"A CROSS SECTIONAL STUDY OF EVALUATION OF ASSOCIATION BETWEEN ACANTHOSIS NIGRICANS AND INSULIN RESISTANCE"

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LIST OF ABBREVIATIONS USED

AN	:	Acanthosis Nigricans
ANA	:	Anti Nuclear Antibodies
BMI	:	Body mass index
CBC	:	Complete Blood Count
DF	:	Degree of freedom
DHEA	:	Di Hydro Epi Androsterone
EGF	:	Epidermal growth factor
EGFR	:	Epidermal growth factor receptor
FBS	:	Fasting Blood Glucose
FGFR	:	Fibroblast growth factor receptor
FSH	:	Follicle Stimulating Hormone
HAIR-AN	:	Hyperandrogenism, insulin resistance and Acanthosis Nigricans
HOMA	:	Homeostatic Model Assessment
HbA1c	:	Hemoglobin A1c
IR	:	Insulin Resistance
IGF	:	Insulin like growth factor
IRS	:	Insulin receptor substrate
IGFBP	:	Insulin like growth factor Binding Protein
LH	:	Luteinizing Hormone
MORFAN	:	Mental retardation, overgrowth, remarkable facies And Acanthosis Nigricans
PCOS	:	Polycystic ovarian syndrome
PUVA	:	Psoralen ultra violet A

QUICKI	:	Quantitative insulin check index
SADDAN	:	Severe achondrodysplasia with developmental delay Acanthosis nigricans
SCD36	:	Soluble CD36
TGF-α	:	Transforming growth factor – α
TNF-α	:	Tumour Necrosis Factor– α
USA	:	United States of America

ABSTRACT

Background: Acanthosis Nigricans is a skin lesion characterized by hyperpigmented velvety cutaneous thickening that can occur in flexural areas like axilla, sides of neck, antecubital and popliteal fosse or groin. Insulin resistance is a reduction in the ability of tissue cells, mainly those in muscle, to use insulin. In this condition, the pancreas is hyperactive to produce more insulin, and hyperinsulinemia develops to maintain blood sugar levels within normal limits. The body cannot use the additional insulin, and the pancreas becomes exhausted. Insulin production then decreases. At this point, a person may be diagnosed with Type 2 diabetes. Some researchers consider acanthosis nigricans to be a predictive marker for 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, insulin resistance (IR) and other metabolic parameters. Thus, screening of patients with acanthosis nigricans for insulin levels becomes relevant and necessary, so as to advice them regarding the diet, life style modifications and weight reduction to prevent occurrence of diabetes mellitus.

Aim: To determine the prevalence of insulin resistance in acanthosis nigricans patients and relation of Acanthosis Nigricans with obesity.

Materials and method: This study was a cross sectional study consisting of 40 patients clinically diagnosed as having acanthosis nigricans irrespective of age or sex. Patients known to have diabetes were excluded from the study. The fasting serum insulin levels and fasting glucose levels were measured. Insulin resistance was

calculated by using homeostasis model of assessment of insulin resistance (HOMA-IR), the values ≥ 2.5 were considered to be positive.

Results: The prevalence of insulin resistance in patients with acanthosis nigricans was found to be 70%. The proportion of females (45%) and males (55%) were almost same. Prevalence of acanthosis nigricans was more in age group between 21 to 30 years. Prevalence of insulin resistance was seen more in the age group of 11 to 20 years.77.78% of obese patients had insulin resistance, 78.94% of overweight patients had insulin resistance and 50% of normal patients had insulin resistance. 80% of patients with positive family history had insulin resistance and 64% with negetive family history had insulin resistance. All patients (100%) had acanthosis nigricans on the neck, next commonest site being axilla (95%). The unusual sites involved were perioral, periorbital and flank regions.

Conclusion: According to our study, raised insulin resistance was found in considerable number of patients with acanthosis nigricans. Prevalence was also more in obese and overweight patients when compared to normal patients. These could be the early indications of impending diabetes in these patients. Thus screening of patients with acanthosis nigricans for insulin levels becomes relevant and necessary.

Keywords: Acanthosis nigricans, Insulin resistance, Obesity

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INTRODUCTION

Acanthosis nigricans is characterized by hyperpigmented velvety plaques of body folds and neck. The most common sites of involvement include axilla, along with flexural areas of the posterior neck, groin, along the belt line, dorsal surface of the fingers, in the mouth, around the areolae, and umbilicus.[1] It is the most common dermatological manifestation of obesity and insulin resistance.[2] Other causes are drugs, benign inherited AN, and, most importantly, malignant or paraneoplastic AN.[3]

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.[4]

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

A study was conducted to determine the prevalence of Acanthosis Nigricans in the central Kerala south Indian population and evaluated its correlations with diabetes, obesity, insulin levels and other factors, and the study showed 16.1% population had acanthosis nigricans.[5] The prevalence of AN varies from 7% in unselected populations to 74% in obese people [6,7]. The prevalence also varies in different racial groups. For example, African Americans are 25 times more likely to have AN than patients of European descent[8]. A study from the USA reports that the

prevalence of AN was 3% among Caucasians, 19% in Hispanics and 28% in American Indians[9].

Early recognition of these conditions is essential for prevention of disease progression. The exact incidence of AN is unknown.

Thus, based on the above 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 life style modification like correction in diet and weight reduction to prevent occurrence of diabetes mellitus.

OBJECTIVES

Primary objective: To study the evaluation of the association between Acanthosis Nigricans and Insulin Resistance

Secondary objective: To study the relation of Acanthosis Nigricans with obesity.

REVIEW OF LITERATURE

Acanthosis nigricans

Acanthosis nigricans is characterized by symmetric, velvety to verrucous, hyperkeratotic and hyperpigmented plaques that have a predilection for the axillae, the nape, and other flexural areas.

Background

The first documented case of acanthosis nigricans was in 1889 in Germany as described by Unna and Pollitzer. By 1909, acanthosis nigricans had been described in approximately 50 patients and was suspected to be associated with internal malignancy. In 1976, Kahn et al published their landmark study in which the association between acanthosis nigricans and insulin resistance was first described. In 2000, the American Diabetes Association established acanthosis nigricans as a formal risk factor for the development of diabetes in children[10].

Epidemiology

Prevalence

The recent increase in the prevalence of AN may well reflect increasing trends in obesity and type 2 diabetes worldwide. The prevalence of AN varies from 7% in unselected populations to 74% in obese people.[6,7] In a study conducted on young American Indians in 2002 the prevalence rate of AN was 34.2%,[11] where as another study from Alabama Coushatta tribal people from Texas and Nebraska showed the prevalence of AN to be 38%. Another study was conducted in the central

Kerala south Indian population and evaluated its correlations with diabetes, obesity, insulin levels and other factors, and the study showed 16.1% population had acanthosis nigricans.[5]

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.[8] A study from the USA reports that the prevalence of AN was 3% among Caucasians, 19% in Hispanics and 28% in American Indians.[9]

Sex

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

Age

Lesions of benign acanthosis nigricans may be present at any age, including at birth, although it is found more commonly in the adult and adolescent population. Malignant acanthosis nigricans occurs more frequently in elderly persons.[3]

Mortality and morbidity

Benign form of acanthosis nigricans have very few, if any, complications of their skin lesions. AN is considered as a simple cutaneous marker of insulin resistance (IR) and hyperinsulinemia helping to identify individuals who are at high risk for developing diabetes or impaired glucose tolerance.[12] The severity of the insulin resistance is highly variable and ranges from an incidental finding after routine blood

studies to overt diabetes mellitus. The severity of skin findings may parallel the degree of insulin resistance, and a partial resolution may occur with treatment of the insulin-resistant state.

Insulin resistance is the most common association of acanthosis nigricans in the younger population. New studies indicate that children with acanthosis nigricans have higher levels of basal and glucose-stimulated insulin compared with obese children without acanthosis nigricans, suggesting an association of acanthosis nigricans with hyperinsulinemia independent of body mass index.[13, 14]

Malignant acanthosis nigricans is much less common than the other types and has a generally poor prognosis, which atleast in part is related to the low survival rate from the neoplasia concerned. It is most commonly associated with intra-abdominal malignancies. Average survival time of patients with signs of malignant acanthosis nigricans is 2 years.

Etiology and pathogenesis

The pathogenesis of acanthosis nigricans is poorly understood. It may be an interplay of factors including insulin-mediated activation of Insulin like growth factor receptors on keratinocytes, and increased growth factor levels.[15]

Various factors that have been proposed in the pathogenesis of acanthosis nigricans are as follows:

- 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 obviously involved in the complex regulations leading to the peculiar epidermal hyperplasia.[16]

Insulin regulates the epidermal balance between keratinocyte proliferation and differentiation and thereby contributes to skin homeostasis[17]. Insulin resistance is mediated by inhibitory serine phosphorylation of insulin receptor substrate-1 (IRS-1), that blocks signalling from the receptor[18]. In AN, keratinocytes are unable to respond to insulin properly, through inhibitory IRS-1 phosphorylation, which could interfere with insulin-dependent skin homeostasis. At the same time the growth promoting effects of insulin via the IGF-1 receptor persist.[19]

Elevated insulin concentrations result in direct and indirect activation of IGF-1 receptors on keratinocytes and fibroblasts, leading to proliferation. Other mediators may also contribute, including other tyrosine kinase receptors such as EGFR and FGFR. (IGF = insulin-like growth factor, BP = binding protein, IGF-1R = insulin-like growth factor 1 receptor, EGFR = epidermal growth factor receptor, FGFR = fibroblast growth factor receptor).[15]

In An hyperinsulinemia is thought to play a pivotal role (Fig. 3). At low concentrations, insulin regulates carbohydrate, lipid, and protein metabolism and can weakly promote growth by binding to "classic" insulin receptors. At high concentrations, however, insulin can exert more potent growth-promoting effects through binding to insulin-like growth factor 1 receptors (IGF-1Rs), which are similar

in size and subunit structure to insulin receptors, but bind IGF-1 with 100- to 1000-fold greater affinity than insulin[20]

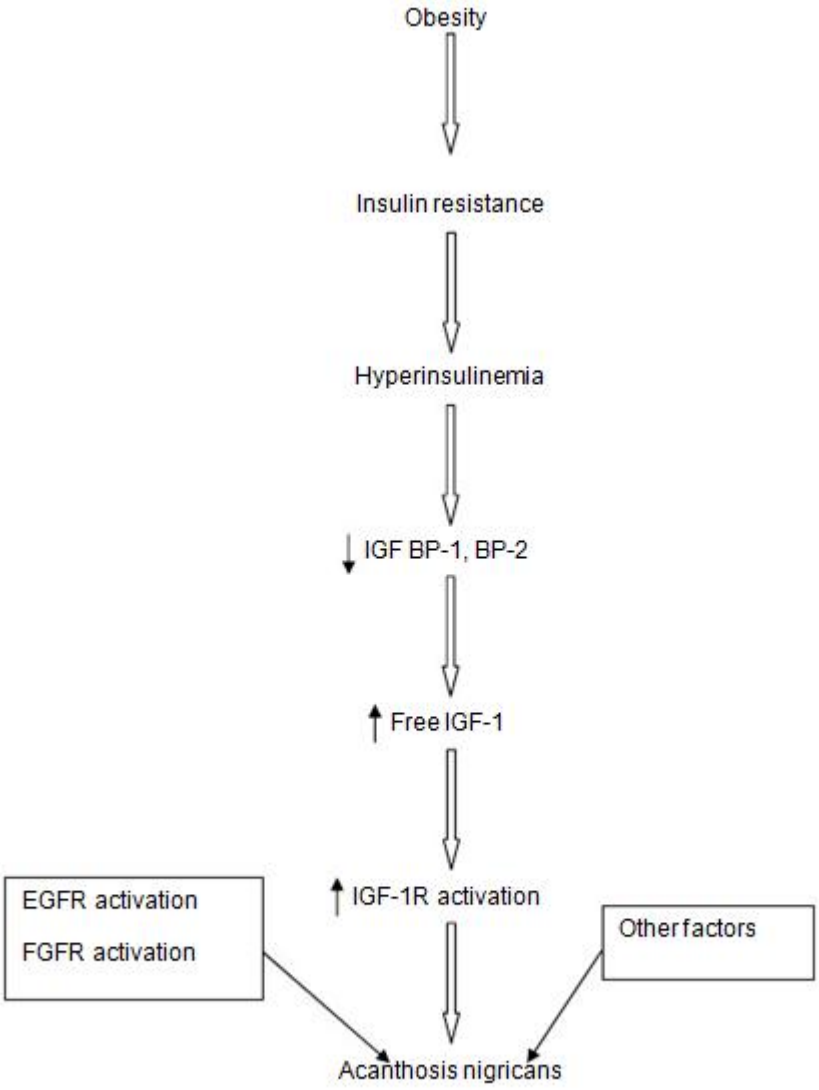


Figure 1: Proposed mechanism for the pathogenesis of acanthosis nigricans [2]

A number of observations suggest that insulin-dependent activation of IGF-1Rs can promote cellular proliferation and facilitate the development of AN. First, IGF receptors are found in cultured fibroblasts and keratinocytes[21]. Second, insulin can cross the dermoepidermal junction, and at high concentrations can stimulate growth and replication of fibroblasts[21, 22]. Finally, the severity of AN in obesity

correlates positively with the fasting insulin concentration[6, 7]. Thus, insulin may promote AN through direct activation of the IGF-1 signaling pathway.

The predilection of AN for areas such as the neck and axillae suggests that perspiration and/or friction also may be necessary cofactors[23].

Hyperinsulinemia may also facilitate the development of AN indirectly by increasing the levels of free IGF-1 in the circulation. The activity of IGF-1 is regulated by IGF binding proteins (IGFBPs), which increase IGF-1 half life, deliver IGFs to target tissues, and regulate the levels of the metabolically active "free" IGF-1[24, 25]. Insulin-like growth factor 1 binding protein and IGFBP-2 are both decreased in obese subjects with hyperinsulinemia, increasing plasma concentrations of free IGF-1[25]. An increase in bioactive IGF-1 promotes cell growth and differentiation[26].

Insulin-like growth factor 1 is expressed within the stratum granulosum and by dermal fibroblasts, but not by epidermal basal keratinocytes[27]. In theory, an insulin-induced systemic reduction of IGFBP-1 and IGFBP-2 could increase local levels of free IGF-1, thereby facilitating the development of hyperkeratosis and papillomatosis.

