"Clinical and Dermoscopic Evaluation to study the Effectiveness of Metformin vs Pioglitazone in Acanthosis Nigricans – A Randomized Control Trial"

BY

REGISTRATION NO: BT0121001

Dissertation

Submitted to
KAHER, Belagavi, Karnataka,
In partial fulfilment of the requirements for the degree of

M.D.

IN

DERMATOLOGY, VENEREOLOGY AND LEPROSY

JAWAHARLAL NEHRU MEDICAL COLLEGE,
KAHER, BELAGAVI – 590010
KARNATAKA.

DECEMBER 2024

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ABBREVIATION LIST

Sr. no	Abbreviation	Full form
1.	AN	Acanthosis Nigricans
2.	IGF-1	Insulin like growth factor 1
3.	FGFR3	Fibroblast growth factor receptor 3
4.	IR	Insulin resistance
5.	PCOS	Polycystic ovary syndrome
6.	HAIR-AN	Hyperandrogenemia, insulin resistance, and AN
7.	SLE	Systemic lupus erythematosus
8.	IRS	Insulin receptor substrate-1
9.	EGFR	Epidermal growth factor receptor
10.	FGFR	Fibroblast growth factor receptor
11.	EGF	Epidermal growth factor
12.	IGR BP-1, BP-2	IGF binding proteins 1,2
13	HIV	Human immunodeficiency virus
14.	Si	Insulin sensitivity
15.	BMI	Body mass index
16.	HOMA-IR	Homeostasis Model Assessment-Insulin Resistance
17.	QUICKI	Quantitative Insulin Sensitivity Check Index
18.	hs-CRP	Highly soluble C- reactive protien
19.	TNF-alpha	Tumour necrosis factor - alpha
20.	DHEAS	Dehydroepiandrosterone-sulfate
21.	LH	Luteinizing hormone
22.	FSH	Follicle stimulating hormone
23.	CBC	Complete blood count
24.	ANA	Antinuclear antibody

25.	GA	Glycolic acid
26.	TCA	Trichloroacetic acid
27.	CO_2	Carbon dioxide
28.	PUVA	Psoralen Ultra Violet A
29.	OCT	Organic cation transporter
30.	GLUT	Glucose transporter type
31.	Cbl	Casitas B-lineage lymphoma protein
32.	CAP	Cbl adapter protein
33.	Src	steroid receptor coactivator
34.	AMPK	Adenosine monophosphate-activated protein kinase
35.	JNK	c-Jun N-terminal kinase
36.	TZD	Thiazolidine-2,4-dione
37.	NIDDM	Non-insulin-dependent diabetes mellitus
38.	PPARy	Peroxisome proliferator-activated receptor
39.	HDL	High density lipoproteins
40.	LDL	Low density lipoproteins
41.	VCAM-1	Vascular cell adhesion molecule 1
42.	ICAM	Intercellular cell adhesion molecule
43.	PAI-1	Plasminogen activator inhibitor 1
44.	NYHA	New York Heart Association
45.	CYP	Cytochrome
46.	CTRI	Clinical Trials Registry India
47.	OCP	Oral contraceptive pill

ABSTRACT

Background and Objectives: Acanthosis Nigricans (AN) is defined by thick, hyperpigmented skin of flexural areas, often indicating underlying systemic conditions like metabolic syndrome. Its prevalence is escalating, notably reaching 6.5% in India. AN severity correlates with insulin resistance, emphasizing the importance of addressing underlying conditions. Dermoscopic examination aids diagnosis by revealing characteristic features. Metformin and pioglitazone are commonly used for insulin resistance in AN, yet comparative efficacy data is lacking. This study evaluates the clinical improvement, metabolic profile, and dermoscopic changes in patients of AN treated with metformin and pioglitazone.

Material and Methods: A randomized open-label trial at a tertiary care centre in Belagavi included consenting AN patients aged above 18. Patients were randomized to receive either metformin 500mg BD or pioglitazone 7.5mg BD for 3 months. Clinical grading, anthropometric measurements, biochemical profile, and dermoscopic features were compared at baseline and follow-up using IBM SPSS v26.

Results: Sixty-six patients, evenly distributed across both the groups having, mean age 35 years, with a female predominance were included in this study. Both drugs significantly improved clinical grading and metabolic profile. Metformin notably reduced BMI and weight, while pioglitazone showed greater reduction in HOMA-IR. No significant differences were observed for other parameters. Both drugs induced significant changes in dermoscopic features, with no notable difference. Morphology of papillary projections and sulci cutis correlated significantly with clinical grading.

Conclusions: Metformin and pioglitazone both led to significant improvement in AN lesions clinically and dermoscopically however, no significant differences were noted amongst the two arms clinically or dermoscopically. Metformin is more effective in reducing weight and BMI, suitable for overweight patients. Pioglitazone demonstrates greater efficacy in reducing HOMA-IR, making it preferable for non-obese patients with insulin resistance. Pioglitazone could be considered for patient's intolerant or unresponsive to metformin. Dermoscopic parameters serve as early treatment response indicators prior to noting visible clinical improvement. Further research with bigger sample size are warranted to validate these findings.

TABLE OF CONTENTS

SR.NO	CONTENT	PAGE NO.
1.	INTRODUCTION	1
2.	OBJECTIVES	3
3.	REVIEW OF LITERATURE	4
4.	METHODOLOGY	44
5.	RESULTS	51
6.	DISCUSSION	90
7.	SUMMARY	101
8.	CONCLUSION	104
9.	REFERENCES	105
10.	ANNEXURES	
	ANNEXURE I – CONSENT FORMS	127
	ANNEXURE II– PATIENT PHOTOGRAPHS	130
	ANNEXURE III – PROFORMA	136
	ANNEXURE IV –KEY TO MASTERCHART	140
	ANNEXURE V – MASTER CHART	143

LIST OF TABLES

TABLE NUMBER	DESCRIPTION	PAGE
1.	Major causes for insulin resistance.	12
2.	Consequences of insulin resistance.	13
3.	Burke et al Classification of AN.	17
4.	Reported adverse effects of metformin.	27
5.	Dermoscopic terminology	40
6.	Dermoscopic Colours of Melanin.	41
7.	Dermoscopic Colours of Keratin.	42
8.	Dermoscopic Colours of hemoglobin.	42
9.	Randomization table.	45
10.	Shows number of patients who had changes in dermoscopy of neck in sulci cutis pre- and post-administration of metformin.	58
11.	Shows number of patients who had changes in crista cutis at the neck pre- and post-administration of metformin.	58
12.	Shows number of patients who had changes in dermoscopy of neck in hyperpigmented dots/globules pre- and post-administration of metformin.	58
13.	Shows number of patients who had changes in dermoscopy of neck in hyperpigmented blotches pre- and post-administration of metformin.	59
14.	Shows number of patients who had changes in dermoscopy of neck in crypts pre- and post-administration of metformin.	59
15.	Shows number of patients who had changes in dermoscopy of neck in white streaks and globules pre- and post-administration of metformin.	59
16.	Shows number of patients who had changes in sulci cutis in right axilla pre- and post-administration of metformin.	60

17.	Shows number of patients who had changes in crista cuti in right axilla pre- and post-administration of metformin.	60
18.	Shows number of patients who had changes in hyperpigmented dots/globules in right axilla pre- and post-administration of metformin.	60
19.	Shows number of patients who had changes in hyperpigmented blotches in right axilla pre- and post-administration of metformin.	61
20.	Shows number of patients who had changes in crypts in right axilla pre- and post-administration of metformin.	61
21.	Shows number of patients who had changes in white streaks/globules in right axilla pre- and post-administration of metformin.	61
22.	Shows number of patients who had changes in sulci cutis in left axilla pre- and post-administration of metformin.	62
23.	Shows number of patients who had changes in crista cuti in left axilla pre- and post-administration of metformin.	62
24.	Shows number of patients who had changes in hyperpigmented dots/globules in left axilla pre- and post-administration of metformin.	62
25.	Shows number of patients who had changes in hyperpigmented blotches in left axilla pre- and post-administration of metformin.	63
26.	Shows number of patients who had changes in crypts in left axilla pre- and post-administration of metformin.	63
27.	Shows number of patients who had changes in white streaks/globules in left axilla pre- and post-administration of metformin.	63
28.	Anthropometric and biochemical at baseline and at 12 weeks of follow-up in metformin group.	65
29.	Shows number of patients who had changes in dermoscopy of neck in sulci cutis pre- and post-administration of pioglitazone.	66
30.	Shows number of patients who had changes in crista cutis at the neck pre- and post-administration of pioglitazone	66

