"A CROSS SECTIONAL STUDY OF ASSOCIATION OF ACANTHOSIS NIGRICANS WITH INSULIN RESISTANCE IN OBESITY AND METABOLIC SYNDROME"

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With reference to the above, we wish to inform you that your proposed research project titled **"A CROSS SECTIONAL STUDY OF ASSOCIATION OF ACANTHOSIS NIGRICANS WITH INSULIN RESISTANCE IN OBESITY AND METABOLIC SYNDROME",** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

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LIST OF ABBREVIATIONS USED

Sl. No.	Abbreviation	Expansion
1.	AN	ACANTHOSIS NIGRICANS
2.	MetS	METABOLIC SYNDROME
3.	IR	INSULIN RESISTANCE
4.	BMI	BODY MASS INDEX
5.	HOMA-IR	HOMEOSTASIS MODEL ASSESSMENT-INSULIN RESISTANCE
6.	DM	DIABETES MELLITUS
7.	CAD	CORONARY ARTERY DISEASE
8.	CVD	CARDIO VASCULAR DISEASE
9.	EGF	EPIDERMAL GROWTH FACTOR
10.	IGF	INSULIN LIKE GROWTH FACTOR
11.	IRS	INSULIN RESISTANCE SYNDROME
12.	ISI	INSULIN SENSITIVITY INDEX
13.	QISI	QUALITATIVE INSULIN SENSITIVITY INDEX
14.	PCOS	POLYCYSTIC OVARIAN SYNDROME
15.	NCEP	NATIONAL CHOLESTEROL EDUCATION PROGRAM

16.	**SD**	**STANDARD DEVIATION**
17.	**HbA1c**	**GLYCOSYLATED HAEMOGLOBIN**
18.	**ANA**	**ANTI- NUCLEAR ANTIBODY**
19.	**CBC**	**COMPLETE BLOOD COUNT**

ABSTRACT

Background: Acanthosis nigricans is a skin lesion characterized by hyperpigmented velvety cutaneous thickening that commonly occurs in flexural areas like axilla, sides of neck, antecubital and popliteal fossa or groin with insulin resistance being the basic underlying pathology. Insulin resistance is reduction in the ability of tissues mainly those in muscles to use insulin. In this condition, the pancreas become hyperactive and produce more insulin and hyperinsulinemia develops to maintain blood sugar levels within normal limits. The body cannot use the additional insulin and the pancreas become exhausted. Insulin production then decreases. At this point a person may be diagnosed with Type 2 diabetes mellitus. Many studies have been done in various parts of the world on subjects with acanthosis nigricans to determine correlations with obesity, diabetes, hyperinsulinemia, hyperlipidemia, and other parameters of metabolic syndrome.

Thus, screening of patients with acanthosis nigricans for insulin levels becomes relevant and necessary, so as to advice the patients regarding the diet, lifestyle modifications and weight reduction to prevent occurrence of any systemic complications.

Objective: To determine the prevalence of insulin resistance in acanthosis nigricans and relation of acanthosis nigricans with obesity or metabolic syndrome.

Materials and method: This was a hospital based cross-sectional study conducted on patients who visited the Dermatology, venereology, and leprosy outpatient department at KLE'S Dr Prabhakar Kore Hospital and Medical Research Centre in Belagavi during December 2020 to December 2021. A total of 50 patients with clinically

diagnosed benign acanthosis nigricans were included in the study. After obtaining consent, clinical examination was done and the participants underwent laboratory investigations like FBS, HDL, triglycerides, fasting insulin level, with values being noted. Clinical scoring was done based on Burke et al grading system for severity of AN along with relevant clinical pictures of lesions. Insulin resistance was calculated using homeostasis model of assessment of insulin resistance (HOMA- IR), the values ≥ 2.5 were taken into consideration. All the data was entered in excel sheet and analysed using SPSS v 21 operating on windows 10. P-value less than or equal to 0.05 signified statistical significance.

Results: Out of 50 patients, 30 (60%) were females and 20 (40%) were males. Majority (40%) (n=20) of them belonged to an age group of 31-40 years. The prevalence of IR in the 50 patients with acanthosis nigricans was found to be 88% (n=44). Out of all acanthosis nigricans patients, 62% patients were obese and 60% patients had insulin resistance with obesity and the association was statistically significant ($p \leq 0.05$). Insulin resistance (IR) and metabolic syndrome (MetS) was also compared, out of all patients (52%) diagnosed with metabolic syndrome, insulin resistance (IR) was seen in all the patients and the association was statistically significant. ($p \leq 0.05$)

Conclusion: According to our study, insulin resistance (IR) was found in considerable number of patients with acanthosis nigricans. Prevalence of insulin resistance was more in obese and metabolic syndrome patients. There is also a statistically significant association of severity of AN observed with prevalence of obesity and metabolic syndrome. Acanthosis nigricans could be the early indicator of

impending diabetes and other cardiovascular diseases. Thus, screening of patients with acanthosis nigricans for insulin levels becomes relevant and necessary.

Limitation: The limitation in our study was that there was no histopathological correlation done. Also, a larger scale study is required to support and verify study outcomes.

Key words: Acanthosis nigricans, insulin resistance, metabolic syndrome, obesity

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INTRODUCTION

Acanthosis nigricans is an easily identifiable dermatoses characterized by thickened, hyperpigmented velvety plaques of body folds and neck. The most common sites of involvement include axilla, along with flexural areas of posterior neck, groin, dorsa of fingers, around areola, and umbilicus; histopathologically characterised by papillomatosis and hyperkeratosis of skin.[1,2] The basic underlying pathology is insulin resistance. It serves as a marker for underlying endocrinopathy.

Insulin resistance (IR) is a metabolic disorder in which target cells fail to respond to normal levels of circulating insulin, which results in compensatory hyperinsulinemia in an attempt to obtain an appropriate physiological response. [3]

The mechanism through which insulin resistance causes acanthosis nigricans is complex. The significant presence of IR produces compensatory hyperinsulinemia. Increased serum insulin levels interact with insulin-like growth receptors (IGF-1) triggering proliferation of keratinocytes and fibroblasts.[4] Hence, AN is mainly caused by factors that stimulate epidermal keratinocytes and dermal fibroblast proliferation.

A study was conducted to determine the prevalence of acanthosis nigricans in the central Kerala and evaluated its correlation with diabetes, obesity, insulin levels and other factors and the study showed up to 20% of adults and 7% of children may have benign AN, making it quite prevalent. [5]

The recognition of connection of AN to IR allows for diagnosis of type 2 DM, metabolic syndrome, polycystic ovarian syndrome. Early recognition of these conditions is essential for prevention of disease progression. [6]

Thus, based on the previous studies conducted to determine the prevalence of AN, screening of patients with acanthosis nigricans for insulin levels becomes relevant and necessary, so as to advice them regarding the lifestyle modification like correction of diet and weight reduction to prevent occurrence of diabetes mellitus.

AIMS AND OBJECTIVES

- **PRIMARY OBJECTIVE**

To evaluate relation between insulin resistance and acanthosis nigricans in patients with obesity or metabolic syndrome.

- **SECONDARY OBJECTIVE**

To grade severity of acanthosis nigricans.

REVIEW OF LITERATURE

ACANTHOSIS NIGRICANS

A velvety skin darkening called AN frequently appears in intertriginous areas. This hyperpigmentation has ill-defined borders, commonly develops in skin fold regions including the axilla, groin and the back of the neck, and may be accompanied with skin thickening. AN is most frequently associated with diabetes and IR, but in rare instances, it can also be an indication of internal malignancy. It can also emerge from hormonal imbalances and the use of specific medications, including oral contraceptives and systemic glucocorticoids.[7–10]

❖ Background

According to Unna and Pollitzer, the first known instance of acanthosis nigricans occurred in Germany in 1889. Acanthosis nigricans, which had been recorded in about 50 patients by 1909, was thought to be linked to an internal cancer. The earliest description of the connection between acanthosis nigricans and insulin resistance was made in a seminal study by Kahn et al., which was published in 1976. Acanthosis nigricans was recognized as a formal risk factor for the onset of diabetes in children by the American Diabetes Association in 2000. [11]

❖ Epidemiology

Prevalence

The current rise in the prevalence of AN may probably be a reflection of global trends toward increased obesity and type 2 diabetes. Between 7% in unselected groups and 74% in obese adults, AN is prevalent. [12,13] A study on young American

Indians from 2002 found a prevalence rate of 34.2%[14]; however, a study on members of the Alabama Coushatta tribe from Texas and Nebraska found a prevalence rate of 38%. Another study looked at the links between acanthosis nigricans and diabetes, obesity, insulin levels, and other variables in the central Keralan population of South India. The study found that 16.1% of the population had the condition.[15] The prevalence of AN is also linked to Cushing's disease, Addison's disease, hypothyroidism, obesity, polycystic ovarian disease, and insulin-resistant diabetes. There are several conditions that are related to AN, including Prader-Willi syndrome, Alstrom syndrome, leprechaunism, lipoatrophic diabetes, Cushing's disease, pineal hyperplasia syndrome, ovarian hyperthecosis, stromal luteoma, and ovarian dermoid cysts. [16,17]

Race

Acanthosis nigricans is much more common in people with darker skin pigmentation. The prevalence in whites is less than 1%. African Americans are 25 times more likely to have AN than patients of European descent.[12] A study from the USA reports that the prevalence of AN was 3% among Caucasians, 19% in Hispanics and 28% in American Indians.[18]

Sex

The incidence of acanthosis nigricans is equal for men and women. Acanthosis nigricans has no known sex predilection.

Age

Although benign acanthosis nigricans lesions can appear at any age, including at infancy, they are more common in adults and adolescents. In older people, malignant acanthosis nigricans is more common. [4]

Mortality and morbidity

There are relatively few, if any, problems from the skin lesions caused by the benign variant of acanthosis nigricans. AN is regarded as a forthright cutaneous indicator of insulin resistance and hence hyperinsulinemia aids in the detection of people who are predisposed to diabetes or poor glucose tolerance. [19]

The degree of insulin resistance is extremely diverse and can range from a chance discovery during normal blood tests to overt diabetic mellitus. A partial resolution may occur with treatment of the insulin-resistant state since the severity of skin abnormalities may correlate with the level of insulin resistance.

The most frequent cause of acanthosis nigricans in younger people is insulin resistance. Recent research suggests that children with acanthosis nigricans had greater baseline and glucose-stimulated insulin levels than obese children without the condition, suggesting a relationship between the two that is independent of body mass index. [20,21]

Malignant acanthosis nigricans is far less frequent than the other forms and has a generally bad prognosis, which is at least partially related to the poor prognosis from the neoplasia in question. The most typical association is with intra-abdominal cancers. Patients with malignant acanthosis nigricans had a 2-year median survival period.

❖ **Etiology**

The development of AN is influenced by a variety of circumstances.[22]

- IGF-1 and other keratinocyte ILGF receptors are stimulated by an increase in the amount of circulating insulin. IGF-1 may be displaced from the IGF binding protein by insulin at higher concentrations. IGF levels in the blood may rise, which could encourage keratinocyte and fibroblast development. Hereditary variations are linked to fibroblast growth factor deficiencies.

1. Familial AN: As a result of an autosomal dominant feature, this disorder might manifest at birth or during infancy. Mutations in the fibroblast growth factor receptor 3 are the root cause (FGFR3).[23]
2. Obesity and AN: Obesity is among the most often occurring diseases linked to AN. Although they can occur at any age, lesions seem to occur more frequently in adults. It was formerly referred to as "pseudo AN" It could be related to IR. An improvement in AN may be seen as a result of diet, weight loss, or medication used to treat obesity.[24,25]

   Most frequently, AN is linked to IR-related conditions such obesity, type 2 diabetes, and polycystic ovary syndrome. Hyperinsulinemia is regarded to be crucial in these situations. Acrochordon (skin tags) are commonly encountered in and around the affected areas. [26]
3. AN and drugs: AN has been connected to a number of medications. Nicotinic acid, systemic glucocorticoids, diethylstilbestrol, combination oral contraceptive pill, growth hormone treatment, estrogen, protease inhibitors and injectable insulin are examples of these. AN normally disappears if the causative drug is discontinued.[7,27,28]

4. AN linked to endocrine dysfunction: It has a slower progression, is less common, and patients are frequently obese. Insulin-resistance disorders are classified as type A (HAIR-AN) or type B. Hyperandrogenemia, IR, and AN are all symptoms of type A syndromes. Females with uncontrolled diabetes, ovarian hyperandrogenism, or autoimmune illness such as SLE, Sjogren's syndrome, or scleroderma are more likely to develop Type B syndrome. AN is linked to polycystic ovarian syndrome (PCOS). IR and hyperandrogenism are common in PCOS patients.[29]
5. Acral acanthotic anomaly: AN seen only over popliteal and cubital fossa and extensor aspect of knuckles and foot surfaces. It is frequently seen in people with Fitzpatrick skin type 4-6.[30]
6. Malignant AN syndrome is linked to gastrointestinal adenocarcinomas as well as genitourinary malignancies such as breast, ovary and prostate, Lung cancer and lymphoma are seldom linked to AN. Internal cancer may be preceded, accompanied, or followed by malignant AN. AN caused by cancer frequently appears suddenly and is accompanied by skin tags, or tripe palms and numerous seborrheic keratoses (an indication of Leser-Trelat). [31,32]
7. AN is linked to autoimmune illnesses such as Hashimoto's thyroiditis, Sjogren's syndrome SLE and Scleroderma.[33]
8. Unilateral AN: It is an extremely uncommon, autosomal dominant condition also known as Nevoid AN arise as unilateral lesions in infancy, childhood or maturity.[34]

❖ **Pathophysiology**

Weak knowledge exists regarding the pathogenesis of acanthosis nigricans. Increased growth factor levels and insulin-mediated activation of insulin-like growth factor receptors on keratinocytes may be contributing factors. [35] Following are a few of the elements that have been suggested as contributing to the pathophysiology of acanthosis nigricans:

- Raised serum insulin levels
- Fibroblast growth factor defects
- Increased TGF-α (Transforming growth factor-α)
- Perspiration or friction
- Drugs

Insulin and insulin-like growth factor-1, and their receptors on keratinocytes are clearly involved in the complex regulations leading to the peculiar epidermal hyperplasia. [36]

Insulin controls the equilibrium between keratinocyte differentiation and proliferation in the epidermis, which helps maintain skin homeostasis[37]. Insulin resistance is caused by insulin receptor substrate-1 (IRS-1) being serine phosphorylated in an inhibitory manner, which prevents the receptor's signal from being sent. [38] Through inhibitory IRS-1 phosphorylation, keratinocytes in AN are unable to respond to insulin as they should, which may affect the insulin-dependent homeostasis of the skin. At the same time, insulin's growth-promoting effects via the IGF-1 receptor continue to exist. [39]

IGF-1 receptors on keratinocytes and fibroblasts are directly and indirectly activated by increased insulin concentrations, resulting in proliferation. Other tyrosine kinase receptors including EGFR and FGFR as well as other mediators could be involved. (IGF, BP, IGF-1R, EGFR, and FGFR stand for insulin-like growth factor, epidermal growth factor receptor, and fibroblast growth factor receptor, respectively.)[35]

Hyperinsulinemia is believed to be crucial in AN. Insulin controls the metabolism of carbohydrates, lipids, and proteins at low concentrations and, by interacting with "traditional" insulin receptors, may also only marginally stimulate growth. IGF-1Rs (insulin-like growth factor I receptors), which resemble insulin receptors in size and subunit structure but bind IGF-1 with 100- to 1000-fold more affinity than insulin, allow insulin to have more robust growth-promoting actions at high concentrations. [40] Numerous findings imply that insulin-dependent IGF-Is activation can boost cellular growth and aid in the emergence of AN. First, cultured fibroblasts and keratinocytes both contain IGF receptors. [41] Second, insulin can pass through the dermo-epidermal interface and, in high doses, can promote fibroblast proliferation and replication. [41, 42] The severity of AN in obese people positively corresponds with the fasting insulin concentration, to conclude. [23,24] As a result, insulin may encourage AN by directly activating the IGF-1 signalling pathway.

The propensity of AN towards regions like the neck and axillae makes it plausible that perspiration and/or friction may also be essential cofactors. [43] By increased amounts of free IGF-1 in the blood, hyperinsulinemia may potentially help AN develop in an indirect manner. IGF binding proteins (IGFBPs), which prolong IGF-1 half-life, transport IGFs to target tissues, and control the concentrations of

metabolically active free IGF-1, are responsible for controlling IGF-1 activity. [44, 45] In obese people with hyperinsulinemia, IGFBP-1 and IGFBP-2 levels are also lowered, which raises plasma concentrations of free IGF-1. [45] IGF-1 that is more bioactive encourages cell growth and differentiation. [46]

Insulin-like growth factor 1 is expressed by dermal fibroblasts and the stratum granulosum, but not by basal keratinocytes of the epidermis. [47] Consequently, an increase in local levels of free IGF-1 caused by an insulin-induced systemic reduction of IGFBP-1 and IGFBP-2 could promote the onset of hyperkeratosis and papillomatosis.

Extreme insulin resistance syndromes, including AN in 5 of 7 patients [48], have by IGF-1 therapy. IGF-1 expression and blood insulin levels may both be decreased by insulin-like growth factor 1 (IGF-1). [44, 49] It's likely that insulin is less effective at downregulating IGF-IRs than IGF-1 because it binds to the IGF-1 receptor with a lower affinity than IGF-1 itself. Not all acanthosis nigricans subtypes are caused by hyperinsulinemia. FGFR deficiencies are the cause of several AN syndromes.

- **History and examination**

Patients often appear with asymptomatic or occasionally itchy, velvety, hyperpigmented to black macules and patches that developing into palpable plaques. Malignant AN manifests as skin alterations in around one-third of patients before any indications of malignancy. Second third of the time, lesions appear at the same time as the tumour. In the remaining one third, lesions appear following any tumor. AN lesions generally appear in skin folds such as the groin, axilla, or posterior neck. The posterior neck is the most prevalent location of AN in youngsters. AN can also

involve the mucosa of the nose, oral cavity, oesophagus, or larynx in rare cases. Nipples may rarely be involved in women. Rarely AN in the conjunctiva have been recorded.

Skin tags in the same location may also be present in certain people. Nail alterations include hyperkeratosis and leukonychia. Clinically, it is impossible to distinguish between benign and malignant AN lesions.

❖ **Evaluation**

AN is clinically diagnosed and corroborated by a skin biopsy. Diabetes or cancer may necessitate complete blood tests, endoscopy or X-rays. The workup is designed to rule out any underlying malignancy. diabetes screening and Glycosylated Haemoglobin testing are indicated because IR and/or obesity are involved in the vast majority of cases. [50,51]

❖ **Algorithm for the evaluation of acanthosis nigricans** [52]

- Patients aged 10 years or younger: Is there a family history of acanthosis nigricans?

A. If yes, consider familial acanthosis nigricans and recommend genetic counseling.
B. If no, look for associated non familial congenital anomalies and suspect underlying insulin resistance.

- Patients aged older than 10 years: What is the severity or extent of acanthosis nigricans?

A. If severe or generalized, characterize onset of acanthosis nigricans.

1. If onset is sudden, Suspect underlying malignancy.

Diagnostic study

(1) Review of systems

(2) Physical examination

(3) Chest roentgenogram

(4) CBC, stool test

Referral

(1) To gynecologist (pelvic examination)

(2) To gastroenterologist (gastroscopy, sigmoidoscopy, or both

2. If onset is insidious, suspect underlying insulin resistance.

B. If mild or localized, characterize onset of acanthosis nigricans.

1. If onset is sudden, does patient take medications?

a. If yes, rule out drug-induced acanthosis nigricans; discontinue drug.

b. If not, suspect underlying insulin resistance.

2. If onset is insidious, is patient obese?

a. If yes, consider obesity as underlying cause.

b. If not, rule out endocrine disorders and suspect underlying insulin resistance.

Diagnostic study

(a) Review of systems

(b) Physical examination

Referral to endocrinologist

Ill. Patients with insulin resistance: What is course of acanthosis nigricans?

A. If progressive, suspect genetic defects of insulin receptor.

Diagnostic study

a. Review of systems

b. Physical examination

c. Plasma levels of glucose and insulin (fasting and 2 hours postprandial)

d. Plasma levels of testosterone, DHEA, FSH, LH

Referral

a. To endocrinologist

b. To appropriate specialist (for congenital anomalies, when present)

B. If characterized by remissions (and exacerbations), suspect acquired defects affecting insulin receptor.

Diagnostic study

a. Review systems

b. Physical examination

c. Plasma levels of glucose and insulin (fasting and 2 hours postprandial)

d. CBC, urinalysis, computer-assisted biochemical analysis

e. Tests for anti-insulin receptor antibody, ANA, other autoantibodies

Referral to appropriate specialist.

