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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/13050
DOI URL: <http://dx.doi.org/10.21474/IJAR01/13050>



RESEARCH ARTICLE

ACANTHOSIS NIGRICANS IN OBESE VERSUS NON-OBESE IN A TERTIARY CARE HOSPITAL; ASSOCIATION WITH BMI AND CENTRAL OBESITY

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Manuscript Info

Manuscript History

Received: 20 April 2021
Final Accepted: 18 May 2021
Published: June 2021

Key words:-

Acanthosis Nigricans, PCO, Obesity,
HAIR-AN Syndrome, Metabolic
Syndrome, BMI

Abstract

Background and objectives: Acanthosis nigricans (AN) is a major cosmetic and pathological condition associated with obesity, hirsutism, polycystic ovary, DM, metabolic syndrome and insulin resistance. This study was conducted to determine frequency of obesity in acanthosis nigricans and the association of BMI and central obesity with gender, age and type of AN.

Methodology: This hospital based observational study was conducted from 1st March to 31st May 2021 at department of Medicine RIHS Islamabad after ethical approval. Sample size was calculated to be 221. **Inclusion criteria:** Adult cases of both the genders presenting with AN in medical OPD.

Exclusion criteria: Diagnosed cases of malignancy, critically ill cases, endocrine disorders and pregnant women were excluded. After detailed history and examination, clinical diagnosis of Acanthosis nigricans was made. The weight in kg and height in meters measured and BMI calculated by formula $\text{weigh in Kg}/\text{height}^2 (\text{m}^2)$. Waist circumference measured in cm by flexible measuring tape from narrowest part of torso, midway between the lowest rib and iliac crest for central obesity and relevant investigations suggested. Data analyzed by SPSS version 21. Chi-square test was used to compare various variables between obese and non-obese AN cases with significant $p < 0.05$.

Results: Among 221 cases with acanthosis nigricans, there were 152 (68.8%) females and 69 (31.2%) males. The mean age was 27 + 13.56 years with a range of 18-64 years. The mean BMI was 31.63 + 6.92 kg/m². Obesity was observed in 144 (65%). Mean waist

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circumference was 37.75 + 13.73 inches. Most frequent site involved was neck (98.6%), followed by groin (80.5%), knuckles (59.7%), sub-mammary (49%) and axilla (47%). The benign acanthosis nigricans was most frequent (98.6%) followed by HAIR AN Syndrome 46% cases, acral AN 14%, Syndromic AN 1.7% and mixed 1.4%. No case had unilateral AN. The types of AN had no association with obesity ($p > 0.05$). Diabetes mellitus observed in 47 (21%) AN cases. Polycystic ovaries (PCOs) in 111 out of 152 females with AN. Autoimmune conditions seen in 53 (24%) AN cases.

Conclusion: Benign and HAIR-AN were most frequent type in our study that was associated with raised BMI, waist circumference, PCOS and diabetes. It is recommended to screen acanthosis nigricans cases regardless of age or gender for obesity, PCOS, DM, hypertension and autoimmune conditions. Hence, early diagnosis may improve quality of life, prevent complications of systemic disease and improve outcome of diseases and quality of life of patients.

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Introduction:-

Acanthosis nigricans is a skin condition characterised by rough, dark brown or black hyperpigmented thickening of skin with appearance of velvety in nature.^[1,2,3,4,5,6,7,8] It presents as bilateral symmetrically on nape of neck, axillae, groin, anti-cubital fossa, popliteal fossa, sub-mammary region, elbows, knees, knuckles and even mucosal surfaces (including oral mucosa, vulva, lips, conjunctiva).^[1,2,3] The first documented case of acanthosis nigricans was found in Germany by Dr. Paul Gerson and Pollitzer^[1,4] while Robinson and Tasker found its association with obesity in 1947 first time.^[1]

The prevalence of acanthosis nigricans varies from 74% in obese people and 7% in non-selected population. It is much more common in black population rather than white population. It varies in different races e.g.; African Americans are 25 times more have acanthosis nigricans than European population. A study from USA showed prevalence of acanthosis nigricans was 3% in Hispanics, in caucasians 19% and 28% in Americans.^[5]

The prevalence in children of age group 2-5 years is 10.4%, 15.3% in 6-11 years, 15.5% in 12-19 years old while it is 62% of children of any races having body mass index above 98th percentile.^[4] Adults having weight above 200% with gross over weight shows 66% of acanthosis nigricans.^[1] The incidence of AN is equal in both males and females^[4] but an Indian study shows 77.8% in females and 22.25% in males.^[1] AN can be present in any age group from time of birth to adolescence but malignant AN mostly seen in elderly age group^[4].