31.	Shows number of patients who had changes in dermoscopy of neck in hyperpigmented dots/globules pre- and post-administration of pioglitazone.	66
32.	Shows number of patients who had changes in dermoscopy of neck in hyperpigmented blotches pre- and post-administration of pioglitazone.	67
33.	Shows number of patients who had changes in dermoscopy of neck in crypts pre- and post-administration of pioglitazone.	67
34.	Shows number of patients who had changes in dermoscopy of neck in white streaks and globules pre- and post-administration of pioglitazone.	67
35.	Shows number of patients who had changes in sulci cutis in right axilla pre- and post-administration of pioglitazone.	68
36.	Shows number of patients who had changes in crista cuti in right axilla pre- and post-administration of pioglitazone.	68
37.	Shows number of patients who had changes in hyperpigmented dots/globules in right axilla pre- and post-administration of pioglitazone.	68
38.	Shows number of patients who had changes in hyperpigmented blotches in right axilla pre- and post-administration of pioglitazone.	69
39.	Shows number of patients who had changes in crypts in right axilla pre- and post-administration of pioglitazone.	69
40.	Shows number of patients who had changes in white streaks/globules in right axilla pre- and post-administration of pioglitazone.	69
41.	Shows number of patients who had changes in sulci cutis in left axilla pre- and post-administration of pioglitazone.	70
42.	Shows number of patients who had changes in crista cuti in left axilla pre- and post-administration of pioglitazone.	70
43.	Shows number of patients who had changes in hyperpigmented dots/globules in left axilla pre- and post-administration of pioglitazone.	70
44.	Shows number of patients who had changes in hyperpigmented blotches in left axilla pre- and post-administration of pioglitazone.	71

45.	Shows number of patients who had changes in crypts in left axilla pre- and post-administration of pioglitazone.	71
46.	Shows number of patients who had changes in white streaks/globules in left axilla pre- and post-administration of pioglitazone.	71
47.	Anthropometric and biochemical at baseline and at 12 weeks of follow-up in pioglitazone group.	72
48.	Comparison of changes in dermoscopic parameters observed at neck in metformin group and pioglitazone group.	73
49.	Comparison of changes in dermoscopic parameters observed in right axilla in metformin group and pioglitazone group.	77
50.	Comparison of changes in dermoscopic parameters observed in left axilla in metformin group and pioglitazone group.	81
51.	Comparison of changes in anthropometric and metabolic parameters in metformin group and pioglitazone group.	85
52.	Shows correlation between Burke's grading with morphology sulci cutis.	86
53.	Shows correlation between Burke's grading with morphology of papillary projection and hyperpigmented dots.	87
54.	Changes in Burke's grading vs changes in papillary projections after treatment.	88

LIST OF FIGURES

FIGURE NUMBER	DESCRIPTION	PAGE
1.	Schematic diagram depicting the relation between IR and AN.	10
2.	Algorithm for evaluation of AN.	19
3.	Algorithm for evaluation of patients with underlying insulin resistance.	20
4.	Bar diagram showing the age distribution.	51
5.	Pie chart showing the gender distribution.	52
6.	Pie chart showing distribution of patients based of residence.	52
7.	Pie chart showing distribution of patients based on marital status.	53
8.	Distribution of patients based on employment status.	53
9.	Distribution of patients based on number of sites involved.	54
10.	Horizonal bar diagram showing prevalence of associated complains with AN.	54
11.	Horizontal bar diagram showing prevalence of associated complains in female patients.	55
12.	Vertical Bar diagram showing prevalence of comorbidities in patients.	55
13.	Vertical bar diagram showing prevalence of habits in patient.	56
14.	Pie chart showing prevalence of positive family history in AN patients.	56
15.	Pie chart showing prevalence of use of OCPs in female participants.	57
16.	Bar diagram showing number of patients who had changes in sulci cutis on neck dermoscopy.	74
17.	Bar diagram showing number of patients who had changes in hyperpigmented dots on neck dermoscopy.	74
18.	Bar diagram showing number of patients who had changes in hyperpigmented blotches on neck dermoscopy.	75
19.	Bar diagram showing number of patients who had changes in crypts dots on neck dermoscopy.	75

20.	Bar diagram showing number of patients who had changes in white streaks/ globules on neck dermoscopy.	76
21.	Bar diagram showing number of patients who had changes in papillary projections on neck dermoscopy.	76
22.	Bar diagram showing number of patients who had changes on dermoscopy of right axilla in sulci cutis after treatment.	78
23.	Bar diagram showing number of patients who had changes on dermoscopy of right axilla in crista cutis after treatment.	78
24.	Bar diagram showing number of patients who had changes on dermoscopy of right axilla in hyperpigmented dots after treatment.	79
25.	Bar diagram showing number of patients who had changes on dermoscopy of right axilla in hyperpigmented blotches after treatment.	79
26.	Bar diagram showing number of patients who had changes on dermoscopy of right axilla in crypts after treatment.	80
27.	Bar diagram showing number of patients who had changes on dermoscopy of right axilla in papillary projections after treatment.	80
28.	Bar diagram showing number of patients who had changes on dermoscopy of left axilla in sulci cutis after treatment.	82
29.	Bar diagram showing number of patients who had changes on dermoscopy of left axilla in cristi cutis after treatment.	82
30.	Bar diagram showing number of patients who had changes on dermoscopy of left axilla in hyperpigmented dots after treatment.	83
31.	Bar diagram showing number of patients who had changes on dermoscopy of left axilla in hyperpigmented blotches after treatment.	83
32.	Bar diagram showing number of patients who had changes on dermoscopy of left axilla in papillary projections after treatment.	84

LIST OF IMAGES

IMAGE NUMBER	DESCRIPTION	PAGE
1.	1a- Sulci cutis (marked with double headed black arrow) and cristae cutis (marked with double headed red arrow). Predominantly polygonal papillary projections present on the crista cuti seen on non-polarized mode. 1b – Same site as 1a seen in polarized mode. Sulci cutis seen as light-coloured areas (double headed black arrow) and cristae cuti as brown globules (double headed red arrow).	131
2.	2a-Predonimantly Triangular Papillary Projections seen in non-polarized mode. 2b - Same site as 2a seen in polarized mode, showing disperse faint hyperpigmented dots.	131
3.	3a-Clinically Burke's grade 4, Neck texture – 1. 3b-Clinically Burke's grade 4. Neck texture – 1. 3c-Non polarised dermoscopy showing narrow sulci cutis with cristae cutis with predominantly polygonal papillary projections. 3d-Non polarised dermoscopy showing wide sulci cutis with cristae cutis with predominantly triangular papillary projections. 3e-Polarised dermoscopy showing light coloured narrow sulci cutis with brown well defined rhomboid shaped cristae cutis. 3f-Polarised dermoscopy showing light coloured wide sulci cutis with brown ill-defined cristae cutis.	132
4.	4a-Clinically Burke's grade 4, Neck texture – 2. 4b-Clinically Burke's grade 3, Neck texture – 1. 4c-Non polarised mode of dermoscopy showing hyperpigmented dots and globules. 4d-Non polarised mode of dermoscopy showing decreased hyperpigmented dots. 4e-Polarised mode of dermoscopy showing hyperpigmented dots and globules. 4f-Polarised mode of dermoscopy showing decreased hyperpigmented dots and globules.	133

5.	5a-Clinically Burke's grade 4, Neck texture – 3. 5b-Clinically Burke's grade 3, Neck texture – 2. 5c-Non polarised dermoscopy showing narrow sulci cutis with pigmented cristae cutis with predominantly circular papillary projections. 5d-Non polarised dermoscopy showing wide sulci cutis with cristae cutis with predominantly circular papillary projections. 5e-Polarised dermoscopy showing sulci cutis with hyperpigmented cristae cutis. 5f-Polarised dermoscopy showing diffuse hyperpigmented globules present.	134
6.	6a-Burke's grade Axilla – 3. 6b-Burke's grade Axilla – 2. 6c-Non polarised dermoscopy showing sulci gyri pattern with papillary projections with numerous hyperpigmented dots. 6d-Non polarised dermoscopy showing sulci gyri pattern with papillary projections with scanty hyperpigmented dots. 6e-Polarised dermoscopy showing numerous hyperpigmented dots. 6f-Polarised dermoscopy showing scanty hyperpigmented dots.	135
7.	7a-Clinically Burke's grade 4, Neck texture -3. 7b-Clinically Burke's grade 4, Neck texture – 3. 7c-Non polarised dermoscopy showing sulci cutis with cristae cutis with predominantly circular papillary projections. 7d-Non polarised dermoscopy showing sulci cutis with rhomboid cristae cutis with predominantly polygonal papillary projections. 7e-Polarised dermoscopy showing sulci cutis with cristae cutis with hyperpigmented globules. 7f-Polarised dermoscopy showing sulci cutis with cristae cutis.	136

INTRODUCTION

INTRODUCTION

Acanthosis Nigricans (AN), defined by hyperpigmented, coarse, velvety, thickened skin is a mirror to several systemic diseases like metabolic syndrome, endocrine disorders, polycystic ovarian disease, drug side effects, malignancy, and genetic disorders.[1,2]

Dermoscopy of AN reveals papillary projections on crista cutis, depressed sulci cutis, and hyperpigmented dots, which aid in differentiating AN from other pigmentary skin disorders which may look like AN in initial stages.[3]

Escalation in the prevalence of AN has been observed recently due to the increasing prevalence of metabolic syndrome, analogous to the expanding epidemic diabetes type 2, hypertension, and obesity.[1]

The occurrence of AN fluctuates significantly, ranging from 7% to 74%. This variance is influenced by factors such as age, race, type frequency, level of obesity, and accompanying endocrine disorders.[1] Research conducted in western India revealed a prevalence rate of 6.5% among the population studied.[4]

Insulin resistance and hyper-insulinemic states contribute to the pathogenesis of AN, therefore the severity of AN is directly proportional to the fasting insulin levels.[5,6]

The main aim of treating AN is correction of the primary pathology. Hence identifying and treating AN will indirectly help in reducing the burden of diseases caused by hyperinsulinemic states.