- **Grading**

1. Curth divided AN into three categories: benign, syndromic, and pseudo-AN.
2. Hernandez-Perez suggested two categories that are more straightforward: basic AN unrelated to malignancy and paraneoplastic AN.

3. Burke et al. graded AN on a scale of 0 to 4 based on the number of afflicted locations and the severity of the condition. This scale is simple to use and corresponds with fasting insulin and body mass index. It also has a high inter-observer reliability (BMI).

Table 1: Burke et al Classification of AN[32]

LOCATION AND SCORE	DESCRIPTION
NECK SEVERITY	
0	Absent: not detectable on close inspection
1	Present: clearly present on close visual inspection, not visible to the casual observer, extent not measurable
2	Mild: limited to the bas of the skull, does not extend to the lateral margins of the neck (usually <3 inches in breadth)
3	Moderate: extending to the lateral margins of the neck (posterior border of the sternocleidomastoid) (usually 3-6 inches), should not be visible when the participant is viewed from font
4	Severe: extending anteriorly (>6 inches), visible when the participant is viewed from the front
AXILLA SEVERITY	
0	Absent: not detectable on close inspection
1	Present: clearly present on close visual inspection, but not visible to casual observer, extent not measurable
2	Mild: localized to the central portion of the axilla, may have gone unnoticed by the participant

3	Moderate: involving entire axillary fossa, but not visible when the arm is against the participant's side
4	Severe: visible from front or back in the unclothed participant when the arm is against the participant's side
NECK TEXTURE	
0	Smooth to touch: no differentiation with normal skin on palpation
1	Rough to touch: clearly differentiated from normal skin
2	Coarseness can be observed visually, portions of skin clearly raised above other areas.
3	Extremely coarse: "hills and valleys" observable on visual examination.
KNUCKLES	Present/ absent
ELBOWS	Present/ absent
KNEES	Present/ absent

❖ **Management**

General measures

The therapy objective is to address the underlying condition. The majority of people seek therapy only for cosmetic reasons. Weight loss and IR treatment can reduce the severity of hyperkeratotic lesions in some people. All provoking factors and drugs should be stopped. Attempts should be made to reduce the lipid profile.

Topical therapy

Podophyllin and topical retinoids like 0.1% tretinoin cream or a mixture of ammonium lactate 12% and 0.05% tretinoin are sometimes suggested as

keratolytics.[55,56] Topical vitamin D analogues (for example, calcipotriol, calcipotriene 0.005%) reduce proliferation of keratinocytes and ameliorate AN lesions.[57] The effectiveness of the above therapies varies.

Oral therapy

Metformin and rosiglitazone, both insulin-sensitizing medications, can be used to treat AN associated with IR.[57,58]. In one study, octreotide demonstrated significant improvement in a patient with IR.[55,58] One patient with acquired generalised lipodystrophy with acanthosis nigricans experienced significant improvement in skin texture and reduced hyperpigmentation after ingesting 10–20g of fish oil containing omega-3 fatty acids daily for six months. [54] Melatonin can aid obese AN patients with their cutaneous symptoms by lowering inflammation and insulin sensitivity. Six months after completing the course, one patient with insulin resistance exhibited persistent improvement in response to Octreotide.[60] Patients with HAIR-AN syndrome (Hvperandrogenemia, Insulin Resistance, and Acanthosis Nigricans Syndrome) may be treated with oral contraceptives and metformin[11]. Malignant acanthosis nigricans patients have taken cyproheptadine as it may prevent the discharge of tumour products. [61] According to reports, PUVA (Psoralen Ultra Violet A) is helpful for symptomatic alleviation in patients of Paraneoplastic Acanthosis Nigricans. [62]

Surgical care

To lessen the severity of the lesion, further treatments including dermabrasion and long pulsed alexandrite laser therapy may be employed. [63] The mainstay of

treatment for malignant acanthosis nigricans is surgical removal of the tumour as there are reports of clearing of lesions after primary malignant tumour excision. [64]

❖ **Prognosis**

When a recognised cause is eliminated, acanthosis nigricans is likely to improve. For instance, weight loss will help with obesity-related acanthosis nigricans, and stopping the drug will probably help with drug-induced acanthosis nigricans. Cancer-associated variants may disappear after a malignancy is removed, while hereditary variants may or may not fade with age. [65]

❖ **Differential diagnosis**

- Tinea
- Candidiasis
- Ichthyosis
- Seborrhea
- Erythrasma
- Granular parakeratosis
- Linear epidermal nevus
- Addison's disease producing cutaneous hyperpigmentation

❖ **Complications**

The complications of AN are determined by the etiology. The majority of instances of AN are caused by IR, however significant consequences such as cancer can also be connected with this illness.[22]

METABOLIC SYNDROME (MetS)

Metabolic syndrome (MetS) is an important cause of morbidity affecting gradually more people in the world. The existence of Insulin-related glucose metabolism disorders in many people having metabolic syndrome (MetS) constituents was supported by epidemiological studies.

Metabolic syndrome (MetS) is also termed as the IR syndrome or syndrome X. It is associated with presence of resistance to the effects of Insulin on peripheral blood glucose levels and also altering the fatty acid utilization. Which often leads to the type 2 diabetes mellitus.

Target cells in IR, a metabolic disorder, do not respond to normal amounts of circulating insulin, which causes compensatory hyperinsulinemia. AN and acrochordons have been linked to IR, and they may serve as an obvious indicator of IR and non-insulin-dependent diabetes. Acanthosis nigricans and IR are always so closely related that acanthosis nigricans has been referred to as a clinical proxy for hyperinsulinemia as diagnosed by a laboratory. [66]

❖ Epidemiology

The prevalence of metabolic syndrome (MetS) varies by age group, as well as by ethnicity. It displays a linear relationship with ageing. It increases between 20 and 50 years and then plateaus.

IR, the associated hyperinsulinemia and hyperglycemia, and adipocyte cytokines (adipokines) may also lead to vascular endothelial dysfunction, an abnormal lipid profile, hypertension, and vascular inflammation, all of which promote the development of atherosclerotic cardiovascular disease (CVD).[41–44] The co-occurrence

of metabolic risk factors in both CVD and T2DM suggested that existence of a metabolic syndrome (MetS).[67,68]

❖ **Definition**

Several definitions for metabolic syndrome (MetS) have been suggested, leading to difficulty in comparing the data from multiple studies which uses different criteria. Hence the national cholesterol education program (NCEP) adult treatment panel III (ATP III) is widely used to maintain a harmonization. Abdominal Obesity is not a prerequisite for diagnosis; the presence of any three of the five criteria listed constitutes a diagnosis of metabolic syndrome (MetS).

❖ **ATP III criteria define metabolic syndrome as the presence of any 3 of the following 5 traits**

1. **Abdominal obesity**: waist circumference ≥102cm (40 in) in men and ≥88 cm (35in) in females
2. **Serum triglycerides** ≥150cm/dL or drug treatment for elevated triglycerides
3. **Serum high-density lipoprotein (HDL) cholesterol** <40 mg/dL in males and <50 mg/dL in females or drug treatment for low HDL cholesterol
4. **Blood pressure** ≥130/85 mmHg or drug treatment for elevated blood pressure
5. **Fasting plasma glucose (FPG)** ≥100mg/dL or drug treatment for elevated blood glucose.

❖ **Other potential markers to detect the metabolic syndrome (MetS):**

The presence of metabolic syndrome (MetS) can be identified by utilizing the proinflammatory, prothrombotic state which are associated with higher level of blood C-Reactive protein (CRP), interleukin (IL)-6 and plasminogen activator inhibitor

(PAI)-1. These markers are also associated with the higher risk of subsequence presence of CVD and type 2 diabetes.[70]

❖ **Clinical implications[71,72]**

Metabolic syndrome (MetS) is a significant contributor to the later onset of type 2 diabetes and cardiovascular disease. Identifying people who require substantial lifestyle changes centred on weight loss and greater physical exercise is the primary clinical implication of the Metabolic syndrome (MetS) diagnosis.

These people are associated with

- Risk of Diabetes mellitus
- Cardiovascular disease
- Fatty liver disease with steatosis, fibrosis and cirrhosis
- Hepatocellular carcinoma and intrahepatic cholangiocarcinoma
- Chronic kidney disease
- Polycystic ovary disease
- Sleep disorders
- Obstructive sleep apnea
- Hyperuricemia and gout

Table 2: Therapeutic goals for management of metabolic syndrome[73]

Lifestyle risk factors	**Goals**
Abdominal obesity	Year 1: Reduce body weight 7 to 10 percent
	Continue weight loss thereafter with ultimate goal BMI <25 kg/m^2
Physical inactivity	At least 30 min (and preferably ≥60 min) continuous or intermittent moderate intensity exercise 5 times per week, but preferably daily
Atherogenic diet	Reduced intake saturate fat, trans fat, cholesterol
Metabolic risk factors	**Goals**
Dyslipidemia	
Primary target elevated LDL cholesterol	High risk*: <100 mg/dL (2.6 mmol/>L); optional <70 mg/dL
	Moderate risk: <130 mg/dL (3.4 mmol/L)
	Lower risk: <160 mg/dL (4.9 mmol/L)
Secondary target elevated non-HDL cholesterol	High risk*: <130 mg/dL (3.4 mmol/L); optional <100 mg/dL (2.6 mmol/L) very high risk
	Moderate risk: <160 mg/dL (4.1 mmol/L)
	Lower risk: <190 mg/dL (4.9 mmol/L)
Tertiary target reduced HDL cholesterol	Raise to extent possible with weight reduction and exercise
Elevated blood pressure	Reduce to at least <140/90 (<130/80 if diabetic)
Elevated glucose	For IFG, encourage weight reduction and exercise
	For type 2 DM, target A1C <7 percent
Prothrombotic state	Low-dose aspirin for high-risk patients
Proinflammatory state	Lifestyle therapies; no specific interventions

OBESITY[74]

❖ Introduction

Obesity is defined as an excess of adipose tissue mass. Although higher adiposity is commonly associated with weight gain, this is not always the case; as muscular people might be overweight by numerical measures without having increased fat deposition. It is relatively arbitrary to choose a medically significant line between lean and obese because body weights vary throughout populations. Obesity is thus characterized by examining its relationship to morbidity or mortality. The presence of AN is more common among the adults with Obesity.

Table 3: Classification of obesity based on BMI

GRADE	BMI (in kg/m^2)
Normal	**18.5 – 24.9**
Overweight	**25 – 29.9**
Obesity grade I	**30 – 34.9**
Obesity grade II	**35 – 39.9**
Obesity grade III	**≥40mg/m^2**

INSULIN RESISTANCE AND ACANTHOSIS NIGRICANS

The most common cause of AN is endocrinopathies, and obesity is frequently associated with IR, hyperinsulinism, and diabetes mellitus. There are several other endocrine disorders that have been linked to AN, some of which are linked to IR, including Cushing's syndrome, polycystic ovaries, thyroid issues, hirsutism, Addison's disease, and acromegaly.

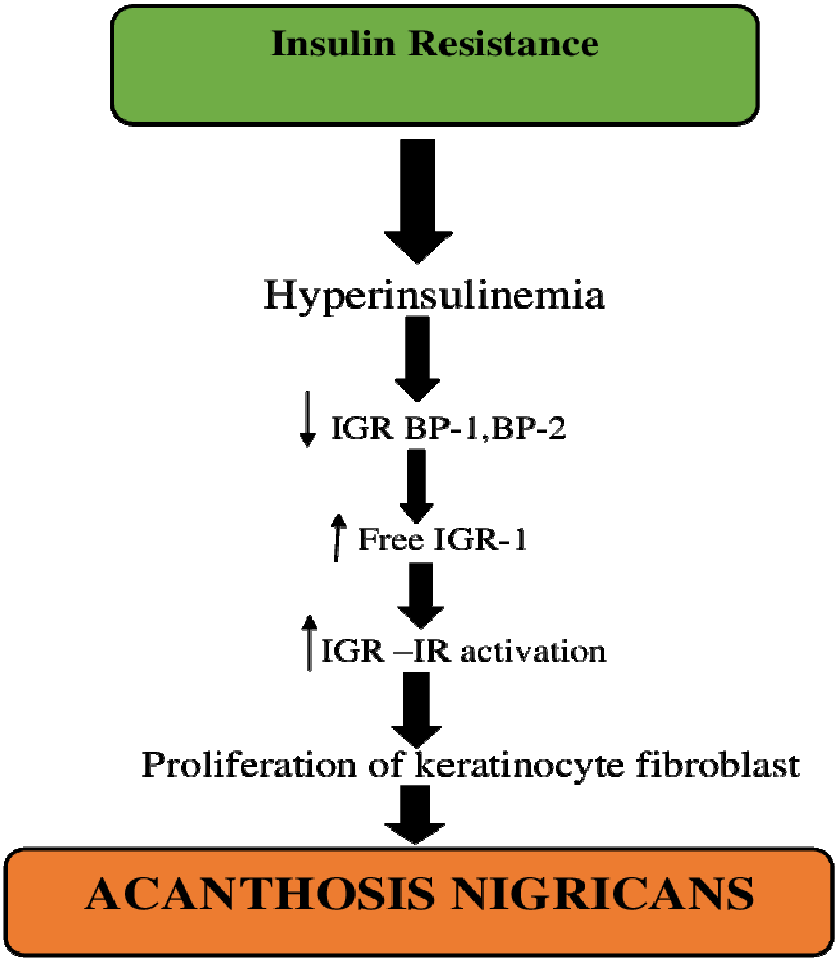


Figure 1: Schematic diagram depicting the relation between IR and AN[75]

Complex steps are involved in how IR causes acanthosis. Significant IR leads to compensatory hyperinsulinemia. IGF-1 receptors and elevated blood insulin levels

work together to promote keratinocyte and fibroblast proliferation. AN is brought on by factors that encourage the proliferation of dermal fibroblasts and epidermal keratinocytes. Substances released by the tumour are hypothesized to operate as stimulating agents in forms linked with malignancy. TGF-alpha, which is generated by tumours and is related to EGF, is thought to have a role in the development of malignant AN.[76]

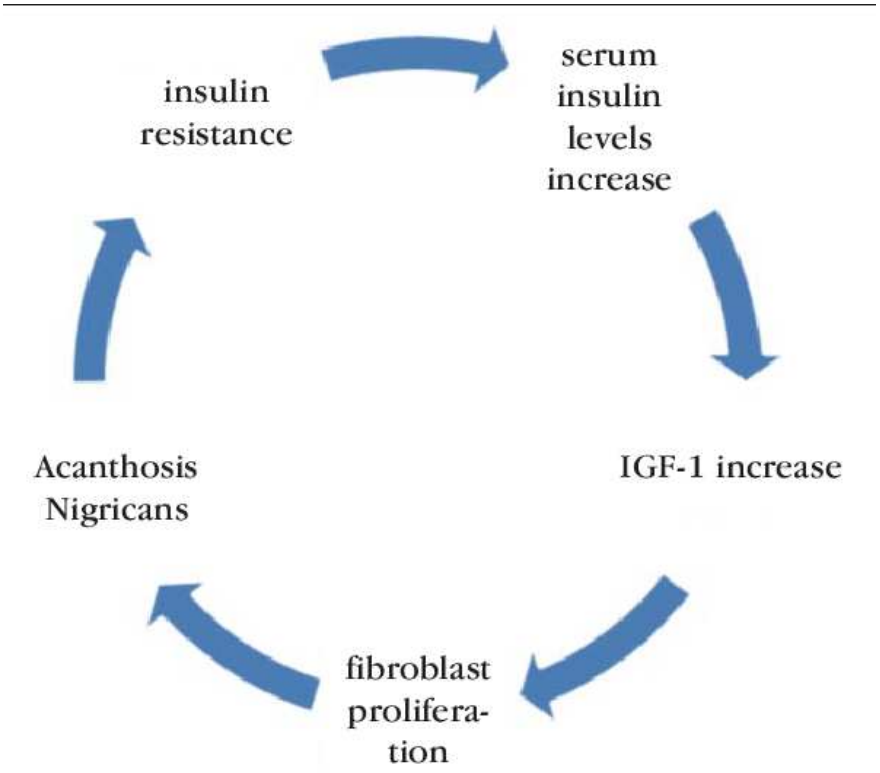


Figure 2: Triggering mechanism of AN lesions[76]

Epidermal growth factor (EGF), which is plentiful in the hyperproliferative epidermis, is a crucial regulator of keratinocyte proliferation in vitro. EGF requires interaction with either high levels of Insulin or Insulin-like growth factor/somatomedin (IGF-1) for keratinocyte proliferation. Since IGF-1 and EGF are thought to play a role in the regulation of epidermal growth and the pathogenesis of

hyperproliferative skin disorders, the basal layer of the epidermis contains the IGF-I receptor.

In a study by Kobaissi HA et al., (2004) to assess the relation between the AN and the Insulin sensitivity. BMI was the most important predictor of Si, accounting for 41% of the variation. The presence of AN explained an extra 4% of the variation in Si; scale grading of AN extent or texture did not enhance prediction considerably. Despite the fact that AN is an independent risk factor for IR in overweight Hispanic children at risk of type 2 diabetes, body adiposity is the predominant predictor of Insulin sensitivity. Furthermore, scale grading AN appears to be of little clinical utility in clinically determining the degree of IR beyond detecting the presence or absence of AN and calculating BMI.[77]

AN was evaluated as a clinical sign of IR in adolescents in a study by Videira-Silva A et al., published in 2019. Adolescents with AN had greater HOMA-IR (d=0.55, P=0.003) and insulin levels than those without (d=0.56, P=0.003). Both the short and long versions of the AN scores failed to adequately describe either IR (P=1.07, P=0.422; =1.10, P=0.374) or hyperinsulinemia (P= 1.10, P= 0.316; P = 1.15, P= 0.251). The presence of AN alone predicted hyperinsulinemia in 7.3% (P= 2.68, P= 0.008) of adolescents and the presence of IR in 7.1% (P=2.59, P=0.009). A non-invasive, affordable technique of identifying asymptomatic overweight teenagers who have IR or are at risk of getting it is to screen for AN at the neck and axilla.[78]

❖ **Manifestations of IR:**

The clinical manifestations of IR include;

- AN
- Metabolic Syndrome (MetS)
- SDB
- Non-alcoholic fatty liver

Table 4 : Major causes for insulin resistance[79]

Inherited states of target cell resistance
Leprechaunism (insulin-receptor mutations)
Rabson-Mendenhall syndrome (insulin-receptor mutations)
Type A syndrome of insulin resistance (insulin-receptor mutations in some, unknown signalling defect in most)
Some lipodystrophies
Secondary insulin resistance
Obesity (free fatty acids and adipocytokines may contribute)
Stress, infection due to excess counterregulatory hormones (cortisol, catecholamines, growth hormone, glucagon)
Medications (eg, glucocorticoids, HIV antiretrovirals, oral contraceptives)
Inactivity

Pregnancy (placental lactogen)
Immune mediated (anti-insulin antibodies, anti-insulin receptor antibodies in type B syndrome)
Miscellaneous (starvation, uremia, cirrhosis, ketoacidosis)

Table 5: Consequences of insulin resistance

Consequences of insulin resistance
Most cases of type 2 diabetes mellitus
Cardiovascular disease, hypertension
Polycystic ovary syndrome
Metabolic syndrome
Obesity-related cancers

- An excess of circulating fatty acids is a significant early contributor to the production of IR. Plasma albumin-bound free fatty acids are primarily derived from triglyceride stores produced by intracellular lipolytic enzymes in adipose tissue. Fatty acids are also generated by lipoprotein lipase, which catalyzes the lipolysis of triglyceride-rich lipoproteins in tissues. Insulin is involved in both anti lipolysis and lipoprotein lipase stimulation in adipose tissue. When IR grows, increased lipolysis releases more fatty acids, reducing Insulin's antilipolytic effect even further. Excess fatty acids increase substrate supply

while also causing IR by altering downstream signaling. Fatty acids inhibit Insulin-mediated glucose absorption and accumulate as Triglycerides in both skeletal and cardiac muscle, while the liver increases glucose production and triglyceride accumulation.

