Co-relation of Acanthosis Nigricans with Insulin Resistance and Type 2 Diabetes Mellitus in a Tertiary Care Hospital

Rakhshinda Jabeen[1*], Tazeen Rasheed[1], Humera Talat[2]

[1]Department of Medicine, Dow University of Health Sciences, Karachi, Pakistan

[2]Department of Dermatology, Dow University of Health Sciences, Karachi, Pakistan

ABSTRACT

Objective: To adjudicate the correlation of Acanthosis Nigricans (AN) with Insulin Resistance (IR) and type 2 diabetes mellitus in a tertiary care hospital.

Methodology: This case control study was administered at Dr. Ruth K. M. Pfau, civil hospital, Karachi between 1st October 2019 to 31st March 2020. A total of 308 patients were enrolled in this study. The patients were disintegrate into two groups, first group having AN of any degree with a BMI of ≥ 25 kg/m², and they were compared with the control group without AN but having same BMI of ≥ 25 kg/m². HbA1c and HOMA-IR were calculated for each patient.

Results: Out of 308 patients involved in the study, 204 (66.23%) were females while 104 (33.77%) were males. Mean age among male patients was 38.39 ± 8.70 years whereas that of female patients was 35.49 ± 9.41 years. While comparing IR with AN in both groups, it was statistically eloquent with p value of 0.000. Diabetes mellitus was seen in 34.6% in AN positive patient while 41.3% without AN had type 2 DM.

Conclusion: IR increases with increasing BMI irrespective of presence or absence of AN. DM is also significantly associated with obesity irrespective of presence or absence of AN.

Key words: Acanthosis nigricans, Insulin resistance, HOMA-IR, Diabetes mellitus type 2, BMI

INTRODUCTION

Acanthosis Nigricans (AN) is a cutaneous presentation, which manifests with thickened, brown to blackish hyperpigmented plaques, typically found on the folds of the body, for example, on the posterior and lateral surface of neck, armpits, navel etc. It is important for clinicians to recognize AN as it occurs in a wide range of disorders such as endocrinologic disturbances and malignancies. Due to rising prevalence of type 2 DM and obesity among patients with AN, their association has been studied multiple times in the past. The prevalence ranges from 7%-74% and it varies among different races, in different age groups and with degree of obesity. Insulin Resistance (IR) is one of the most important pathological mechanism that lead to the formation of plaques of AN [1].

IR is defined as a metabolic disorder in which target receptors do not respond to normal levels of circulating insulin which causes increase blood insulin levels. IR can be found in extreme insulin resistance syndrome type B, certain uncommon disorders, such as, leprechaunism and lipodystrophic states. It is also associated with impaired glucose tolerance, type 2 DM, obesity, glucocorticoid excess, stress, infection and pregnancy.

The confederation of AN with Diabetes Mellitus (DM) because of insulin resistance in adults and children presents in the form of syndrome. These syndromes may present with hyper androgenism. Insulin and insulin like growth factor-1, act on receptors present on keratinocytes that lead to hyperplasia of epidermis. Control of obesity might likely reverse this process, probably by reducing IR and compensatory hyperinsulinemia [2].

AN is strongly weighed as a cutaneous marker of IR. IR is also thought to be the underlying cause of non-alcoholic fatty liver disease. In a study it was reported that there is worsening of IR with increasing severity of AN, and patients having severe AN (score ≥ 3) are at higher risk of developing IR. It has been further aggravated if associated with increased BMI. In a study done among children, 62% of children presented with AN of any degree had greater risk of IR, and it further increases to 80% with associated high BMI [3].

Our objective was to determine the co-relation of AN with IR for the determination of pre-diabetes or diabetes mellitus type 2 and compare it with control group without AN, with same Body Mass Index (BMI) in each group. This will help to diagnose diabetes mellitus type 2 at a much earlier stage. Earlier diagnosis may help in delaying complications of diabetes [4].

MATERIALS AND METHODS

This case control study was administered at Dr. Ruth K. M. Pfau, Civil hospital, Karachi between 1st October 2019 to 31st March 2020. Non-probability consecutive sampling was used as a tool for selection of patients. Prior approval from the institutional review board of Dow university of health sciences was taken [5].

Inclusion criteria

- All patients between ages of 18-55 years of both genders having BMI>25 Kg/m^2 were included in the study.
- All patients between age of 18-55 years of both genders having AN of any degree were included in the study.

