag for insulin resistance, Journal of Endocrinology, Metabolism and Diabetes of South Africa 2014; 19:2, 68-74.
16. 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; 7: 498-503.
17. Burke JP, Hale DE, Hazuda HP, Stern MP. A quantitative scale of acanthosis nigricans. Diabet Care 1999; 22(10): 1655-9.
18. Ramachandran A, Snehalatha C, Yamuna A. Insulin resistance and clustering of cardiometabolic risk factors in urban teenagers in southern India. Diabetes Care 2007; 30(7): 1828-33.
19. Nsiah-Kumi PA, Beals J, Lasley S, et al. Body mass index percentile more sensitive than acanthosis nigricans for screening Native American children for diabetes risk. J Natl Med Assoc 2010; 102(10): 944-9.
20. Srinivasa Nageswara Rao G, Prema G, Priya G, et al. Comparison between serum insulin levels and its resistance with biochemical, clinical and anthropometric parameters in South Indian children and adolescents. Indian J Clin Biochem 2011; 26(1): 22-7.
21. Sharquie KE, Al‑Ogaily SM. Acanthosis Nigricans as a Cause of facial melanosis (Clinical And histopathological Study). IOSR J Dent Med Sci 2015; 1: 84‑90.
22. Sharquie K, Noaimi A, Mahmood H, Al‑Ogaily S. Clinical and Biochemical Evaluation of Facial Acanthosis Nigricans. JCDSA 2015; 5: 231‑7.
23. Sierra‑Johnson J, Johnson BD. Facial fat and its relationship to abdominal fat: Amarker for insulin resistance? Med Hypotheses 2004; 63: 783‑6.