- Another hypothesized pathophysiologic mechanism for the metabolic syndrome (MetS) is leptin resistance. Leptin reduces hunger, boosts energy expenditure, and enhances insulin sensitivity. Leptin can also affect cardiovascular and vascular health through a nitric oxide-dependent mechanism.
- Obesity, on the other hand, causes hyperleptinemia, with reports of leptin resistance in the brain and other tissues leading to inflammation, IR, hyperlipidemia, and a slew of cardiovascular diseases such as CHD, atherosclerosis, hypertension and heart failure.
- The oxidative stress hypothesis offers a unifying explanation for aging and the metabolic syndrome predisposition. A defect in mitochondrial oxidative phosphorylation that contributes to the accumulation of triglycerides and associated lipid molecules in muscle has been reported in studies of insulin resistant individuals with obesity or type 2 diabetes, the offspring of type 2 diabetes patients, and the elderly.[80]

❖ **IR measurement**

- **Hyperinsulinemic- euglycemic glucose clamp technique**

This technique is a gold standard and reference method for quantifying insulin sensitivity because it directly measures effects of insulin in promoting glucose utilization under steady-state conditions in vivo. However, its calculation is complicated and impractical.

- **Homeostasis model assessment-insulin resistance**

The mathematical model of the normal physiological dynamics of insulin and glucose produced the homeostasis model assessment (HOMA), which provided equations for estimating IR (HOMA-IR) and -cell function from simultaneous fasting measures of insulin and glucose levels. HOMA was first developed in 1985 by Matthews et al. It has been proved to be a robust clinical and epidemiological tool for the assessment of IR. It has a good and linear correlation with the hyperinsulinemic - euglycemic clamp method[81]

It is calculated as HOMA-IR = [fasting serum insulin UI/ml × fasting plasma glucose mg/d1] ÷ 405. IR is diagnosed when the result is >2.5.

- **Fasting insulin level**

Measurement of fasting insulin level has been considered most practical approach for the measuring of IR as it correlates well with I. Its use is limited because of a high proportion of false-positive results and lack of standardization. Glucose/insulin This ratio has been used in studies as an index of IR. It is a highly sensitive and specific measurement of insulin sensitivity. In adults, a ratio of <4.5 is abnormal, whereas in prepubertal children <7 is abnormal. [82]

- **Quantitative insulin sensitivity check index**

Quantitative insulin sensitivity check index (QUICKI) proves to be a first-rate index of IR in comparison with clamp-IR. It provides a consistent and precise index of insulin sensitivity with better positive predictive power. It is calculated as:

QUICKI = 1/ (log[Insulin U/mL] + log[Glucose mg/dL]) Patients with QUICKI index below 0.357 tend to have a higher risk of IR or frequently present with manifestations typical of metabolic syndrome.

- **Glucose insulin product**

Product of plasma glucose and insulin concentrations has been considered an index of whole-body insulin sensitivity and it provides better index of insulin sensitivity. If plasma glucose level is higher, along with higher plasma insulin response, state of IR tends to be more severe.

- **Log (homeostasis model assessment-insulin-insulation resistance)**

Log (HOMA-IR) is useful for assessment of IR. In research studies it may be appropriate to use log (HOMA-IR) instead of HOMA Several novel markers such as IGFBP-1, hs-CRP, adiponectin, ferritin, HbAlc, C3 complement, TNF alpha and sCD36 are now surfacing as surrogate markers of IR, Other investigations for IR are fasting glucose and lipoprotein profile, hemoglobin Alc, body weight, blood pressure, and an alanine transferase test for evaluation of fatty liver.[82]

ACANTHOSIS NIGRICANS AND METABOLIC SYNDROME

In research to evaluate the prevalence of AN in an urban community with metabolic syndrome (MetS) patients, Dassanayake AS et al. (2011). There are 2957 participants in this study. 17.4%, 34.8%, and 19.6% of the population, respectively, had AN, metabolic syndrome (MetS), or type 2 diabetes mellitus. A direct connection existed between AN and metabolic syndrome (MetS). In order to identify metabolic syndrome (MetS) in men, AN had the following sensitivity, specificity, positive predictive value, and negative predictive value of 28.2%, 89.0%, 45.9%, and 79.0%, respectively, and 29.2%, 88.4%, 65.6%, and 62.3%, respectively. The presence of AN significantly predicts the presence of Metabolic Syndrome, even though it did not have a high enough sensitivity to be used as a screening test for the condition.[83]

In a review article by Maguolo A et al., (2019) to assess the AN in childhood as a cutaneous marker of IR. Obesity is linked to the majority of AN cases. Obesity incidence is increasing globally, which is accompanied by a rise in the frequency of metabolic syndrome (MetS) in children. [84]

In a study by Shah NG et al., (2019) to assess the AN as cutaneous marker for metabolic syndrome (MetS). The average age of the patients was 32.4 years, with females (62%) outnumbering males (38%). All of the patients had neck AN. There was a statistically significant relationship between increasing AN severity and each component of metabolic syndrome. When comparing patients and controls, each component of metabolic syndrome was higher in cases than in controls. Metabolic syndrome was present in 70% of the patients, which was statistically significant. In people with metabolic syndrome, there was a significant frequency of AN. There was also a link between the severity of AN and metabolic syndrome.[85]

❖ ACANTHOSIS NIGRICANS AND OBESITY

Patients with AN, especially children with benign AN, are more likely to develop type 2 diabetes, IR, obesity, hypertension, and hyperinsulinemia. An accurate index of IRS can be found in AN. However, obesity is a more significant predictor of IR than AN, so AN shouldn't be used as the only diagnostic to identify whether obese children have elevated insulin levels.

According to Urutia-Rojas et al., mothers of AN-positive children are more likely than mothers of AN-negative children to have anomalies of fuel metabolism. Fathers with blood glucose levels below 126 mg/dL are more likely to have children who are AN positive. They proposed that AN screening in children is a useful tactic for detecting prediabetes in adults. Fasting lipoprotein profile, fasting glucose, haemoglobin, fasting insulin, and alanine aminotransferase tests are performed on all overweight adults and kids.[86]

IR and AN are inextricably linked. Evidence suggests that AN is a valuable clinical diagnostic for identifying obese and overweight patients with IR who are at risk of developing type 2 diabetes and Metabolic Syndrome (MetS). In clinical practice, recognizing AN is important for identifying patients who are predisposed to the Insulin-resistant Obesity phenotype and might benefit from early treatments.[84]

MATERIALS AND METHODOLOGY

- **Study source**: This study was conducted in the Department of Dermatology, Venereology and Leprosy, in tertiary care hospital, Belgaum as a part of the MD academic curriculum.
- **Study duration**: The study was conducted between 1st January 2021 to 31st December 2021
- **Ethical clearance:** Clearance was taken from the Ethical Committee of the institute.
- **Study design:** Hospital based cross sectional study.
- **Sample size:**

Formula used for sample size calculation is

$$n = \frac{p(100-p)Z^2}{E^2}$$

n is the sample size required, p is the percentage occurrence of a state or condition (proportion or prevalence), E is the percentage maximum error required, Z is the value corresponding to level of confidence required.

Prevalence of metabolic syndrome is assumed as 15%, with percentage of maximum error as 10% at 95% confidence level sample size is given

$$n = \frac{15 \times 85 \times (1.96)^2}{10^2}$$

$$n = 48.98 \approx 49$$

Minimum sample size required is 49. Larger the sample size, better the precision.

❖ **Sample selection criteria:**

Random sampling method

❖ **Inclusion criteria:**

The study included all clinically diagnosed cases of benign acanthosis nigricans between the age group 18-60 years.

❖ **Exclusion criteria:**

- Patients not willing / not consenting for blood investigations.
- Children below the age of 18 years.
- Pregnant and lactating women up to 6 months.
- Patients on medications like oral contraceptive pills, systemic corticosteroids, insulin, anti-retroviral drugs, nicotinic acid, fusidic acid, which can cause drug induced AN.
- Patients with AN due to malignancy associated conditions
- Patients with autoimmune causes of AN
- Patients with inherited causes of AN.

❖ **Data collection:**

- All patients with clinically diagnosed cases of benign acquired AN attending KLE's Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi were recruited.
- Informed consent was taken from all the patients included in the study.
- Data was collected by a single examiner and recorded in case record proforma.

- All patients in study underwent a detailed history taking, general physical like height, weight, waist circumference, BMI, BP, systemic and dermatological examination.
- All participants underwent laboratory investigations like FBS, serum HDL, serum Triglycerides, serum Fasting Insulin level with values being noted.
- Clinical scoring was done based on Burke et al grading system for severity of AN along with relevant clinical pictures of lesions.
- Insulin resistance was determined using HOMA-IR calculation and a value above or equal to 2.5 was taken into consideration.
- Records were maintained and analysed statistically and relevant pictures attached.
- Informed consent was taken from all the study patients.
- All the study subjects were made to go through a detailed history taking, general physical, systemic and dermatological examination.
- Data was collected by a single examiner and recorded in case record proforma.

❖ **Statistical Method for Data Analysis**

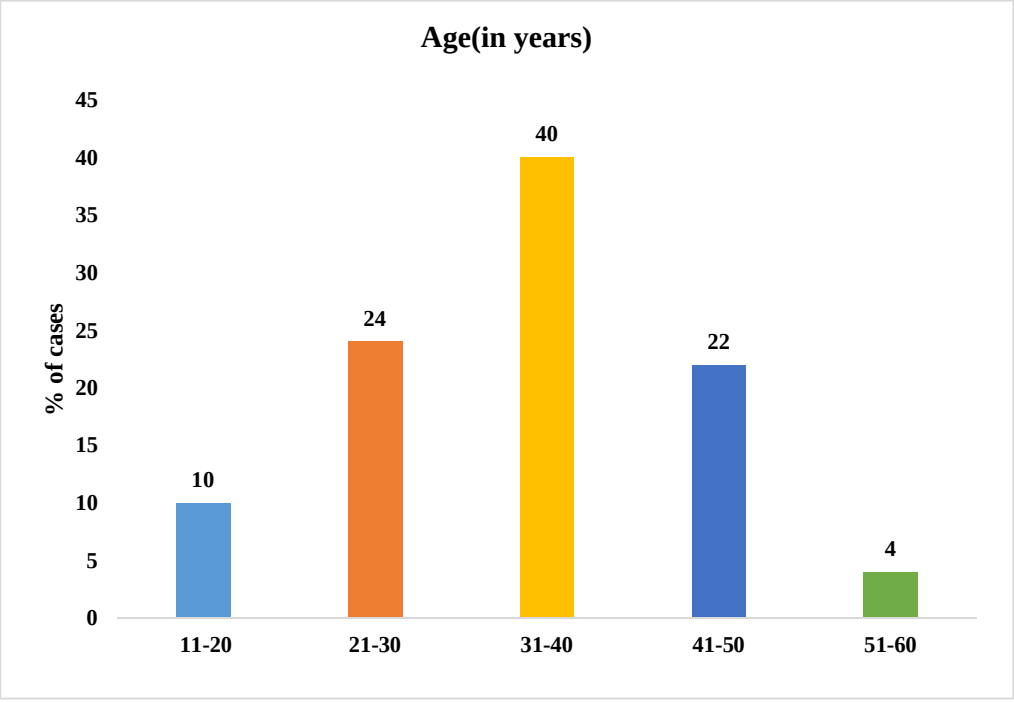
- All the data was entered in excel sheet and analysed using SPSS v 21 operating on windows 10.
- Results on continuous measurement is presented as Mean & SD and categorical as Frequency & percentage.
- Inferential statistics like Chi-square/Fisher exact test is applied. $P < 0.05$ was considered statistically significant.
- P-value less than or equal to 0.05 shows statistical significance.

RESULTS

In the present study, a total of 50 clinically diagnosed cases of benign AN, fulfilling inclusion criteria were included. P value of < 0.05 was considered statistically significant.

1. Age distribution:

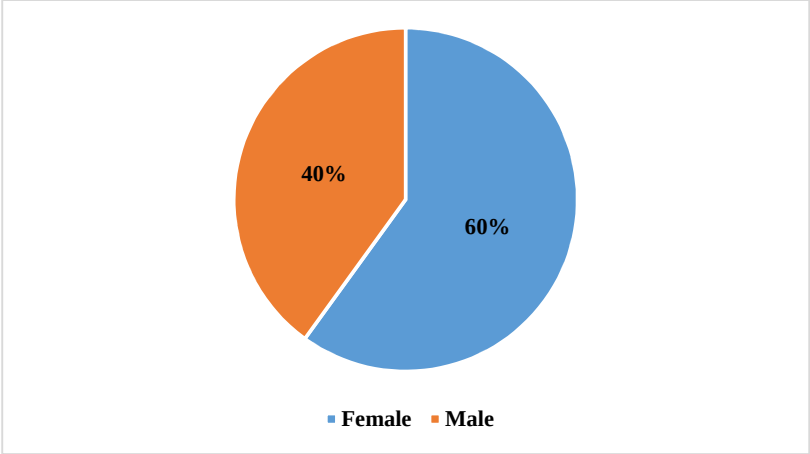
Out of a total of 50 patients, majority patients have been observed between the age group of 31- 40 years (40%) followed by 21-30 years (24%) and the findings were consistent with the other studies.



Graph 1: Distribution of subjects by age

2. Gender distribution:

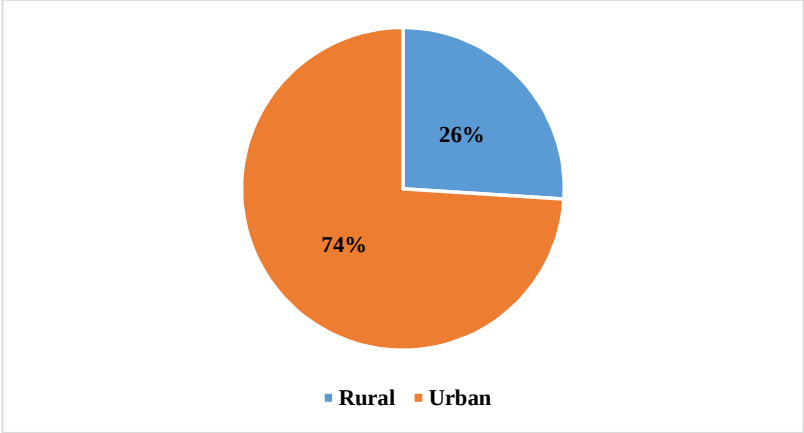
Out of 50 patients, 30 females and 20 males which is 60% and 40% respectively with a slight female preponderance.



Graph 2: Distribution of subjects by gender

3. Distribution of subjects based on residence:

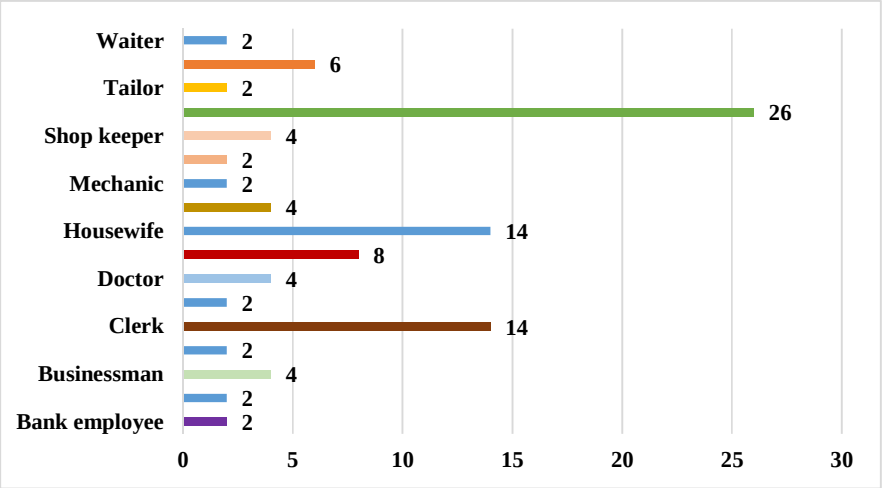
In the present study, 26% (n=13) belonged to rural area and 74% (n=37) belonged to urban area.



Graph 3: distribution of subjects based on residence

4. Distribution of subjects based on occupation:

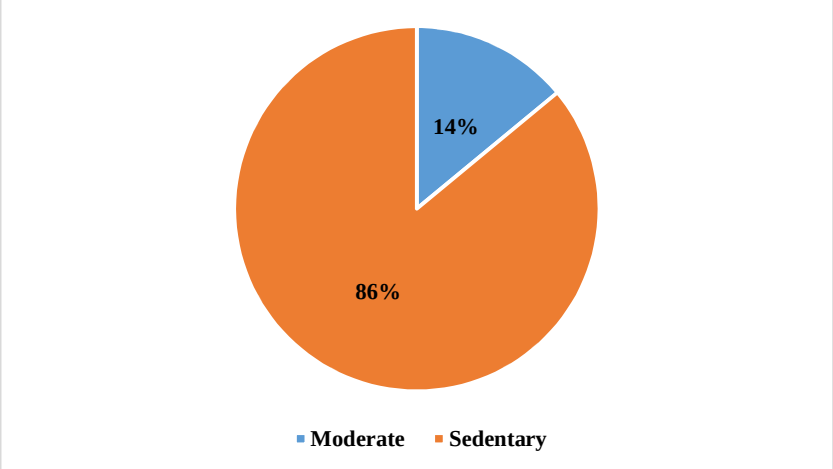
Out of 50 patients, majority were students i.e. 26% (n=13), followed by 14% (n=7) were housewives and clerks, each respectively.



Graph 4: Occupation of the patients included

5. Physical activity of subjects:

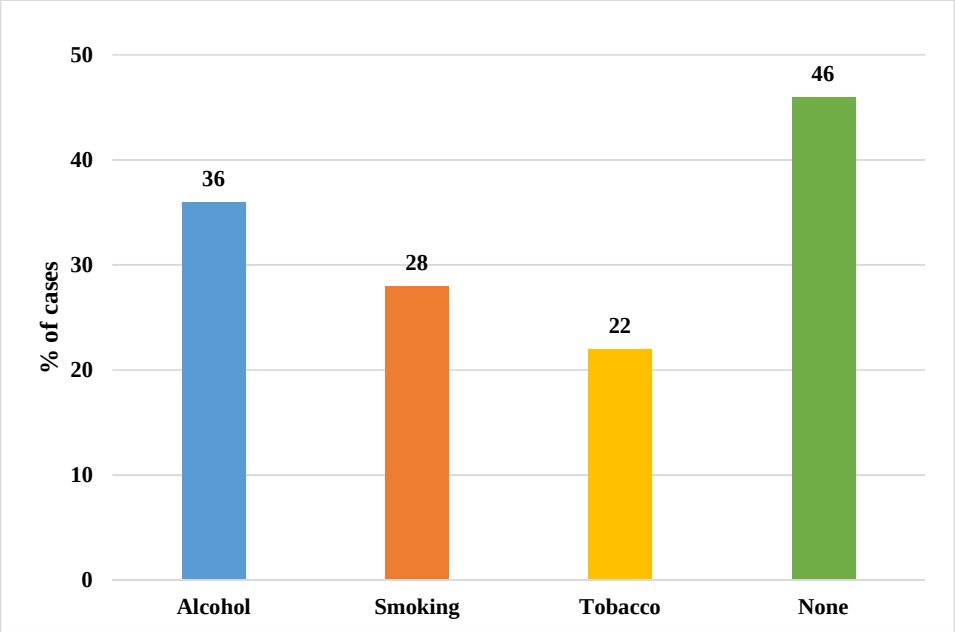
In the present study, 14% (n=7) showed moderate and 86% (n=43) showed low physical activity.



Graph 5: Distribution of subjects based on physical activity

6. Distribution of subjects based on habits:

Out of 50 patients, 36% (n=18) were known alcoholics, followed by 28% (n=14) smokers and 22% (n=11) being tobacco users. 46% (n=23) had no habits.



Graph 6: Distribution of presence of addiction among patients

7. Age of onset and duration of disease:

The average age of onset of AN in patients was 28.76 ranging from 13-50.5 years.

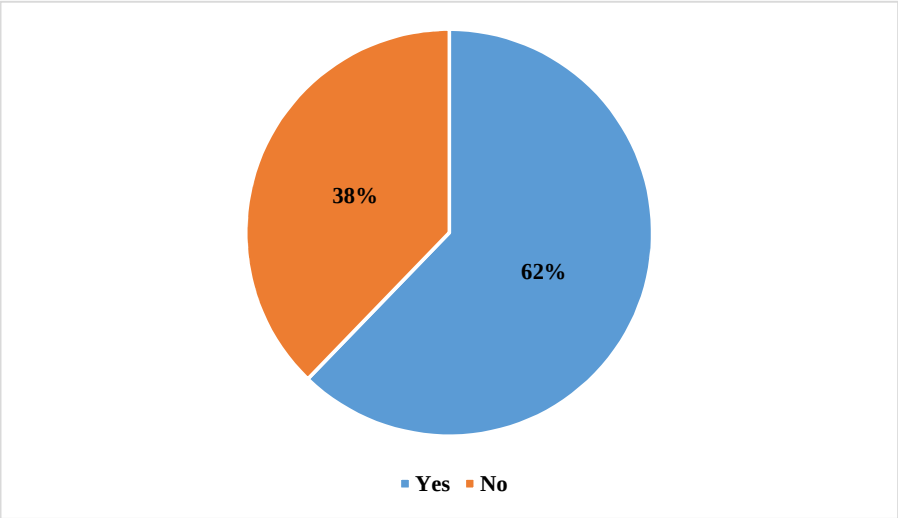
Average duration of disease at the time of presentation was 3 years.

