



## TO STUDY THE PREVALENCE OF THE ACANTHOSIS NIGRICANS IN TYPE 2 DIABESTES AND METABOLIC SYNDROME

**Dr Vishal Marwaha**

Amrita institute of Medical sciences, Kochi

**Dr. Anuj Singhal**

Armed Forces Medical College, Pune

**Dr. Prashant Jambunathan\***

Armed Forces Medical College, Pune \*Corresponding Author

### KEYWORDS :

#### INTRODUCTION:

Acanthosis nigricans (AN) is a skin disorder presenting as dark thickened skin in various areas of body like nape of neck, axillae, elbows, knees, knuckles, groin and other intertriginous areas. It is seen in certain conditions like obesity, Type-2 diabetes mellitus (T2DM), endocrine disorders like hypothyroidism, polycystic ovarian disease (PCOD)1, pregnancy and in certain malignancies1,2. Presence of AN is considered as a marker of insulin resistance. In hyperinsulinemia, insulin crosses the dermo-epidermal junction, binds to insulin like growth factor-1 receptors (IGF-1Rs) with much greater affinity than insulin receptors which are similar in size and structure to insulin receptors. On binding, it promotes proliferation and growth of fibroblasts and keratinocytes leading to hyperpigmentation and skin thickening. Other mechanisms responsible for AN are direct toxicity due to hyperinsulinemia and increase of insulin like growth factors. Markers of IR will help in identifying the individuals at an early stage who are at high risk of developing such metabolic diseases especially in high risk population with family history of T2DM and obesity.

Presence of IR markers like AN in patients of T2DM and overweight/obesity requires early intervention in form strict glycemic control, weight reduction, diet control and frequent monitoring to reduce the development of complications which causes significant morbidity and mortality.

Presence of AN should warrant an intensive evaluation to rule out underlying metabolic disorders associated with insulin resistance (IR). Various studies have validated the fact that clinical T2DM is preceded by long duration of IR. Hence clinical markers like AN can be of paramount importance in primary prevention of major group of non-communicable diseases (NCD) like T2DM and MS. This cross sectional study was done to evaluate the prevalence of AN in T2DM and MS in patients attending medical out patient department (OPD) of a tertiary care hospital.

#### MATERIAL AND METHODS:

This study is carried out in tertiary care hospital in Pune, Maharashtra from Sep 2014 to Aug 2016. Ethical clearance was obtained from the Institutional ethical committee. The objective of the study was to determine the prevalence of AN in patients of T2DM and MS, attending various medical OPD of this hospital. The secondary objective was to assess the correlation of AN with anthropometric measurements and laboratory parameters.

All the patients of T2DM above 18 years of age attending medical OPD were included in the study after taking informed consent. Patients with known thyroid disorders, PCOD, malignancies, dermatological disorders and pregnancy were excluded from the study. Patients were screened for presence of AN in various parts of body like nape of neck, axillae, elbows, knuckles and other intertriginous areas. AN on nape of neck was graded according to its severity based on Burke et al scale of grading of AN. Grade-0 was defined as absence of AN; grade-1 was visible AN on close inspection of nape of neck; grade-2 was clearly visible on nape of neck and with no lateral extension; grade-3 was clearly visible on nape of neck and extending laterally; and grade-4 was clearly visible on nape of neck and extending laterally and

anteriorly, visible from front. Subjects were also checked for presence of skin tags on nape of neck. Height (cm), weight (kgs), waist circumference (WC), hip circumference (HC), waist-hip ratio (WHR) and blood pressure were measured by standard method. Body mass index (BMI) was calculated by weight in kgs divided by height in metres squared. Hematological & biochemical lab parameters (complete blood count (CBC), liver function tests(LFT), renal function test (RFT), total cholesterol(TC), triglycerides(TG), High density lipoprotein (HDL) of all subjects were recorded. South Asian modified NCEP ATP-III criteria (SAM NCEP ATP-III) was used to screen patients for presence of MS. The compiled data of 500 subjects was analyzed using Microsoft excel 2013 and SPSS software version 20 (statistical package for the social sciences for windows). Data was analyzed for correlation of AN with age, sex, anthropometric measurements and laboratory parameters among patients with T2DM. Similar analysis was also done for this group of patients who met the criteria of MS as per SAM NCEP ATP-III criteria. The baseline characteristics of patients is shown in table 1.