There are three classifications regarding types of AN. **Curth** classifies AN into 3 types: malignant type, benign type and syndromic or pseudo acanthosis nigricans. **Hernandez-Perez** classified as simple and paraneoplastic AN. **Schwartz classification** is more common and has 8 types: Benign, malignant, associated with obesity, syndromic, unilateral, drug induced, mixed and acral AN

The Benign AN is inherited as autosomal dominant and present at the time of birth or during childhood or adolescence, usually unilateral and sparing palms & soles but progressive until puberty. **Obesity associated AN**, previously called as pseudo AN, common in childhood and in adults, associated with obesity in prepubertal children. This type is indicator of early type 2 DM because higher insulin resistance and pancreatic cell dysfunction. Hence this type of AN is indicator of obesity, hyperinsulinemia, insulin resistance and type 2 diabetes mellitus. **The type A insulin resistance syndrome** is called as HAIR-AN syndrome.^[1] This type is familial involving young women (especially black women) and is associated with polycystic ovary (PCO) (includes acne, hirsutism, seborrhea, androgenic alopecia or signs of virilization).^[1,4,9]

The **type B insulin resistance syndrome** appears in 4th decade. This type is associated with autoimmune conditions such as SLE, scleroderma, Sjogren syndrome, autoimmune thrombocytopenia and Hashimoto thyroiditis.^[1,4] The circulating antibodies may be found in serum against insulin leading to insulin resistance in these cases.^[4] The **Malignant AN** is seen in old age group and associated with gastric carcinoma and very rarely associated

with Wilm's tumor and osteosarcoma. In 25-50% of cases, oral cavity (tongue and lips) may be involved.^[4] and Tripe palms (characterized by rugose thickening of palms with increased dermatoglyphic lines of skin) is the early presentation of gastric cancers.^[9] **Acral AN** remains localized to knee, ankle, fingers and tarsophalangeal joints, more commonly seen in dark skin person and associated NFP, non-Hodgkin lymphoma^[11]

The **Unilateral or Nevoid AN** is clinically present at childhood or later, remained to unilateral, similar to classical AN, not associated with any systemic, endocrine or syndromic condition.^[11] **Drug induced AN**, certain drugs like nicotinic acid, OCP, diethylstilbestrol, fucidic acid and hydantoin like derivatives may develop AN which may start at abdomen and flexure surfaces of body and resolve 4-10 weeks after stopping of drug.^[1,4] **Mixed type AN**, If more than one type of lesions are present in same patient then it is known as mixed type AN eg; obesity associated AN may be associated with malignant type.^[1,4] **Facial AN**: A multicentric study of India shows that this variety could be manifestation of increased level of HOMA 2 IR, increase waist hip ratio, impaired glucose tolerance test and increase body mass index so thoroughly workup these patients for cardiovascular disease and metabolic syndrome if there are no such sign and symptoms of such disease.^[11]

Associations of AN is with the obesity, endocrinopathies, malignancy, genetic syndrome and drugs. Obesity is a benign condition associated with AN along with metabolic conditions such as hyperinsulinism, insulin resistance (IR), DM type 2, impaired glucose tolerance test, dyslipidemia, PCO, arterial hypertension, acromegaly, Cushing's syndrome, hirsutism, hyperthyroidism, hypothyroidism, Addison's disease, fatty liver and lipotrophic DM.
[2,3,5,8,11,12,13,14]

Regarding prognosis of malignant AN is usually poor because of advanced malignancy and survival rate is usually 2 years. Patient of benign AN usually suffers very few skin complications but majority of benign AN usually suffers with insulin resistance and DM. Severity of skin findings are directly proportions to IR and partial resolution of lesion may occur if treatment of IR condition occurs.^[15]

So far, very few local studies are available regarding AN associated with obesity with increased BMI and waist circumference so in our study we determined the frequency of AN in obese versus non obese in accordance with BMI and waist circumference. This will help us identify the cases of AN to be screened for obesity and its associations like obesity, PCOS, DM, hypertension on the basis of gender, age group and types of AN. Also, this may help us develop a clinical approach to diagnose and manage obesity, PCOS, DM that are the systemic associations via cutaneous manifestation.