Table 6: Onset and duration of the disease

(In years)	Mean ± SD	Range
Age of onset of AN	28.76±8.60	13.0-50.5
Duration of AN	3.08±2.62	0.25-12

8. History of weight gain:

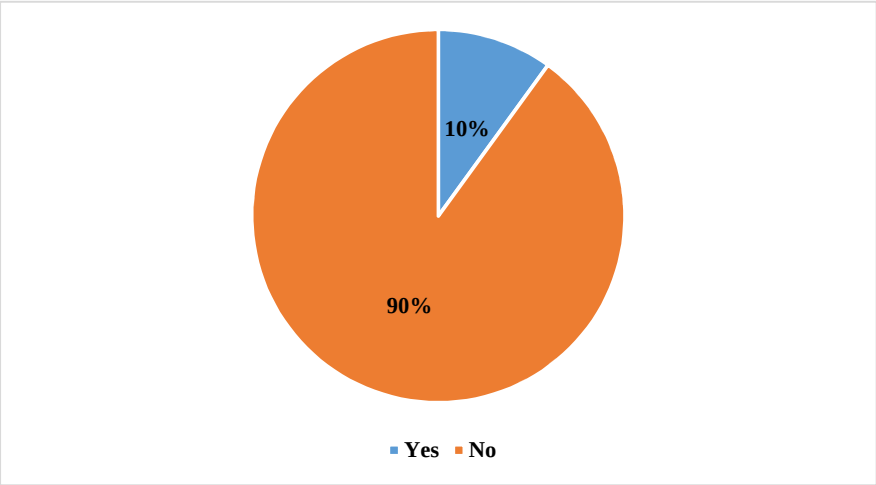
In the study, 56% patients (n=28) gave history of weight gain.



Graph 7: Presence of history of weight gain

9. History of irregular mensus:

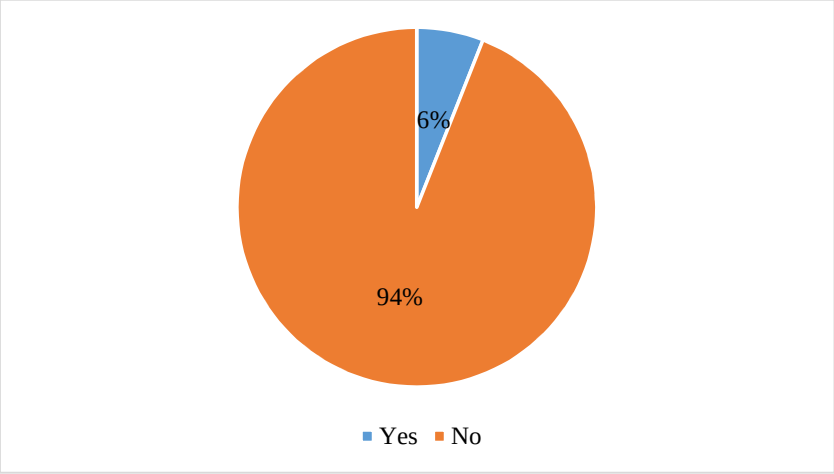
Out of 50 patients, 30 were females. Out of 30 female patients, 10% (n=5) had irregular mensus.



Graph 8: Showing the history of irregular menstrual cycle

10. History of itching:

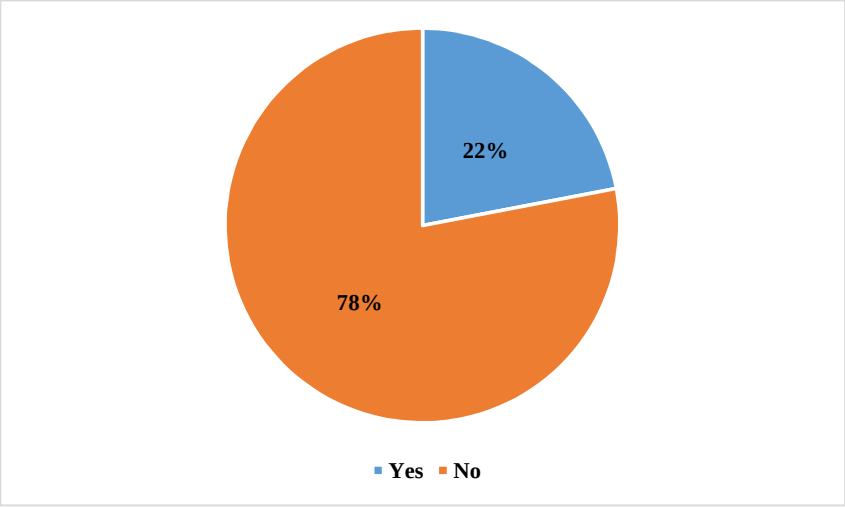
In the present study, 6% patients (n=3) were associated with itching.



Graph 9: Presence of associated itching among patients

11. Family history of AN:

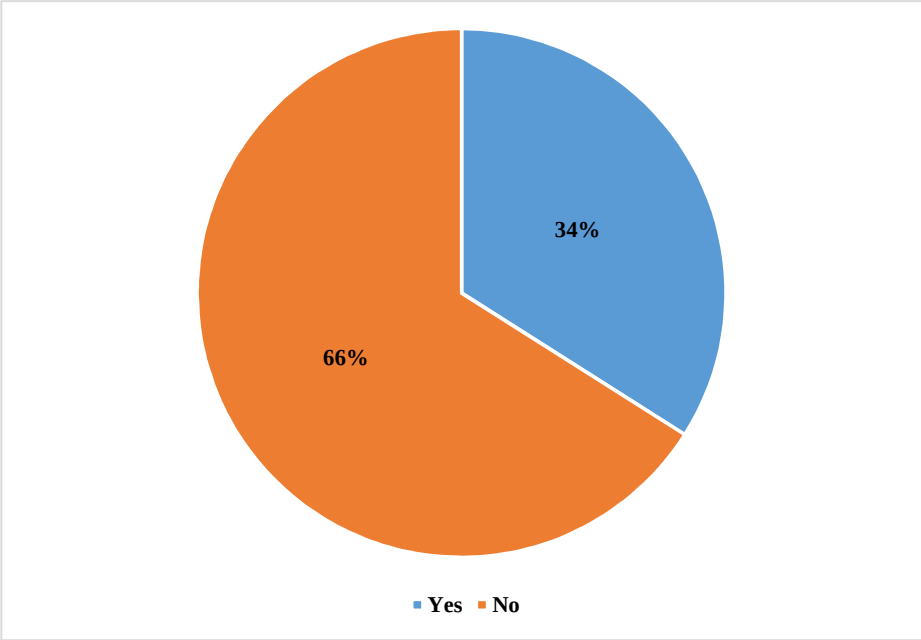
Out of 50 patients, 22% (n=11) patients showed positive family history of AN.



Graph 10: Showing the presence of family history of AN

12. Family history of diabetes mellitus:

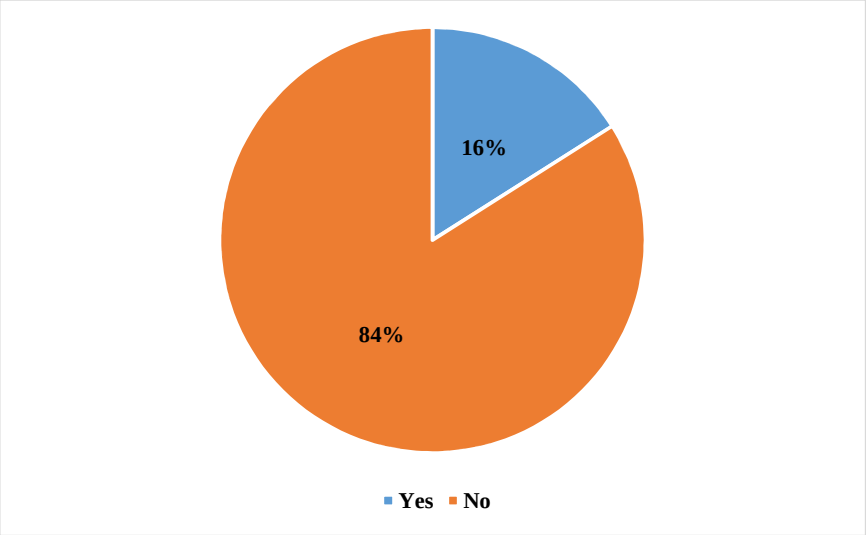
Out of 50 patients, 34% (n=17) patients gave positive family history of diabetes mellitus.



Graph 11: Showing the presence of family history of diabetes mellitus

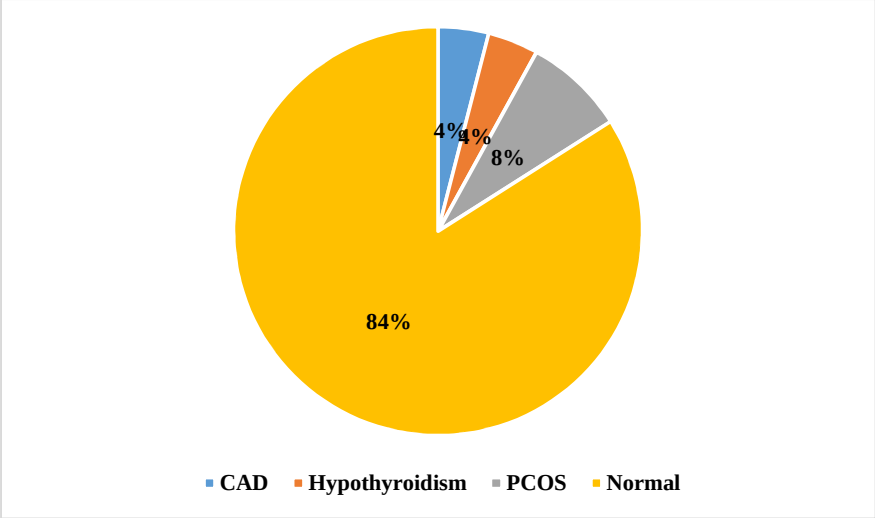
13. History of systemic diseases:

In the present study, 16 % (n=8) patients had associated systemic diseases.



Graph 12: Showing the presence of family history of systemic disease

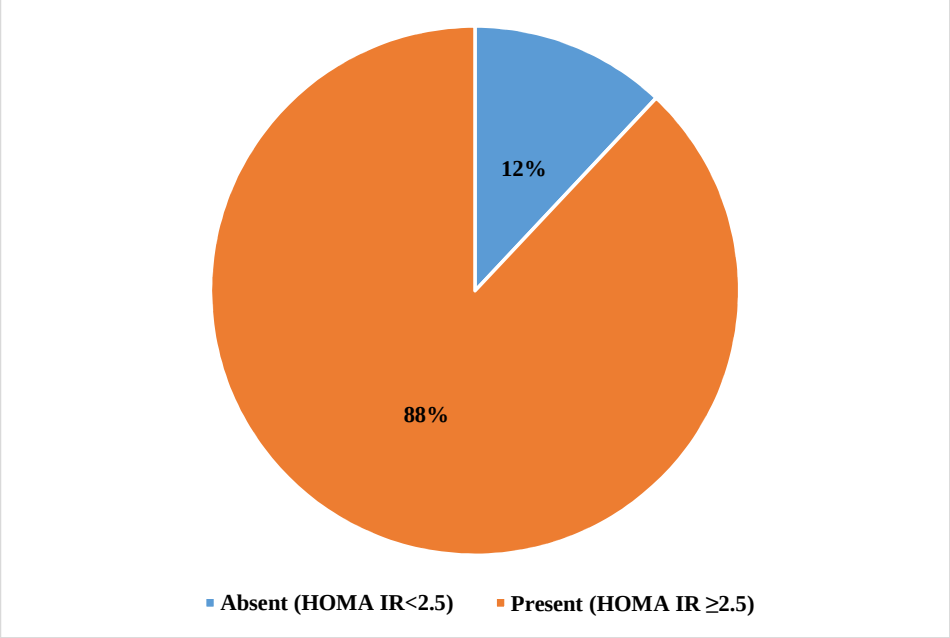
Out of 16% patients with systemic diseases, majority had 8% (n=4) PCOS followed by hypothyroidism and CAD seen in 4% (n=2) each respectively.



Graph 13: Showing the presence of systemic disease

14. Presence of insulin resistance:

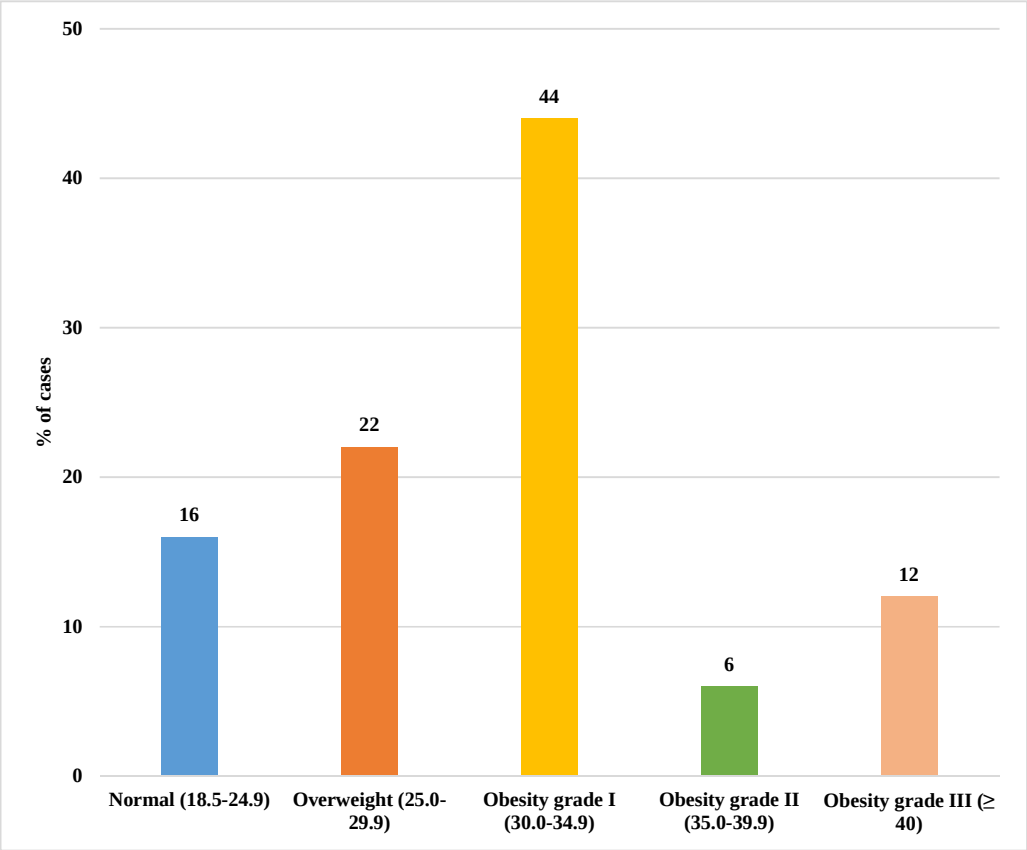
Out of 50 patients, 88% (n=44) had insulin resistance with HOMA- IR ≥2.5.



Graph 14: Showing the presence of IR

15. Distribution of subjects based on BMI:

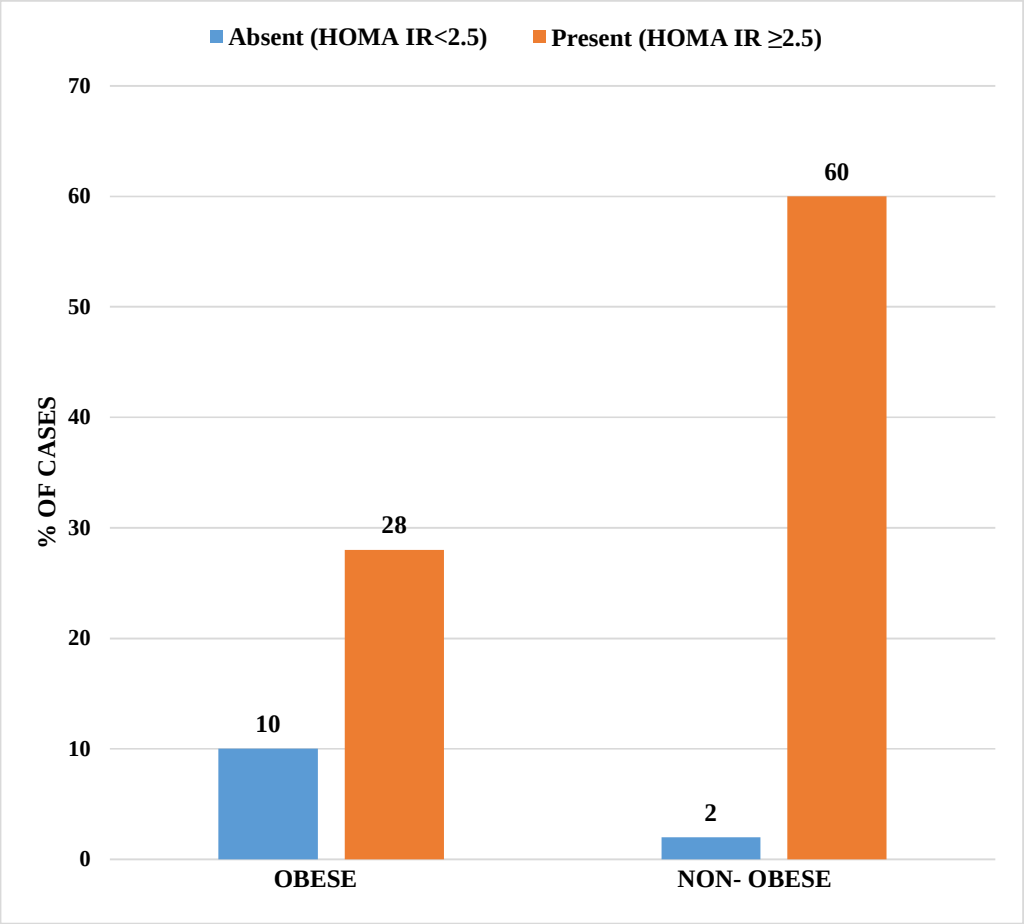
Out of 50 patients, 44% (n=22) belonged to Obesity grade I (30.0-34.9), followed by Overweight (25.0-29.9) in 22% (n=11), 12% (n=6) belonged to Obesity grade III (≥ 40), Obesity grade II (35.0-39.9) in 6% (n=3) patients.



Graph 15: Showing the distribution of BMI of patients

16. Presence of insulin resistance in subjects with obesity

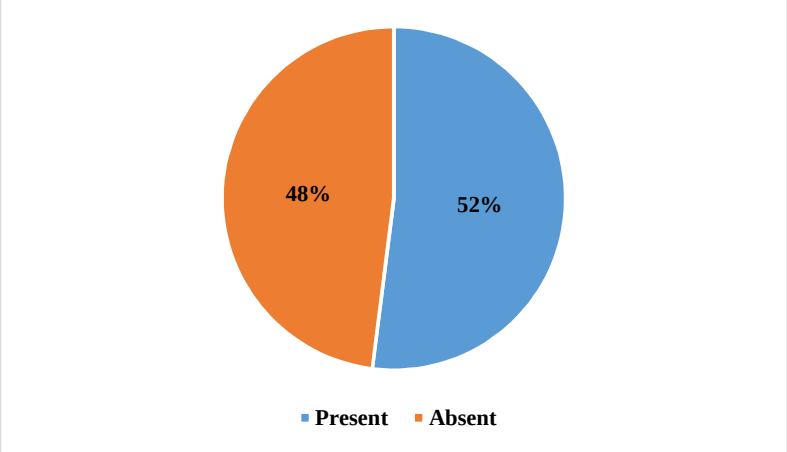
In our study, out of 50 AN patients, 31(62%) were found to be obese. Out of these 31 patients, 30 patients had insulin resistance and the association was statistically significant. ($p<0.05$)



Graph 16: Comparison of the presence of IR and Obesity in patients with AN

17. Distribution of subjects based on presence of metabolic syndrome:

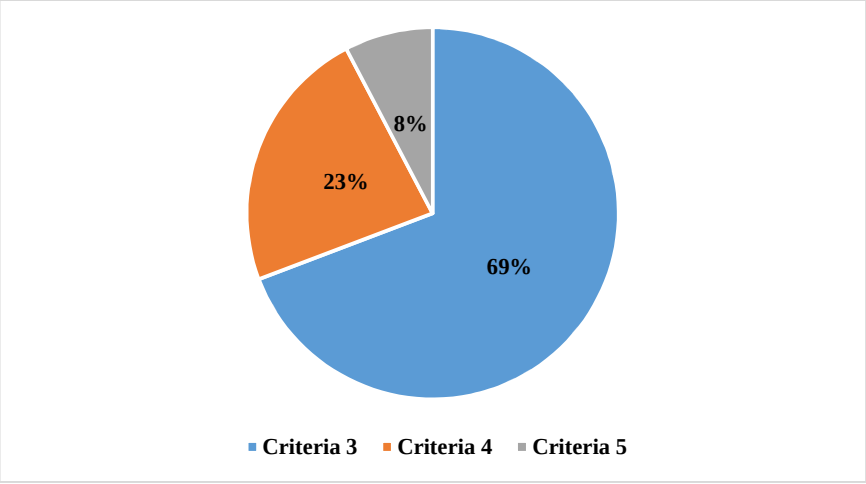
Out of 50 AN patients, 52% patients were diagnosed to have metabolic syndrome.