**Table 1: Baseline characteristics of subjects in study**

Parameters	Males	Females	Total
Age(yrs)	51.6±11.27	52.4±10.05	
BMI(kg/m <sup>2</sup> )	25.27±3.79	25.42±3.83	25.33±3.81
WC(cm)	90.39±8.95	89.86±8.53	90.21±8.84
WHR	0.92±0.11	0.91±0.10	0.92±0.10
TG(mg%)	150.2±81.11	149.2±65.02	151.2±75.21
HDL(mg%)	42.5±8.18	43.17±8.46	42.66±8.28

BMI, body mass index; WC, waist circumference; WHR, Waist hip ratio; TG, triglycerides; HDL, high density lipoprotein;

#### RESULTS:

In our study, among 500 subjects, 266(53.2%) were males and 234(46.8%) were females. The mean age in males was 51.6±11.27 years and females was 52.4±10.05 years. Obesity (BMI ≥ 25 kg/m<sup>2</sup>) seen in 207(41.4%) subjects while 152(30.4%) individuals were overweight (BMI ≥ 23–24.9 kg/m<sup>2</sup>). Among study subjects, 289(57.8%) individuals had abnormal WC (males ≥ 90 cm, females ≥ 80 cm). Raised serum TG levels (≥ 150 mg/dl) was seen in 217 (43.4%) subjects and 312(62.4%) subjects had low HDL levels (males <40 mg/dl and females <50 mg/dl) and 116(23.2%) subjects had hypertension. Table 2 summarizes the prevalence of AN in T2DM.

ACANTHOSIS NIGRICANS					
PARAMETERS		n	PRESENT (n=330)	ABSENT (n=170)	P VALUE
GENDER	Female	234	166(50.30%)	68(40%)	0.03
	Male	266	164(49.69%)	102(60%)	
WC	Abnormal(>90 cm in males, > 80 cm in females)	289	205(62.12%)	84(49.41%)	0.007

	Normal	211	84 (37.87%)	86(50.58%)	
HDL(mg/dl)	Low(males<40mg/dl, females<50 mg/dl)	312	205(62.12%)	107(62.94%)	0.922
	Normal	188	125(37.87%)	63(37.05%)	
HTN	Present	116	100(30.30)	16(9.41%)	0.922
	Absent	383	229(69.39%)	154(90.58%)	
BMI(kg/m <sup>2</sup> )	≥ 25.00	209	192(58.18%)	17(10%)	< 0.001
	23.00 - 24.99	152	92(27.87%)	60(35.29%)	
	≤ 22.99	141	48(14.54%)	93(54.70%)	
TG(mg/dl)	Abnormal(<150 mg/dl)	217	163(49.39%)	54(31.76%)	< 0.001
	Normal	283	167(50.60%)	116(68.25%)	
WHR	Abnormal(males >0.9, females>0.85)	330	229(69.39%)	101(59.41%)	0.029
	Normal	170	101(30.60%)	69(40.58%)	

**Table 2: Prevalence of AN and correlation with subject parameters in T2DM.**

Among study population, 330 subjects (66%) had AN. Out of 330 subjects with AN, 164 (61.15%) were males and 166 (70.94%) were females and had a significant difference in prevalence of AN between male & female gender (P 0.03). Among 330 subjects with AN, 190(57.57) subjects found to be obese (BMI ≥ 25 kg/m<sup>2</sup>), 92(27.87) subjects were overweight (BMI ≥ 23 kg/m<sup>2</sup>). Among 28 subjects with grade-4 AN, 27(96.42%) were found to be obese. Obese individuals with grade-4 AN also had AN in axilla & other areas. AN is observed in significantly higher frequency compared to patients with normal BMI (P<0.01).