Therapy with IGF-1 has resulted in improvement of extreme insulin resistance syndromes, including improvement of AN in 5 of 7 patients[28]. Insulin-like growth factor 1 may reduce serum insulin concentrations and downregulate expression of IGF-1R[24, 29]. Since insulin binds with lower affinity to the IGF-1 receptor than IGF-1 itself, it is possible that insulin may be less proficient than IGF-1 at downregulating IGF-1Rs.

Hyperinsulinemia does not mediate all forms of acanthosis nigricans. Certain AN syndromes are due to FGFR defects.

Table 1: Syndromes associated with acanthosis nigricans:

- **Insulin Resistance Syndromes**
    - Acral hypertrophy and muscle cramps
    - Acromegaly
    - Alström syndrome
    - Ataxia-telangiectasia (Louis-Bar syndrome)
    - Cushing syndrome
    - Diabetes Mellitus Type 2
    - Gonadal dysfunction
    - Ovarian hyperthecosis
    - Polycystic ovary syndrome (PCOS, Stein-Leventhal syndrome)
    - Hyperplasia of the adrenal cortex, diabetes mellitus, and hypertrophy of the pineal body (Rabson-Mendenhall syndrome)
    - Leprechaunism
    - Lipodystrophy
    - Congenital lipodystrophic diabetes with acanthosis nigricans (Lawrence-Seip syndrome)
    - Congenital generalized lipodystrophy (Seip-Berardinelli syndrome)
    - Familial partial lipodystrophy (Kobberling-Dunnigan syndrome)
    - Mental retardation, overgrowth, remarkable faces, and acanthosis nigricans (MORFAN)
    - Prader-Willi syndrome
    - Type A syndrome (Hyperandrogenism, insulin resistance, and AN syndrome, or HAIR-AN) and Type B syndrome

- Hashimoto's thyroiditis
- Scleroderma
- Sjögren's syndrome
- Systemic lupus erythematosus
- Type C syndrome

➢ **Fibroblast Growth Factor Receptor Defect Syndromes**

- Beare-Stevenson cutis gyrata syndrome
- Crouzon's syndrome with acanthosis nigricans
- Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN)
- Thanatophoric dysplasia

➢ **Other Associations**

- Benign encephalopathy
- Congenital adrenal hyperplasia
- Costello syndrome
- Hepatolenticular degeneration (Wilson's disease)
- Hirschowitz syndrome
- Hypothyroidism
- Kabuki syndrome
- Ichthyosis with hypogonadism (Rud's syndrome)
- Primary biliary cirrhosis

Very little is known about the etiology and pathophysiology of acral-type malignant acanthosis nigricans. It has been speculated, however, that tumor-secreted TGF-α (which acts on tumor cells in an autocrine fashion) is transported via the blood

to the skin, where it binds to receptors on epidermal keratinocytes, thereby promoting their proliferation[33]. Elevated urinary transforming growth factor-a (TGF-a) and increased expression of epidermal growth factor (EGF) receptors in lesional skin were noted in a patient with acanthosis nigricans and Leser-Trélat sign[31]. More recently, a pathogenic role has been proposed for a tyrosine kinase receptor expressed in the basal cells of the epidermis[34]. The observation that following chemotherapy, there was an apparent disappearance of papillomatosis suggests a chemotherapeutic effect on the factor determining epidermal growth leading to acanthosis.

Among the neoplastic associations with pan , abdominal carcinomas are the most frequent (the preponderance being gastric adenocarcinomas)[3, 35], although a broad spectrum of cancers have been documented.

Table 2: List of other malignancies associated with acanthosis nigricans:

- Bile duct cancer
- Bladder cancer
- Breast cancer
- Colon cancer
- Endometrial cancer
- Esophageal cancer
- Gall bladder cancer
- Hodgkin disease
- Kidney cancer
- Liver cancer
- Lung cancer

- Mycosis fungoides
- Non-Hodgkins lymphoma
- Ovarian cancer
- Pancreatic cancer
- Pheochromocytoma
- Prostate cancer
- Rectal cancer
- Testicular cancer
- Thyroid cancer
- Wilms tumor

Drug-induced acanthosis nigricans, although uncommon, may be induced by several medications, including nicotinic acid, insulin, pituitary extract, systemic corticosteroids, and diethylstilbestrol. Nicotinic acid is most widely recognized association, with acanthosis nigricans, developing on abdomen and flexor surfaces and resolving within 4-10 weeks of discontinuation[10]. Rarely, triazinate, oral contraceptives, fusidic acid, and methyltestosterone have also been associated with acanthosis nigricans. Fibroblast growth factor receptor ligands such as palifermin may cause drug-induced acanthosis nigricans[36].

Clinical features

History

Patients usually present with an asymptomatic area of darkening and thickening of the skin. Pruritus occasionally may be present. Lesions begin as hyperpigmented macules and patches and progress to palpable plaques. In

approximately one third of cases of malignant acanthosis nigricans, patients present with skin changes before any sign of cancer. In another one third of cases, the lesions of acanthosis nigricans arise simultaneously with the neoplasm. In the remaining one third of cases, the skin findings manifest sometime after the diagnosis of cancer. Malignant acanthosis nigricans has been reported to appear abruptly and exuberantly and may be associated with a higher rate of pruritus[10]. Onset may be related to medication or supplemental usage.

Cutaneous findings

The "classic" presentation of acanthosis nigricans is symmetric, velvety to verrucous, hyperkeratotic and hyperpigmented plaques that have a predilection for the axillae, the nape, and other flexural areas. The degree of cutaneous involvement varies from subtle hyperpigmentation and papillary thickening, affecting few areas, to a deeply pigmenting and vermcoid process that involves the entire integument, including mucous membranes, palms, and soles. It is commonly seen on the neck, in the armpit and groin. It may also affect dorsal hands, knuckles, knees, elbows, inframammary regions, areola of the nipple, face, eyelids, lips, scalp, palms, vulva, mucosal surfaces (oral, esophageal, pharyngeal, laryngeal, conjunctival and anogenital)[37, 38].

The lesions of malignant and benign acanthosis nigricans are indistinguishable. However there are subtle differences regarding the age of onset, distribution and speed of onset that may assist in recognizing the paraneoplastic form. The benign form typically presents at a younger age and has a gradual progression of flexural surfaces. The malignant form has rapid appearance in an older individual over typical sites such as oral mucosa and palms. The lesions over oral mucosa appear

as verrucous papillomas and are not pigmented. The lesions over the palms have a rugated appearance and are called tripe palms. Many consider tripe palms and Leser-Trélat Sign (sudden development of multiple eruptive seborrheic keratoses associated with intense itching) to be along a spectrum of malignant acanthosis nigricans given a high degree of co-occurrence and histologic similarities. Florid cutaneous papillomatosis is also a part of this same spectrum.

Classification of acanthosis nigricans

Table 3: Curth's clinical classification of AN[39]

- Benign
- Malignant
- syndromic and
- pseudo-acanthosis nigricans.

More recently, Sinha and Schwartz have proposed a classification for AN[10]

Table 4: Classification of acanthosis nigricans is based on cause[10]

- Obesity associated acanthosis nigricans
- Syndromic acanthosis nigricans
- Acral acanthosis nigricans
- Unilateral acanthosis nigricans
- Generalized acanthosis nigricans
- Familial acanthosis nigricans
- Drug induced acanthosis nigricans
- Malignant acanthosis nigricans
- Mixed-type acanthosis nigricans

Obesity associated acanthosis nigricans

It is also called pseudo-acanthosis nigricans and is the most common type of acanthosis nigricans. The lesions commonly appear in adulthood but can be seen at any age. The dermatosis is weight dependent, and lesions regress completely with weight reduction. Insulin resistance is present in these patients; however it is not universal.

Syndromic acanthosis nigricans

It is the name given to acanthosis nigricans that is associated with a syndrome [table 1]. Type A syndrome and Type B syndromes are special examples.

The type A syndrome is also termed as the hyperandrogenemia, insulin resistance and acanthosis nigricans syndrome (HAIR-AN syndrome). This syndrome is often familial, affecting primarily young women (especially black women). It is associated with polycystic ovaries or signs of virilization (e.g., hirsutism, clitoral hypertrophy). High plasma testosterone levels are common. The lesions of acanthosis nigricans may arise during infancy and progress rapidly during puberty.

The type B syndrome generally occurs in women who have uncontrolled diabetes mellitus, ovarian hyperandrogenism or an autoimmune disease such as Systemic lupus erythematosus, Scleroderma, Sjogren syndrome or Hashimoto thyroiditis. Circulating antibodies to the insulin receptor may be present. In these patients, the lesions of acanthosis nigricans are of varying severity.

Acral acanthosis nigricans

It occurs in individuals who are otherwise in good health. Acral acanthosis nigricans is most common in dark skinned individual, especially those of African American or sub-Saharan African descent. The hyperkeratotic velvety lesions are most prominent over dorsal aspect of the hands and feet, with knuckle hyperpigmentation often most prominent.

Unilateral acanthosis nigricans

It is sometimes called nevoid acanthosis nigricans and is believed to be inherited as an autosomal dominant trait. Lesions are unilateral in distribution and may become evident during infancy, childhood or adulthood. Lesions tend to enlarge gradually before stabilizing or regressing. Unilateral acanthosis nigricans lesions may represent a unilateral epidermal nevus.

Generalized acanthosis nigricans

Generalized acanthosis nigricans is rare and has been reported in pediatric patients without underlying systemic disease or malignancy

Familial acanthosis nigricans

It is a rare genodermatosis that seems to be transmitted in an autosomal dominant fashion. The lesions typically begin during early childhood but may manifest at any age. It often progresses till puberty, at which time it stabilizes or regresses.

Drug induced acanthosis nigricans

In this type, acanthosis nigricans lesions develop following intake of drugs. The lesions of acanthosis nigricans may regress following discontinuation of the offending medication.

Malignant acanthosis nigricans

Malignant acanthosis nigricans is associated with internal malignancy [list 2]. Regression of acanthosis nigricans has been seen with treatment of the underlying malignancy, and reappearance may suggest recurrence or metastasis of the primary tumor.

Mixed-type acanthosis nigricans

Mixed type acanthosis nigricans refers to those situations in which a patient with one of the above types of acanthosis nigricans develops new lesions of a different etiology. An example of this would be an overweight patient with obesity-associated acanthosis nigricans who subsequently develops malignant acanthosis nigricans.

Histopathology

Histologic examination reveals hyperkeratosis and papillomatosis but only slight, irregular acanthosis and usually no hyperpigmentation. Thus, the term acanthosis nigricans has little histologic justification.

In a typical lesion, the dermal papillae project upward as finger like projections. The valleys between the papillae show mild to moderate acanthosis and are filled with keratotic material. Horn pseudocysts can occur in some cases. The epidermis at the tips of the papillae and often also on the sides of the protruding papillae appears thinned[40]. The brown color of the lesions is caused more by hyperkeratosis than by melanin.

Differentiation of acanthosis nigricans from other benign papillomas, particularly from linear epidermal nevi and from the hyperkeratotic type of seborrheic keratosis, may be difficult. As a rule, however, linear epidermal nevi show more marked acanthosis than acanthosis nigricans and have a more compact orthokeratotic stratum corneum. Furthermore, the pilosebaceous units in linear epidermal nevi are rudimentary. Acanthosis nigricans cannot be distinguished histologically from confluent and reticulated papillomatosis.

Evaluation and Management

Algorithm for the evaluation of acanthosis nigricans[41]

I. 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* (**Table 5**) and suspect underlying *insulin resistance* (go to item IIIA, below).

II. 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*.

a. Diagnostic study

(1) Review of systems

(2) Physical examination

(3) Chest roentgenogram

(4) CBC, stool test

b. Referral

(1) To gynecologist (pelvic examination)

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

2. If onset is insidious, suspect underlying *insulin resistance* (go to item III, below).

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* (go to item III, below).

2. If onset is insidious, is patient obese?

a. If yes, consider *obesity* as underlying cause (go to item IIIB, below).

b. If not, rule out *endocrine disorders* (**Table 6**) and suspect underlying *insulin resistance.*

(1) Diagnostic study

(a) Review of systems

(b) Physical examination

(2) Referral to endocrinologist

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

A. If progressive, suspect *genetic defects* of insulin receptor (**Tables7**).

1. 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

2. 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 (**Tables 8**).

1. 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

2. Referral to appropriate specialist

Table 5: Nonfamilial congenital anomalies associated with acanthosis nigricans

- AlstrSm syndrome
- Ataxia telangiectasia
- Bloom syndrome
- Capozucca syndrome
- Crouzon's disease (craniofacial dysostosis)
- Lawrence-Seip syndrome (total lipodystrophy)
- Lepreehaunism
- Prader-Willi syndrome
- Rabson's syndrome
- Rud's syndrome
- Syndrome of acral hypertrophy and muscle cramps

Table 6: Endocrine disorders associated with acanthosis nigricans

- Acromegaly
- Addison's disease
- Cushing's disease
- Diabetes mellitus
- Hypothyroidism
- Insulin-resistant states (type A, type B, other)
- Obesity
- Ovarian hyperthecosis
- Pinealoma or pineal hyperplasia (Rabson-Mendenhall)
- Polycystic ovary disease (Stein-Leventhal syndrome)

Table 7: Type A syndrome of insulin resistance

Demography
20 cases reported
Predominantly female, 19:1
Mostly black persons
Onset in infancy or childhood
Clinical manifestations
Acanthosis nigricans, usually generalized.
Hyperandrogenic features (hirsutism, clitoromegaly, masculine habitus, increased somatic growth)
Laboratory evaluation
Inappropriately high plasma levels of insulin
High plasma testosterone levels in majority of cases
Polycystic ovarian syndrome diagnosed in several cases
Genetic defect in post insulin receptor pathway shown in some cases
No immunologic abnormalities

Table 8: Type B syndrome of insulin resistance

Demography
19 cases reported
Predominantly female, 6:1
Mostly black persons
15 to 64 yr of age, mean age at onset 39 yr

Clinical manifestations

Acanthosis nigricans of varying severity

Associated autoimmune disorders

Systemic lupus erythematosus

Scleroderma

Sjogren's syndrome

Mixed connective tissue disease

Hashimoto's thyroiditis, vitiligo

Laboratory evaluation

Hyperinsulinemia, insulin resistance,

Autoantibodies against insulin receptor

Other immune abnormalities: positive for ANA,

Hypergammaglobulinemia,

Hypocomplementemia, positive for rheumatoid factor

High plasma testosterone without clinical evidence of virilization

Management

There is no specific treatment for AN. The treatment plan focuses on management of the underlying disorder. This usually results in partial or complete regression of the AN. Researchers recently showed that regression of AN correlates with the disappearance of anti–insulin receptor antibodies in patients with diabetes. They demonstrated that the achievement of euglycemia in diabetic patients is accompanied by marked regression of AN[42]. Similarly, malignant AN usually improves after the underlying malignancy is treated. Researchers have also shown that patients presenting with AN secondary to underlying congenital adrenal hyperplasia

show symptomatic resolution of the skin lesions after effective treatment of the adrenal hyperplasia[43]. Similarly, investigators have reported dramatic improvements of AN lesions in patients with congenital generalized lipodystrophy following leptin replacement therapy. This clearly demonstrates the need to address and treat the underlying etiology in all patients with AN[44].