Graph 17: Showing the presence of Metabolic Syndrome among the patients

Out of a total of 50 AN patients, 26 patients satisfied the criteria of metabolic syndrome.

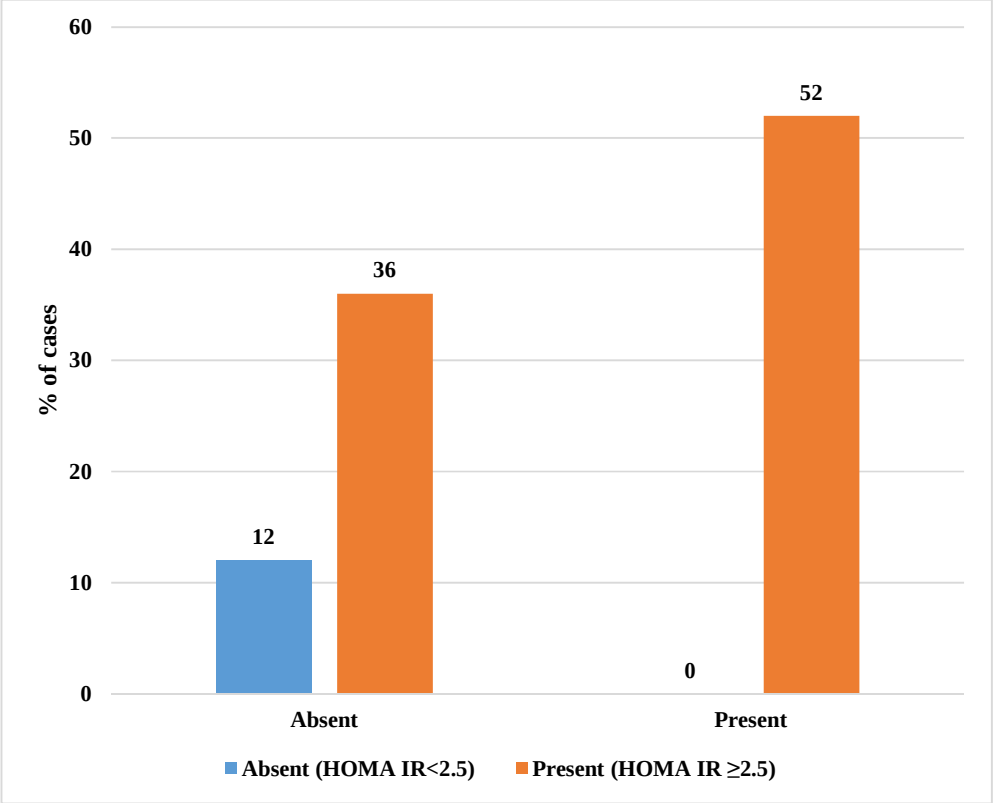
36% satisfied 3/5 criteria, 12% met 4/5 criteria and 4% patients met all 5/5 criteria for diagnosing metabolic syndrome.



Graph 18: Showing the presence of Metabolic Syndrome parameters

18. Presence of insulin resistance in subjects with metabolic syndrome

Out of 50 AN patients, 26 patients had metabolic syndrome and all of them had insulin resistance. The association was statistically significant. ($p<0.05$)



Graph 19: Comparison of IR and Metabolic Syndrome in patients with AN

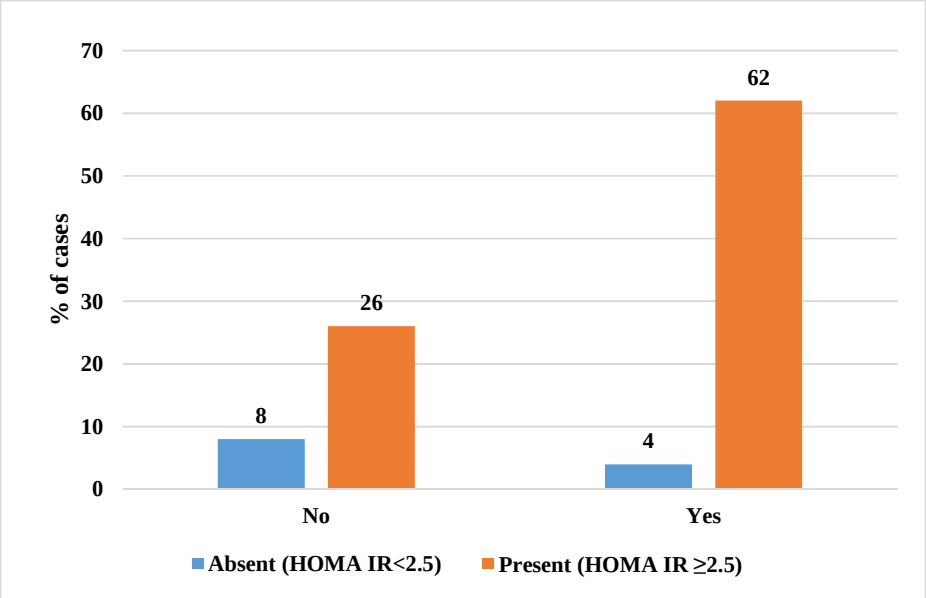
19. Presence of insulin resistance in subjects with dyslipidemia:

Out of 50 patients, 33 patients had dyslipidemia.

Out of these 33 patients, 31 patients had IR but the association was not statistically significant.

Table 7: Comparison of IR and dyslipidemia in patients with AN

Dyslipidemia HDL< 50 males <40 females or TDL>150mg/dl	IR (HOMA IR≥2.5)		Total
	Absent	Present	
No	04(08)	13(26)	17(34)
Yes	02(04)	31(62)	33(66)
Total	06(12)	44(88)	50(100)
P=0.093			



Graph 20: Comparison of IR and dyslipidemia in patients with AN

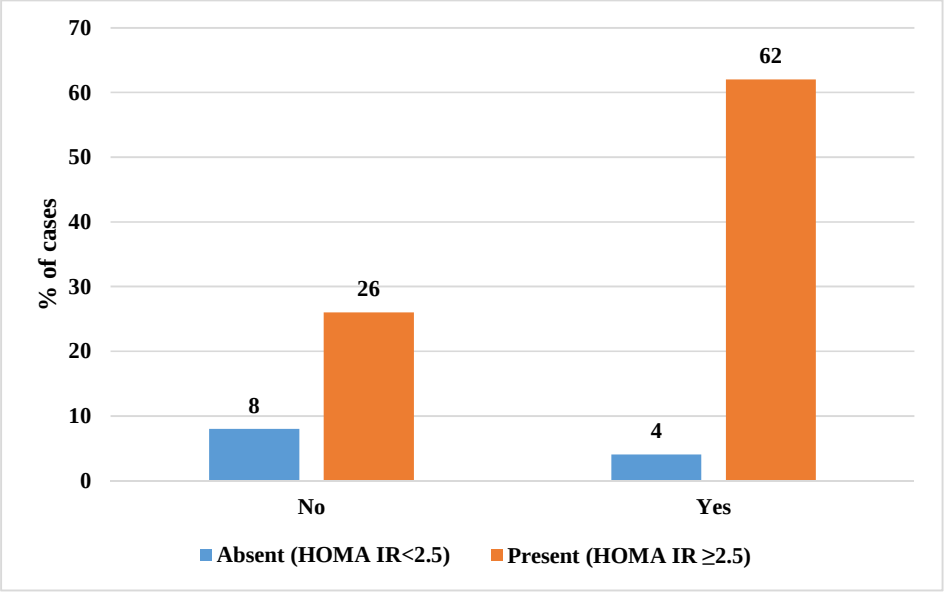
20. Presence of insulin resistance in subjects with hyperglycemia:

Out of 50 patients, 21 patients showed hypergylcemia.

Out of which 20 patients had IR. The association was not statistically significant.

Table 8: Comparison of the IR and hyperglycemia among patients

Hyperglycemia	IR		Total
	Absent (HOMA IR<2.5)	Present (HOMA IR ≥2.5)	
No (FBS≤100mg/dl)	05(10)	24(48)	29(58)
Yes (FBS>100mg/dl)	01(02)	20(40)	21(42)
Total	06(12)	44(88)	50(100)
P=0.187			



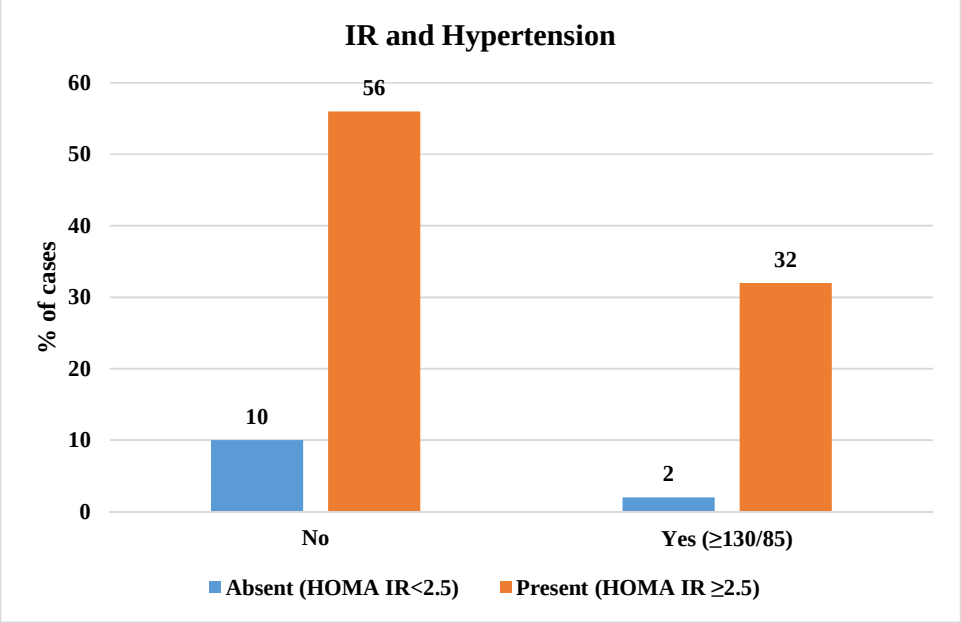
Graph 21: Comparison of the IR and hyperglycemia among patients

21. Presence of insulin resistance in subjects with hypertension:

Out of 17 patients with HTN, 16 patients (32%) showed IR. **No** significant association is observed between IR and hypertension

Table 9: Comparison of the IR and Hypertension among patients

Hypertension	IR		Total
	Absent (HOMA IR<2.5)	Present (HOMA IR ≥2.5)	
No	05(10)	28(56)	33(66)
Yes (≥130/85)	01(02)	16(32)	17(34)
Total	06(12)	44(88)	50(100)
P=0.324			



Graph 22: Comparison of the IR and Hypertension among patients

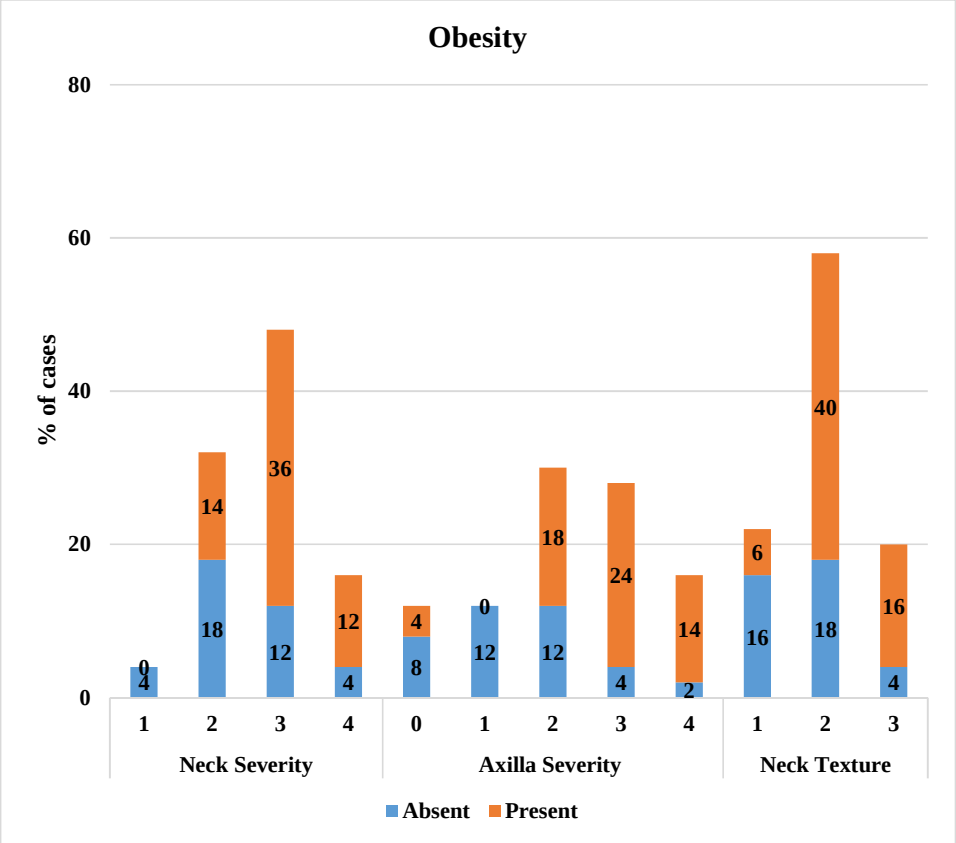
22. Comparison of obesity and AN severity:

In our study, it was noticed that with increasing severity grading of AN there was increased prevalence of obesity. The association was statistically significant.

Table 10: Comparison of the Obesity and Neck Severity, Axilla Severity and Neck texture

	Score	Obesity		P value
		Absent	Present	
Neck Severity	1	02(04)	0	0.042*
	2	09(18)	07(14)	
	3	06(12)	18(36)	
	4	02(04)	06(12)	
Axilla Severity	0	04(08)	03(04)	0.001*
	1	06(12)	0	
	2	06(12)	09(18)	
	3	02(04)	12(24)	
	4	01(02)	07(14)	
Neck Texture	1	08(16)	03(06)	0.024*
	2	09(18)	20(40)	
	3	02(04)	08(16)	
(*Statistically significant p<0.05)				

Statistically significant association is observed between neck severity, axilla severity, neck texture and Obesity.



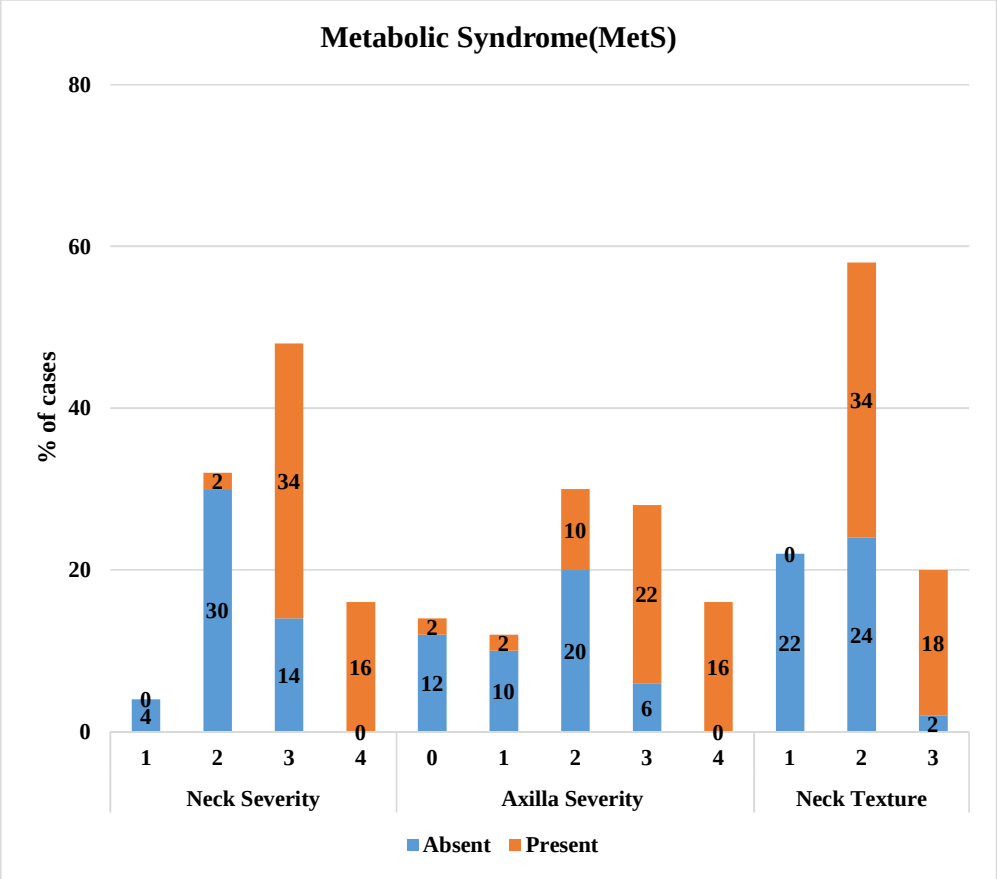
Graph 23: Comparison of the Obesity and Neck Severity, Axilla Severity and Neck texture

23. Comparison of metabolic syndrome and AN severity:

With increasing severity of acanthosis nigricans, it was noted that there was increased prevalence of metabolic syndrome and the association was statistically significant.