A significant difference is seen in prevalence of AN in subjects with raised TG levels compared to patients with normal TG levels(P <0.001). Out of 163(60.37%) had AN which is significant compared to those with normal TG levels (P < 0.001). Out of 312 individuals with low HDL levels, 205(65.70%) had AN. Among 289(57.80%) subjects with abnormal WC, 205 (70.93%) had AN.

Out of 500 subjects with T2DM, 210(42%) met the criteria of MS as per SAM NCEP ATP-III criteria<sup>4</sup>. 98(46.66%) were female and 112(53.33%) were male. Among 210 subjects of MS, 121(57.61%) were obese (BMI ≥ 25 kg/m<sup>2</sup>) and 42 (20%) were overweight. AN is seen in 173(82.38%) subjects of MS. In patients of MS with AN, 117(55.71%) were obese. In subjects of MS, abnormal WC is seen in 120(57.14%) subjects with AN compared to 05 subjects without AN. Raised TG levels seen in 129(61.42%) and low HDL levels seen in 130(61.90%) individuals of MS with AN. The prevalence of AN in MS and its correlation with subject parameters is depicted in table 3.

METABOLIC SYNDROME					
PARAMETER		TOTAL	PRESENT (n=210)	ABSENT (n=290)	P VALUE
GENDER	Female	234	98(46.66%)	136(46.89%)	0.999
	Male	266	112(53.33%)	154(53.10%)	
WC(cm)	Abnormal(>90 cm in males, > 80 cm in females)	289	136(64.76%)	153(52.77%)	0.008

	Normal	211	74(35.23%)	137(47.24%)	
HDL(mg/dl)	Low(males<40mg/dl, females<50 mg/dl)	312	162(77.14%)	150(51.72%)	< 0.001
	Normal	188	48(22.85%)	140(48.27%)	
HTN	Present(≥ 130/85 mm Hg)	383	119(56.66%)	264(91.0%)	< 0.001
	Absent	116	91(43.30%)	25(8.65%)	
BMI(kg/m <sup>2</sup> )	≥ 25.00	207	121(57.61%)	86(29.65%)	< 0.001
	23.00 - 24.99	152	42(20%)	110(37.93%)	
	≤ 22.99	141	47(22.30%)	94(32.41%)	
TG(mg/dl)	Abnormal	217	155(73.80%)	62(31.37%)	< 0.001
	Normal	283	55(26.19%)	228(78.62%)	
WHR	Abnormal(males > 0.9, females > 0.85)	330	170(80.95%)	160(55.17%)	0.002
	Normal	170	55(26.19%)	115(39.65%)	

**Table 3: Prevalence of AN and correlation with subject parameters in MS.**

**DISCUSSION:**

Diabetes mellitus is one of the most common NCD seen in world affecting about 422 million population in 2014 with doubling of prevalence since 1980 rising from 4.7% to 8.5%. The main risk factors for T2DM are obesity, sedentary life style, physical inactivity and change in dietary habits. T2DM is responsible for premature death by increasing the risk of its complications, especially cardiovascular diseases and drains significant amount of resources<sup>6,7</sup>, MS comprises of group of risk factors like hyperglycemia, hypertension, dyslipidemia, obesity with insulin resistance and obesity. MS and T2DM are leading cause of mortality due to cardiovascular diseases globally and prevalence of these is expected to rise in coming times. Individuals with metabolic disorders like T2DM, MS and dyslipidemia have high insulin resistance. They are prone to develop stroke, Cardiovascular diseases and Nonalcoholic fatty liver disease (NAFLD),..Therefore, it is imperative to device and recognize easily identifiable clinical markers and biomarkers which can aid in early diagnosis. Recognition of such markers would also help medical fraternity to better understand this impending epidemic of NCD and to device novel therapeutic interventions.