Metformin, classified as a biguanide, primarily reduces the glucose produced by liver, and enhances glucose utilization by boosting peripheral insulin sensitivity.[7] This leads to a decrement in resistance to insulin and hyperinsulinemia, and is used for the treatment of AN.

Pioglitazone, belonging to the thiazolidinedione class, primarily enhances glycemic regulation by boosting peripheral insulin sensitivity.[8]

Metformin and pioglitazone both reduce insulin resistance and hyperinsulinemia but have separate mechanisms of action and there is no data that directly compares their clinical efficacy on AN. Therefore, we primarily aim to compare the effectiveness of monotherapy with pioglitazone to metformin clinically, dermoscopically and their role in improving insulin resistance profile indicated by fasting insulin levels, fasting glucose level and serum triglyceride levels. in AN. This study will aid in knowing the efficacy of pioglitazone in AN in comparison to metformin. It will form a basis to use pioglitazone as a substitute for metformin in AN not responding to metformin.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

- To compare the clinical effectiveness of metformin vs pioglitazone on skin lesions in acanthosis nigricans.
- To compare the pre-treatment and post treatment dermoscopic findings in patients of Acanthosis nigricans taking metformin 500 mg BD.
- To compare the pre-treatment and post treatment dermoscopic findings in patients of Acanthosis nigricans taking Pioglitazone 7.5mg BD.
- To compare the effectiveness of metformin vs pioglitazone at baseline and at completion of treatment dermoscopically.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Skin has a unique structure, where environmental factors and its anatomical position mostly determine its functional variability. Highly specialized signal recognition and interaction are needed to keep the skin in a state of homeostasis. The cutaneous neuroendocrine system, the pigmentary system, and the skin immune system are the main systems at play. Different hormones are produced by and/or have hormone receptors on many skin cells. Thus, a lot of endocrine diseases initially manifest at the skin level.[9] Acanthosis nigricans (AN) serves as a distinctive skin indicator for numerous systemic and endocrine disorders. It manifests as symmetrical, dark, rough, thickened patches with a velvety appearance, typically found on neck, armpits, inner elbows, and knees, beneath the breasts, and in the groin region.

ACANTHOSIS NIGRICANS

Acanthosis nigricans, manifests as symmetric, coarse, thickened velvety pigmentation of the skin, often seen in flexural areas, like the armpits, groin, and back of the neck. AN is a cutaneous marker of many systemic diseases. While commonly linked to obesity, diabetes and insulin resistance, AN can also signal hormonal irregularities or result from certain medications, such as oral contraceptives or systemic glucocorticoids. In rare cases, it might even hint at an underlying malignancy.[10–12]

❖ Background

According to historical records, acanthosis nigricans was first documented in Germany in 1889 by Unna and Pollitzer. Kahn et al, in 1976 established its connection to insulin resistance. Acanthosis nigricans was formally identified by the American Diabetes Association (2000) as a risk factor for diabetes in children.[13]

❖ Epidemiology

The rising incidence diabetes and obesity globally are probably reflected by the increasing prevalence of AN. The prevalence ranges from 7-74% according to factors such as age, race, AN type, degree of obesity, and related endocrine problems.[1,4,14] A study conducted in 2002 among young American Indians revealed a prevalence rate of 34.2%. [15] A study done in Texas and Nebraska among members of the Alabama Coushatta tribe reported a prevalence rate of 38%. In another study conducted in South India among the central Kerala population, 16.1% were found to have acanthosis nigricans.[16] AN is associated with conditions such as Cushing's disease, Addison's disease, hypothyroid, obesity, polycystic ovarian disease, and insulin-resistant diabetes. Additionally, it is also related to inherited conditions (Table 1) along with pineal hyperplasia syndrome, ovarian hyperthecosis, stromal luteoma, and ovarian dermoid cysts.[17,18]

Race

People with darker coloured skin have a greater probability to be diagnosed with Acanthosis nigricans. Compared to those of Caucasians having less than 1% prevalence of AN, blacks are 25 times at a higher risk of developing AN.[14] In USA, research indicates a prevalence of 3% in Caucasians, 19% in Hispanics, and 28% in American Indians.[19]

Sex

The occurrence of acanthosis nigricans affects both genders equally, showing no discernible preference for either sex.

Age

While benign acanthosis nigricans lesions may manifest at any age, they are more frequently encountered in adults and adolescents. Conversely, malignant acanthosis nigricans tends to be more prevalent among older individuals.[13]

Morbidity and Mortality

Benign acanthosis nigricans skin lesions typically pose minimal problems. They serve as an indication of insulin resistance, aiding in the recognition of individuals who may develop diabetes or glucose intolerance.[20] Insulin resistance varies widely, ranging from incidental findings in routine blood tests to overt diabetes. Treatment of insulin resistance may lead to partial or even complete improvement in skin lesions, as their severity often correlates with insulin resistance levels. In younger individuals, insulin resistance is the primary cause of acanthosis nigricans. Recent research suggests that, independent of body mass index, there is a correlation between the two variables: obese children with acanthosis nigricans had greater baseline and glucose-stimulated insulin levels than obese children without the condition.[21,22]

The prognosis for malignant acanthosis nigricans is poor, primarily because of the underlying malignancy. It is less prevalent and is typically linked to intra-abdominal malignancies.[23]

❖ Etiology

The onset of AN can be affected by multiple factors. An increase in circulating insulin stimulates insulin like growth factor-1(IGF-1) and other keratinocyte IGF receptors. Higher insulin concentrations may remove IGF-1 from its binding protein, leading to elevated blood levels of IGF-s, which could promote the proliferation of keratinocytes and fibroblasts.

Additionally, genetic variations with deficiencies in fibroblast growth factors are associated with AN.

1. **Familial Acanthosis Nigricans (AN):** It can manifest from birth or infancy it is attributed to an autosomal dominant inheritance pattern. The root cause lies in mutations affecting the fibroblast growth factor receptor 3 (FGFR3).[24]
2. **Obesity and AN:** There is often an association between obesity and AN, particularly in adults, sometimes referred to as "pseudo-AN" lesions. This connection might be influenced by insulin resistance (IR). Strategies like dietary modifications, weight reduction, or medication for obesity management have demonstrated effectiveness in improving AN. Hyperinsulinemia is a significant factor linking AN with IR-related conditions such as obesity, diabetes type 2, and polycystic ovarian syndrome (PCOS). Additionally, acrochordon, also known as skin tags, are frequently observed in, and around affected areas.[25,26]
3. **Drug induced AN:** AN has been correlated with various medications, including nicotinic acid, corticosteroids, diethylstilbestrol, combination OCPs, growth hormone treatments, estrogen, protease inhibitors, and injectable insulin. Discontinuation of the causative drug typically results in the resolution of AN.[27,28]
4. **AN Linked to Endocrine Dysfunction:** AN associated with endocrine dysfunction progresses slowly, is less common, and is often observed in obese individuals. Insulin-resistant disorders are categorized into type A or type B, with symptoms such as hyperandrogenemia, insulin resistance, and AN. Women with diabetes not in control, ovarian hyperandrogenism, or underlying diseases of autoimmunity are more susceptible to developing Type B syndrome. AN is also associated with PCOS, characterized by common occurrences of IR and hyperandrogenism.[29]

5. **Acral Acanthotic Anomaly:** Acral acanthotic anomaly manifests exclusively over specific areas like the popliteal and cubital fossa, as well as the extensor aspect of knuckles and foot surfaces. It is frequently observed in individuals with Fitzpatrick skin types 4-6.[30]
6. **Malignant AN Syndrome:** Malignant AN syndrome is related with breast cancer, ovary cancer, and prostate cancer, pulmonary cancer and lymphoma are seldom linked to AN. Malignant AN may appear before or accompany, or maybe followed by an internal cancer. AN induced by cancer often appears suddenly and is associated with acrochordons, tripe palms, and numerous seborrheic keratoses, which may indicate Leser-Trelat syndrome.[31,32]
7. **AN and Autoimmune Illnesses:** There is a correlation between AN and autoimmune conditions such as Hashimoto's thyroiditis, Sjogren's syndrome, Systemic lupus erythematosus (SLE), and Scleroderma.[33]
8. **Unilateral AN (Nevoid AN):** Unilateral AN, also known as Nevoid AN, is an exceedingly rare autosomal dominant condition characterized by unilateral lesions appearing in infancy, childhood, or adulthood.[34]

❖ Pathophysiology

The underlying mechanisms of acanthosis nigricans remain unclear. Elevated levels of growth factors and insulin mediated activation of insulin-like growth factor receptors present on corneocytes are two potential contributing elements.[35]

Several factors have been implicated in the pathophysiology of AN:

- Elevated serum insulin levels

- Fibroblast growth factor defects
- Elevated TGF-α (Transforming growth factor-α)
- Perspiration or friction
- Drug induced effects