Table 11: Comparison of Metabolic Syndrome and Neck Severity, Axilla Severity and Neck texture

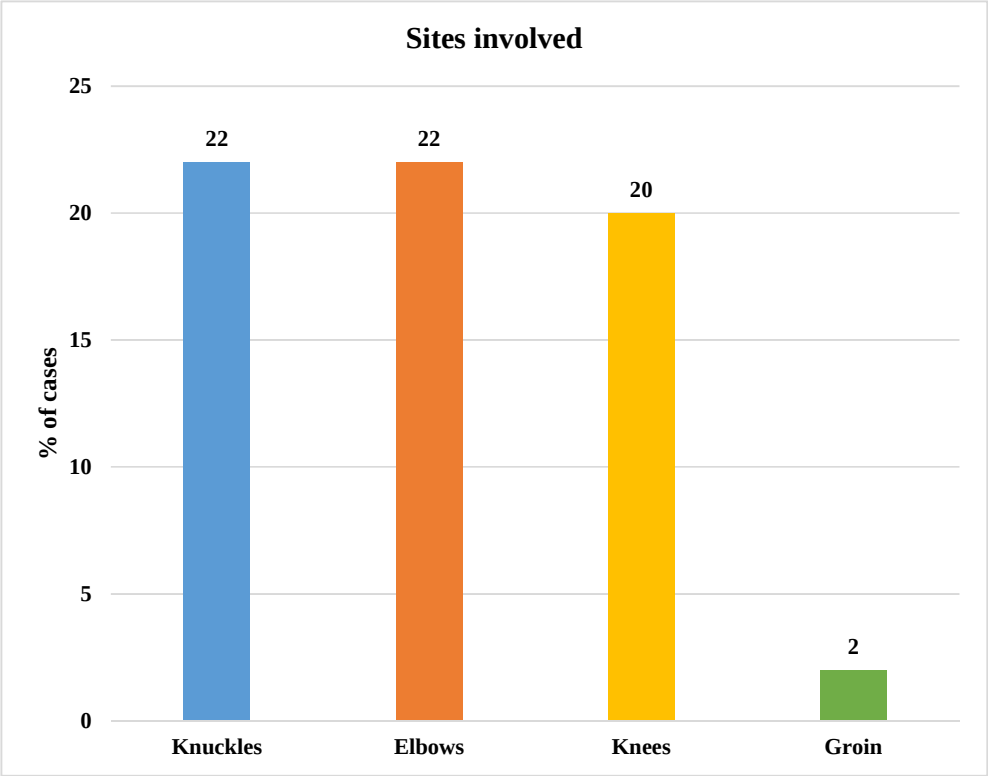
	Score	Metabolic Syndrome		P value
		Absent	Present	
Neck Severity	1	02(04)	0	0.001*
	2	15(30)	01(02)	
	3	07(14)	17(34)	
	4	0	08(16)	
Axilla Severity	0	06(12)	01(02)	0.001*
	1	05(10)	01(02)	
	2	10(20)	05(10)	
	3	03(06)	11(22)	
	4	0	08(16)	
Neck Texture	1	11(22)	0	0.001*
	2	12(24)	17(34)	
	3	01(02)	09(18)	
(*Statistically significant p<0.05)				



Graph 24: Comparison of Metabolic Syndrome (MetS) and Neck Severity, Axilla Severity and Neck texture

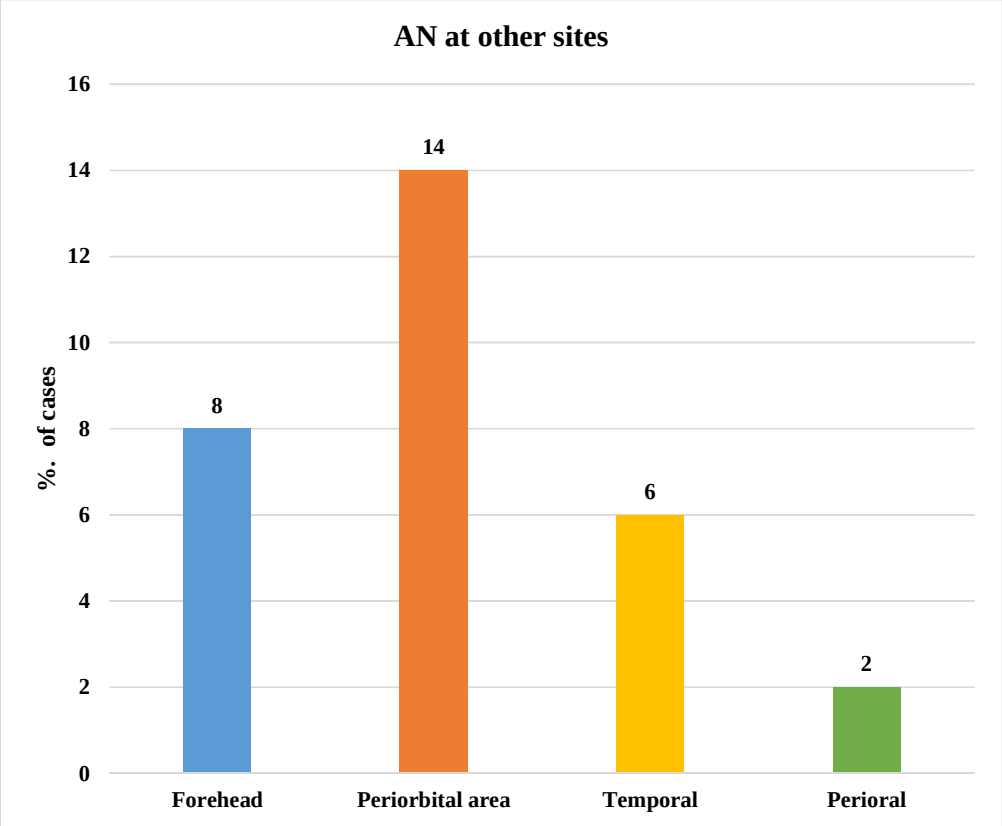
24. Distribution of lesions based on site of involvement:

Neck was the commonest site of involvement in 100% (n=50) in the study subjects followed by axilla in 92% (n=46), knuckles and elbows in 22% (n=11) each and knees in 20% patients(n=10).



Graph 25: Site of involvement

In our study we noticed that patients had facial acanthosis nigricans in decreasing frequency 14% over periorbital area (n=7) followed 8% by forehead (n=4), 6% temporal (n=3) and 2% perioral area(n=1).



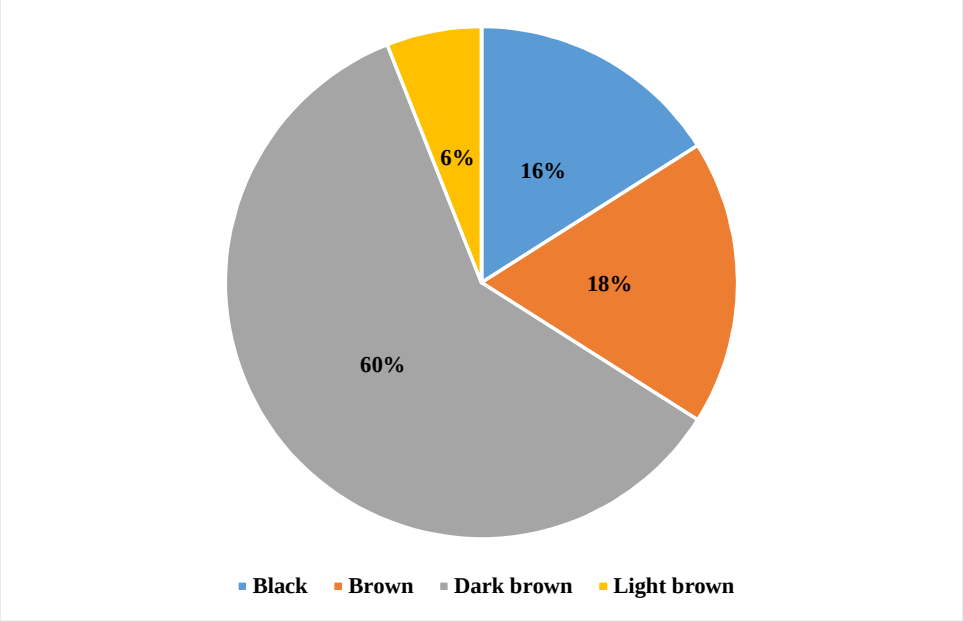
Graph 26: Presence of AN at other sites

25. Colour of lesions:

The colour of lesion was found to be 60% dark brown, 18% with brown, 16% with black and 6% with light brown.

Table 12: Showing the Colour of lesion

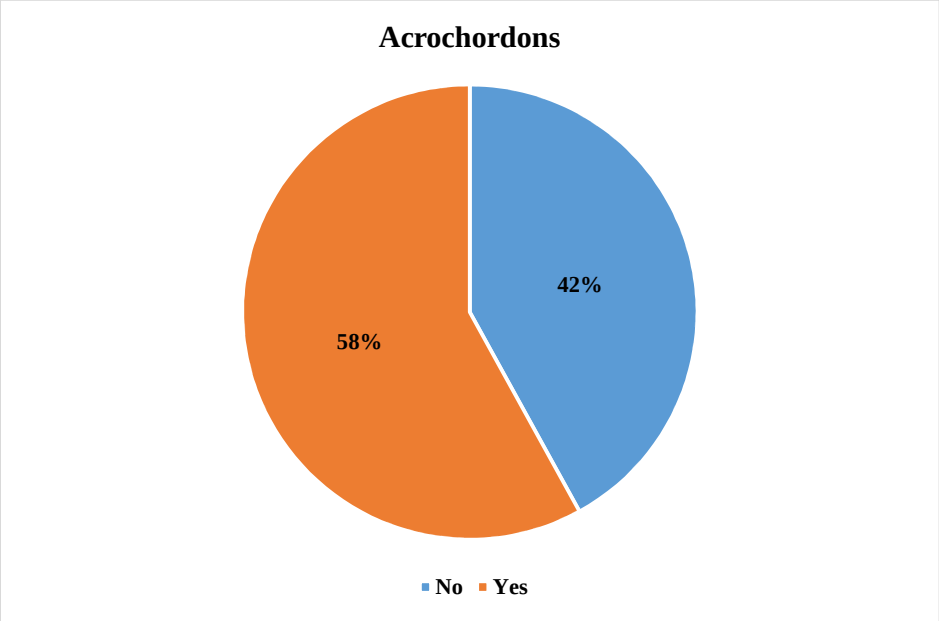
Colour of lesion	No. of Cases (N)	Percentage (%)
Black	08	16.0
Brown	09	18.0
Dark brown	30	60.0
Light brown	03	06.0
Total	50	100.0



Graph 27: Showing the Colour of lesion

26. Other co existing dermatosis:

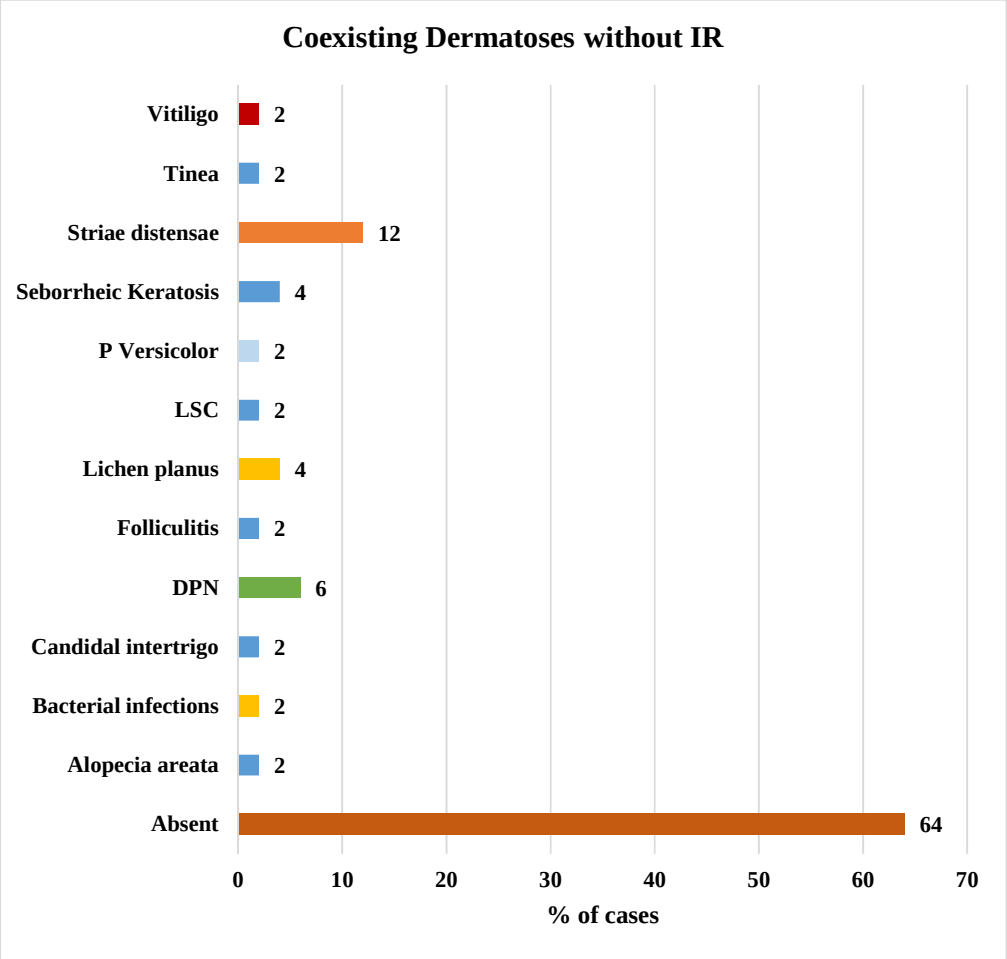
Out of 50 AN patients, 29 patients (58%) has associated acrochordons.



Graph 28: Showing the presence of acrochordons

Majority of patients (12%) had striae distansae (n=6), followed by DPN seen in 6% of patients(n=3).

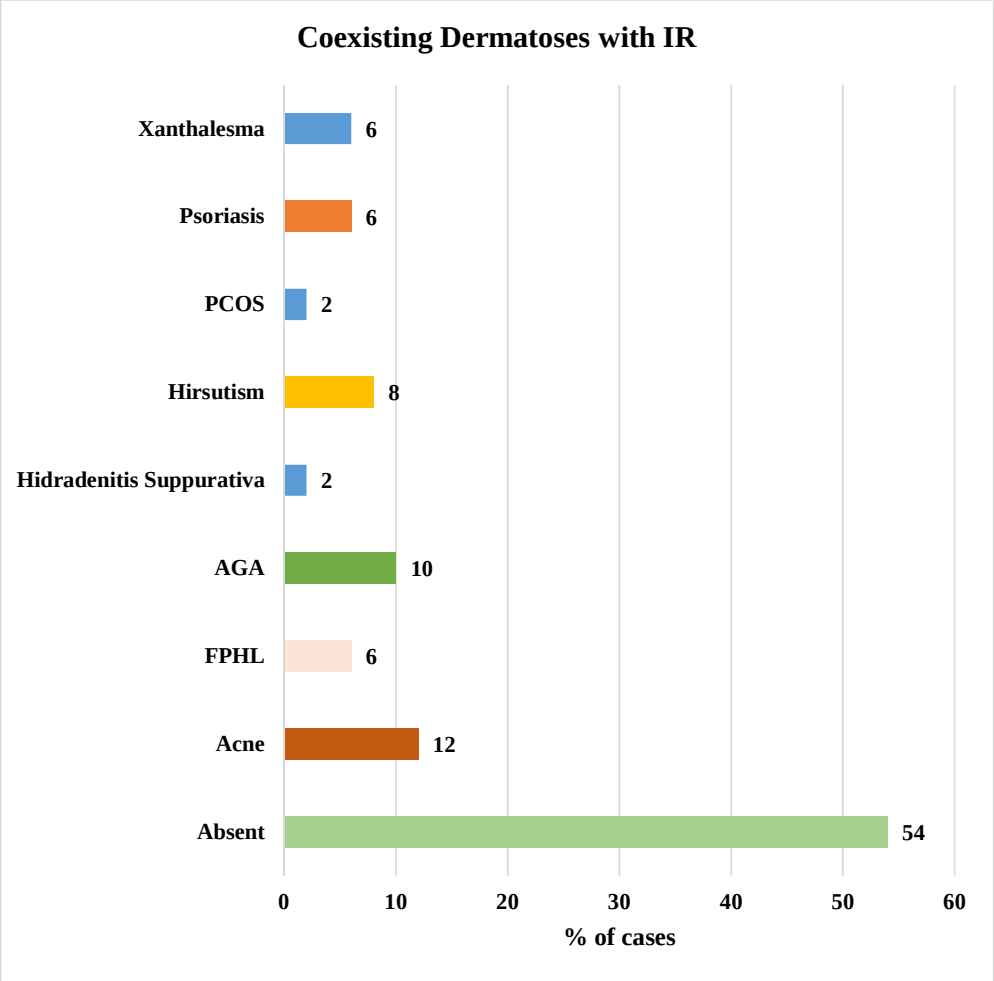
Other associated dermatological conditions seen in our patients include alopecia areata, candidal infections (2%)(n=1), bacterial infections (4%)(n=2), lichen planus (4%)(n=2), LSC (2%)(n=1), tinea (2%)(n=1), vitiligo (2%)(n=1), seborrheic keratosis (4%)(n=1), p versicolor (2%)(n=1).



Graph 29: Showing the Coexisting Dermatoses without IR

Out of 50 patients, Acne was most commonly seen in 12% patients (n=6), followed by AGA in 10% (n=5), hirsutism in 8% (n=4) patients. FPHL, Psoriasis and xanthalesma was seen in 6% of patients (n=3) each, respectively.

1 patient (2%) had hidradenitis suppurativa.



Graph 30: Presence of Coexisting Dermatoses with IR

DISCUSSION

The association of acanthosis nigricans and insulin resistance has been reported by many authors, but most of the studies have been conducted on diabetics. The present study was done only on nondiabetics with acanthosis nigricans and its prevalence in obese and metabolic syndrome patients was noted.

It is a hospital based cross sectional study carried out on a total of 50 patients and the results were compared with studies done in the past which include studies conducted by

Age wise distribution:

Table 13: Comparison of age distribution in various studies

Age (Years)	Present study	PK Varthakavi et al[87]	Neerja Puri[88]
11-20	05 (10%)	10 (27.8%)	10 (33.3%)
21-30	12 (24%)	9 (25%)	9 (30%)
31-40	20 (40%)	13 (36.1%)	5 (16.6%)
41-50	11(22%)	3 (8.3%)	3 (10%)
51-60	02	0	0
Total	50	36	30

Out of a total of 50 patients, majority patients have been observed between the age group of 31- 40 years (40%) followed by 21-30 years (24%) and the findings were consistent with the other studies.

Sex distribution:

Table 14: comparison of sex distribution in various studies

Sex	Male	Female
Present study	20 (40%)	30 (60%)
PK Varthakavi et al[87]	8	28
Neerja Puri[88]	12	18

In the present study there were 30 females and 20 males which is 60% and 40% respectively with a slight female preponderance. The results are similar to study conducted by PK Varthakavi et al probably because it can be cosmetically more unappealing for females[87]. But in the study conducted by Neerja Puri[88] there was no difference.

Place of residence:

37 (74%) Were from urban area whereas 13 (26%) were from rural area. In the study conducted by R Sudaven et al[89] 84% belonged to urban and 16% belonged to rural area which is similar to our studies.

Prevalence of habits:

Table 15: Prevalence of habits

Addiction	No. of Cases (N)	Percentage (%)
Alcohol	18	36.0
Smoking	14	28.0
Tobacco	11	22.0
None	23	46.0

In the present study, alcoholism was the predominant form of addiction seen in 18 patients (36%), followed by smoking by 14 patients (28%) and tobacco by 11 patients (22%). 23 patients (46%) showed no form of addictions.

These findings have not been observed in any previous studies.

Family history of acanthosis nigricans:

In our study, 22 % patients had a positive history of acanthosis nigricans and the results are similar to the study conducted by R Sudaven et al [89] which was conducted on 400 adolescents.

History of weight gain:

In the present study, 56% of the patients gave positive history of weight gain and the results are consistent with the study conducted by MM Phiske[53] et al on obese individuals with acanthosis nigricans.

Physical activity:

Table 16: physical activity of subjects

Physical activity	No. of Cases (N)	Percentage (%)
Moderate	07	14.0
Low	43	86.0
Total	50	100.0

In our study, majority patients had low physical activity, probably due to sedentary lifestyle.

The results are consistent with the findings in the study conducted by R Savuden et al [89] where 43/58 patients had low physical activity.

Family history of diabetes:

17(34%) patients had positive history of diabetes in the family.

In a similar study conducted by AS Kong et al[18], prevalence rates of family history of diabetes was 63.7% of all patients included in the study.

Prevalence of systemic disorders:

Table 17: Prevalence of systemic diseases

Systemic Diseases	No. of Cases (N)	Percentage (%)
CAD	02	4.0
Hypothyroidism	02	4.0
PCOS	04	8.0
Normal	42	84.0

In our study it was observed that out of 50 patients, 4 patients (8%) had PCOS, followed by hypothyroidism and CAD seen in (4%) 2 patients each, respectively.

Prevalence of coexisting dermatoses:

In the present study, Coexisting Dermatoses was seen with total 66% of participants, of which, acne (24%) was most common followed by AGA (20%). Hirsutism was seen in 8 patients (16%) which is comparatively less than the study conducted by Neerja et al wherein in it was evident in 26.6% of the cases.[88]

Presence of acrochordons:

Associated presence of Acrochordons was seen in 58% of the patients. Singh SK et al., study found that AN and acrochordons were discovered to be linked to IR.[59]

Colour of lesions:

The colour of lesion was found to be 60% dark brown, 18% with brown, 16% with black and 6% with light brown.

According to study conducted by S panda et al, the most common pigmentation was brown- black (78.86%) and grayish brown in remaining ones.[90]

Site of involvement:

Table 18: site of involvement

Other areas involved	No. of Cases (N)	Percentage (%)
Knuckles	11	22.0
Elbows	11	22.0
Knees	10	20.0
Groin	01	02.0

Neck was the commonest site of involvement in 100% in the study subjects followed by axilla in 92%, knuckles and elbows in 22% each and knees in 20% patients.

Acanthosis nigricans over face:

Table 19: acanthosis nigricans over face

Other areas involved	No. of Cases (N)	Percentage (%)
Forehead	04	08.0
Periorbital area	07	14.0
Temporal	03	06.0
Perioral	01	02.0

Periorbital was most common site for facial AN followed by forehead (8%), temporal area (3%) and perioral area (2%).