Table 9: Selected case reports in which acanthosis nigricans improved with treatment of the underlying condition[15]

Condition	**Treatment**
Obesity/ hypertension	Diet/ weight loss Octreotide
HAIR-AN syndrome	Bariatric surgery Hypocaloric diet and weight loss Ketoconazole
Cushing syndrome	Trans sphenoidal surgery
Congenital generalized lipodystrophy	Leptin
Nicotinic acid use	Nicotinic acid discontinued Substitution with acipimox
Amprenavir use	Substitution with efavirenz
Triazinate (folate antagonist) use	Triazinate discontinued
Gastric adenocarcinoma	5-fluorouracil, cisplatin, epirubicin
Melanoma	Excision
Primary biliary cirrhosis	Liver transplantation

Medical care

Topical medications have been effective in some cases of acanthosis nigricans. These include keratolytics (e.g., topical tretinoin 0.05%, ammonium lactate 12% cream or a combination of the two) and triple combination depigmenting cream (tretinoin 0.05%, hydroquinone 4%, flucinolone acetonide 0.01%) at night with daily

sunscreen[45]. Calcipotriol, podophyllin, urea and salicylic acid also have been reported with variable results[10]. An obese man had acanthosis nigricans in the flexural areas that improved after 3 months of calcipotriol 0.005 percent cream twice daily[46]. Another obese woman improved with calcipotriol ointment twice daily, for 3 months[47]. Topical tretinoin 0.1% reduced acanthosis nigricans in two case reports. An eighteen year old woman with acanthosis nigricans experienced clearing of her neck in 10 days, with improvement in color and hyperkeratosis of her axillae within 2 weeks[48]. Another patient had clearing of her axillae within 2 weeks. The right axilla, used as a control, did not show any improvement[49].

Oral agents that have shown some benefit include, oral retinoids, insulin sensitizers and dietary fish oils. A randomized, open-label trial that compared the insulin sensitizers metformin and rosiglitazone in 30 overweight Mexican patients for 12 weeks demonstrated only minimal improvement in acanthosis nigricans lesions with either agent[50]. A smaller, 6 month trial of metformin in obese patients resulted in improvement of acanthosis nigricans in 3 of 5 patients[51]. Oral retinoids such as isotretinoin and acitretin, can be effective[52, 53, 54]. Improvement required large doses and extended courses, and relapses were described. One obese woman improved with isotretinoin 3mg/kg/day, but relapsed when this was stopped. An 18 year old man with generalized idiopathic acanthosis nigricans experienced complete recovery after 45 days with acitretin 0.8mg/kg divided into 2 daily doses. After starting maintenance therapy of 25 mg daily for 2 months, lesions recurred but subsequently resolved with topical retinoic acid 0.1%. An obese man taking isotretinoin 80mg/day noted 90 percent improvement of his palms and 50 percent improvement of his axillae within 2 months. After gradually tapering this dose over more than a year and receiving over 30g, he experienced an exacerbation of his skin lesions that improved with metformin

1000mg twice daily. Fish oil containing omega-3 fatty acids effectively reduced hyperpigmentation and normalized the skin texture in one woman with acquired generalized lipodystrophy and acanthosis nigricans. This occurred after taking 6 months of 10 to 20g per day of fish oil[55]. Octreotide showed sustained improvement in one patient with insulin resistance 6 months after completing the course. Hyperandrogenemia, insulin resistance and acanthosis nigricans syndrome (HAIR-AN syndrome) patients may be treated with oral contraceptives and metformin[10]. Cyproheptadine has been used in cases of malignant acanthosis nigricans because it may inhibit the release of tumor products[56]. PUVA (Psoralen ultra violet A) has been reported as beneficial for symptomatic relief in cases of paraneoplastic acanthosis nigricans[57].

Surgical care

Dermabrasion and long pulsed alexandrite laser therapy may also be used to reduce the bulk of the lesion, with some long term remission[58]. Surgical removal of the tumor is the main stay of treatment for malignant acanthosis nigricans, because clearance following excision of primary malignant tumor has been described[59].

Prognosis

Acanthosis nigricans is likely to improve in circumstances where a known cause is removed. For example, obesity-related acanthosis nigricans will improve with weight loss, and drug-induced acanthosis nigricans is likely to resolve when the drug is withdrawn. Hereditary variants may or may not fade with age, and malignancy-associated variants may, after a malignancy is removed, fade[60].

Complications

Complications vary depending on the eitiology of acanthosis nigricans. Appearance of acanthosis nigricans during childhood usually is associated with a benign condition, and no important sequel are described.

Adult onset acanthosis nigricans is more worrisome and an underlying malignancy must be ruled out. However, most cases of adult onset acanthosis nigricans are benign and often are associated with insulin resistance.

Acanthosis nigricans and insulin resistance

Insulin resistance is a metabolic disorder in which target cells fail to respond to normal levels of circulating insulin, resulting in compensatory hyperinsulinemia. IR has been associated with AN and acrochordons which may represent an easily identifiable sign of IR and noninsulin-dependent diabetes. AN is so closely associated with IR that it has been called a clinical surrogate for laboratory determined hyperinsulinemia. Katie S in their study observed that posterolateral neck texture had the highest sensitivity (96%) for IR compared with neck/axillary texture and pigment and proposed the term insulin neck (visibly increased texture on posterolateral neck appearing as visible lines and/or furrows and ridges) for this finding. They concluded that neck texture exhibits both greater sensitivity and specificity than neck pigment for AN detection, because visible roughness of the neck is recognizable without touching or disrobing patient, affording an instant assessment of AN. They suggested that all patients with elevated BMI should be examined for insulin neck and if neck texture is normal, IR is less likely to be present[61].

Methods for detecting insulin resistance:

- **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 β-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[62].

It is calculated as

HOMA-IR = [fasting serum insulin μUI/ml × fasting plasma glucose mg/dl] ÷ 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 IR. 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[63].

- **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 μU/mL] + log[Glucosemg/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, HbA1c, C3 complement, TNF alpha and sCD36 are now surfacing as surrogate

markers of IR[64]. Other investigations for IR are fasting glucose and lipoprotein profile, hemoglobin A1c, body weight, blood pressure, and an alanine transferase test for evaluation of fatty liver[63].

Acanthosis nigricans and obesity

Patients with AN, especially childhood benign AN, are at risk for obesity, hypertension, hyperinsulinemia, IR and type 2 diabetes. AN may be used as reliable index of IR[65]. But obesity is a more important determinant of IR than AN, hence AN should not be used as exclusive marker for predicting which overweight children have excess insulin levels.

Urrutia-Rojas *et al*. suggested that mothers of AN-positive children are likely to have abnormalities of fuel metabolism compared with mothers of AN-negative children. Fathers of AN-positive children are more likely to have blood glucose levels ≥26 mg/dL. They suggested that screening children for AN is an effective strategy for identifying adults with prediabetes[66]. Investigations for all overweight adults and children include fasting lipoprotein profile, fasting glucose, hemoglobin, fasting insulin, and alanine aminotransferase.

METHODOLOGY

We adopted a *cross-sectional design* for this study. The details of the study methodology are described below:

- *Study source:* The study was conducted in the Department of Dermatology Venereology and Leprosy, KLE's Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum as a part of the MD academic curriculum.
- *Study duration* – The study was done between January 2013 to December 2013
- ***Ethical clearance:*** It was granted by the J.N.M.C. Institutional Ethics Committee of Human Subjects Research.
- ***Study design:*** Cross sectional study
- ***Sample size:*** 80% of average cases of Acanthosis nigricans (AN) in 3 years.

  No. of cases in 2009- 52

  No. of cases in 2010- 48

  No. of cases in 2011- 50

  Total cases in last 3 years- 150

  Average cases of AN in 3 years = 50

  80% of 50 = **40**

  The resultant sample size was 40
- ***Data collection*** **-** A detailed history regarding the age, sex, occupation, family history, personal habits and duration of the disease was be taken. Dermatological and systemic examination was carried out. Diagnosis of Acanthosis Nigricans was made on clinical examination. The data was noted

in a pre-tested and pre-designed proforma after taking informed and written consent.

The fasting serum insulin and fasting plasma glucose levels were measured by collecting the blood samples. Insulin resistance was calculated by using homeostasis model of assessment of insulin resistance (HOMA-IR)

HOMA-IR = [fasting serum insulin μUI/ml × fasting plasma glucose mg/dl] ÷ 405.

HOMA-IR value ≥ 2.5 is considered insulin resistant.

- ***Sample selection criteria:*** All acanthosis nigricans patients attending KLE's Dr. Prabhakar Kore Hospital and MRC, Belgaum, were recruited as per the Inclusion and Exclusion criteria.

- ***Inclusion criteria:*** All new cases of acanthosis nigricans presenting to the outpatient Department of Dermatology.

- ***Exclusion criteria:*** All known cases of Diabetes Mellitus.

- ***Statistical Method for Data Analysis :*** Chi Square Test

RESULTS

All the 40 patients in the present study were cases of acanthosis nigricans.

All the manifestations seen were statistically correlated with insulin resistance. Statistical value (p) of <0.05 was considered significant.

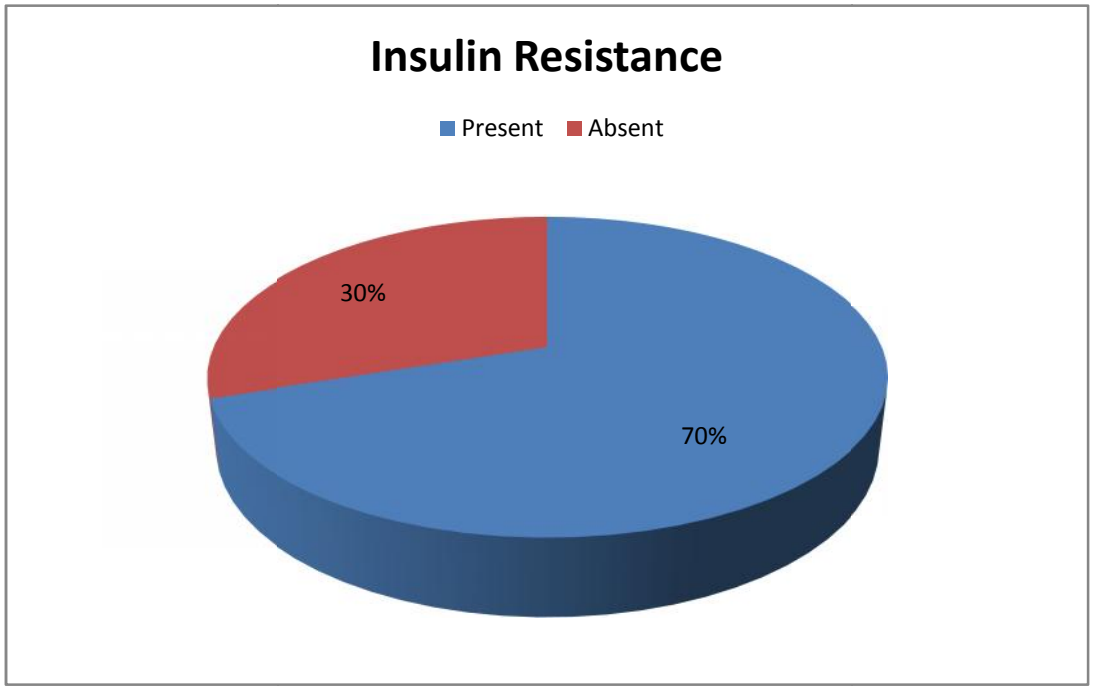
Insulin resistance:

Insulin resistance was considered present if the values were equal to or more than 2.5. A total number of 40 patients were included in the study where insulin resistance was present in 28 (70%) patients and absent in 12 (30%) patient

Table 10: Prevalence of IR in patients with Acanthosis nigricans

Insulin resistance	Number of patients	Percentage out of total number of patients
Present	28	70%
Absent	12	30%

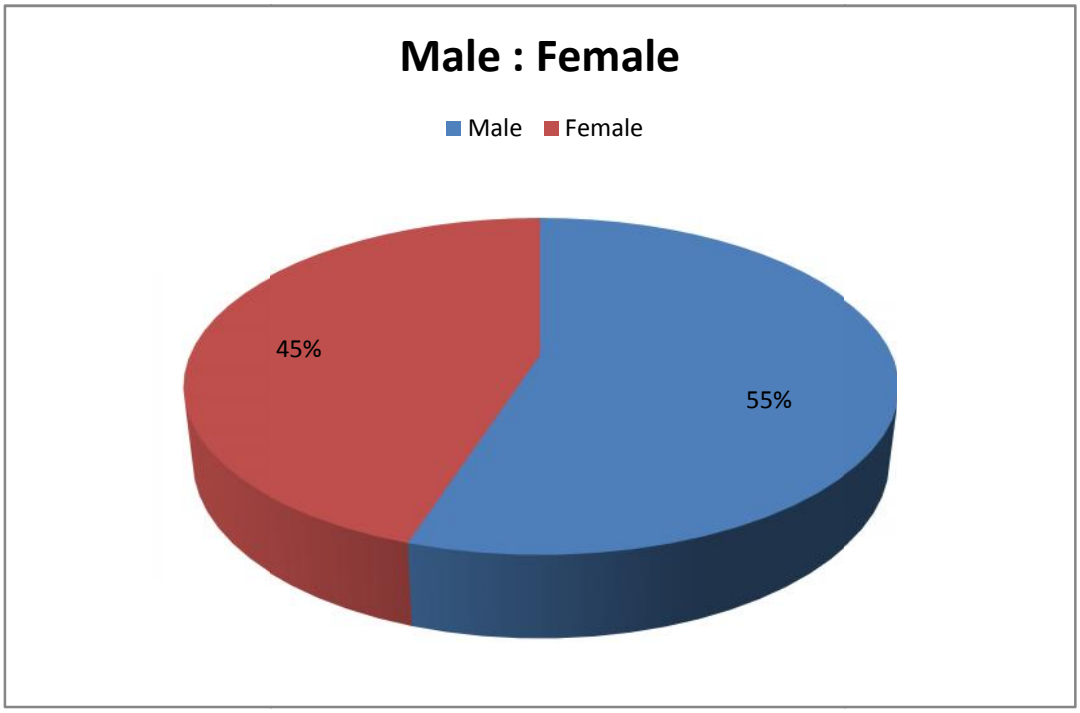
Graph1: Prevalence of insulin resistance



Sex distribution:

Out of 40 patients that were included in the study 22 (55%) were males and 18 (45%) were females.