Methodology:-

This was hospital based observational study conducted in the department of Medicine over a period of three months at Rawal institute of Health Sciences Islamabad after ethical approval from 1st March to 31st May 2021. The minimum sample size was calculated 221 cases by WHO calculator taking 17.5% prevalence of acanthosis nigricans, 5% precision and 95% confidence interval. Total number of cases were 250. Sample was collected via non probability purpose sampling. The cases presented to Medical OPD with clinical appearance of acanthosis nigricans were included after informed consent.

Inclusion criteria:

Adult cases of both the genders presented with AN.

Exclusion criteria:

Diagnosed cases of malignancy, critically ill cases, underlying known endocrine disorders and pregnant women were excluded.

After informed consent of patients, detailed history taken regarding onset, duration and progression of pigmentation, systemic co-morbidities, medications, dietary habits, medications used in the past, personal and family history and its association like DM, PCOS, obesity. Menstrual and reproductive history were taken in female patients. General physical, systemic and skin examination were done in detailed to make a diagnosis of Acanthosis nigricans. The weight in kg and height in meters were measured and BMI was calculated by formula $\text{weigh in Kg/height (m}^2\text{)}$. Waist circumference was measured by flexible measuring tape from narrowest part of torso, midway between the lowest rib and iliac crest and noted in cm for central obesity. The patients were classified on the basis of BMI criteria by WHO(1998) as normal: 18.5-22.9, overweight :23-24.9 and obese >25 kg/m², pre-obese 25-29, obese

class 1 30.0-34.0, obese class II: 35.0-39.9, obese class III: >40.0. Relevant investigations were suggested as per indication in individual cases and data recorded in specifically design proforma.

Data were analyzed by SPSS version 21. Frequency and percentages were calculated for qualitative variables i.e., gender, obesity grade, co-morbid, type of AN, etc and mean with standard deviation were calculated for quantitative variables i.e., age, height, weight, BMI, waist circumference. Chi-square test was used to compare various variables between obese and non-obese AN cases.

Results:-

Among 221 cases with acanthosis nigricans, there were 152(68.8%) females and 69(31.2%) males. The mean age was 27 + 13.56 years with a range of 18-64 years. Regarding marital status 156(70.6%) patients were unmarried and 65(29.4%) were married. The mean height was 4feet 9 inches and mean weight was 71.79 + 14.75 kg. Mean waist circumference was 37.03+3.74 inches. The BMI was calculated to have mean value of 31.63 + 6.92 kg/m²(**table 1**).

Based on BMI cut-off value of 30 kg/m², obesity was observed in 144(65%) and 77(34.8%) were non-obese with BMI less than 30 kg/m². The obesity grade I was observed in 51%, Obesity grade II in 5% and obesity grade III in 9%. 27% cases were overweight and 8% had normal weight. No case was found to be underweight i.e., BMI < 18 kg/m²(**Fig 1**).

The mean waist circumference was 37.75 + 13.73 inches in obese AN cases Vs 23.77 + 12.67 inches in non-obese AN cases (**p<0.0001**).

Female gender was found to be associated with obesity in AN cases. 69.5% females were obese Vs 55.2% males (**p=0.041**). Regarding the marital status the married AN cases were found to have significantly higher obesity (76.9%) as compared to unmarried cases (60.3%) (**p=0.018; table 1**)

The frequency of various sites of acanthosis nigricans showed maximal involvement of neck (98.6%) followed by groin (80.5%), knuckles (59.7%), sub-mammary (49%) and axilla (47%) (**Fig 2**). The neck and groin AN involvement weren't associated with obesity (**p>0.05**), however knuckles, axilla and sub-mammary involvement was significantly associated with obesity (**p<0.05, table 1**)

The benign acanthosis nigricans was seen in 98.6%. The HAIR AN Syndrome; i.e., hyperandrogenism (HA), insulin resistance (IR) and acanthosis nigricans (AN) was seen in 46% cases. Acral AN in 14%. Syndromic AN was seen in 1.7% and mixed in 1.4%. No case had unilateral AN (**Fig 3**).The various types of AN had no association with obesity (**p>0.05**).