Insulin has a role in maintaining skin homeostasis, it regulates the balance between keratinocyte differentiation and proliferation in the epidermis.[36,37] Insulin, IGF-1, along with their receptors on keratinocytes, are implicated in epidermal hyperplasia.[36] Insulin receptor substrate-1 (IRS-1) gets serine phosphorylated in an inhibitory manner that stops the receptor's signal from being transmitted, which results in insulin resistance.[38] Insulin-dependent skin homeostasis in AN is affected by inhibitory IRS-1 phosphorylation, which prevents keratinocytes from responding to insulin as they should. Meanwhile, elevated insulin levels cause proliferation by directly and indirectly activating keratinocyte and fibroblast IGF-1 receptors (Figure 1). Other tyrosine kinase receptors, such as the fibroblast growth factor receptor (FGFR) and the epidermal growth factor receptor (EGFR), may also be implicated, as mediators.[35,39,40]

The hyperproliferative epidermis contains large amounts of epidermal growth factor (EGF), a crucial regulator of keratinocyte proliferation in vitro. EGF interacts with elevated insulin or insulin-like growth factor/somatomedin for keratinocyte proliferation. The basal layer of the epidermis has the IGF-I receptor because it is thought that IGF-1 and EGF regulate epidermal growth and have a role in the etiology of hyperproliferative skin disorders.[41]

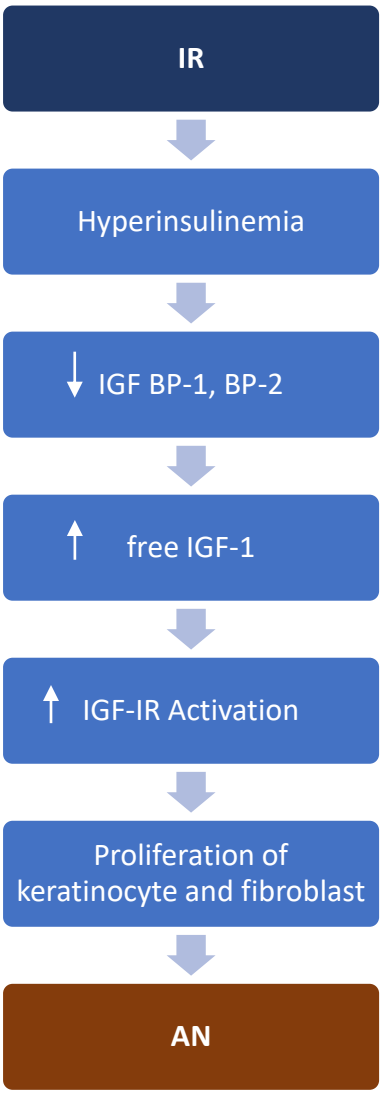

Figure 1: Schematic diagram depicting the relation between IR and AN[35,42]

Hyperinsulinemia might play a part in the indirect advancement of AN by elevating free IGF-1 in the bloodstream. The function of IGF binding proteins (IGFBPs) includes prolonging the half-life of IGF-1, transporting IGFs to target tissues, and moderating the concentration of free IGF-1.[43,44]

Individuals who are obese and exhibit hyperinsulinemia tend to have reduced levels of IGFBP-1 and IGFBP-2, resulting in elevated amounts of free IGF-1 in the bloodstream. This heightened bioactivity of IGF-1 encourages cellular division and proliferation.[45]

IGF-1 is formed by fibroblasts in the dermis and the stratum granulosum, and not in basal corneoocytes in the epidermis. Consequently, a rise in local free IGF-1 levels due to a systemic reduction in IGFBP1 and IGFBP2, initiated by insulin, could lead to hyperkeratosis and papillomatosis.[46]

Extreme insulin resistance syndromes have been managed via IGF-1 treatment. IGF-1 may lower blood insulin levels and IGF-1 expression. Because insulin binds to the IGF-1 receptor less securely than IGF-1 itself, it is probably less effective than IGF-1 at downregulating IGF-IRs. Not every subtype of acanthosis nigricans is brought on by hyperinsulinemia. Most AN syndromes are caused by defects in FGFR.[43,47]

Substances released by tumours can act as stimulants in cancer-related conditions. Malignant AN may be influenced by TGF-alpha, a tumour-produced factor associated with EGF.[41]

In conclusion, there is a relation among the fasting insulin levels and the severity of AN relative to body mass.[24,48] Insulin may therefore promote AN by directly initiating the IGF-1 signalling pathway.

AN is more prevalent in regions like the neck and axillae, suggesting that friction and sweating could be significant contributing factors.[49]

- **Insulin Resistance**

Insulin resistance, or reduced insulin sensitivity, refers to tissues reacting abnormally to normal insulin levels. Tables 1 and 2 detail the causes and consequences of insulin resistance.[50]

Table 1: Major causes of insulin resistance[51]

Primary insulin resistance -Inherited causes of resistance in target tissue
Mutation of insulin-receptor - Leprechaunism - Rabson-Mendenhall syndrome - Insulin resistance Syndrome Type -A
Lipodystrophies
Secondary insulin resistance
Obesity
Stress
Drugs (corticosteroids, antiretrovirals, OCPs)
Infections
Pregnancy
Immune regulated due to anti-insulin antibodies, anti-insulin receptor antibodies in type B syndrome
Miscellaneous(starvation/uremia/cirrhosis/ketoacidosis)

Table 2: Consequences of insulin resistance[51]

Consequences of insulin resistance
Diabetes mellitus type 2
Heart diseases, HTN
PCOS
Metabolic syndrome
Cancers due to obesity

In Kobaissi et. al.'s (2004) study, BMI emerged as the primary predictor (41%) of insulin sensitivity (Si). AN presence explained an additional 4% Si variation, but grading AN did not notably improve prediction accuracy.[52]

In their 2019 study, Videira-Silva et. al. investigated AN as an indicator of IR in teenagers. They found that AN patients exhibited higher insulin and HOMA-IR values compared to non-patients. However, Burke's grading, whether in its short or full form, did not accurately reflect hyperinsulinemia or IR. Interestingly, AN alone predicted hyperinsulinemia in 7.3% of adolescents and IR in 7.1%. This suggests that AN screening at the neck and axilla, a non-invasive and cost-effective technique, could identify overweight children who are asymptomatic but at risk of IR.[53]

Insulin Resistance Measurement Techniques:[53–59]

1. Hyperinsulinemic Euglycemic Glucose Clamp Technique.[56]

   Is the gold standard for estimating insulin sensitivity since it assesses insulin's direct impact on increasing glucose uptake in vivo during steady-state settings. Its computation is difficult and unfeasible, though.

2. Homeostasis Model Assessment-Insulin Resistance (HOMA-IR)[54]

   Developed by Matthews et. al. in 1985, HOMA estimates beta-cell function and insulin resistance from fasting insulin and glucose levels using mathematical models. The hyperinsulinemic-euglycemic clamp method and this method have a high linear association. It has proven to be useful in both clinical and epidemiological settings. When the value surpasses 2, IR is diagnosed. HOMA-IR is computed as [fasting serum insulin (UI/mL) × fasting plasma glucose (mg/dl)] ÷ 405.

3. Fasting Insulin Level[55]

   Measuring fasting insulin levels is an easy practical approach for assessing IR due to its correlation with Si. However, its utility is restricted by a high rate of false-positive results and absence of standardization.

4. Glucose/Insulin Ratio[57]

   Sensitive and specific indicator of Si, with abnormal values defined as <4.5 in adults and <7 in prepubertal children.

5. Quantitative Insulin Sensitivity Check Index (QUICKI)[58]

   - QUICKI: excellent measurement of IR compared to the clamp method, providing a constant and accurate measure of Si with good positive predictive value.

   - QUICKI is measured as 1/(log[Insulin U/mL] + log[Glucose mg/dL]), with a QUICKI index <0.357 indicating an increased risk of IR or metabolic syndrome.

6. Glucose Insulin Product[59]

Derived from serum glucose and insulin levels, serves as a measure of whole-body Si and offers a more comprehensive measure of Si. A higher product indicates a more severe state of IR when accompanied by elevated serum glucose and insulin levels.

7. Log (HOMA-IR)[55]

Log (HOMA-IR) is utilized to assess IR and may be preferred in research trials over HOMA-IR alone.

Various surrogate indicators of IR are emerging like IGFBP1, hsCRP, adiponectin, ferritin, HbA1C, C3 complement, TNF alpha, and sCD36. Other tests to identify IR include fasting glucose and lipoprotein profiles, hbA1C, body-weight, blood pressure, and alanine transferase tests for evaluating fatty liver.

❖ **Assessment**

A skin biopsy validates the clinical diagnosis of AN. X-rays, endoscopies, and comprehensive blood testing may be required in cases of diabetes or malignancy. The goal of the workup is to rule out any underlying cause. Because insulin resistance and/or obesity are associated in the great majority of cases, glucose tolerance tests and HbA1c testing are recommended.[60]

❖ **Histopathology**

Histological examination typically reveals hyperkeratosis and papillomatosis, with only minimal and irregular acanthosis and generally no hyperpigmentation. Therefore, the term

"acanthosis nigricans" lacks substantial histological support. In a typical lesion, the dermal papillae extend upward projections. The crevices between these papillae exhibit mild to moderate acanthosis and contain keratotic material. Additionally, horny pseudocysts may be present in some cases. The epidermis at the apex of the papillae and often on the sides of the protruding papillae appears thinner.[61]

❖ **Grading**

1. Curth classified AN patient into three groups: syndromic, pseudo-AN, and benign cases. [62]

2. Hernandez-Perez proposed two simpler categories: paraneoplastic AN and basic AN unrelated to malignancy.[63]

3. Sharqie's Facial AN grading is based on texture/colour.[64]

Grade 1: Colour is light-brown.