Unlike the previous studies, the current study has a large sample size. The prevalence of AN varies widely in patients due to underlying conditions with prevalence of 7% in general population and increase of prevalence to 74% in obese individuals. The prevalence of AN is found to be 62.6% in T2DM and 40% in general population<sup>5</sup>. Prevalence of AN and baseline characteristics compared to two earlier studies<sup>5</sup>, (from India is shown in table 4.

Parameters	Grandhe et al, 20055	Patidar et al, 20128	Our study
n (100%)	150	150	500
Study groups	T2DM and general population	T2DM	T2DM
Age(yrs)	52.2	45.2	51.98
BMI(kg/m <sup>2</sup> )	25.7	27.42	25.34
WC (cm)	90.9±11.08	-	90.21± 8.84
WHR(cm)	0.96±0.07	-	0.91±0.10

AN prevalence	62.6%	71.79	66%
AN in males	62.5%	56.67%	61.2%
AN in females	62.9%	86.92%	70.94%
MS	Not studied	Not studied	289(57.8%)

In our study the prevalence of AN is found to 66% in T2DM and with prevalence of 61.15% in males and 70.94% in females which is statistically significant (P value 0.03) which is not observed in previous studies<sup>5</sup>. The higher prevalence of AN in female sex can be attributed to higher IR among women<sup>1,15</sup>.

In our study, high prevalence of AN is seen with increase in BMI of T2DM patients and the correlation is statistically significant (P 0.001) which corroborates with previous studies. Increased WC results in increased prevalence of AN in T2DM patients and had a statistically significant correlation (P 0.007) as similar to previous studies. AN is more frequently seen in T2DM patients with raised WHR (P 0.02). No significant correlation in prevalence of AN is seen in T2DM with hypertension and with low HDL levels. A statistically significant higher prevalence of AN is observed in patients with raised serum TG levels (P<0.001).

Out of 210 subjects of MS, 173(82.38%) had AN. The prevalence of AN in MS is 82.38%. There is no significant difference in prevalence of MS between males and females. Increased prevalence of AN is seen in patients of MS with increase in WC which is statistically significant (P 0.008). Similarly higher prevalence of AN is noted in patients of MS with increase in BMI (P<0.001), with raised triglycerides TG levels (P <0.001), low HDL levels (0.001) and with increase of WHR (P 0.002) which is statistically significant.

Prevalence of AN in severity of grading has been studied in T2DM and MS patients. Out of 330(66%) T2DM patients with AN grade-1 AN is seen in 76(23.03%) and grade-2, grade-3 and grade-4 AN is seen in 152(46.06%), 74(22.42%), 28(8.48%) respectively. Out of 173(82.30%) MS patients with AN, grade-1, grade-2, grade-3 and grade-4 AN is seen in 24(13.82%), 72(41.61%), 52(30.05%) and 25(14.45%) respectively. Table 4 enumerates the results of grades of AN in T2DM and MS

T2DM (n= 500)	AN	AN n=330(66%)	P Value
	Gd 1	76(23.03)	0.001
	Gd2	152(46.06)	
	Gd3	74(22.42)	
	Gd4	28(8.48)	
MS (n=210)		173 (82.3%)	0.001
	Gd 1	24(13.82%)	
	Gd2	72(41.61)	
	Gd3	52(30.05%)	
	Gd4	25(14.45%)	

**Table 4: Grades of AN in T2DM and MS patients**

The weakness of this study is that IR levels was not calculated. Further studies with simultaneous recording of IR levels should be undertaken in future

**CONCLUSION:**

Presence of AN requires intensive evaluation for early detection of metabolic disorders because they are preceded by long period of IR, before patient becomes symptomatic. This study reveals that, AN is more frequently seen in females than in male patients with T2DM and is statistically significant (P 0.03). Our study has also revealed that patients with T2DM and MS who are obese, have higher TGs levels, lower HDL and who has higher WC have statistically significant prevalence of AN. The severity (grades) of AN on nape of neck correlates with increasing BMI, waist circumference and presence of MS. Presence of IR markers like AN may aid physicians in early diagnosis of T2DM and MS, which in turn can reduce the global burden of these NCD.

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