Regarding co-morbid and associated conditions, diabetes mellitus was observed in 47 (21%) AN cases and 174(78.7%) AN cases were non-diabetic. There wasn't significant association of diabetes with obesity in AN case (**p=0.131**). Polycystic ovaries (PCOs) were seen in 111 females out of total 152 females with AN included in study, i.e., 73% females had PCOs. Autoimmune conditions were seen in 53(24%) AN cases and wasn't associated with obesity (**p=0.134**).

Table 1:- Presenting demographic variables, anthropometric measurements, site and types of acanthoses nigricans in obese Vs. non-obese cases with (AN) acanthoses nigricans (n=221).

VARIABLES	n (%) n=221	OBESE n=144	NON-OBESE n=77	P-value
1. Age	27.06+13.56 (10-64yrs)	28.83+13.73 (12-64yrs)	23.77+12.67 (10-57yrs)	<0.0001
2. Height (ft)	4.94+0.61	4.82+0.69	5.17+0.32	<0.0001
3. Height (m)	1.51+0.18	1.47+0.21	1.57+0.09	0.003
4. Weight (kg)	71.79+14.75	74.29+16.68	67.10+8.53	<0.0001
5. BMI	31.63+6.92	34.4+6.92	26.45+2.66	<0.0001
6. Waist circumference	37.03+3.74	37.75+4.25	35.69+1.93	<0.0001
7. Gender	69(31.2%)	37(55.2%)	30(44.8%)	0.041

• Male	152(68.8%)	107(69.5%)	47(30.5%)	
• Female				
8. Marital status				
• Married	65(29.4%)	50(76.9%)	15(23.1%)	0.018
• Unmarried	156(70.6%)	94(60.3%)	62(39.7%)	
9. Site of AN				
• Neck	218(98.6%)	141(64.7%)	77(35.3%)	0.202
• Groin	178(80.5%)	118(66.3%)	60(33.7%)	0.472
• Knuckles	132(59.7%)	96(72.7%)	36(27.3%)	0.004
• Axilla	104(47.1%)	76(73.1%)	28(26.9%)	0.020
• Sub-mammary	108(48.9%)	82(75.9%)	26(24.1%)	0.001
10. Types of AN*				
• HAIR AN	102(46.2%)	67(65.7%)	35(34.3%)	0.879
• Acral	31(14%)	21(67.7%)	10(32.3%)	0.745
• Mixed AN	3(1.4%)	03(100%)	0(0%)	0.202
• Unilateral AN	0(0%)	0(0%)	0(0%)	-
• Syndromic	6(2.7%)	03(50%)	03(50%)	0.429
• Benign AN	218(98.6%)	144(66.1%)	74(33.9%)	0.017
11. History of				
• Diabetes mellitus				
✓ Diabetic	47(21.3%)	35(74.5%)	12(25.5%)	0.131
✓ Non-diabetic	174(78.7%)	109(62.6%)	65(37.4%)	
• PCO (n=152 females)	95(62.5%)	65(61%)	30(65%)	0.648
• Autoimmune	53(24%)	30(56.6%)	23(43.4%)	0.134
• Drug induced	0(0%)	0(0%)	0(0%)	-
• Familial	0(0%)	0(0%)	0(0%)	-

(test of significance Chi-square test; significant $p < 0.05$)