Graph 2: Sex distribution



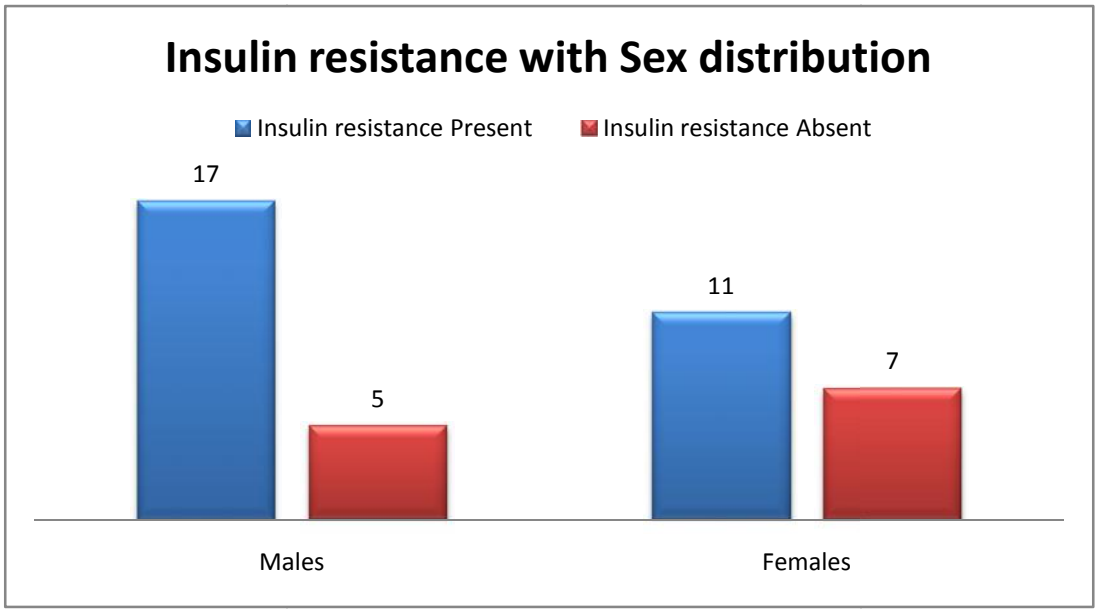
Relation of insulin resistance with sex distribution:

Total number of male patients were 22, insulin resistance was present in 17 (77.27%) of them and absent in 5 (22.73%). Total number of female patients were 18, insulin resistance was present in 11 (61.11%) of them and absent in 7 (38.89%).

Table 11: Relation of insulin resistance with sex distribution

Sex	Insulin resistance present	Insulin resistance absent	Total	
Male	17 (77.27%)	5 (22.73%)	22	x^2= 1.231
Female	11 (61.11%)	7 (38.89%)	18	P = 0.267

Graph 3: Insulin resistance with sex distribution

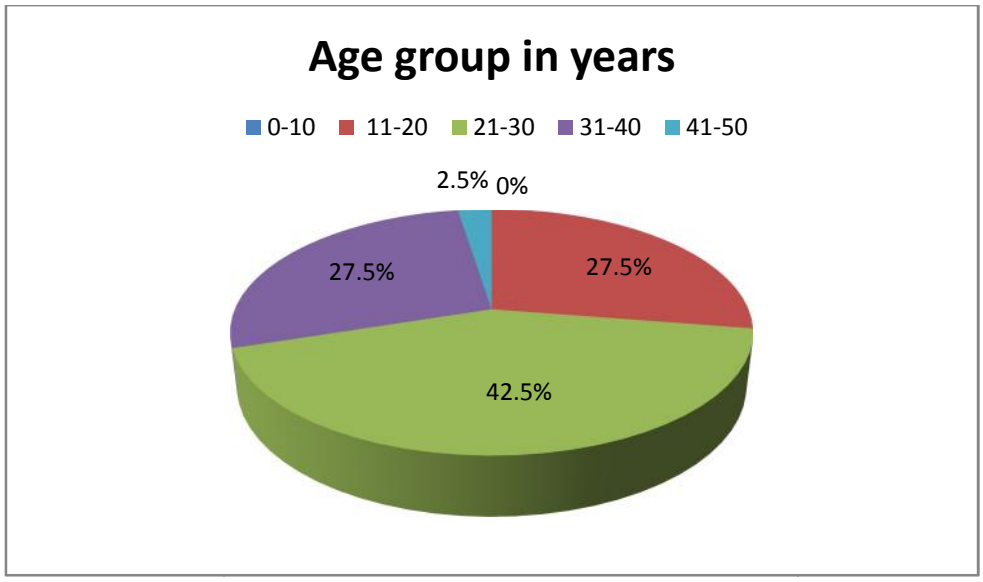


Age distribution: The youngest person in the study was 12 years old whereas the oldest was 41 years old. The average age of all the patients enrolled in the study was 25.6 years.

Table 12: Age distribution

Age in years	Number of patients	Percentage out of total no. of patients
0-10	0	0%
11-20	11	27.5%
21-30	17	42.5%
31-40	11	27.5%
41-50	1	2.5%

Graph 4: Age distribution



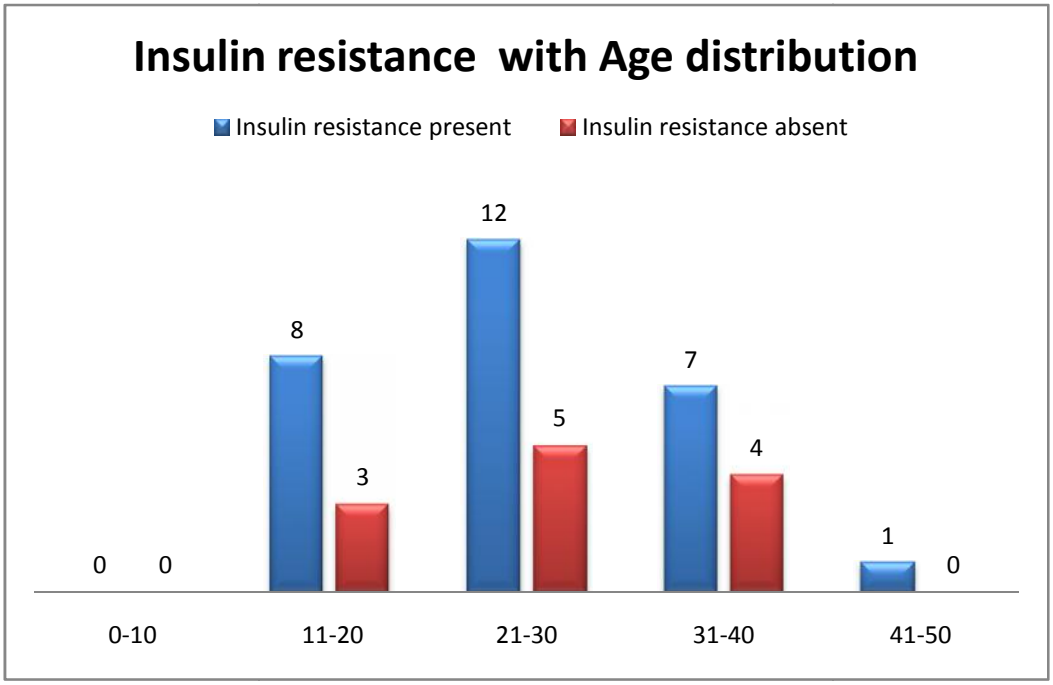
The above data suggests that out of 40 patients of acanthosis nigricans, 17 (42.5%) of patients were between the age group of 21-30 years, 11 (27.5%) in 11 to 20 and 31 to 40 years each and 2.5% in 41 to 50 years. So the maximum number of

patients was in between the age group of 21 to 30 years. Mean age duration± standard deviation was found to be 25.6±7.81. x

Table 13: Relation of insulin resistance with age distribution

Age group	Insulin resistance present	Insulin resistance absent	Total	
0-10	0(0%)	0(0%)	0	
11-20	8(72.73%)	3(27.27%)	11	$x^2 = 0.105$
21-30	12(70.59%)	5(29.41%)	17	DF = 2
31-40	7(63.64%)	4(36.36%)	11	P = 0.949
41-50	1(100%)	0(0%)	1	

Graph 5: Insulin resistance with age distribution



Body mass index (BMI):

BMI of all the 40 patients were calculated. The value 18.5 – 24.9 was considered normal, 25 – 29.9 was considered overweight and that above 30 was considered to be obese.

Total numbers of obese patients were 9 (22.5%), those who were overweight were 19 (45%) and those who were normal were 12 (32.5%).

Graph 6: Body mass index

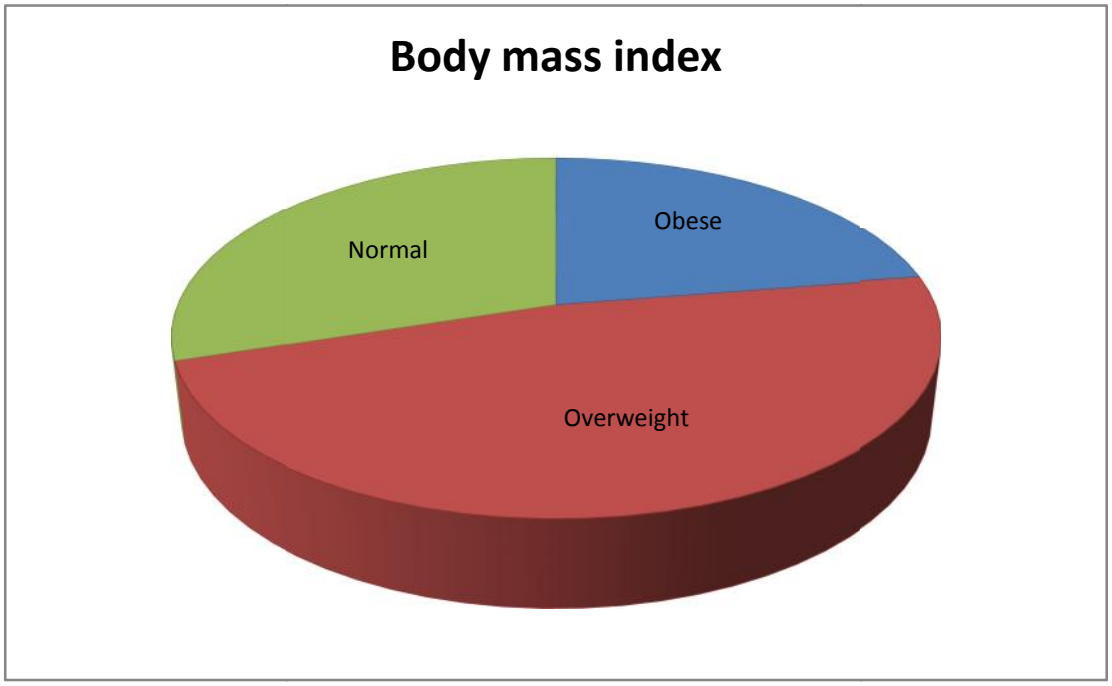
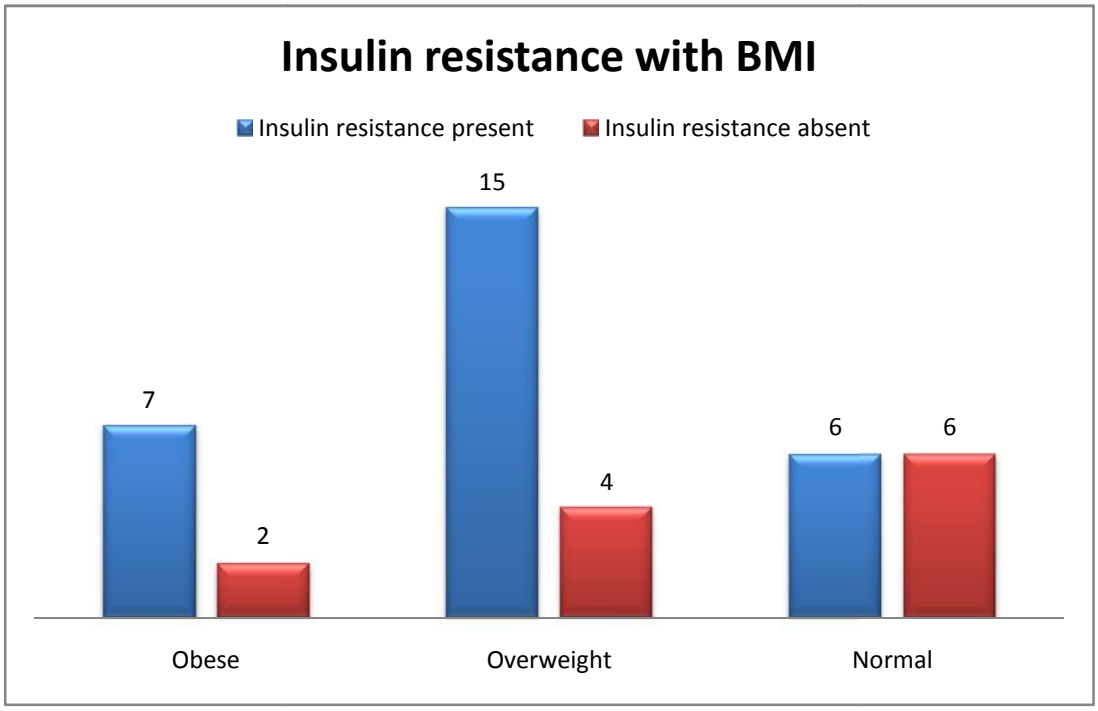


Table 14: Relation of insulin resistance with body mass index

Body mass index	Insulin resistance present	Insulin resistance absent	Total	
Obese	7 (77.78%)	2 (22.22%)	9	x^2= 3.264
Overweight	15 (78.94%)	4 (21.06%)	19	DF= 2
Normal	6 (50%)	6 (50%)	12	P = 0.195

Graph 7: Insulin resistance with BMI



Family history

All 40 patients in the study were asked for family history of acanthosis nigricans.