Grade 2: Texture is mild, with a brown colour.

Grade 3: Texture is moderate (velvety), and the colour is dark brown.

Grade 4: Texture is severe with a pronounced velvety feel, and the colour is black.

4. Burke et. al. graded AN on a range of 0 to 4 depending on the number of affected sites and the severity. This measure is simple to apply and has a correlation to both fasting insulin and body mass index.[65] (Table 3)

Table 3: Burke et al Classification of AN[65]

SCORE/ LOCATION	DESCRIPTION
NECK SEVERITY	
0	Not seen even when viewed from a short distance.
I	Seen – evidently seen from near, not seen otherwise, extent cannot be measured.
II	Mild -restricted to the base of the head, not reaching the sides of the neck (usually less than three inches in width).
III	Moderate- reaching the sides of the neck (usually 3-6 inches), not seen when the patient is seen from front.
IV	Severe-reaching front aspect of neck (>6 inches), visible when the patient is viewed from the front.
AXILLA SEVERITY	
0	Not seen when viewed from a short distance.
I	Seen evidently when observed from a short distance, but not seen otherwise, extent cannot be measured.
II	Mild-limited to axilla centre, at times not noticed by the patient.
III	Moderate-involving complete axilla, but not seen when the arm is against patient's side.
IV	Severe-visible from both front and back in the when the arm is against the patient's side.
NECK TEXTURE	
0	Smooth to feel cannot be differentiated with normal skin on

	palpation
I	Rough to feel and clearly differentiated from normal skin
II	Coarseness can be seen, parts of skin evidently raised.
III	Extremely coarse, mountains and depressions seen.
KNUCKLES	Seen or not seen
ELBOWS	Seen or not seen
KNEES	Seen or not seen

Algorithm for the assessment of acanthosis nigricans[66,67]

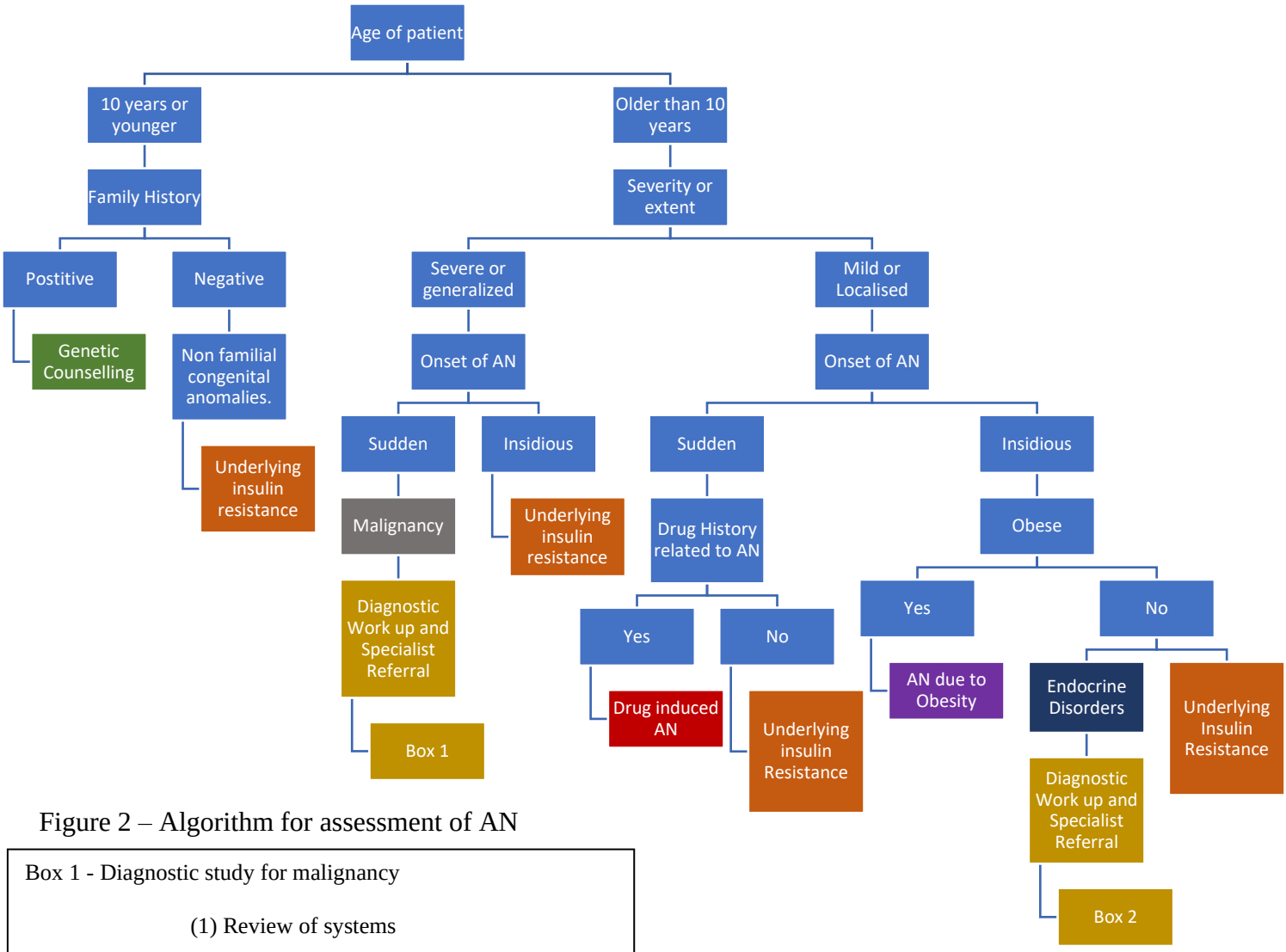

Figure 2 – Algorithm for assessment of AN

Box 1 - Diagnostic study for malignancy

(1) Review of systems

(2) Examination

(3) Chest xray

(4) CBC, stool test

Refer

(1) Gynaecologist

(2) Gastroenterologist

(gastroscopy/sigmoidoscopy, or both)

Box 2 - Diagnostic study for endocrine causes.

(a) Review of systems

(b) Examination

Refer to endocrinologist

Algorithm for assessment of patients with underlying insulin resistance.[66,67]

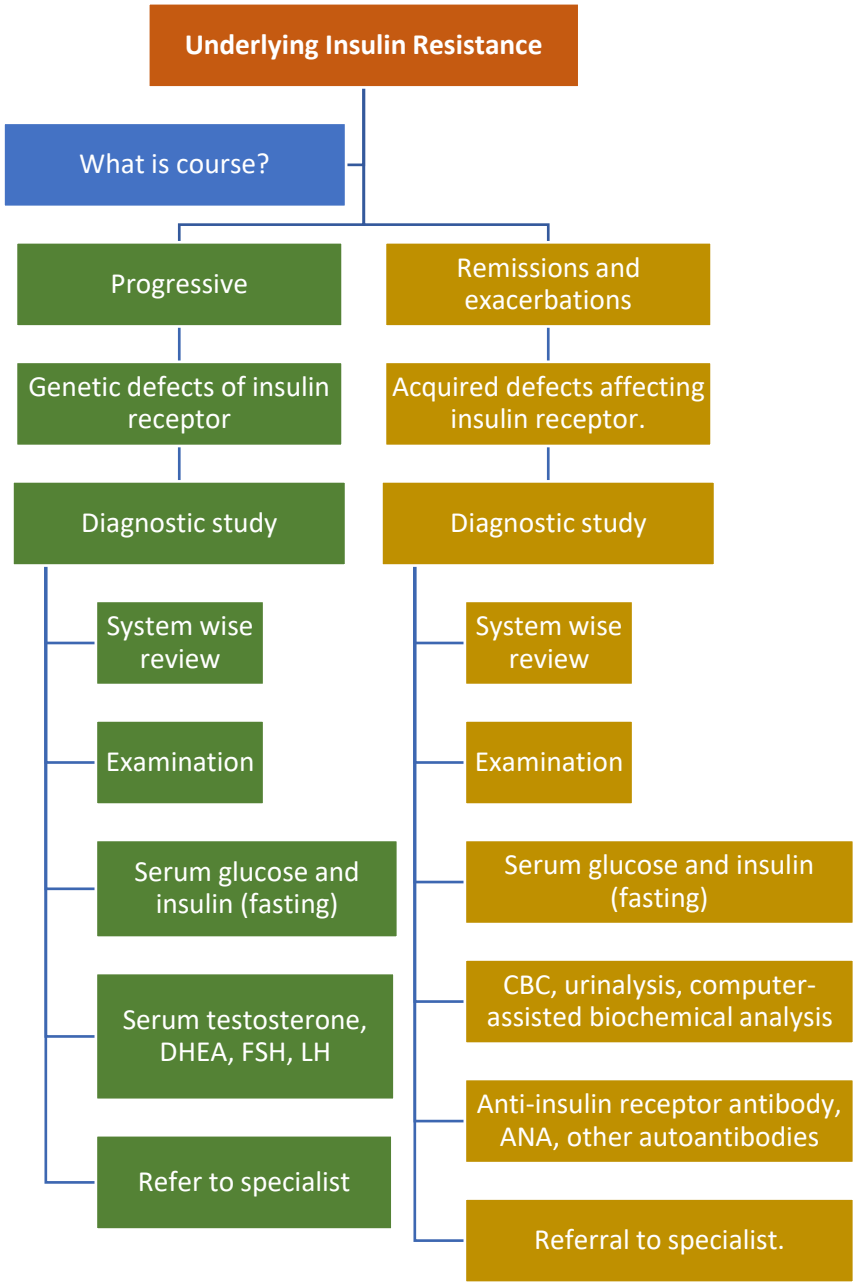

Figure 3 – Algorithm for assessment of patients with underlying insulin resistance.