*Acanthosis nigricans, **Polycystic ovaries

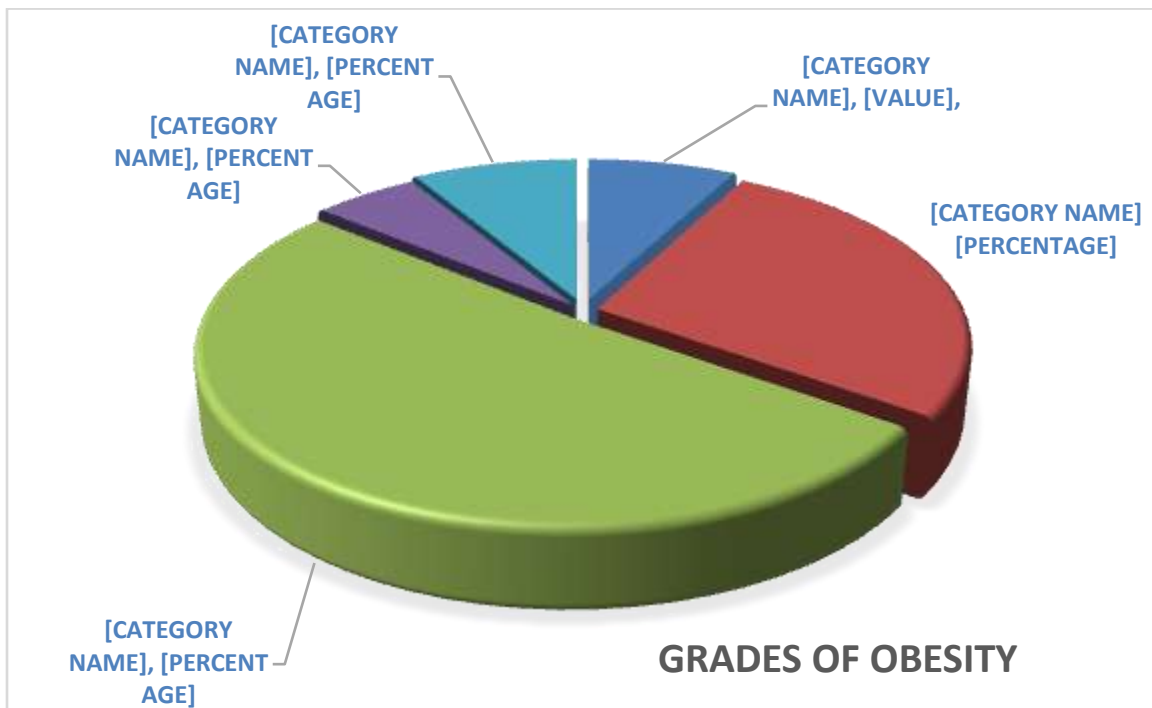


Fig 1:- Pie chart presenting various grades of obesity based on body mass index (BMI) of patients with acanthosis nigricans (n=221).