The most common site of face involved was the forehead and temporal region (69%) followed by zygomatic area (57%), and 14% cases with peri oral and periocular involvement in the study conducted by Saumya Panda et al[90]

Prevalence of Insulin resistance as per HOMA-IR:

Table 20: Prevalence of insulin resistance as per HOMA-IR

	No. of Cases (N)	**Percentage (%)**
Absent (HOMA IR<2.5)	06	12.0
Present (HOMA IR ≥2.5)	44	88.0
Total	50	100.0

Of the biochemical data available for 50 cases, 88 % of the patients with acanthosis nigricans had HOMA- IR ≥ 2.5 and these patients were considered to have insulin resistance.

Obesity:

Table 21: grading of obesity based on BMI

Grade	**No. of Cases (N)**	**Percentage (%)**
Obesity grade I (30.0-34.9)	22	44.0
Obesity grade II (35.0-39.9)	03	06.0
Obesity grade III (≥ 40)	06	12.0
Total	31	62

The Obesity of different grade was seen in 62% of the patients with grade I in 44%, grade II in 12% and grade III Obesity in 6% of the patients. In the study by Sharquie[80] and A-Ogaily[91], 33,3 % patients were overweight and 53.3% were found to be obese.Verma et al[92] found that 85.29% of the males were obese and 7.8% were overweight. In case of females, 100% belonged to obese category.

Correlation of insulin resistance and obesity

Table 22: Comparison of the presence of IR and Obesity in patients with AN

Obesity	Insulin Resistance		Total
	Absent (HOMA IR<2.5)	Present (HOMA IR ≥2.5)	
No (BMI <30)	05(10)	14(28)	19(38)
Yes (BMI ≥30)	01(02)	30(60)	31(62)
Total	06(12)	44(88)	50(100)

In our study, out of 50 AN patients, 31(62%) were found to be obese.

Out of these 31 patients, 30 patients had insulin resistance and the association was statistically significant. ($p<0.05$)

Correlation of Obesity and AN severity:

Statistically significant association is observed between neck severity, axilla severity, neck texture and obesity ($p<0.05$) and the results are similar to the study conducted by HY Ng et al.[56]

Metabolic syndrome:

Table 23: prevalence of metabolic syndrome

Metabolic Syndrome	Criteria	Frequency(n)	Percentage
Present	03	18	36.0
	04	06	12.0
	05	02	4.0
Absent		24	48
Total		50	100

Out of a total of 50 AN patients, 26 patients satisfied the criteria of metabolic syndrome.

36% satisfied 3/5 criteria, 12% met 4/5 criteria and 4% patients met all 5/5 criteria for diagnosing metabolic syndrome.

Correlation of insulin resistance and metabolic syndrome:

Table 24: Comparison of IR and Metabolic Syndrome in patients with AN

Metabolic Syndrome	Insulin Resistance		Total
	Absent (HOMA IR<2.5)	Present (HOMA IR ≥2.5)	
Absent	06(12)	18(36)	24(48)
Present	0	26(52)	26(52)
Total	06(12)	44(88)	50(100)

In our study 26 patients had metabolic syndrome, and all of them had insulin resistance and the association was statistically significant. ($p<0.05$) and none of the patients without insulin resistance had metabolic syndrome.

In a similar study conducted by NE Philip et al, metabolic syndrome was found to be present in 78.3% which is much higher than that found in our study.[93]

Metabolic syndrome and AN severity:

In our study, statistically significant correlation was seen between severity of AN and metabolic syndrome ($p<0.05$) and the findings are similar to that of NE Philip et al[93] ($p=0.001$) and AS Kong et al[18] studies.

In study by Dassanayake AS et al., documented the presence of the AN in urban population with metabolic syndrome (MetS) and stated that the AN can substantially predict the existence of metabolic syndrome (MetS).[83] scale grading AN appears to be of little clinical utility in clinically determining the degree of IR beyond detecting the presence or absence of AN and calculating BMI.[74]

There was a statistically significant relationship between increasing AN severity and each component of metabolic syndrome (MetS) as noted by Shah NG et al. each component of metabolic syndrome (MetS). Metabolic syndrome (MetS) was present in 70% of the patients and there was a significant frequency of AN. There was also a link between the severity of AN and metabolic syndrome (MetS).[94]

IR and AN are inextricably linked. Evidence suggests that AN is a valuable clinical diagnostic for identifying obese and overweight patients with IR who are at risk of developing type 2 diabetes and metabolic syndrome (MetS). In clinical

practice, recognizing AN is important for identifying those who are predisposed to the Insulin-resistant Obesity phenotype and might benefit from early treatments.[84]

According to Videria-Silva A et al., screening for AN at the neck and axilla is a non-invasive, inexpensive technique of detecting overweight patients who are asymptomatic and either have IR or are at risk of getting it.[95]

CONCLUSION

This study showed that among 50 patients with acanthosis nigricans, insulin resistance was present in 44 patients (88%) and absent in 6 patients (12%). Out of 50 patients, 30 were females (60%) and 20 (40%) were females showing slight female preponderance.

Maximum number of patients were in the age group of 31-40yrs (40%) followed with 24% in 21-30yrs.

Total number of overweight patients were 22% (n=11), Obesity grade I in 44%, 12% with Obesity grade III and 6% in Obesity II. Insulin resistance was seen in 60% (n=30) of the patient with Obesity. It shows that insulin resistance is more prevalent in obese and overweight patients.

Metabolic syndrome was present with criteria 3 components in 36%, with 4 components in 12% and 4% with 5 components of metabolic syndrome. Total number of patients with metabolic syndrome were 42% (n=21). Insulin resistance was seen in all patients with metabolic syndrome.

All patients had acanthosis nigricans over neck, 96% had in axilla, other sites were knuckles, groin, flexors, submammary region, umbilicus. Rare sites involved were perioral, periorbital, temporal and flanks.

Associated presence of Acrochordons was seen in 58% of the patients. systemic disease was seen in 8% with PCOS, 4% with CAD and hypothyroidism.

Thus, based on the above findings of higher prevalence of insulin resistance in patients with acanthosis nigricans and obesity/ metabolic syndrome, screening of patients with acanthosis nigricans for insulin levels becomes relevant and necessary, so as to advise them regarding life style modifications like correction un diet and weight reduction to prevent occurrence of diabetes mellitus or other cardiovascular complications.

Perhaps, studies on a larger number of acanthosis nigricans patients with control group from general population would strengthen theses associations.

SUMMARY

- The present cross sectional study random sampling method is conducted among the patients attending the Dermatology OPD, KLE'S Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi during January 2021 to December 2021.

- All clinically diagnosed cases of Benign acquired AN were included in the study.

- The mean age of the 50 patients who met the inclusion criteria in the current study was 34. ±10 years. Majority were in age group of 31-40yrs (40%) followed with 24% in 21-30yrs.
- There were 60% women and 40% men among them, with a female to male ratio of 1.5:1.
- Among the included patients, 26% were rural and 74% were urban location.
- By occupation, majority were students (26%), followed with 14% housewife and clerk.
- Life styles were assessed, 86% were with sedentary life style and 14% were moderate.
- Onset of age was seen with 28.76±8.60, duration was 3.08±2.62.
- History of weight gain was seen 56%.
- Menstrual history was seen irregular in 10% of the female patients.
- Associated itching was seen in 6% of the patients.
- Positive family history of AN seen in 22%.
- Family history of diabetes was seen in 34% of patients.

- History of systemic disease was seen 16%.
- In present study, systemic disease was seen in 8% with PCOS, 4% with CAD and hypothyroidism.
- HOMA IR was seen in 88% of the patients and absent in 12% of patients.
- In the present study, BMI was normal in 16%, overweight in 22%, Obesity grade I in 44%, 12% with Obesity grade III and 6% in Obesity II.
- IR and obesity was compared, IR was seen in 60% of the patient with obesity. ($p<0.05$) There is significant association between the IR and obesity among the patients.
- IR and metabolic syndrome (MetS) was compared, IR was seen in 52% of the patient with presence of metabolic syndrome (MetS).($p<0.05$) Statistically significant association is observed between IR and metabolic syndrome (MetS)
- IR and dyslipidemia was compared, IR was seen in 62% of the patient with presence of dyslipidemia. ($p>0.05$) though the prevalence was more in these patients, No significant association is observed between IR and Dyslipidemia
- IR and hyperglycemia was compared, IR was seen in 40% of the patient with presence of hyperglycemia. ($p>0.05$) but the association was statistically insignificant.
- IR and hypertension was compared, IR was seen in 32% of the patient with presence of hypertension. ($p>0.05$) The association was statistically not significant.
- In the study, the severity of disease with the Obesity, there is statistical significant association is observed between neck severity, axilla severity, neck texture and obesity.

- In the study on assessment of the severity with metabolic syndrome (MetS), there is significant association is observed between neck severity, axilla severity, neck texture and metabolic syndrome (MetS)
- AN on other side, 22% were on the knuckles, elbows and 20% in knee and 2% groin. Forehead in 8%, periorbital in 14%, temporal in 6% and 2% in perioral area.
- The color of lesion was found to be 60% dark brown, 18% with brown, 16% with black and 6% with light brown.
- Associated presence of Acrochordons was seen in 58% of the patients.
- Coexisting Dermatoses without IR was associated with striae distensae, seborrheic keratosis, lichen planus, DPN, and others like alopecia areata, bacterial infections, LSC, P Versicolor, candidal intertrigo.
- Coexisting Dermatoses with IR was seen with total 66% of participants, among them 12% with acne, 10% with AGA, 8% with hirsutism, 6% with psoriasis, xanthelasma. Others included PCOS, FPHL.
- Metabolic syndrome was present with criteria 3 components in 36%, with 4 components in 12% and 4% with 5 components of metabolic syndrome.

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ANNEXURE I – INFORMED CONSENT FORM

Title of the study: **"A Cross sectional study of association of acanthosis nigricans with insulin resistance in obesity and metabolic syndrome" attending KLE's Dr Prabhakar Kore Hospital & MRC, Belagavi**

The study is conducted by _____, Post Graduate (M.D) student in Dermatology under the guidance of _____, Professor and Head, Department of Dermatology, Venereology and Leprosy, JNMC, Belagavi.

Respected Sir/Madam,

We invite you to participate in our study as you are eligible for the same. During the study you will be asked some questions in detail regarding your present complaints.

Purpose of the study:

To study the association of AN with insulin resistance in obesity and Metabolic syndrome.

Procedure:

You will be asked to give a detailed history of your disease, undergo a physical examination and laboratory investigations.

Risks and Benefits:

The result of you taking part in this research would help health care providers towards a better understanding and early diagnosis of this disease, and thus we will be able to provide improved patient care.

Alternatives:

If you decide not to participate in this study, you will still be receiving the usual standard care for your disease.

Privacy and confidentiality:

Your privacy will be respected and all information collected about you during the course of this study will be kept confidential. Your identity will remain undisclosed.

Relations with the Institutional policy:

The J N Medical College will provide, within the limitations of the laws of the State of Karnataka, facilities and medical attention to patients who suffer injuries as a result of participating in this project.

Financial incentives: You shall not be receiving any payment or any financial incentives for participating in this study.

Authorization to publish results:

The results of this study may be published for scientific purpose or presented to a scientific group. Your identity, however, will be maintained confidential at all times.

Voluntary participation:

Your participation in this study is voluntary. Your decision whether or not to participate will neither affect the care of your current disease, nor your future relations with the doctor or the hospital. In the event if you suffer any physical injury as the result of your participation in this study, you may contact

In case you need further information regarding your rights as a study participant, you may please contact **Dr. Harsha Hegde**, chairman of the ethical committee, J N Medical College, Belagavi. 9480422500

STATEMENT OF CONSENT

I.D.NO: | | | |

I Mr/Ms/Mrs ---------- volunteer and consent to participate in this study. I have read the consent document or it has been read to me in my vernacular language. I accept to participate in the study. All the information regarding this study is provided to me and I have understood the same. I have been given the opportunity to ask questions and obtain appropriate answers.

Participant's name:

Signature or left thumb print of participant:

Witness name:

Signature of witness:

Signature of the investigator:

Date: | | | |

ANNEXURE II –PROFORMA

Study: "A cross-sectional study of association of acanthosis nigricans with insulin resistance in obesity and metabolic syndrome" attending KLE's Dr. Prabhakar Kore hospital and MRC, Belagavi"

Case no: **OP no:**

Name:

Age:

Sex:

Occupation:

Address with phone number:

Chief complaints:

History of present illness:

Duration of onset:

Age of onset:

Mode of onset: sudden / gradual

Progression: progressive / stationary

Precipitating factors, if any: PCOS / hypothyroidism / hyperthyroidism / cushing's disease

Site of lesion-	**present**	**absent**
1. nape of neck	☐	☐
2. axilla	☐	☐
3. groin	☐	☐
4. knuckles	☐	☐
5. cubital fossa	☐	☐
6. popliteal fossa	☐	☐
7. face	☐	☐
8. Other sites	_____	

Any associated factors:

asymptomatic / itching / pain / burning

Systemic complaints:

fatigue / loss of concentration / weight gain / sleepiness / depression / increased hunger

Past history:

DM / HTN / thyroid disorders / cushing's disease / PCOS / other medical illnesses

Family history:

Similar complaints / diabetes mellitus

Personal history:

Diet:

Appetite:

Bowel and bladder habits:

Sleep:

Habits/ addictions: alcohol / smoking / tobacco chewing

Treatment / Drug history:

Menstrual history:

General physical examination:

Vitals:

Pulse: _____/min

BP: _____/mmHg

Temp: _____^{o}F

Anthropometric measurements:

Height: _____ m

Weight: _____ kgs

Waist circumference: _____inches

BMI: _____kg/m^{2}

Signs:

Pallor:

Icterus:

Cyanosis:

Clubbing:

Lymphadenopathy:

Edema:

Mucocutaneous examination:

Type of lesion: patch / plaque

Colour of lesion: light brown / dark brown / brown- black / black

Site of lesion:

Acrochordon: present / absent

Other associated dermatoses:

Hair:

Nails:

Oral cavity:

Genitals:

Burke's AN severity grading:

Neck severity: 1 2 3 4

Neck texture: 1 2 3

Axilla severity: 1 2 3 4

- **FBS: _____mg/dL**

- **TG: _____**

- **HDL: _____**

- **Fasting insulin: _____**

- **HOMA-IR = _____ × _____ |405 =**

Diagnosis:

- **Insulin resistance.** + / -
- **Obesity-** + / - **and grade:**
- **Metabolic syndrome ___/ 5**
- **AN grade:**

ANNEXURE III – PHOTOGRAPHS

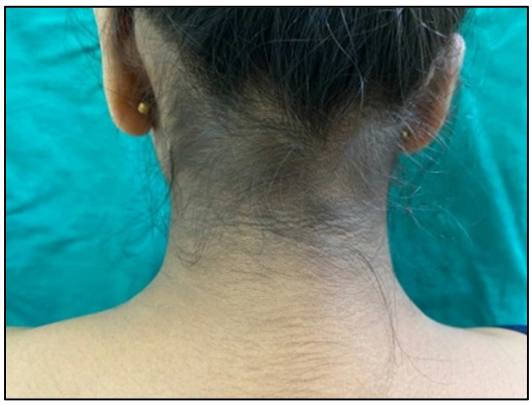

Figure: 3a

Figure:3b

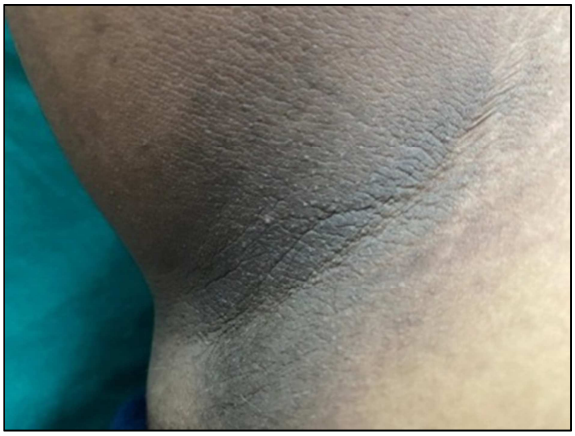

Figure: 3c

Figure 3a and 3b acanthosis nigricans over neck & 3c acanthosis nigricans over axilla. According to burke grading, Neck severity-3, neck texture-2, axilla grading-2.

Figure: 4a

Figure: 4b

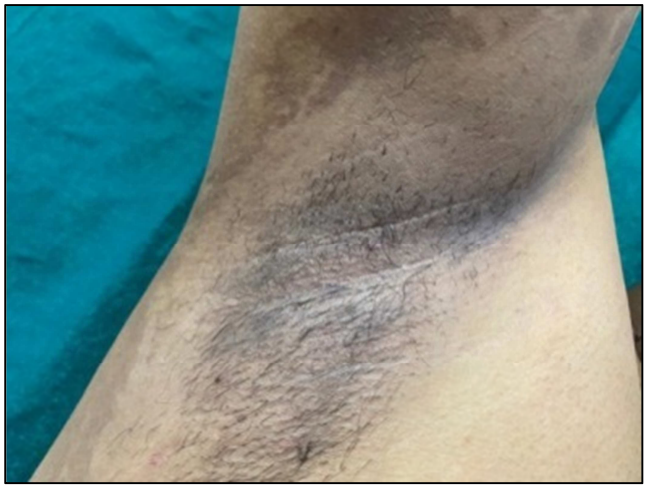

Figure: 4c

Figure 4a and 4b acanthosis nigrians over neck & 4c acanthosis nigricans over axilla. According to burke grading, Neck severity-2, neck texture-1, axilla grading-1, with associated acrochordons- neck, pityriasis versicolor- axilla

Figure: 5a

Figure: 5b

Figure: 5c

Figure 5a and 5b acanthosis nigricans over neck & 5c acanthosis nigricans over axilla. According to burke grading Neck grading-4, neck texture- 2, axilla grading- 3 with multiple acrochordons over neck and axilla, pityriasis versicolour over neck and chest.

Figure 6a- Facial AN- involvement of periorbital and zygomatic area.

Figure 6b- Facial AN – involvement of forehead and periorbital area.

Figure 7a

Figure 7b

Figure 7a and 7b – Acanthosis nigricans in axilla with striae alba.

Figure 8a

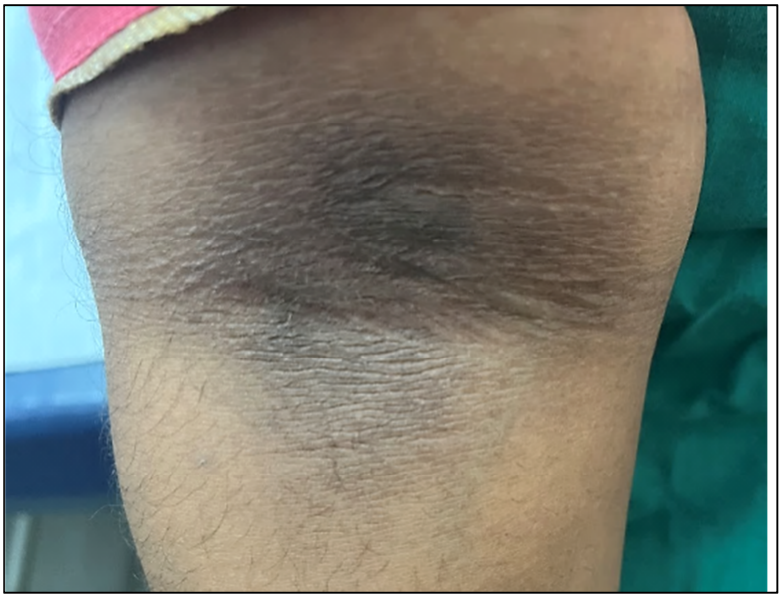

Figure: 8b

Figure 8a, 8b – Acanthosis nigricans over other sites- knuckles and cubital fossa.