❖ **Management**

The agenda is to treat the underlying illness. Most people solely opt for treatment for aesthetic purposes. Losing weight and lowering insulin resistance can, for some people, diminish the severity of hyperkeratotic lesions. Drugs and other contributing factors must to be avoided. It is recommended to lower the lipid profile.

1. Topical treatment

Topical retinoids such as 0.1% tretinoin cream or a combination of 12% ammonium lactate and 0.05% tretinoin are occasionally recommended as keratolytic. Vitamin D analogs, such as calcipotriol and 0.005% of calcipotriene, lessen keratinocyte growth and improve AN lesion.[68,69,70] The above-mentioned treatments differ in their efficacy. Urea cream (10-20%), a compound derived from carbonic acid, is a keratolytic agent and has emollient properties. It acts on AN by facilitating keratinolysis and exerting a proteolytic effect, skin irritation is the most common reported adverse reaction.[71]

2. Chemical Peels

Glycolic acid (GA) peels are known for their multifaceted benefits, including anti-inflammatory, antioxidant, and keratolytic properties. GA works via concentrating on the corneosome, where it helps to break down and lessen the cohesiveness of skin cells, resulting in exfoliation. The acid concentration, the carrier material, the amount applied, and the application method are some of the variables that affect the peel's strength.[72]

In research led by Md Zeeshan et al.[73], they checked the efficacy of a treatment regimen combining salicylic acid-mandelic acid peels for axillary acanthosis nigricans lesions, accompanied by application of a blend containing GA, urea, and acetylated fat-esters to

sustain the effects. Results revealed notable enhancements in both pigmentation reduction and lesion thickness, indicating promising outcomes for this combined approach.[73]

Trichloroacetic acid (TCA) stands out as a potent chemical exfoliant, inducing controlled epidermal damage followed by regeneration. TCA causes epidermal necrosis by causing the coagulation and precipitation of skin proteins. This, in turn, sets off an inflammatory response and activates wound healing mechanisms, all of which contribute to the appearance of smoother skin.[5]

3. Lasers

Fractional CO_2 laser treatment enhances both pigmentation and texture irregularities by gently removing superficial layers of skin with minimal heat-induced damage. The skin heals from dermal wounds because of this process, which also stimulates the synthesis of new collagen, which is essential for the noticeable post-treatment changes. Furthermore, the unbroken skin around the injury acts as a natural reservoir, hastening the healing process of the epidermis. The treatment parameters were tailored for superficial peeling and targeted ablation, aiming to utilize the melanin shuttle mechanism and facilitate transepidermal elimination of melanin. This approach involved employing low-density (500μm), short dwell time (500μs), low-power (10 J), and a double stacking technique with a single pass over the affected part. Remarkably, complete healing occurred within a week, with the maximum peeling effect evident by the second week. However, no additional improvements were observed thereafter.[72]

The utilization of the Alexandrite laser presents another viable cosmetic intervention for improving acanthosis nigricans lesions. Promising results were observed, with over 95% clearance in the left axilla following 7 sessions spaced at 4 to 8-week intervals using a

long-pulsed Alexandrite laser (5 msec). This laser, originally developed to target hair melanin, was believed to alleviate skin pigmentation in affected areas. While it may not currently rival the price-effectiveness of alternative topical or oral treatments, the potential of the Alexandrite laser in AN treatment suggests a hopeful avenue for future advancements.[5]

4. Systemic Medication

Medication that sensitizes insulin, including rosiglitazone and metformin, can be utilized to treat AN associated with IR.[69] In one trial, octreotide dramatically reduced IR.[68,74] Taking 10–20g of fish oil constituting omega-3 fatty acids every day for 6-months resulted in a significant improvement in texture and decreased hyperpigmentation in one patient with acanthosis nigricans and acquired generalized lipodystrophy.[75] Melatonin helps obese AN patients with their cutaneous symptoms by reducing inflammation and insulin sensitivity. After completing the course, one patient with insulin resistance continued to respond favorably to octreotide six months later.[76] Metformin and OCPs may be utilized to treat patients with HAIR-AN syndrome. Since cyproheptadine may prevent the release of tumor products, it is administered to patients with malignant acanthosis nigricans.[77] Psoralen Ultra Violet A (PUVA) is purported to alleviate symptoms in patients with paraneoplastic AN.[78]

5. **Surgery**

To reduce the severity of the lesion dermabrasion can be used. The mainstay of treatment for malignant acanthosis nigricans is surgery to remove the tumour leading to resolution of AN lesions.[79,80]

❖ **Prognosis**

Acanthosis nigricans is expected to become better after the underlying cause is found and removed. For example, losing weight will assist in improving acanthosis nigricans associated with obesity, and discontinuing the medication will likely help with acanthosis nigricans associated with drug use. Hereditary variations may or may not diminish with age, but cancer-associated mutations may vanish after a tumour is eradicated.[81]

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METFORMIN

❖ Introduction

Metformin (1,1-dimethylbiguanide) is a commonly recommended medication for individuals with diabetes. It comes Galega officinalis, which has been used in traditional medicine for centuries.[82]

❖ Pharmacokinetics

Metformin has a 40–60% absorption when taken orally. The drug's gastrointestinal absorption concludes approximately six hours after ingestion. Plasma membrane monoamine transporter promotes metformin's intestinal absorption.[83] Metformin has a half-life of five hours and is not metabolized. Organic cation transporter 2 (OCT2) aids in the absorption from the blood into kidney epithelial cells, whereas OCT1 and OCT3 aid in the liver uptake of the medication.[83,84] The kidneys eliminate metformin through active tubular secretion.

❖ Mechanism of Action

Metformin's positive effects on disease states including acanthosis nigricans and hyperinsulinemia are likely mediated, at least partially, by its interaction with the glucose transporter type 4 (GLUT4).[85] Insulin normally promotes the absorption of glucose by muscle and adipose cells by stimulating the movement of GLUT4 vesicles from intracellular space to the cell membrane. There is a downregulation of GLUT4 expression in target tissues, Metformin promotes endocytosis of GLUT4, and the hindrance of GLUT4 translocation to the cell membrane when there is prolonged insulin resistance or hyperinsulinemia, such as obesity PCOS.[86]

Metformin effects on GLUT4 translocation pathway - Metformin regulates GLUT4 translocation by modulating Cbl (Casitas B-lineage lymphoma protein) and CAP (Cbl adapter protein) signals via AMPK (AMP-activated Protein Kinase).[87]

Short-term metformin treatment:

1. Rapidly increases Cbl phosphorylation through AMPK
2. Enhances Src (Steroid receptor coactivator) phosphorylation in an AMPK-dependent manner.
3. Src inhibition blocks metformin-induced Cbl phosphorylation.

Long-term metformin treatment:

1. Stimulates CAP mRNA and protein expression.
2. Increases JNK (c-Jun N-terminal kinase) phosphorylation and downstream c-Jun activation.
3. AMPK/JNK knockdown impairs metformin-induced CAP expression.

Metformin Effects on GLUT4 Translocation:

1. AMPK knockdown weakens Cbl/CAP complex formation.
2. CAP or Cbl knockdown suppresses metformin-induced GLUT4 translocation.

Promoter Activity:

Metformin boosts CAP promoter activity via AMPK/JNK.