Exclusion criteria

Diagnosed cases of DM type1 and type 2 were excluded. Patients with other reasons of AN like hypothyroidism, cushing's disease, acromegaly, any malignancy like gastric carcinoma and patients taking drugs that cause AN were excluded [3].

A written informed consent was taken from all patients. The patients were taken into 2 groups with presence or absence of AN: Group 1 having AN and group 2 having no AN. HbA1c and HOMA-IR was calculated for each patient [6].

AN over neck was graded according to Burke et al grading as follows:

- Grading 0: Not visible.
- Grade 1: Clearly present on close visual inspection, not visible to the casual observer, extent not measurable.
- Grade 2: Mild, limited to the base of the skull, does not extend to the lateral margin of the neck (usually, 3 inches in breadth).
- Grade 3: Extending to the lateral margins, not visible from the front.
- Grade 4: Extending anteriorly.

HOMA IR: HOMA-IR was calculated using the formula (fasting glucose × fasting insulin)/405. A HOMA-IR value of 2.5 was considered as an indicator of IR.

Data analysis

Statistical values were expressed as mean ± SD for continuous variables and % for categorical variables. Comparison of groups for categorical variables was done by Pearson correlation test [7]. All data was compared using an analysis of variance and p values were calculated. P-value<0.05 was considered significant. Data was analyzed on SPSS version 22.

RESULTS

This study was concurred in a tertiary care hospital of Karachi during the period of 1st October 2019 to 31st March 2020. Among 308 patients who were enrolled in the study 153 patients had AN while 155 who were taken as controls and were without AN. Out of 308 patients 204 (66.23%) were females while 104 (33.77%) were males (Table 1). The age range among these patients was 18 years to 55 years with mean age in male in 38.39 ± 8.70 years, while in females it was 35.49 ± 9.41 years [8]. All patients incurred in the study were obese with BMI grading according to Asian population. In patients with positive AN most of them were in the category of grade 1 (n=61, 39.9%) and grade 2 (n=51, 33.3%) of BMI with mean of 31.62 ± 4.76 while in group of patients with negative AN mostly patients were in grade 2 and 3 with mean BMI of 35.59 ± 6.59 (Table 2) [9].

While comparing IR with AN in both groups, it was statistically significant with p value of <0.001. In various metabolic profile studied in both groups in the study were statistically significant with p value of <0.001 (Table 3). Most the patients in both groups had either prediabetes or diabetes irrespective of BMI (Table 4) [10].

Table 1: Gender distribution among patients in both groups.

Parameters	Male		Female		Total
AN +VE	55	35.90%	98	64.10%	153
AN -VE	49	31.60%	106	68.40%	155
Total	104	33.77%	204	66.23%	308

Table 2: BMI categorization in both groups.

Parameters	AN +VE		AN -VE		BMI Total	
	Total	%	Total	%	Total	%

Grade 1	61	39.90%	26	16.80%	87	28.25%
Grade 2	51	33.30%	44	28.90%	95	30.84%
Grade 3	27	17.50%	49	31.60%	76	24.67%
Grade 4	14	9.20%	30	23.20%	44	14.28%

Table 3: Metabolic parameters in both groups.

Parameters	AN +VE		AN -VE	
	Mean	P-value	Mean	P-value
FBS	106.78 ± 24.39	0	117.14 ± 41.92	0
Fasting insulin	13.16 ± 6.91	0	18.91 ± 10.74	0
HOMA-IR	3.59 ± 2.25	0	8.96 ± 41.65	0.039
HbA1c	6.32 ± 1.04	0	6.56 ± 1.21	0
Cholesterol	195.68 ± 58.29	0	204.96 ± 63.11	0
Triglycerides	157.63 ± 65.64	0	178.34 ± 39.56	0
ALT	37.22 ± 21.57	0	42.04 ± 24.46	0
BMI	31.62 ± 4.76	0	35.59 ± 6.56	0
WHR	0.891 ± 0.061	0	0.89 ± 0.072	0

Table 4: Diagnosis of diabetes mellitus in both groups.