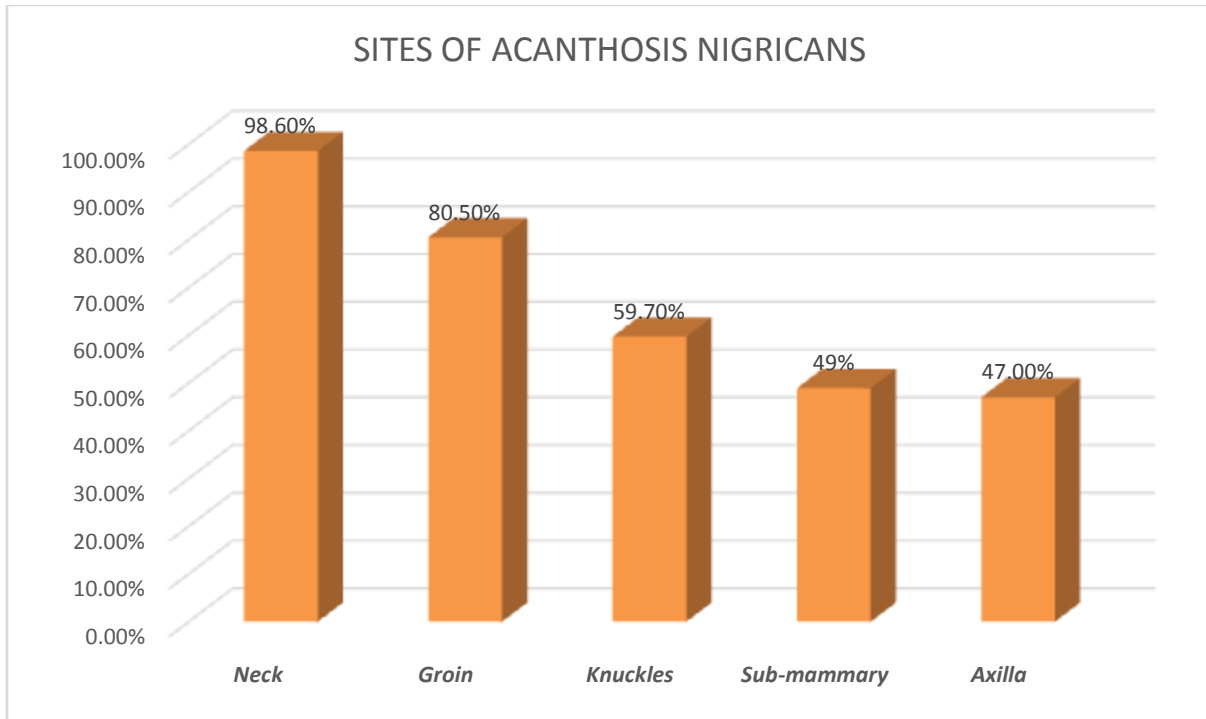


Fig 2:- Bar graph representing sites of Acanthosis Nigricans involvement (n=221).

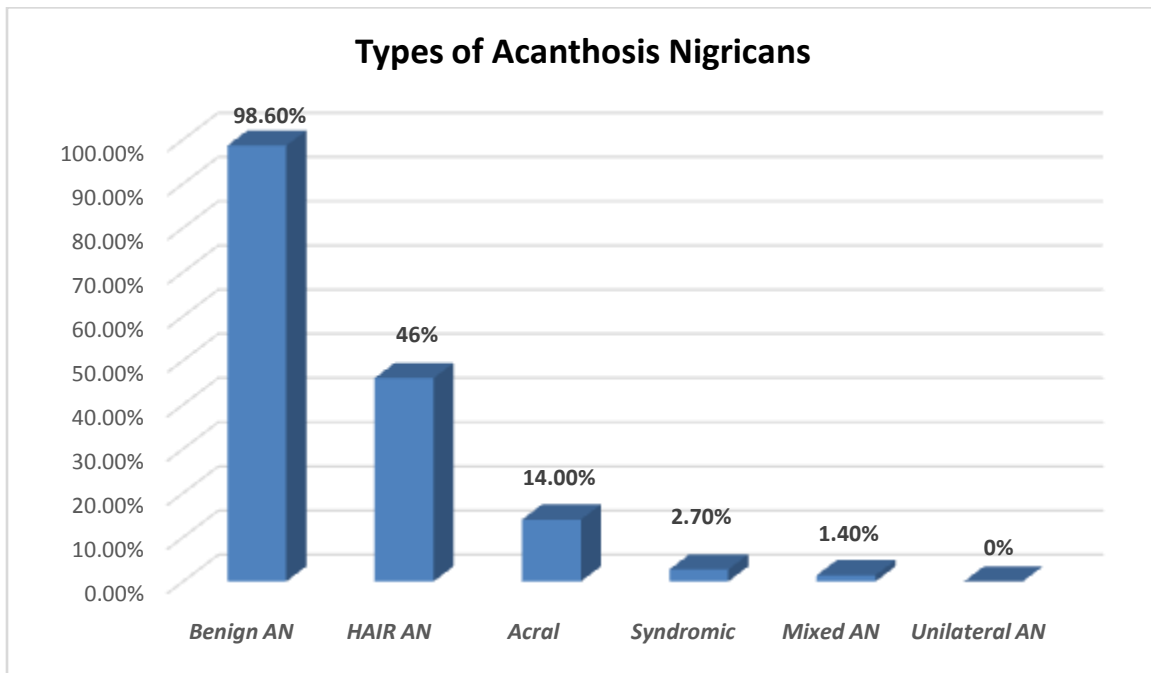


Fig 3:- Bar graph presentation of various type of acanthosis nigricans (n=221).

Discussion:-

Skin as endocrine organ considered as a mirror for many systemic diseases. Hormones in excess or in deficiency/resistance may lead to certain skin diseases or skin changes. AN is a skin condition which itself is poorly defined as a common manifestation of systemic diseases.^[16]

AN is a classical skin condition which is characterized by hyperkeratosis, hyperpigmentation and papillomatosis with involvement of posterior sides of neck, axillae, groins, elbows and knees. The most common association with benign AN are obesity, metabolic syndrome and IR. Metabolic syndrome (Mets) includes central obesity, hypertriglyceridemia, low levels of HDL, cholesterol, hyperglycemia & hypertension.^[17]