❖ Adverse Effects

Table 4 – Reported adverse effects of metformin[88–91]

Adverse Effect	Description
Cutaneous	Bullous pemphigoid: Reported in a patient receiving gliptins alongside metformin. However, causality of metformin in this dermatosis remains unclear. [87]
	Metformin-induced lichen planus.[88]
	Leukocytoclastic vasculitis: Several reports suggest metformin's involvement in the development of this condition.[89]
Non-cutaneous[90]	Flatulence
	Myalgia
	Nausea
	Vomiting
	Indigestion

❖ Drug Interactions

There is a considerable chance that cationic medications, such as frusemide, nifedipine, and cimetidine, which are excreted by renal tubular secretion, will interact with metformin. In tubular epithelial cells, they compete with OCT2, which may raise the blood concentration of metformin. Consequently, to reduce the chances of lactic acidosis in individuals taking these medications concurrently, close observation and dose modifications of metformin are required.[91]

❖ **Dosing and monitoring**

Metformin administration typically commences in adults with an initiating dose of 500 mg two times daily, with slow increments of 500 mg per week or 850 mg every alternate week, until reaching a maximum daily dosage of 2550 mg. Likewise, in children aged 10 to 16 years, treatment commences with 500 mg two times daily, with weekly increments of 500 mg, reaching the highest dose of 2000 mg daily in divided doses. Regular monitoring of complete blood picture and renal tests is imperative for all individuals receiving metformin. Monitoring should occur at least annually following the initial evaluation to ensure optimal management and safety.[92]

❖ **Contraindications**

Metformin should be given with caution in patients with blood creatinine levels of 150μmol/l or greater, in patients who are hypersensitive to the medication, and in situations where tissue hypoxia is suspected, such as myocardial infarction or sepsis. Furthermore, metformin should only be resumed after establishing normal renal function, and it should be stopped for three days before iodine-containing contrast media is supplied.[93]

PIOGLITAZONE

❖ Introduction

In 1982, Takeda Pharmaceuticals in Japan developed derivatives of clofibrate, discovering that adding the acidic thiazolidine-2,4-dione (TZD) moiety improved hypoglycemic and hypolipidemic effects in yellow KK mice, a model for non insulin dependent DM (NIDDM).

Ciglitazone was identified as an anti-diabetic medication, effectively lowering blood glucose levels without elevating insulin secretion. Subsequent research based on this discovery resulted in the creation and regulatory authorization of troglitazone, rosiglitazone, and pioglitazone for the management of NIDDM. [94,95]

❖ Pharmacokinetics

The drug is efficiently absorbed and undergoes metabolism through the hepatic cytochrome P450 enzyme system. Its $t_{1/2}$ is about nine hours, with two metabolites that are active prolonging its glucose-decreasing effects. After getting absorbed, the drug reaches peak levels in the hepatic, renal and plasma, in animals. It has a high absolute bioavailability of 83%, with a t(max) of 1.5 hours and a wide absorption rate constant range. Clearance is moderate at 2.4 L/hr, and its pharmacokinetics exhibit linearity with dose and are unaffected by food intake. The drug has a large volume of distribution, mainly attributed to extensive protein binding. Importantly, there is no substantial interaction with cytochrome P450 enzymes, indicating a low potential for drug interactions.[96]

❖ **Mechanism of action**[97]

The thiazolidinediones, commonly known as glitazones, activate a specific nuclear receptor complex called Peroxisome Proliferator-Activated Receptor (PPARγ). Within the PPAR family, which comprises PPARα, PPARγ, and PPARδ, only PPARγ is affected by thiazolidinediones, as confirmed by binding assays. Among the three thiazolidinediones, rosiglitazone exhibits the highest affinity for PPARγ, followed by pioglitazone and then troglitazone. This affinity pattern correlates with their effectiveness in treating insulin-resistant diabetes mellitus type 2.

Thiazolidinediones act by binding to the nuclear receptor PPARγ, forming a complex with RXR, which regulates lipid and carbohydrate metabolism. This complex binds to specific regions of target genes, altering their interactions with regulatory elements, thus affecting gene transcription. PPARγ has two subtypes, with PPARγ2 predominantly found in adipocytes and PPARγ in muscle, the latter containing additional amino acids. PPARγ agonists promote adipocyte differentiation and affect various cell types where PPARγ receptors are abundant, such as macrophages, endothelium, vascular smooth muscle, and colon epithelium.

1. **Effect of Pioglitazone on adipose tissue**[97]

   - **Adipose Tissue Differentiation**: Pioglitazone, promotes adipose tissue cell differentiation. When exposed to pioglitazone, fibroblast cells differentiate into adipocytes, expressing genes for various adipose-related proteins.
   - **Adipose Tissue Redistribution:** Pioglitazone may cause a re-distribution of fat from central compartments to the peripheral subcutaneous compartment. This redistribution could potentially reduce insulin resistance associated with central adipose tissue.

2. **Effect of Pioglitazone on Insulin resistance**[97,98]

Increases Si in resistant patients. Improvements in insulin sensitivity can range from 25%-68%, based on the study type and assessment technique used. Examples of assessment methods include the Bergman minimal model, the euglycemic-hyperinsulinemic clamp, and the HOMA-IR. It is hypothesized that PPARγ's action on adipose tissue may be related to the betterment in insulin action in muscle. Improved insulin action can result from thiazolidinediones' ability to reduce adipose tissue's release of TNFα and free fatty acids.

3. **Impact of Pioglitazone on lipid profile**[98]
    - Reduced serum free fatty acids by 25%-35%
    - Increases serum HDL cholesterol by 10%-20%
    - Reduces serum triglycerides, particularly if initial levels are over 200 mg/dL
    - Converts LDL particles to large buoyant LDL particles
    - Elevates adiponectin levels
4. **Impact of Pioglitazone on vessel endothelium and smooth muscles:**[97–99]

    In vitro and in vivo studies on animal models suggest that insulin resistance can disrupt usual vasodilation and endothelial function. It is hypothesized that the improvement in Si and metabolic parameters achieved with pioglitazone probably contributing to the normalization of vascular cell function and potentially reduce the atherosclerotic burden in individuals with insulin resistance and diabetes.
    - Enhanced vasodilation.
    - Reduction in systolic (SBP) and diastolic blood pressure (DBP) by 4-5 mmHg.
    - Decreased formation of VCAM-1 and ICAM-1.
    - Inhibition of proliferation of vascular smooth muscle cell.
5. **Impact on inflammation:**[97]
    - Decreases average plasma C-reactive-protein (CRP) levels by 25–30%.

- Decreases white blood cell, counts and metalloproteinase levels.

6. **Impact on procoagulant state:**[97]
    - Lowers plasminogen activator inhibitor 1(PAI-1) levels by nearly 25%.
    - Decreases plasma fibrinogen.
7. **Impact on glycemic control:**[98,100]
    - Thiazolidinediones reduce glycated hemoglobin (HbA1c) by addressing both fasting and postprandial hyperglycemia.
    - Reduction in HbA1c correlates with improved insulin resistance and residual insulin secretion.
    - In large trials like PROactive[101], HbA1c was decreased by 0.8% from a baseline of 7.8%, accompanied by a 53% decrement in insulin requirement.
    - Data from the ADOPT[102] trial demonstrates that rosiglitazone maintains better glycemic control over 5 years compared to glyburide or metformin.
8. **Impact on maintaining beta-cell functionality:**[103]

    Pioglitazone reduce the chances of conversion from prediabetes to diabetes by 60% after median durations of 2.4 years to 3 years.

    The reduction in the transition from prediabetes to diabetes in both studies is tightly correlated with the maintenance of beta-cell insulin secretory activity.

❖ **Adverse Effects** [97,98]

1. **Hepatotoxicity:** Although pioglitazone isn't strongly linked to liver toxicity, rare cases of liver injury also reported. Regular liver function tests are recommended for patients on pioglitazone to monitor for elevated liver enzymes.

2. **Cardiovascular Effects:**

- Congestive Heart Failure: Pioglitazone at times may lead to higher risk of congestive heart failure, particularly in people with known cardiac comorbidities. Vigilant monitoring is advised for signs of retention of fluid and exacerbation of heart failure symptoms.
- Cardiovascular Events: Reports suggest a potential risk of nonfatal heart attacks in patients using pioglitazone, particularly those with a history of cardiovascular disease. Prescribing should be cautious after assessing the patient's cardiovascular risk profile.

3. **Edema and Fluid Retention:**

Pioglitazone can cause peripheral edema and fluid retention, leading to swelling and weight gain. Most cases are manageable with diuretics, but severe edema may require discontinuation of pioglitazone.

4. **Bone Health:**

Long-term pioglitazone use is related with an elevated risk of fractures, particularly postmenopausal women. Healthcare providers should evaluate bone health and fracture risk, particularly in vulnerable populations.

5. **Weight Gain:**

Pioglitazone may induce weight gain due to increased adipose tissue and fluid retention. The extent of weight gain varies among individuals and should be

considered in treatment decisions, especially for those with higher chances of obesity-related complications.

❖ **Dosing and monitoring**[104]

Pioglitazone is administered orally and can be taken with or without food.

Initial adult oral dosage is usually 15 mg or 30 mg one time every day, with potential increments of 15 mg as needed for inadequate response. The maximum daily dose is 45 mg orally.

The recommended dose for persons with asymptomatic heart disease who have heart failure risk factors, or those in NYHA Class I or II heart failure, less than 15 mg once day.

Maximum daily dose for adults is 45 miligrams.

Safety and efficacy of pioglitazone in adolescents and children remain uncertain.

Monitoring

i. Liver function tests should be conducted before starting pioglitazone and periodically thereafter due to its potential impact on liver function. Monitoring frequency can be decided based on clinical judgment. Pioglitazone may improve liver function in people having non alcoholic fatty liver disease. Patients should be counselled to seek urgent medical help for unexplained symptoms such as nausea, vomiting, pain in abdomen, fatigue, anorexia, or dark coloured urine.
ii. Caution is advised when using pioglitazone in those diagnosed with NYHA Class I and II heart failure. Patients should be counseled to watch for signs such as

shortness of breath, rapid weight gain, and/or peripheral or pulmonary edema after starting or changing the dose of the medication.

iii. Bone health should be assessed and maintained according to current standards, particularly in female patients.

iv. Patients should be encouraged to report any warning signs of bladder cancer, including red-colored urine (hematuria), increased urge or frequency of urination, and unexplained weight loss.