Total number of patients with positive family history of acanthosis nigricans were 15 that is 37.5% and those with negative family history of acanthosis nigricans were 25 that is 62.5%.

Graph 8: Family history

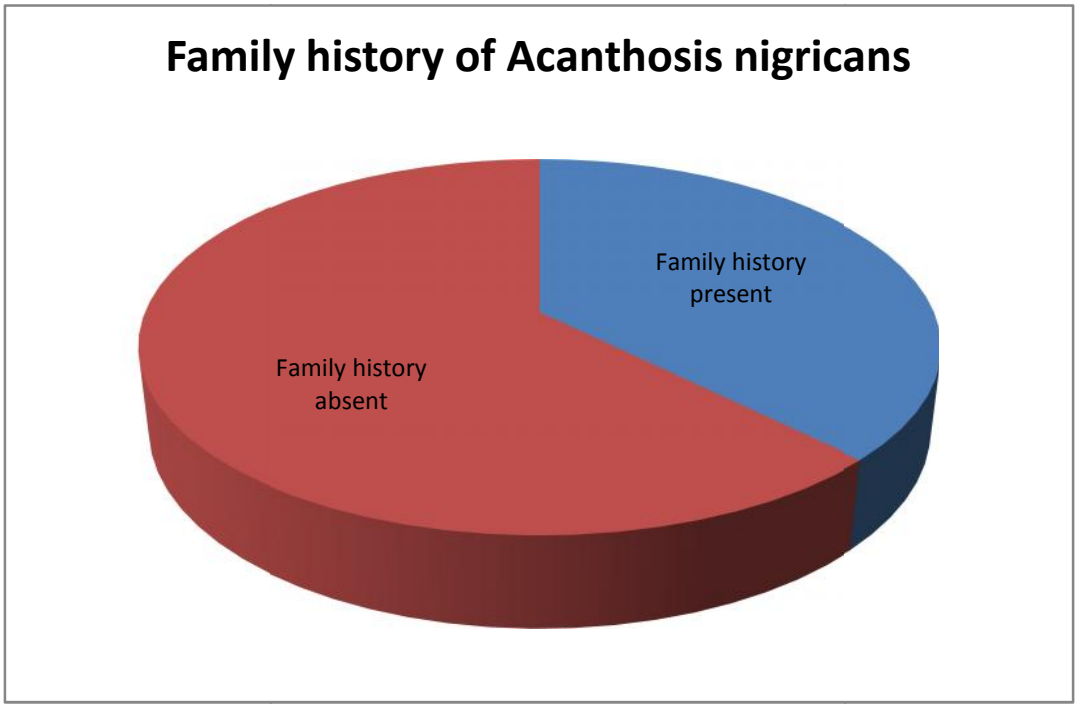
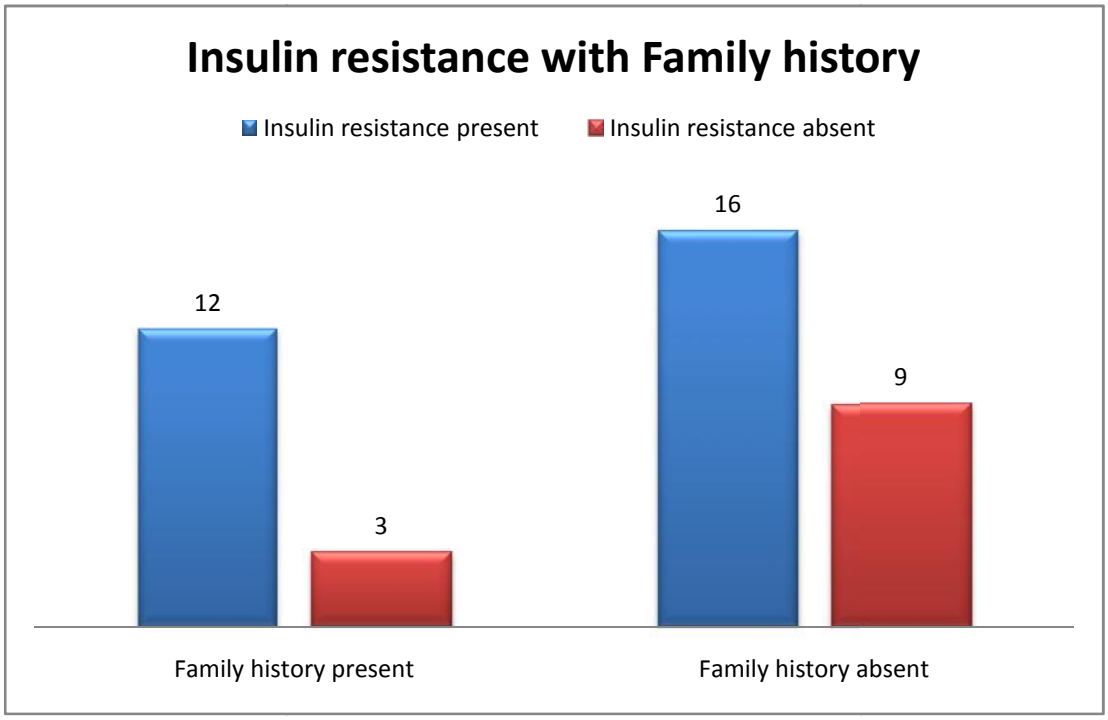


Table15: Relation of Insulin resistance with family history of Acanthosis nigricans

Family history of Acanthosis nigricans	Insulin resistance present	Insulin resistance absent	Total	
Present	12 (80%)	3 (20%)	15	x^2= 0.508 P = 0.476
Absent	16 (64%)	9 (36%)	25	

Graph 9: Insulin resistance with family history



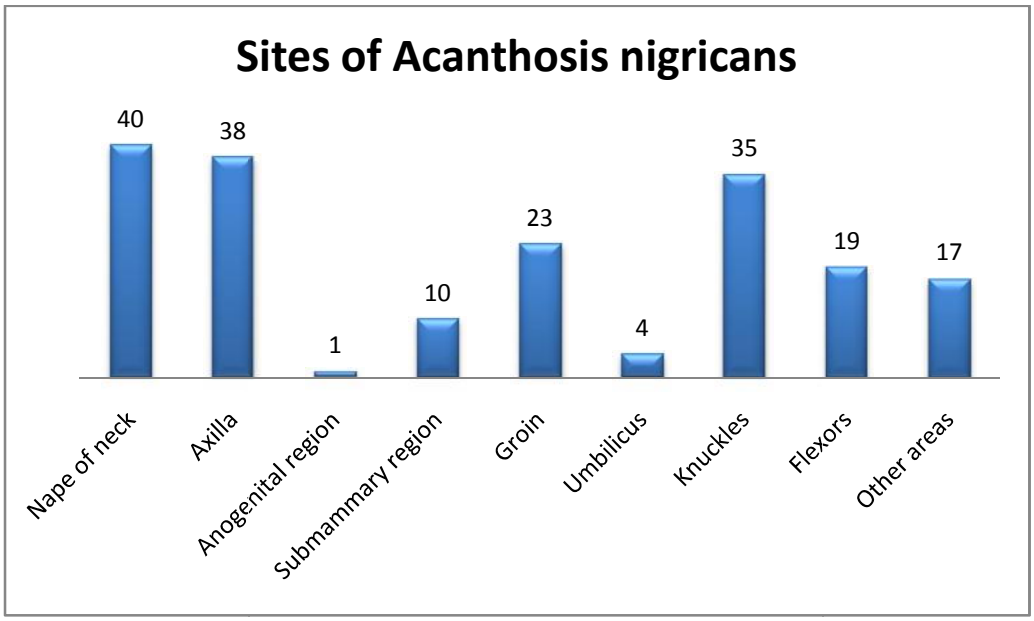
Sites of Acanthosis nigricans

The sites that were examined were nape of neck, axilla, anogenital region, submammary region, groin, umbilicus, knuckles, flexors and other areas like flanks, perioral and periorbital region. The most commonest site involved in all patients in the study was nape of neck.

Table 16: Sites of acanthosis nigricans

Sites of acanthosis nigricans	Number of patients having AN at these sites	Percentage out of 40 patients
Nape of neck	40	100%
Axilla	38	95%
Anogenital region	1	2.5%
Submammary region	10	25%
Groin	23	57.5%
Umbilicus	4	10%
Knuckles	35	87.5%
Flexors	19	47.5%
Other areas	17	42.5%

Graph 10: Sites of acanthosis nigricans



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. Present study was done only on non diabetics who have acanthosis nigricans to know the association with insulin resistance. It is a cross sectional study in which a total number of 40 patients were studied. Very few studies have been carried out on this subject. Here we have compared the present study with a few related studies.

Table 17: Comparision of sample size of various studies

Studies	**Sample size**
Present study	40
PK Varthakavi et al[67]	36
Neerja Puri[68]	30

Larger the sample size, more is the significance of the study. However due to time restriction only 40 patients were examined.

Sex distribution

In the present study there were 22 males and 18 females which is 55% and 45% respectively. This shows there is not much difference in the prevalence of the disease in either sex. In a study conducted by PK Varthakavi et al[67] there were more females than males, possibly because it can be cosmetically more unappealing and upsetting for females. But in the study conducted by Neerja Puri[68] there was no difference.

Table 18: Comparison of sex distribution in various studies

Study	Male	Female
Present study	22	18
PK Varthakavi et al[67]	8	28
Neerja Puri[68]	12	18

Age distribution

More number of patients have been observed between the age group of 20 to 30 years as they have comparatively higher cosmetic consciousness than the other age groups. In the present study 17 patients were in the age group of 21 to 30 years. There is clustering of patients in between the age group 11 to 40 years in all studies.

Table 19: Comparison of age distribution in various studies

Age in years	Present study	PK Varthakavi et al[67]	Neerja Puri[68]
0-10	0 (0%)	1(2.8%)	3(10%)
11-20	11 (27.5%)	10(27.8%)	10(33.3%)
21-30	17 (42.5%)	9(25%)	9(30%)
31-40	11 (27.5%)	13(36.1%)	5(16.6%)
41-50	1 (2.5%)	3(8.3%)	3(10%)
Total	40	36	30

Insulin resistance

Valeria Hirschler et al[69] has conducted a study on 74 obese children with and without acanthosis nigricans, there were greater fasting insulin levels and HOMA-IR in the group with AN, the difference between both groups was not statistically significant. Sixty-six obese women (32 patients with acanthosis nigricans and 34 patients without acanthosis nigricans) were selected randomly in a study conducted by Sadeghian G et al[70] where five (15.6%) patients with acanthosis nigricans and no (0%) patient without acanthosis nigricans had insulin resistance ($P < 0.05$). In present study where only patients with acanthosis nigricans were studied insulin resistance was present in 28 patients (70%) and absent in 12 (30%). It can be interpreted that insulin resistance was present in most of the cases with acanthosis nigricans indicating that it is important to screen these patients to avoid further complications.

Body mass index

In present study total numbers of obese patients were 9 (22.5%), those who were overweight were 19 (45%). Obese and overweight patients together were 67.5% which is comparable with the other two studies (PK Varthakavi et al[67] – 69.4%; Neerja Puri[68] – 66.6%). In present study 77.78% of obese patients had insulin resistance, 78.94% of overweight patients had insulin resistance and 50% of normal patients had insulin resistance. Though the prevalence was more in obese and overweight patients compared to normal patients, the values were not statistically significant ($p= 0.195$)

Table 20: comparision of Sites of acanthosis nigricans in various studies

Sites of acanthosis nigricans	Number of patients having AN at these sites		
	Present study	**PK Varthakavi et al[67]**	**Neerja Puri[68]**
Nape of neck	40 (100%)	100%	28 (93.3%)
Axilla	38 (95%)	80.6%	20 (66.6%)
Anogenital region	1 (2.5%)		1 (3.3%)
Submammary region	10 (25%)	10.3%	
Groin	23 (57.5%)	61.1%	12 (40%)
Umbilicus	4 (10%)		
Knuckles	35 (87.5%)		2 (6.6%)
Flexors	19 (47.5%)		
Other areas	17 (42.5%)		

In almost all studies nape of the neck was found to be the highly affected area. In present study all patients had acanthosis nigricans on nape of the neck (100%) which is comparable to the other two studies (PK Varthakavi et al[67] 100% and Neerja Puri[68] 93.3 %). The next commonest site was found to be axilla 95% in present study, 80.6% in PK Varthakavi et al[67] and 66.6% Neerja Puri[68] study.

Family history

In present study total number of patients with positive family history of acanthosis nigricans were 15 in them 12 (80%) had insulin resistance and 3 (20%) had no insulin resistance. Total number of patients with negative family history of acanthosis nigricans were 25 in them 16 (64%) had insulin resistance and 9 (36%) had no insulin resistance. The prevalence was more in those who had a positive family when compared to negative family history.

CONCLUSION

This study showed that among 40 patients with acanthosis nigricans insulin resistance was present in 28 (70%) patients and absent in 12 (30%) patient. Out of 40 patients 22 (55%) were males and 18 (45%) were females showing no significant difference in the sex distribution.

Maximum number of patients (42.5%) were in the age group of 21 to 30 years. Prevalence of insulin resistance was more in the age group of 11 to 20 years (72.73%).

Total numbers of obese patients were 9 (22.5%) and those who were overweight were 19 (45%). These obese and overweight patients together were 28 amongst them 22 patients had insulin resistance making it 78.5 % of patients. It shows insulin resistance is more prevalent in obese and overweight patients.

Total number of patients with positive family history of acanthosis nigricans were 15 amongst them 12 (80%) had insulin resistance and 3 (20%) had no insulin resistance.

All patients (100%) had acanthosis nigricans over neck and 95% had in axilla, other sites were knuckles, groins, flexors, submammary region, umbilicus and anogenital region in their order of predilection. Rare sites involved were perioral, periorbital, temple region and flanks.

None of our patients had any other associated illnesses.

Thus, based on the above findings of high prevalence of insulin resistance in patients with acanthosis nigricans and obesity, screening of patients with acanthosis

nigricans for insulin levels becomes relevant and necessary, so as to advice them regarding the life style modification like correction in diet and weight reduction to prevent occurrence of diabetes mellitus.