Diagnosis	AN +VE		AN -VE		Total	
	Total	%	Total	%	Total	%
No DM	43	28.10%	29	18.70%	72	23.37%
Pre-DM	57	37.30%	62	40.00%	119	38.63%
DM	53	34.60%	64	41.30%	117	37.98%

DISCUSSION

Acanthosis Nigricans (AN) is a cutaneous presentation that is often linked with a variety of disorders, for example, endocrine disorders such as an overproduction of corticosteroids, diabetes, pineal tumors and other malignancies [11]. The term acanthosis nigricans was first coned by Umma, however, the first case highlighting the skin condition was not reported till 1891 by Pollitzer and Janovsky. Similarly, according to Hud et al., the prevalence of AN is higher in black women compared to white women, with a prevalence of less than 1%. Diabetes is still one of the leading cause of not only increasing morbidity but also a high mortality in adults worldwide with a prevalence of 33% in adults in the USA by the year 2050. It is also rising in the Pakistani population at an alarming rate with a current prevalence of 11.77%. The incidence of diabetes is relatively higher among males with a prevalence of 11.20%, whereas in females the prevalence is 9.19% [12]. Additionally, while comparing disease rates in different provinces of Pakistan, the prevalence of diabetes is found to be higher in Sindh, with 16.2% males and 11.70% females suffering with the disease. However, in Punjab the prevalence is

relatively lower with 12.14% males 9.83% females affected [13].

The severity of AN is significantly correlated with Insulin Resistance (IR). Therefore, the severity of IR can be measured based on the grading of AN. The term insulin resistance was first described in 1923 after the introduction of insulin, when patients failed to respond to insulin, requiring much higher doses for controlling diabetes mellitus [14]. Most patients developed autoantibodies as the insulin was not extracted by humans. The relationship between obesity and diabetes mellitus type 2 was established several decades ago. The increase in adipose tissue storage in obese individuals results in an increase in free fatty acids and triglyceride level in tissues [15]. This causes not only insulin resistance but other adverse effects as well like lipotoxicity. IR in obese and thus in type 2 diabetic patients is due to decreased suppression of hepatic glucose release, a decrease in insulin-stimulated transport of glucose and impaired metabolism in fat cells and skeletal muscle [16].

For further confirmation of DM type 2 along with physiological reason are certain laboratory tests are used

to early identification of DM type 2. In this context HOMA-IR is used religiously for the assessment of IR [17]. Various studies done before to evaluate or diagnose DM type 2 by using HOMA-IR, and all showed a significant result. In same context this study is done to arbitrate the co-relation of AN with IR to determine pre-diabetes or diabetes mellitus and compare it with control group without AN [18]. Both groups had the same BMI>25 Kg/m^2.

The results of our study exhibit that there was significant IR in both groups. Our results also display a strong correlation of increasing BMI in both groups (p value<0.001) with all metabolic profiles, including FBS, HbA1c, HOMA-IR and fasting insulin levels [19]. The results of the study are similar to a study previously conducted by Martinez KE et al. The study concluded that both an increase in BMI and body fat percentage are significantly related to insulin resistance. A gradual increase is seen in IR with increasing BMI levels. The study further concluded that including body fat percentage with BMI does not have a significant impact on the utility of BMI for measuring insulin resistance [20].

In a study conducted in South Indian population it was reported that 16.1% of population had AN, the findings were much higher among females than males. They also reported that AN is more prevalent in females, obesity, diabetes mellitus and increasing triglyceride levels [21]. Cutaneous manifestation of AN was also significantly associated with increase fasting insulin levels. They further stated that the stronger clinical relevance of AN makes it a suitable marker of insulin resistance along with obesity and a family history of diabetes. The study also delineates that 71.9% among positive AN had either pre-diabetes or DM type 2 [22].

In a study by Patidar PP et al it was reported that the severity of acanthosis over the neck leads to much higher IR values, fasting glucose and insulin levels. In addition, they are all statistically significant, too (P<0.05). The same study also reported that the presence of acanthosis over other parts of the body including axilla and knuckles does not have a significant association with insulin resistance. Patients included in the study mostly had grade 1 or grade 2 AN.

CONCLUSION

Controlling obesity results in the reversal of AN, by reducing both IR and compensatory hyper insulinemia. Early initiatives such as focusing on lifestyle changes may slow the progress of AN and burden of IR and diabetes mellitus. Our study suggests that not only obesity but also AN is significantly associated with DM type 2. The basic reason among them is IR which can easily be calculated to get an inference. By just doing good physical examination one can identify AN which may help in early detection of DM type 2. By early evaluation of obesity and DM one can delay the complications of DM.

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