Insulin binds with insulin receptors in low concentration in circulation while in insulin resistance and compensatory hyperinsulinemia, insulin binds with IGF-1 (insulin like growth factor) receptors whereas receptors are found in fibroblast and keratinocytes. In obese patients with high insulin resistance, IGF-1 receptors are overexpressed so high concentration of insulin lead to indirect activation of IGF-1 receptors in fibroblasts and in keratinocytes, leading to their proliferation which resultant in AN.^[18]

AN is a asymptomatic skin lesion and appear before the age of forty years and more common in black women than white women. AN may also lead to psychological disturbances due to its appearance with morbidity, depression and self-esteem problems as well.^[19]

In our study, among 221 cases of AN, in which 152(68.8%) females and 69(31.2%) were males. Females were higher than males. In study by parkash^[3] ratio between female: male as same as in our study and females were higher than males but in some previous literature there is no sex predilection for AN^[11]. In our study mean age was 27 ± 13 years while in study by parkash showed slight higher mean age group that is 29.8 ± 8.44 years^[3]. In our study, we found AN more in married patients 156(70.6%) than unmarried 65(29.4%).

Regarding BMI in our study, we found 31 ± 6.92 had normal BMI, while 144 obese cases had 34.4 ± 6.92 BMI and 77 non obese cases had 26.4 ± 2.6 BMI which is less than 30 kg/m^2 (that is normal BMI) .

We had 75% obese cases on the basis of WHO criteria of weight & BMI while parkash found 47% obese in his study that is much less than our study^[3].

The waist circumference in our study was 37.7 ± 4.25 in obese cases while 35.69 in nonobese cases. We found 37(55%) obese males and 30(44.8%) nonobese males while on contrary side 107(69.5%) females were obese and 47(30.5%) were non obese. ShayamVerma in his study found increase prevalence of obesity, 87.5% in males and 100% in females which is less percentage of obesity than our study. There is an increased risk of obesity, hypertension and cardiovascular diseases if waist circumference is more than 36 inches in males and 32 inches in females.^[17]

The current study showed AN to be associated with obesity and increased BMI: that is weight gain which creates a major health issue and need to be immediate attention. The strong relation found in between AN and BMI in major ethnic groups. In Argentina, Hirscher et al, studied 1250 young Hispanic subjects and established strong association of AN and BMI.^[18] AN has been found more commonly in obese or overweight individuals in ethnic groups in Asians and Middle East populations. Previous literatures showed strong association between BMI and AN.^[18]

In our study ,most common site was neck 218(98.6%) followed by groin 178 (80.5%), knuckles 132(59.7%), axillae 104(47.1%) and sub-mammary 108(48.9%). Previous studies by Nisha^[3] and ShayamVerma^[17] showed involvement of neck was the most commonest site of AN which coincides with our study.^[18] Rodriguez found knuckles was most commonest site(21.6%) of AN in his study which is not coincides with our study.^[19] The previous literature showed that in Latino adults (18-23 years), the knuckles was the common site of AN and it indicates one of the first sign of insulin resistance(IR), however neck and axillae are the most common sites and individuals are at high metabolic risk and need early life style modifications.^[19]

Hence , exclusion of knuckles may delay diagnosis of IR until it appears it commonest sites such as neck and axillae thereby time may be loose to start early management of IR as soon as possible. In our study 47(21.3%) were diabetic cases in which 35(74.3%) were obese and 12(25%) were non obese. Shiva Parkash in his study showed that obesity is the known risk factor for DM and IR. Study from Brazil showed all the patients were obese and frequencies of DM (5.8%) and impaired glucose tolerance test (12.6%) were higher in AN groups. In other studies, increased BMI was significantly associated with type 2 DM and AN.^[20] Martha L found 73% prevalence of AN in type 2 DM.^[21]

In our study, we found 62.5% patients with PCOS in which 61% were obese and 30(43%) were non obese while Shabaras et al^[22] found 37% obese in PCOS and Vishali^[23] found 38% obesity in PCOS cases that showed less obesity cases in PCOS patients as compare to our study. Khalifa and Sharquie^[24] found benign AN in 75% unmarried female patients with PCOS. ^[24]PCO's is characterized by obesity, infertility, acne, hirsutism, amenorrhea or oligomenorrhea^[25]