Perhaps, studies on a larger number of acanthosis nigricans patients with control group from general population who can be followed up for a considerable time, would further strengthen these associations and also bring forth if any other specific clinical parameters of acanthosis nigricans could raise suspicion for the association of insulin resistance.

SUMMARY

- This was a cross-sectional study was carried out from January 2013 to December 2013.
- The source of data were acanthosis nigricans patients attending the Dermatology OPD, at KLES Dr. Prabhakar Kore Hospital and MRC, Belgaum.
- The objectives of the study were evaluation of the association between Acanthosis Nigricans and Insulin Resistance and the relation of Acanthosis Nigricans with obesity.
- The proportion of females (45%) and males (55%) were almost same.
- The youngest person in the study was 12 years old whereas the oldest was 41 years old. The average age of all the patients enrolled in the study was 25.6 years.
- Prevalence of acanthosis nigricans was more in age group between 21 to 30 years.
- Prevalence of insulin resistance was seen more in the age group of 11 to 20 years.
- In the present study obese patients were 22.5% and those who were overweight were 45%. 77.78% of obese patients had insulin resistance, 78.94% of overweight patients had insulin resistance and 50% of normal patients had insulin resistance. Though the prevalence was more in obese and overweight patients compared to normal patients, the values were not statistically significant

- 80% of patients with positive family history of acanthosis nigricans had insulin resistance and 64% with negative family history of acanthosis nigricans had insulin resistance. The values were not statistically significant.
- All patients (100%) had acanthosis nigricans on the neck, next commonest site being axilla (95%). The unusual sites involved were perioral, periorbital and flank regions.

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ANNEXURE I

INFORMED CONSENT FORM

I.D.NO.

A One year cross sectional study of evaluation of association between acanthosis nigricans and insulin resistance

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:

The purpose of this study is to find out the association of acanthosis nigricans and insulin resistance. You are being asked to participate in this research because you have been diagnosed to have acanthosis nigricans. All patients attending the outpatient department, who are diagnosed to have this disease, will be requested to participate in this study during the period of one year.

Procedure and treatment:

Should you choose to participate, you will be asked to give a detailed history of your disease, undergo a physical examination, and consent to a few routine investigations.

Risks and benefits:

You may undergo some amount of discomfort during the process of investigations, which may include slight pain. However all necessary steps and precautions will be taken to ensure your safety. The result of you taking part in this research would help health care providers towards a better understanding 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. In the event if you suffer any physical injury as the result of your participation in this study, you should contact KLE'S Dr. Prabhakar Kore Hospital and MRC on Telephone No. 08312473777.

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.

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:

If the participants are Minors (under 18), the parents sign the form, rather than the participants.

ANNEXURE II

PROFORMA

Study: A One year cross sectional study of evaluation of association between Acanthosis nigricans and Insulin resistance.

Case No:____ **OP No._____**

Name:

Age:

Sex:

Occupation:

Address with phone no. :

Chief complaints:

History of present illness:

Duration of onset:- _____

Mode of onset:

1. Sudden ☐
2. Gradual ☐

Precipitating factors if any:

1. PCOS ☐
2. Hypothyroidsm ☐
3. Hyperthyroidsm ☐
4. Cushing's disease ☐

Site of onset:

1. Nape of neck
   - Present ☐
   - Absent ☐
2. Axilla
   - Present ☐
   - Absent ☐
3. Anogenital region
   - Present ☐
   - Absent ☐
4. Submammary region
   - Present ☐
   - Absent ☐
5. Groin
   - Present ☐
   - Absent ☐
6. Umbilicus
   - Present ☐
   - Absent ☐
7. Knuckles
   - Present ☐
   - Absent ☐
8. Flexors
   - Present ☐
   - Absent ☐
9. Other site _____

Any associated factors:

1.Itching ☐
2.Pain ☐
3.Burning ☐
4.Asymptomatic ☐

Systemic complaints:

1.Fatigue ☐
2.Loss of concentration ☐
3.Gain of weight ☐
4.Sleepiness ☐
5.Depression ☐
6.Increased hunger ☐

Past history:

1.History suggestive of Diabetes Mellitus

Present ☐
Absent ☐
If present duration _____

2.) History suggestive of Hypertension:

Present ☐
Absent ☐
If present duration _____

3.) History suggestive of Thyroid Disorders:

Present ☐
Absent ☐
If present duration _____

4.) History suggestive of Cushing's Disease

Present ☐
Absent ☐
If present duration _____

5.) History suggestive of PCOS

Present ☐
Absent ☐
If present duration _____

6.) History of any other Medical Disorders:

Present ☐
Absent ☐
If present _____

Family History:

History of Similar complaints:

Present
Absent

Personal History:

Diet: Vegetarian ☐
Mixed ☐
Appetite: Normal ☐
Poor ☐
Increased ☐
Sleep : Normal ☐
Reduced ☐
Increased ☐

Addictions/Habits (if any)_____

General Physical Examination:

Vitals: Pulse:_____/min

BP :_____mmHg

Temp:_____ºF

Height (m):_____

Weight(kgs):_____

BMI : _____ (weight in kgs)÷ (height in meter)^2

Signs :

- Pallor ☐
- Icterus ☐
- Cyanosis ☐
- Clubbing ☐
- Lymphadenopathy ☐
- Oedema ☐

Mucocutaneous Examination:

Types Of Lesion:

- Patch: ☐
- Plaque: ☐

Associated Features:

- Dryness ☐
- Roughness ☐
- Velvety Texture ☐
- Scaling ☐

Mucosal Examination:

Genital Mucosa

Oral Mucosa

Hair Changes :

Nail Changes:

Systemic Examination:

CVS:_____

RS:_____

Per Abdomen:_____

CNS:_____

Investigations:

Fasting plasma glucose: _____mg/dl

Fasting Serum Insulin: _____µIU/ml

Insulin Resistance = "Fasting Serum Insulin µIU/ml × Fasting plasma glucose mg/dl"