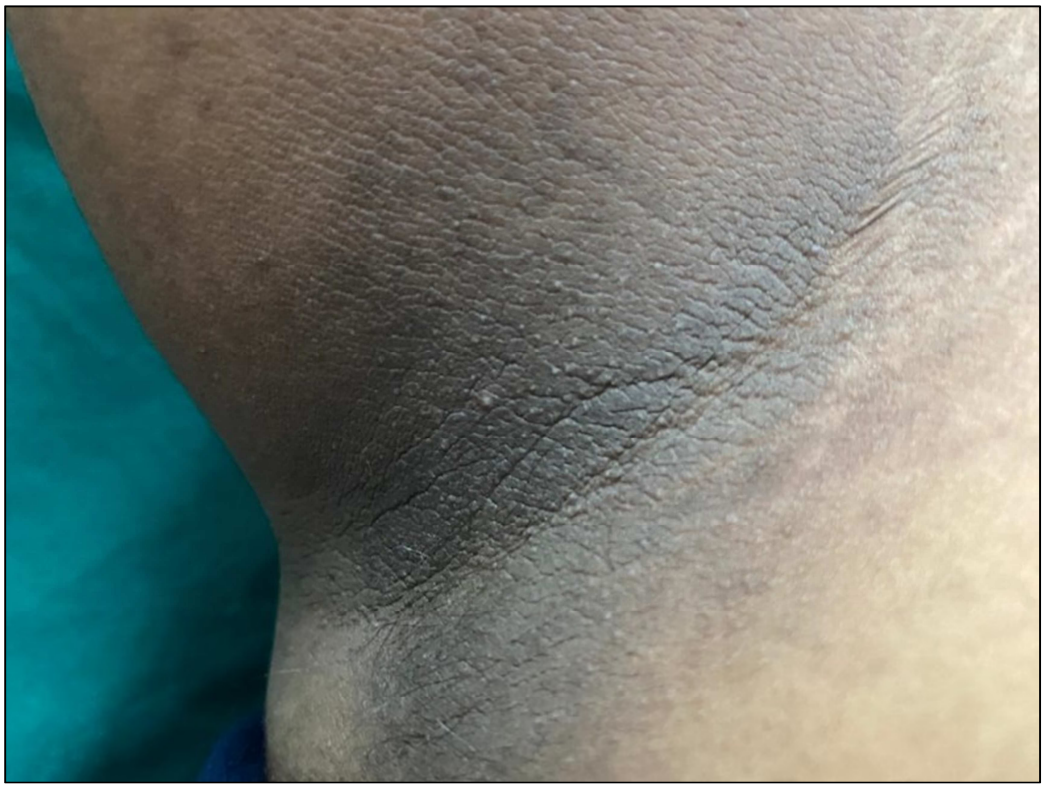

Figure 9: Typical velvety hyperpigmented appearance

ANNEXURE IV – KEY TO MASTER CHART

Y - YES

N - NO

S - SMOKING

A - ALCOHOL

T - TOBACCO

P - PRESENT

A - ABSENT

IR - INSULIN RESISTANCE

ANNEXURE V –MASTER CHART

	PATIENT DETAILS					RELEVANT HISTORY									CLINICAL EXAMINATION																		ANTHROPOMETRY				LABORATORY INVESTIGATIONS											
															BURKE'S QUANTITATIVE SCALING								OTHER AREAS					COLOUR OF AN NECK	CO EXISTING DERMATOSES																				
SL NO	NAME	AGE	RESIDENCE	OCCUPATION	LIFESTYLE	ADDICTIONS	DURATION OF DISEASE	AGE OF ONSET	HISTORY OF WEIGHT GAIN	HISTORY OF IRREGULAR MENSUS	ASSOCIATED WITH ITCHING	FAMILY HISTORY OF AN	F/H/O DIABETES	H/O SYSTEMIC DISEASES	NECK SEVERITY	NECK TEXTURE	AXILLA SEVERITY	KNUCKLES	ELBOWS	KNEES	BURKES TOTAL SCORE	FOREHEAD	PERIORBITAL AREA	FACE	TEMPORAL	PERIORAL	GROIN		ACROCHORDONS	WITHOUT IR	WITH IR	HEIGHT(CMS)	WEIGHT(KGS)	BMI	WC(INCHES)	FBS(MG/DL)	F INSULIN	HOMA2-IR (>=2.5)	HDL(<40MG/DL IN MEN, <50MG/DL IN WOMEN	TRIGLYCERIDES	OBESITY	HYPERTENSION	DYSLIPIDEMIA	HYPERGLYCEMIA/ DM-2	METABOLIC SYNDROME	INSULIN RESISTANCE
1	VARSHA SHARMA	19	U	STUDENT	SEDENTARY	A	4 YEARS	15	Y	N	N	N	Y	N	2	2	3	0	0	0	7	A	A	A	A	A	DARK BROWN	Y		ACNE, STRIAE DISTENSAE	143	69	33.74	34	81	10.8	2.56	42	143	YES	NO	YES	NO	A	P
2	SANTOSH DASARADDI	25	U	STUDENT	SEDENTARY	AS	3 YEARS	22	N	N	N	Y	N	N	3	2	3	1	0	0	9	A	A	A	A	A	DARK BROWN	Y	LICHEN PLANUS		150	69	30.67	40.9	78	16.9	3.25	40	151	YES	NO	YES	NO	P-3	P
3	MEESAHEB NADAF	22	U	STUDENT	SEDENTARY	AS	1 YEAR	21	Y	N	N	N	Y	N	3	2	2	0	0	0	7	A	A	A	A	A	DARK BROWN	N			172	82	27.7	36	80	15.7	3.1	38	143	NO	NO	YES	NO	A	P
4	VAIBHAV HOSUR	15	RURAL	STUDENT	MODERATE	AST	2 YEARS	13	Y	N	N	N	N	N	2	2	1	0	1	1	7	A	A	A	A	A	LIGHT BROWN	Y		STRIAE DISTENSAE	163	63	23.7	36.22	72	8.27	1.47	49	89	NO	NO	NO	NO	A	A
5	VINOD DODAMANI	42	U	CLERK	MODERATE	ST	3 YEARS	27	Y	N	N	N	N	N	3	3	3	0	0	0	9	A	A	A	A	A	BROWN	Y	LICHEN PLANUS	STRIAE DISTENSAE	168	88	31	38	109	28.6	6.28	54	131	YES	YES	NO	YES	P-3	P
6	KARUNA HADUPAD	14	U	STUDENT	SEDENTARY	N	3 MONTHS	14	N	Y	N	N	N	PCOS	2	2	0	0	0	0	4	A	A	A	P	A	LIGHT BROWN	Y		HIRUSTISM, PCOS, FPHL	155	56	23.3	30	76	4.8	0.9	47	113	NO	NO	YES	NO	A	A
7	SANDESH ACHITAL	32	U	CLERK	SEDENTARY	S	5 YEARS	26	N	N	N	N	N	N	3	2	3	0	0	0	8	A	A	A	A	A	DARK BROWN	N	LSC		155	80	33.2	42	110	23.9	6.49	39	152	YES	NO	YES	YES	P-3	P
8	PRIYANKA PATIL	37	U	ENGINEER	SEDENTARY	A	4 YEARS	28	Y	N	N	N	N	N	4	3	4	1	0	0	12	A	A	A	A	A	BLACK	N		XANTHALESMA, STRIAE DISTENSAE	156	102	41.91	47	120	65.39	19.37	37	353	YES	NO	YES	YES	P-4	P
9	SARANSH AGARWAL	21	U	STUDENT	SEDENTARY	N	3 YEARS	18	Y	N	N	N	Y	N	3	2	0	1	0	0	6	A	A	A	A	A	DARK BROWN-BLACK	Y	DPN, STRIAE DISTENSAE		154	117	49.3	42	91	36.62	8.22	26	201	YES	NO	YES	NO	P-3	P
10	ARUN	32	R	SHOP KEEPER	MODERATE	AST	2 YEARS	30	N	N	N	N	N	N	4	3	4	0	0	1	12	A	A	A	A	A	BLACK	Y			175	95	31	41.2	114	36.1	10.16	36	148	YES	NO	YES	YES	P-4	P
11	BHARATI	38	R	CLERK	SEDENTARY	AT	1 YEAR	31	N	N	N	Y	Y	N	3	2	3	0	0	0	8	A	P	P	A	A	DARK BROWN	N	CANDIDIAL INTERTRIGO		152	80	34.2	42.9	108	25.9	6.9	37	132	YES	NO	YES	YES	P-3	P
12	SACHIN	45	U	CLERK	SEDENTARY	T	5 YEARS	24	Y	N	N	Y	N	N	2	2	1	0	1	0	6	A	A	A	A	A	BROWN	N			170	79	27.3	38.9	98	37.6	3.2	29	96	NO	YES	NO	NO	A	P
13	SHIVAKUMAR	25	U	BUSINESSMAN	SEDENTARY	A	3 MONTHS	25	Y	N	N	N	N	N	3	2	2	0	0	0	7	P	P	A	A	A	DARK BROWN-BLACK	Y	STRIAE DISTENSAE		168	80	28.34	39	122	27	8.1	43	165	NO	NO	YES	YES	A	P
14	RAJASHEKAR	33	U	MECHANIC	MODERATE	AS	7 YEARS	28	N	N	N	Y	N	N	3	3	4	0	0	0	10	A	A	A	A	A	BLACK	Y		AGA	174	97	32.03	48.03	106	44.2	11.56	45	166	YES	NO	YES	YES	P-3	P
15	DEEPA	29	U	BANK EMPLOYEE	SEDENTARY	N	2 YEARS	27	Y	N	N	N	N	N	2	2	3	0	0	0	7	A	A	A	A	A	DARK BROWN	N	BACTERIAL INFECTIONS		158	62	24.8	32	96	17.65	4.1	47	140	NO	NO	YES	NO	A	P
16	IQRA	26	U	STUDENT	SEDENTARY	N	3 YEARS	23	Y	Y	N	N	N	N	2	1	1	0	0	1	5	A	A	A	A	A	BROWN	Y		ACNE, FPHL	153	57	24.3	34	90	14.5	3.2	48	93	NO	NO	YES	NO	A	P
17	SHARADA	39	U	HOUSEWIFE	SEDENTARY	N	8 YEARS	31	N	N	Y	N	N	N	3	2	3	0	0	0	8	A	P	P	A	A	DARK BROWN	Y			153	76	32.46	42	96	38.6	9.1	39	154	YES	NO	YES	NO	P-3	P
18	VEERESH	48	U	SHOPKEEPER	MODERATE	AST	12 YEARS	26	N	N	N	N	Y	CAD,HTN	3	2	3	0	0	0	8	P	A	P	A	A	DARK BROWN-BLACK	N	STRIAE DISTENSAE		169	98	34.31	45.9	102	31.2	7.85	41	151	YES	NO	YES	YES	P-3	P
19	SUJITH	38	U	CLERK	SEDENTARY	ST	8 MONTHS	27	Y	N	N	Y	N	N	2	1	2	0	1	0	6	A	A	A	A	A	BROWN	N		HIDRADENITIS SUPPURATIVA	160	76	29.68	39.8	89	16.3	3.5	35	127	NO	NO	YES	NO	A	P
20	MOHIT	21	U	STUDENT	SEDENTARY	AS	6 MONTHS	21	Y	N	N	Y	Y	N	3	3	3	0	0	1	10	A	A	A	A	A	DARK BROWN	Y	STRIAE DISTENSAE		169	82	28.7	38	105	23	5.9	40	122	NO	NO	NO	YES	A	P
21	ANITA	38	R	TEACHER	SEDENTARY	A	7 YEARS	31	Y	N	N	N	Y	N	4	3	4	1	0	0	12	A	P	A	A	A	BLACK	Y		PSORIASIS	152	99	42.8	52	169	47.08	19.6	38	339	YES	YES	YES	YES	P-5	P
22	MIRAJ BEGUM	48	U	HOUSEWIFE	SEDENTARY	N	3 YEARS	45	N	Y	Y	N	N	PCOS	3	2	2	1	0	0	8	P	P	A	A	A	BROWN	Y	FOLLICULITIS	HIRSUTISM, FPHL	156	90	36.98	45	91	35.27	7.8	45	134	YES	YES	YES	NO	P-3	P
23	ARSHYA	35	U	HOUSEWIFE	SEDENTARY	N	2 YEARS	33	N	Y	N	N	N	PCOS	2	2	2	0	0	0	6	A	A	A	A	A	DARK BROWN	N		HIRSUTISM	160	96	37.5	46	75	21.35	3.8	40	68	YES	NO	YES	NO	A	P
24	SHOEB	37	R	COOK	SEDENTARY	T	4 YEARS	33	N	N	N	N	Y	N	4	3	4	0	1	0	12	A	A	A	A	A	DARK BROWN	N	STRIAE DISTENSAE	AGA	180	124	39.5	60	73	32.23	5.7	33	154	YES	NO	YES	NO	P-3	P
25	NADEEM	30	U	TEACHER	SEDENTARY	ST	2 YEARS	28	Y	N	N	Y	N	N	2	1	2	0	1	0	6	A	A	A	A	A	BROWN	N		AGA	167	86	30.8	42	87	8.58	2.8	45	71	YES	NO	NO	NO	A	P
26	JHANAVI	18	U	STUDENT	SEDENTARY	N	1 YEARS	17	Y	N	N	N	Y	N	2	2	2	0	0	0	6	A	A	A	A	A	DARK BROWN	Y	ALOPECIA AREATA	ACNE	165	82	30.1	43	70	17.91	3.09	37	60	YES	NO	YES	NO	A	P
27	PADMAVATI	60	R	LECTURER	SEDENTARY	N	10 YEARS	50	Y	N	N	N	N	CAD	2	1	2	1	0	1	7	A	A	A	A	A	DARK BROWN	Y	SEBORRHEIC KERATOSIS, DPN		165	70	25.7	35	70	10.66	1.83	56	122	NO	YES	NO	NO	A	A
28	HAMEERA	42	R	CLERK	SEDENTARY	N	2 YEARS	40	Y	N	N	N	N	N	3	2	2	0	1	0	8	A	A	A	A	A	DARK BROWN	Y		XANTHALESMA, STRIAE	180	118	36.4	47	225	11.8	6.5	40	223	YES	YES	NO	YES	P-4	P
29	PRABHAKAR	37	R	WAITER	MODERATE	N	11 MONTHS	36	Y	N	Y	N	Y	N	1	1	0	0	0	0	2	A	A	A	A	A	LIGHT BROWN	Y		AGA	174	84	27.7	38	81	10.8	2.16	45	180	NO	NO	YES	NO	A	A
30	YALLAWA	43	U	TAILOR	SEDENTARY	A	5 MONTHS	42	N	N	N	N	N	N	2	2	2	0	0	1	7	A	A	A	A	A	DARK BROWN	Y	SEBORRHEIC KERATOSIS, DPN		143	69	33.74	34	78	16.9	3.25	56	156	YES	YES	YES	NO	P-3	P
31	HARSHITHA	52	R	HOUSEWIFE	SEDENTARY	N	9 YEARS	43	N	N	N	N	N	HYPOTHYROIDISM	3	2	3	0	1	0	9	A	A	A	A	A	DARK BROWN	N	TINEA		150	69	30.67	40.9	80	15.7	3.1	45	123	YES	NO	YES	NO	A	P
32	SHIVABAI	23	U	STUDENT	SEDENTARY	N	2 YEARS	26	N	N	N	Y	N	N	2	1	2	1	0	0	6	A	A	A	A	A	BROWN	N	STRIAE DISTENSAE		172	82	27.7	36	72	8.27	1.47	56	123	NO	NO	NO	NO	A	A
33	BASAVVA	37	U	STUDENT	SEDENTARY	N	2 YEARS	20	Y	N	N	N	N	N	4	3	3	0	0	0	10	P	P	A	A	A	DARK BROWN-BLACK	N		ACNE	163	63	23.7	36.22	109	28.6	6.28	58	188	NO	YES	YES	YES	P-3	P
34	SHIVANI	39	U	ENGINEER	SEDENTARY	A	4 YEARS	25	Y	N	N	Y	Y	N	2	1	1	0	0	0	4	A	A	A	A	A	DARK BROWN	Y			168	88	31	38	76	4.8	0.9	76	110	YES	NO	NO	YES	A	A
35	BHAVYA	33	U	HOUSEWIFE	SEDENTARY	N	1 YEAR	38	N	N	N	N	Y	N	3	1	2	0	0	0	6	A	A	A	A	A	DARK BROWN	Y			155	56	23.3	30	110	23.9	6.49	55	121	NO	NO	YES	NO	A	P
36	BHAGYASHREE	40	U	HOUSEWIFE	SEDENTARY	N	2 YEARS	38	N	N	N	N	N	N	4	3	4	0	1	0	12	A	A	A	A	A	BLACK	N	VITILIGO		155	80	33.2	42	120	65.39	19.37	34	90	YES	YES	YES	NO	P-4	P
37	VIJAYRATNA	37	R	TEACHER	SEDENTARY	T	2 YEARS	35	N	N	N	N	N	N	3	2	3	1	0	0	9	A	A	A	A	A	DARK BROWN	N			156	102	41.91	47	91	36.62	8.22	39	129	YES	YES	YES	NO	P-3	P
38	NEHA	30	U	BEAUTICIAN	SEDENTARY	N	1 YEAR	29	Y	N	N	N	N	N	3	2	3	0	1	0	9	A	A	A	A	A	DARK BROWN	N			154	117	49.3	42	114	36.1	10.16	45	186	YES	NO	YES	NO	P-4	P
39	SAVITA	35	R	DOCTOR	SEDENTARY	AS	1 YEAR	34	Y	N	N	N	N	N	3	2	2	0	0	0	7	A	A	A	A	A	DARK BROWN	Y		PSORIASIS	175	95	31	41.2	108	25.9	6.9	39	98	YES	NO	YES	YES	P-3	P
40	RAJASHREE	45	U	ENGINEER	SEDENTARY	A	3 YEARS	42	Y	N	N	Y	Y	N	3	2	3	1	0	0	9	A	A	A	A	A	DARK BROWN	Y			152	80	34.2	42.9	98	37.6	9.09	49	110	YES	NO	YES	NO	P-3	P
41	SRI SAI	41	U	RECEPTIONIST	SEDENTARY	N	2 YEARS	39	Y	N	N	N	N	HYPOTHYROIDISM	2	1	3	0	0	0	6	A	A	A	A	A	BROWN	Y	P VERSICOLOR		170	79	27.3	38.9	122	27	8.1	60	120	NO	YES	NO	YES	A	P
42	GAURI	49	U	CHARTERED ACCOUNTANT	SEDENTARY	A	9 MONTHNS	38	Y	N	N	N	N	N	4	2	4	0	0	1	11	A	A	A	A	A	DARK BROWN- BLACK	Y			168	80	28.34	39	106	44.2	11.56	51	120	NO	YES	YES	YES	P-4	P
43	MUKTA	22	U	STUDENT	SEDENTARY	N	6 MONTHS	22	Y	N	N	N	Y	N	3	2	2	0	0	0	7	A	A	A	A	A	DARK BROWN	Y		ACNE	174	97	32.03	48.03	96	17.65	4.1	55	110	YES	NO	NO	NO	A	P
44	USHA	29	U	HOUSE WIFE	SEDENTARY	N	4 YEARS	25	Y	N	N	N	Y	N	2	1	1	0	0	0	4	A	A	A	A	A	BROWN	Y			158	62	24.8	32	90	14.5	3.2	45	129	NO	NO	YES	NO	A	P
45	REKHA	40	U	LECTURER	SEDENTARY	S	1 YEAR	29	N	Y	N	N	Y	PCOS	3	2	2	0	0	0	7	A	A	A	A	A	DARK BROWN	Y		HIRSUTISM	153	57	24.3	34	96	38.6	9.1	37	165	NO	YES	NO	NO	P-3	P
46	MAYA	39	U	DOCTOR	SEDENTARY	N	4 YEARS	25	N	N	N	N	N	N	3	2	3	1	0	0	9	A	A	A	A	A	DARK BROWN	N		PSORIASIS	153	76	32.46	42	102	31.2	7.85	55	132	YES	YES	NO	YES	P-3	P
47	JAYASHREE	19	U	STUDENT	SEDENTARY	A	3 YEARS	16	N	N	N	N	Y	N	2	1	2	0	0	0	5	A	A	A	A	A	DARK BROWN	N			169	98	34.31	45.9	89	16.3	3.5	56	165	YES	NO	NO	NO	A	P
48	MADHURI	42	R	ENGINEER	SEDENTARY	N	5 YEARS	17	N	N	N	N	N	N	3	2	3	0	1	1	10	A	A	A	A	A	DARK BROWN	N		ACNE	160	76	29.68	39.8	105	23	5.9	56	226	NO	YES	YES	YES	P-3	P
49	MAMTA	35	U	BUSSINESSMAN	SEDENTARY	N	6 YEARS	29	N	N	N	Y	N	N	4	3	4	1	0	1	13	A	A	A	A	A	BLACK	N			152	99	42.8	52	169	47.08	19.6	38	339	YES	YES	YES	YES	P-5	P
50	RAJESH	48	R	CLERK	MODERATE	ST	2 YEARS	36	Y	N	N	N	N	N	3	2	0	0	1	1	7	A	P	A	A	A	DARK BROWN	Y		AGA	154	76	31	38	89	11.9	2.6	48	109	YES	NO	NO	NO	A	P