In PCOS patients, there is a raised LH:FSH ratio of more than 2:1. Pathogenesis of PCOS is multifactorial. It is associated with abnormalities in the metabolism of steroid and production of androgens. LH hormones from pituitary gland stimulates theca cells in the ovaries produces androgens and cytochrome P-450c17 (an enzyme with hydroxylase and 17,20 lyase activity) causes production of androstenedione and then this converted by 17 β hydroxy steroid dehydrogenase into testosterone or into estrone by aromatase while from pituitary FSH controls aromatase enzyme activity in the granulosa cells of ovary and produces estrogen. In patient with PCOS, there is an increase level of LH rather than FSH, which results in increased production of androgens (testosterone) in the ovaries by inhibition of aromatase and stimulation of 17 β -hydroxy steroid dehydrogenase^[23]. Hyperandrogenism accounts 75-80% of PCOS and prevalence of hirsutism in PCOS is about 77-83%.

Regarding types of AN, the most common type was benign AN (98.6%) in which 144 (66%) were obese and 74 (33%) were non obese. This type may present at the time of birth or after birth in the childhood or adolescence. There is a doubt that this type is associated with IR but still unknown and needs further investigations^[1]

We found 46% HAIR-AN syndrome is the 2nd most common type, in which 67 were obese (65.7%) and 35 (34.3%) non obese cases of HAIR-AN syndrome. HAIR-AN syndrome; hyperandrogenism (HA), insulin resistance (IR), acanthosis nigricans (AN) is a sub-phenotype of PCOS, seen in 5% with patients of hyperandrogenism.^[26]

The main pathogenesis is thought to be insulin resistance and increased insulin levels and then subsequent increased production of androgens from ovaries. Long periods of hyperandrogenism and insulinism may result in skin changes of AN and signs of virilization. HAIR-AN syndrome is found to be associated with mood disorders, depression and hypothalamic abnormalities. Hypothalamic abnormalities cause disturbance in insulin regulation and depression which explain the abnormalities in both the condition IR and HAIR AN syndrome.^[27]

Acral AN 14% in our study, in which 03 were obese and no non obese case were found in our study. Significance of acral AN is doubtful and needs more literature to explain this type but study by Schwart showed acral AN may be found in normal healthy individuals in dark complexion people and need for workup for internal malignancies and its associations like dermatofibrosarcoma protuberans, non-Hodgkin's lymphoma, gastric adenocarcinoma^[1]. Six cases were found of syndromic type of AN and three cases of mixed types but no case were found of unilateral type^[1]

There are limited regional studies addressing acanthosis nigricans with obesity in accordance to BMI and waist circumference. This study provides us associations of AN with obesity in our population. There are certain limitations in our study like sample size and shorter duration of study and inability to obtain hormone profiles due to financial constraints and further work up for its association like PCOS, DM, hypertension, insulin resistance etc. Authors recommend further regional studies with better sample size, extended study duration and hormone profile and its associations related workup in future studies. The results of this study will help us regarding earlier diagnosis of acanthosis nigricans associated with obesity, hence diagnosing and managing obesity i.e., a systemic problem in patients presenting with dermatological complaint. This can help preventing long term complications and improving quality of life in our patients.

Conclusion:-

Acanthosis nigricans is a major cosmetic and pathogenic problem among obese in our population. Benign and HAIR-AN were most frequent types in our study which associated with obesity, raised BMI and waist circumference. Hence, it is recommended to screen all acanthosis nigricans cases regardless of age or gender for obesity, PCOS, DM, hypertension and autoimmune conditions, IR in particular patients with obesity. This may lead to identification of systemic disorders in dermatologically presenting acanthosis nigricans cases. We may conclude that the early diagnosis of acanthosis in obese cases may improve quality of life, prevent complications of systemic disease and improve outcome of diseases and quality of life of a patient as well.

Acknowledgement:-

We are thankful to all participants who were involved in this study and those who have helped either directly or indirectly.

Grant support & financial disclosure:

None

Conflicts of interest:

There was no conflict of interest of any authors

Abbreviations:DM:DiabetesMellitus,AN:acanthosisnigricans,NFP:Neurofibromatosisprotuberance,

OCP:Oralcontraceptive,IR:Insulinresistance,PCO:Polycysticovary,Mes;Metabolicsyndrome,IGF:Insulin like growth factor,FSH:follicle stimulating hormone,LH:leutinizinghormone

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