405

= _____

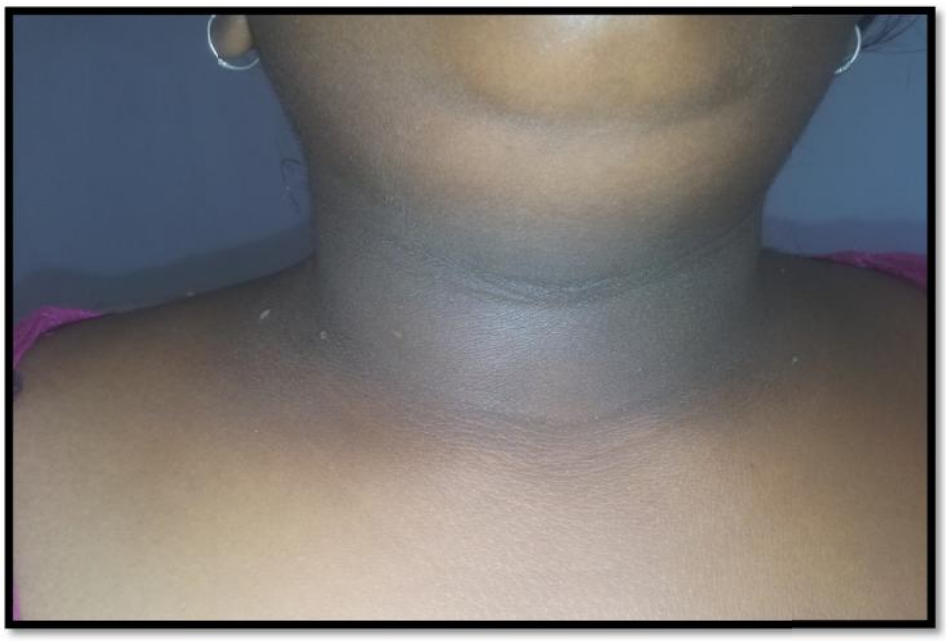
Diagnosis: _____

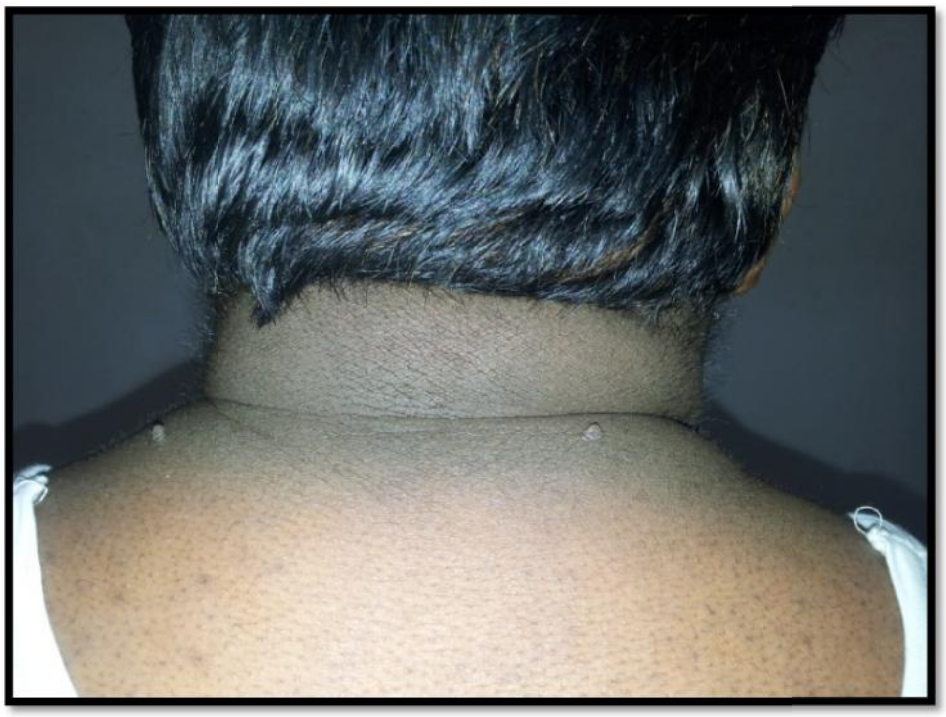
Candidate's Signature: _____

Guide's Signature:_____

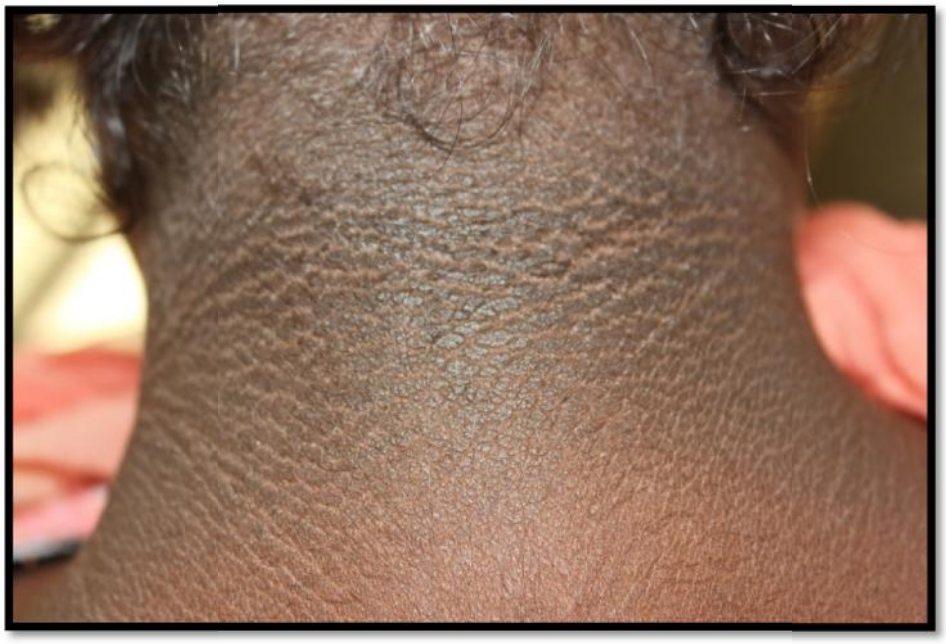
ANNEXURE III

PHOTOGRAPHS

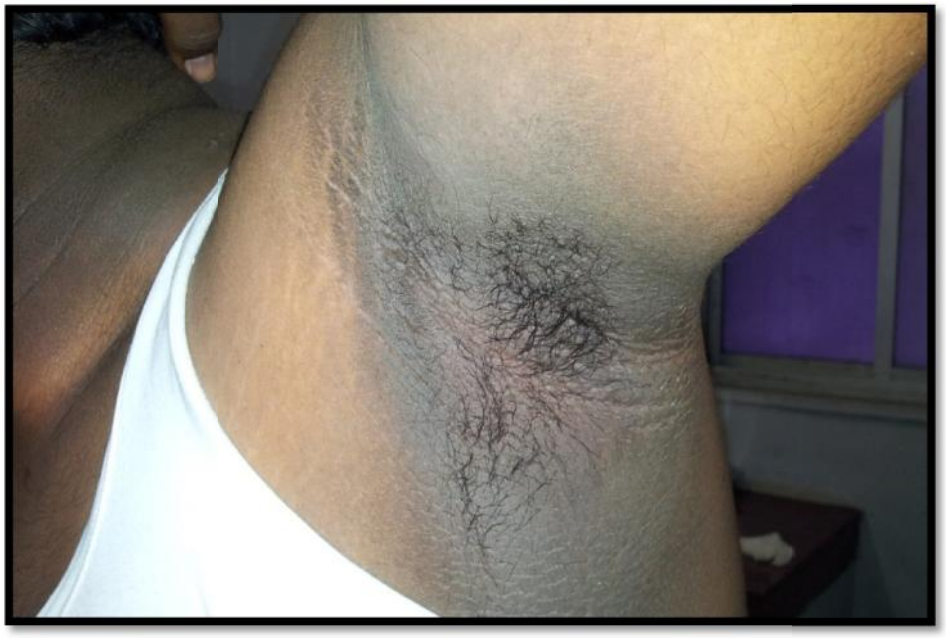


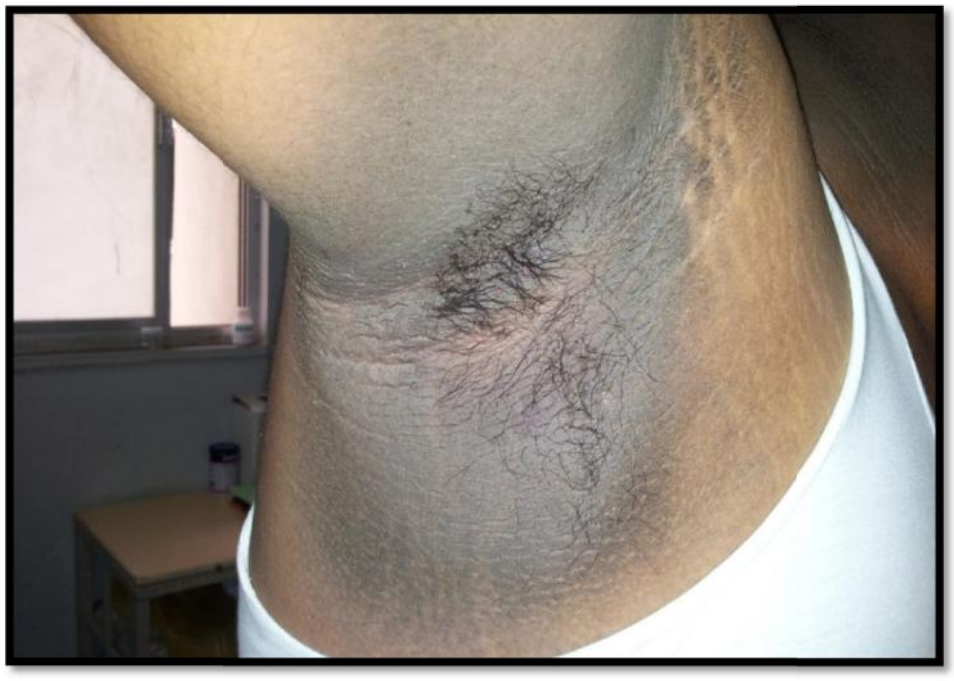


Photographs 1 & 2: Acanthosis nigricans on neck

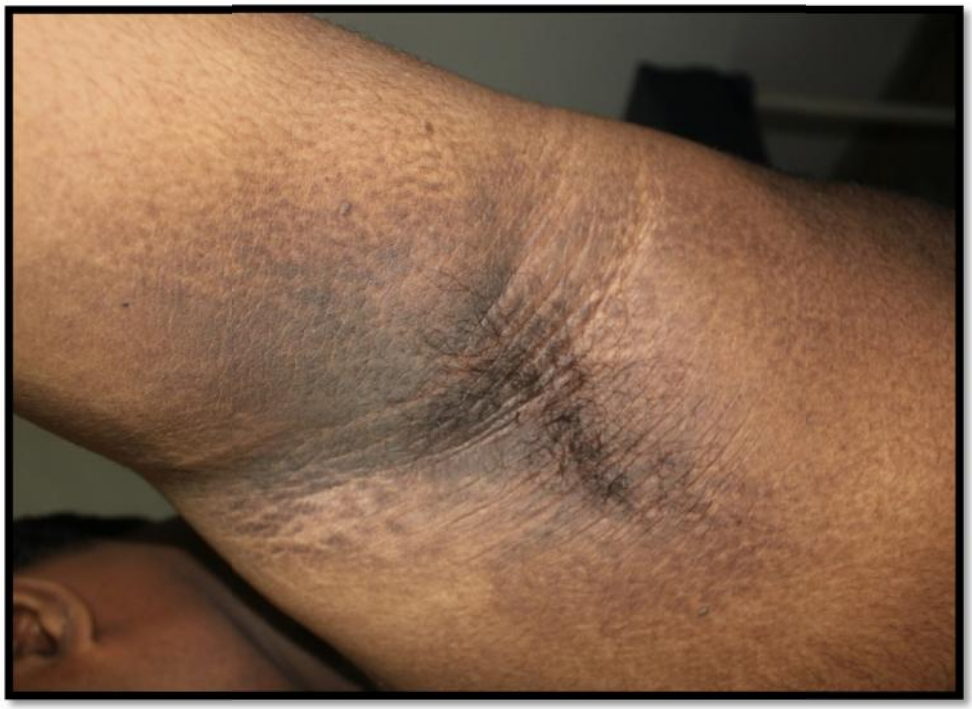


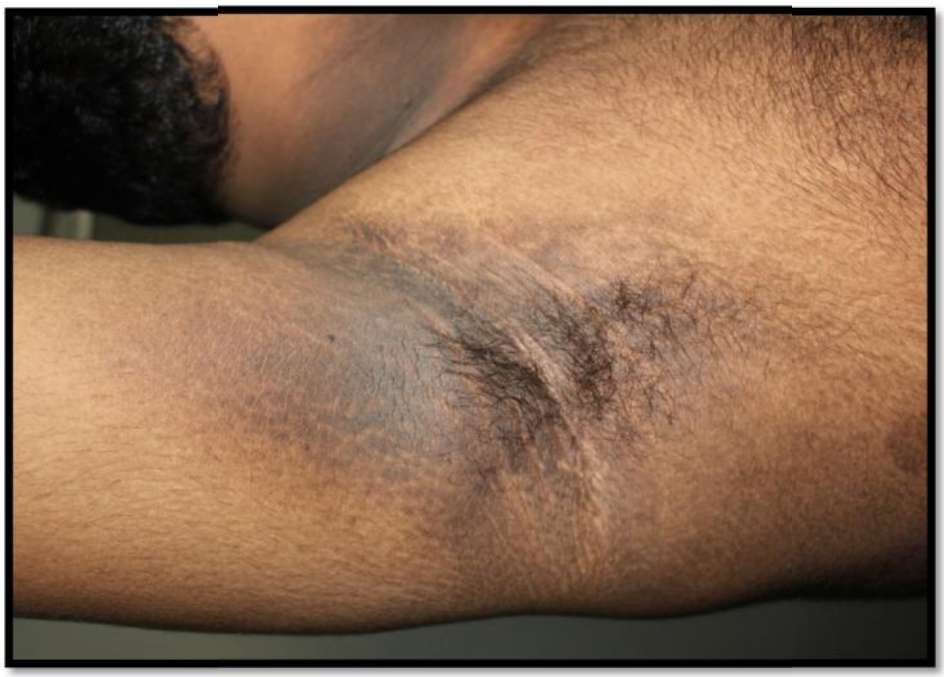
Photographs3: Typical hyperpigmented velvety appearance



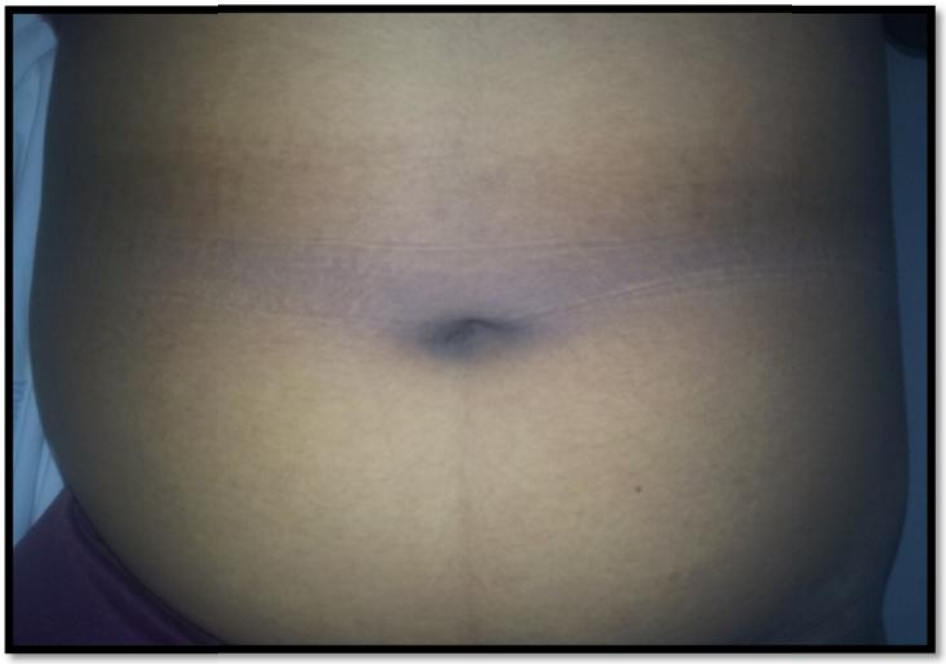


Photographs 4& 5: Acanthosis nigricans in the axilla

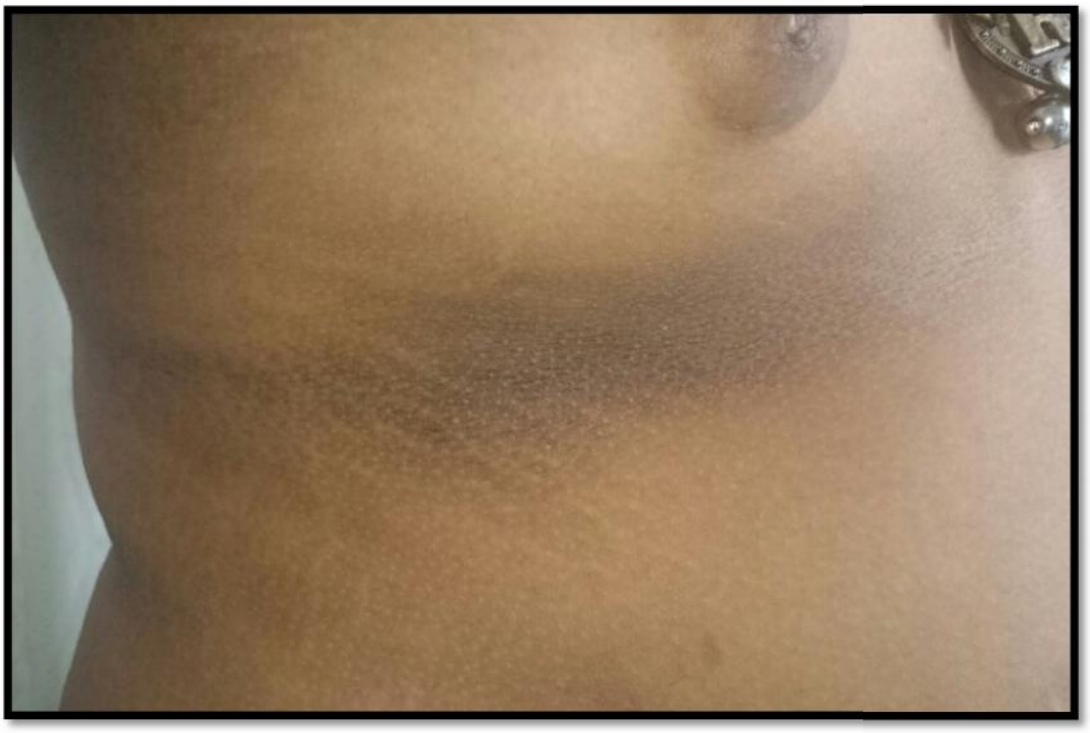




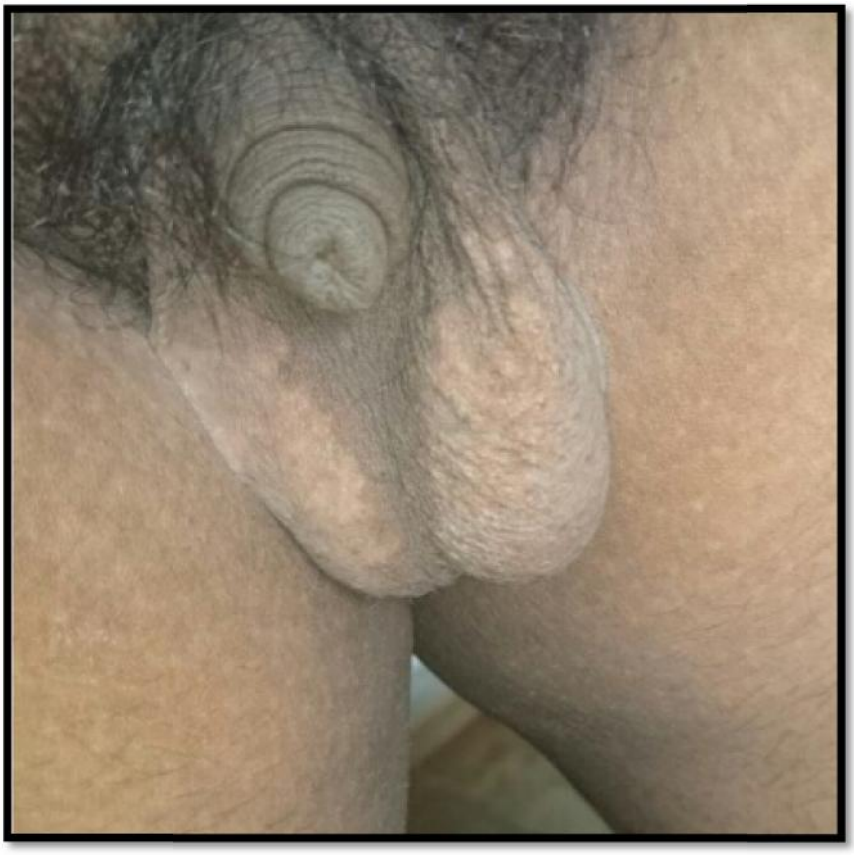
Photographs 6 & 7: Acanthosis nigricans in the axilla



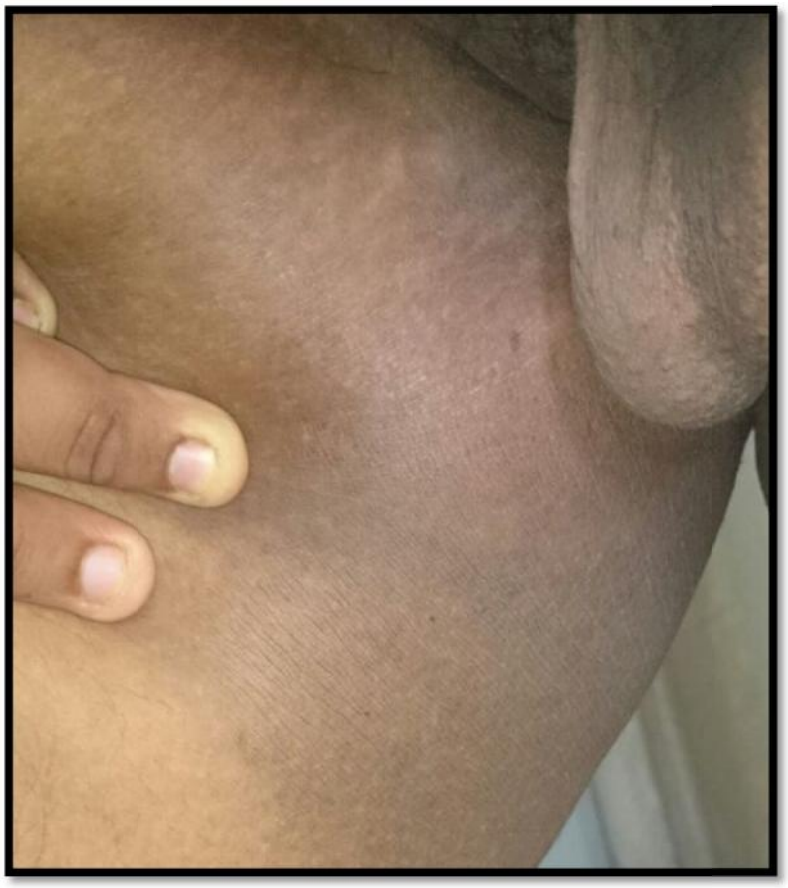
Photographs 8: Acanthosis nigricans over umbilical region



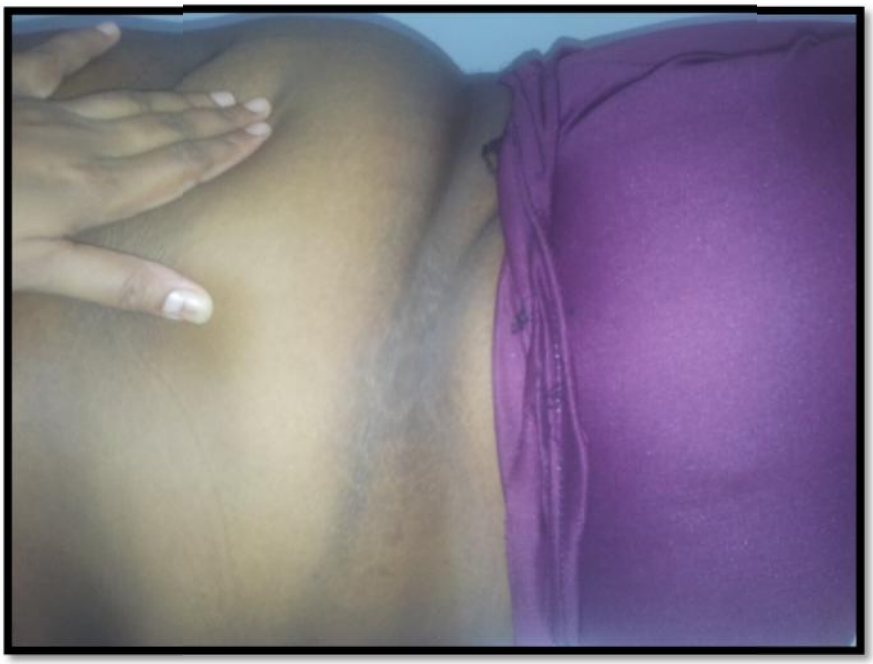
Photographs 9: Acanthosis nigricans over inframammary region



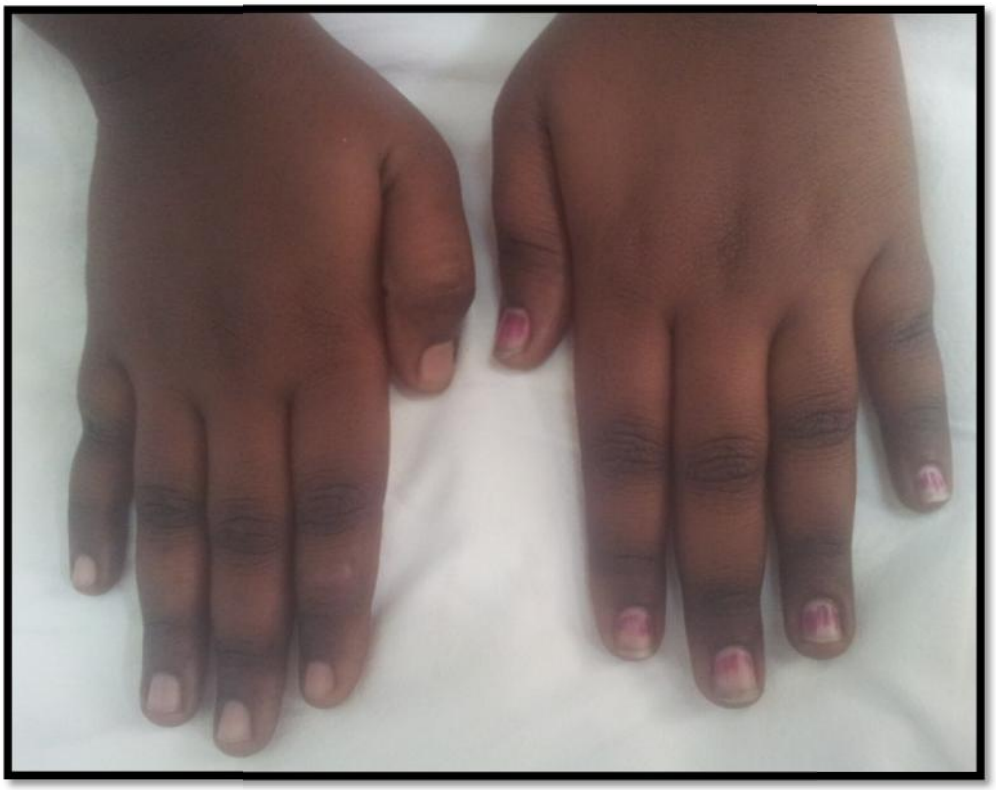
Photographs 10 & 11: Acanthosis nigricans over genitalia



Photographs 12: Acanthosis nigricans over inner thighs



Photographs 13: Acanthosis nigricans over the flanks



Photographs 14: Acanthosis nigricans over the knuckles

ANNEXURE - IV

KEY TO MASTER CHART

SL No. - Serial number

OPD No. – Out patient department number

Sex –

M – Male

F – Female

Occupation –

H – House wife

S – Student

O – Others

Mode of onset

G – Gdual

Su – Sudden

PCOS – Poly cystic ovarian syndrome

Inference of BMI

Nr – Normal

Ow – Over weight

Ob – Obese

Rest

A – Absent

P – Present

Sl. No	OPD No.	Age	Sex	Occupation	Mode of Onset	SITES FOR ACANTHOSIS NIGRICANS									MEDICAL ILLNESS						Family History	ANTHROPOMETRY				INVESTIGATIONS			
						Nape of neck	Axilla	Anogenital region	Submammary region	Groin	Umblicus	Knuckles	Flexors	Others	Diabetes Mellitus	Hypertension	Thyroid disorders	Cushing's Disease	PCOS	Others		Height In (mts)	Weight in (kgs)	Basal metabolic Index(BMI)	Inference of BMI	Fasting Glucose Level (mg/ dl)	Fasting serum insulin level (mcU/	Insulin resistance (IR)	Inference of IR
1	2037505	12	F	S	G	P	P	A	A	A	A	P	P	P	A	A	A	A	A	A	A	1.58	48	19.27	Nr	84	7.19	1.49	A
2	2307501	20	M	O	G	P	P	A	A	P	A	P	P	P	A	A	A	A	A	A	A	1.73	110	36.78	Ob	87	10.6	2.27	A
3	2369701	36	F	H	G	P	P	A	A	P	A	P	A	P	A	A	A	A	A	A	P	1.61	63	24.3	Nr	81	2	0.4	A
4	2455121	38	M	O	G	P	P	A	A	A	A	P	A	A	A	A	A	A	A	A	A	1.7	91	31.48	Ob	105	23.6	6.12	P
5	2368578	38	F	H	G	P	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	1.67	69	24.82	Nr	89	3.86	0.848	A
6	644826	34	M	O	G	P	P	A	A	A	A	P	A	A	A	A	A	A	A	A	A	1.67	80	28.77	Ow	104	16.4	4.211	P
7	932652	21	M	S	G	P	P	A	A	A	A	A	A	A	A	A	A	A	A	A	A	1.76	74	23.94	Nr	90	8.05	1.788	A
8	2497635	19	F	H	G	P	P	A	P	P	A	A	A	P	A	A	A	A	A	A	A	1.64	65	24.25	Nr	82	24.1	4.879	P
9	2472576	32	M	O	G	P	P	A	A	P	A	P	A	A	A	A	A	A	A	A	A	1.68	78	27.65	Ow	73	11.1	2	A
10	2385671	36	M	O	G	P	P	A	A	P	A	P	P	P	A	A	A	A	A	P	A	1.71	85	29.1	Ow	88	11.7	2.542	P
11	2510659	24	M	O	G	P	P	A	A	A	A	P	P	P	A	A	A	A	A	A	A	1.76	102	33	Ob	81	25.8	5.16	P
12	2550876	22	M	S	G	P	P	A	A	A	A	P	A	A	A	A	A	A	A	A	A	1.67	83	29.85	Ow	85	14.2	2.98	P
13	2559875	28	M	O	G	P	P	A	A	P	A	P	P	A	A	A	A	A	A	A	A	1.7	78	26.98	Ow	84	8.29	1.719	A
14	2599160	23	M	S	G	P	P	A	A	P	A	P	A	A	A	A	A	A	A	A	P	1.73	85	28.42	Ow	94	15.3	3.55	P
15	2595180	26	F	S	G	P	P	A	P	A	A	P	A	P	A	A	A	A	A	A	A	1.52	53	22.94	Nr	85	28.42	5.96	P
16	2614351	25	F	S	G	P	P	A	A	A	A	P	P	A	A	A	A	A	A	A	A	1.58	70	27.88	Ow	95	11.2	2.6	P
17	2697879	14	F	S	G	P	P	A	A	A	A	P	P	P	A	A	A	A	A	A	P	1.55	62	25.72	Ow	97	26.1	6.25	P
18	2343510	13	F	S	G	P	P	A	A	A	A	P	A	A	A	A	A	A	A	A	A	1.615	63	24.15	Nr	88	5.22	1.134	A
19	2735843	35	F	H	G	P	P	A	P	P	A	P	P	A	A	A	A	A	A	A	A	1.55	68	28.16	Ow	86	28.8	6.11	P
20	2734320	24	M	O	G	P	P	A	A	P	A	P	A	A	A	A	A	A	A	A	A	1.706	78	26.8	Ow	83	6.61	1.354	A
21	2693090	27	F	H	G	P	P	A	P	P	A	A	A	P	A	A	A	A	A	A	P	1.58	62	24.7	Ow	82	9.37	1.89	A
22	2760163	13	F	S	G	P	P	A	P	P	P	P	P	P	A	A	A	A	A	A	P	1.49	65	29.27	Ow	105	57.8	14.9	P
23	2759499	21	M	S	G	P	P	A	A	A	A	P	A	A	A	A	A	A	A	A	A	1.52	70	30.17	Ob	76	19.3	3.62	P
24	2763545	38	M	O	G	P	P	A	A	A	A	P	P	A	A	A	A	A	A	A	A	1.706	96	32.98	Ob	103	78.6	19.99	P
25	2765115	15	M	S	G	P	P	A	A	A	A	A	A	A	A	A	A	A	A	A	P	1.7	83	28.52	Ow	104	26.8	6.88	P
26	2788259	23	F	S	G	P	P	A	A	A	P	P	A	A	A	A	A	A	A	A	P	1.645	60	22.38	Nr	108	4.9	1.306	A
27	2423837	32	M	O	G	P	A	A	A	P	A	A	A	P	A	A	A	A	A	A	A	1.61	72	27.79	Ow	132	8.17	2.66	P
28	2613406	41	M	O	G	P	P	A	A	A	A	P	A	A	A	A	A	A	A	A	A	1.7	75	25.95	Ow	99	11.9	2.9	P

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						Nape of neck	Axilla	Anogenital region	Submammary region	Groin	Umblicus	Knuckles	Flexors	Others	Diabetes Mellitus	Hypertension	Thyroid disorders	Cushing's Disease	PCOS	Others		Height in (mts)	Weight in (kgs)	Basal metabolic Index(BMI)	Inference of BMI	Fasting Glucose Level (mg/ dl)	Fasting serum insulin level (mcU/	Insulin resistance (IR)	Inference of IR
29	2748827	22	F	S	G	P	P	A	A	A	A	P	P	P	A	A	A	A	A	A	P	1.55	48.8	20.21	Nr	96	21.16	5.01	P
30	2851975	18	F	S	G	P	P	A	A	P	A	P	A	A	A	A	A	A	A	A	P	1.58	53	21.28	Nr	91	34.9	7.84	P
31	2548960	32	F	O	G	P	P	A	A	P	A	P	P	P	A	A	A	A	A	A	A	1.6	78	30.46	Ob	83	5.4	1.1	A
32	2875230	23	F	S	G	P	P	A	A	P	A	P	P	A	A	A	A	A	A	A	P	1.63	62	23.39	Nr	90	20.11	4.47	P
33	2808802	19	F	S	G	P	P	A	P	P	A	P	A	A	A	A	A	A	A	A	P	1.63	54	20.37	Nr	86	19.49	4.138	P
34	2905968	31	M	O	G	P	P	A	P	P	A	P	P	P	A	A	A	A	A	A	A	1.62	96	36.92	Ob	103	30.39	7.728	P
35	2905229	30	M	O	G	P	P	A	A	P	A	P	P	A	A	A	A	A	A	A	A	1.69	96	33.61	Ob	92	24	5.45	P
36	2767266	24	M	S	G	P	P	A	A	P	A	P	A	A	A	A	A	A	A	A	A	1.7	75	25.95	Ow	99	30.21	7.38	P
37	2434999	30	F	H	G	P	P	A	P	P	P	P	P	P	A	A	A	A	A	A	P	1.63	78	29.43	Ow	94	32.9	7.63	P
38	2038632	27	M	O	G	P	P	A	A	P	A	P	P	P	A	A	A	A	A	A	P	1.7	75	25.9	Ow	85	52	10.19	P
39	2365872	19	M	S	G	P	P	P	P	P	A	P	P	A	A	A	A	A	A	A	P	1.58	101	40.26	Ob	89	36.4	7.99	P
40	2970560	19	M	S	G	P	P	A	P	P	P	P	P	P	A	A	A	A	A	A	P	1.67	80	28.77	Ow	105	56.57	14.66	P