❖ **Drug Interactions**[97]

Thiazolidinediones undergo hepatic metabolism through oxidative cytochrome pathways. Pioglitazone undergoes metabolization through CYP 3A4, CYP 2C8, and CYP 1A1. When drugs that are metabolized by CYP 3A4 are given together, there is a chance that they will interact. Nevertheless, neither the pharmacokinetics nor the pharmacodynamics of pioglitazone's interactions with medications such as warfarin, glipizide, metformin, or digoxin are impacted. While pioglitazone's effect on CYP 3A4 induction or inhibition is not fully understood, ketoconazole may inhibit its metabolism.

❖ **Contraindications**[104]

i. Known allergy to pioglitazone.

ii. Patient in Diabetic ketoacidosis (DKA) or type 1 diabetic.

iii. Hypoglycemia, necessitating regular blood sugar monitoring.

iv. New York Heart Association Class III/IV heart failure.

v. Symptomatic failure of heart (NYHA Class I, II, III, IV).

vi. Presence of fluid overload.

vii. Carcinoma of bladder cancer or unexplained microscopic hematuria.

viii. Past history of fracture or high tendency of fracture.

ix. Active hepatic issues, with elevated enzymes more than 2.5 times more than normal limit.

x. Pregnancy

xi. Older people with heart/kidney failure according to the Beers Criteria.

DERMOSCOPY

❖ Introduction

Dermoscopy is a non-invasive technique involving transillumination of skin lesions and high-magnification visualization of subtle features, that shows distinctive patterns in a variety of dermatoses, greatly enhancing diagnostic capabilities.[105,106] Surface microscopy for pigmented lesions was first described in the first half of the 20th century, drawing from previous work on colposcopy for cervical visualization. Dermoscopy, once a technique primarily used for evaluating dysplastic changes in suspicious nevi, has evolved significantly since its inception.[107,108]

❖ Tool – Dermoscope

There are two different kinds of instruments: (i) a handheld dermoscope, which is like an ophthalmoscope in size and portability, and (ii) a videodermoscope, that has a universal serial bus connector that must be connected to a laptop/computer to view the patterns. Videodermoscopes need to be connected to a computer system, while handheld dermoscopes are portable and easy to use while examining a skin lesion.[106,109]

The dermoscope consists of three main components: the lighting system, magnification system, and power supply. LED lamps are usually utilized in handheld dermoscopes, replacing earlier halogen lamps. Magnification is achieved through achromatic lenses in the faceplate of the dermoscope. Handheld dermoscopes are powered by rechargeable lithium batteries, while videodermoscopes utilize electric power. Handheld dermoscopes are often connected to smartphones for image capture, while videodermoscopes allow simultaneous visualization on a computer screen and image saving. Magnification ranges up to 14x in handheld dermoscopes and can reach up to 160x to 220x in videodermoscopes.[106]

❖ **Principle**

Human eye cannot visualize structures beneath the skin's surface layer because of the disparity in the refractive indices (RI) of the stratum corneum (1.55) and air (1.0), causing light to reflect upon hitting the skin's surface and rendering structures invisible to the human eye. To minimize light reflection and enhance light penetration, a liquid interface dermoscope is employed alongside the skin. The liquid must possess a RI nearer to that of the stratum corneum. This is can be accomplished using interface media or noncontact polarized light, both of which facilitate improved visualization of skin structures.[106,110,111]

❖ **Technique**[112–115]

Polarized and nonpolarized dermoscopy are distinct techniques allowing physicians to visualize various skin structures for detailed analysis of dermoscopic patterns. In natural light, skin surface reflection prevents deep structure visualization. Polarized dermoscopy or a glass plate with the ideal refractive index and interface material are employed to prevent this.

1. **Nonpolarized dermoscopy** requires skin contact and interface medium, offering better visualization of superficial structures like comedones and scales.
2. **Polarized dermoscopy -** two orthogonal filters maintain the polarization of light passing through the initial filter. Deeper skin structures absorb and scatter this polarized light, causing it to lose polarization and readily pass through the next filter, enabling visualization up to 100 microns depth, known as cross-polarization.
3. **Contact dermoscopy** – (wet dermoscopy) Interface fluid is used to blur surface irregularities. Common interface liquids are ethanol (70%), isopropanol (90%), ultrasound gel, liquid paraffin, and plain water, with ultrasound gel being the

preferred choice due to its viscosity and non-reacting nature, especially for nail visualization and lesions close to the eyes.

Contact-polarized dermoscopy includes keeping the dermoscope to the skin's surface to improve brightness and visibility. Drawbacks include blood vessel compression and cross-infection, mitigated by suspending the dermoscope in viscous gel and using disposable contact caps or tapes. Performing various dermoscopic techniques ensures thorough examination without missing minor details.

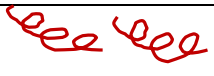
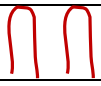
4. **Non-contact dermoscopy** – (dry dermoscopy) No interface fluid is used, employed to identify surface irregularities. Above drawbacks are prevented by non-contact dermoscopy but at the cost of decreased illumination and resolution.

❖ **TERMINOLOGY – Table 5**[106,116]

In dermoscopy, "structures" refer to well-defined, solid objects with specific shapes and sizes, each with histological correlates. Meanwhile, "structureless" areas lack discernible elements but are large enough to form patterns. Dermoscopic "patterns" are formed by repeating these structures, with lesions exhibiting one or multiple patterns, often with one pattern dominating. The distribution of structures and patterns can vary (regular, irregular, central, marginal, etc.). Additionally, follicular, and eccrine openings, along with dilated blood vessels, contribute to dermoscopic features. Abnormalities in follicular openings (plugging, fibrosis) and perifollicular skin (redness, scaling, colour changes) should be noted. Eccrine openings appear as small white interfollicular dots. Dilated vessels exhibit different morphologies and distributions, categorized as monomorphic or polymorphic

based on the predominance of a single morphology or the presence of multiple morphological types. These vessels can also generate various patterns.

Table 5 – Dermoscopic terminology

Term	**Description**	**Schematic Representation**
Line	Solid structures with length significantly greater than breadth	
Clod	Solid structures with specific shape and size • Globules • Lacunae	
Pseudopod	Bulbous extending margin	
Dot	Tiny solid objects smaller than globules	
Circle	Solid annular objects with equal distant margins from the center	
Structureless area	Areas big enough to form patterns but lack specific elements	
Blood Vessels		
Schematic Representation		
Straight		
Curved		
Spiral		
Looped		
Dotted		
Red clods		
Coiled		

Branching	
Wavy	

Colours on Dermoscopy[109,116]

The colours observed through dermoscopy can be attributed to chromophores in skin, primarily keratin, melanin, and haemoglobin. Chromophores impart white, black, and red colours respectively, but variations with contrast occur due to factors like their depth, biological state, and the individual's skin type. Additionally, certain Colours may signify other phenomena or histological elements. For instance, white can indicate dermal sclerosis or pigment absence, while yellow may result from fat or sebum. Black may represent thrombosed capillaries, and brown may indicate hemosiderin. Histologically, white, and yellow correspond to acanthosis and hyperkeratosis respectively. Therefore, interpreting dermoscopic colours, alongside other features, necessitates considering the clinical context of the lesion.

Table 6 - Dermoscopic colours of Melanin[109,116]

Melanin	**Stratum corneum**	**Malpighian layer**	**Papillary dermis**	**Reticular dermis**
Colour	Black	Brown	Grey	Blue

Table 7 - Dermoscopic colours of Keratin[109,116]

Keratin	**Less and laminated**	**More and compact**	**Admixed with sebum**	**Admixed with oxygenated blood**	**Admixed with deoxygenated blood**
Colour	White	Yellow	Orange	Red	Black

Table 8 - Dermoscopic colours of Haemoglobin[109,116]

Haemoglobin	**Oxygenated**	**Deoxygenated**
Colour	Red	Black

❖ **Dermoscopy of Acanthosis Nigricans**

Dermoscopy reveals distinct linear structures known as crista cutis and sulcus cutis. Crista cutis appear as linear gray to brown pattern, while sulcus cutis appears as linear dull white structures.[117,118] Cristae cutis and sulci cutis both are visualized better in non-polarized mode, while hyperpigmented dots/globules, are more easily observed in polarized mode.[119] Typically, darker brown or black dots are visible within the crista cutis, irregular brown globules and pigmentation around the follicle may be present. In lesions of long duration, exophytic papillary structures and brownish invaginations filled with keratin may be observed. The backdrop colour is typically gray-brown in the crista cutis and white in the sulcus cutis.[61,118]

❖ **Dermoscopy and histopathology correlation**

Histopathological examination reveals epidermal hyperplasia, hyperkeratosis, and papillomatosis, accompanied by evident melanin accumulation in the basal epidermal layer. Dermal papillae extend upwards, creating epidermal valleys. Linear crista cutis is indicative of an elevated and pigmented epidermis due to dermal papillary projections, while sulcus cutis suggests uniformly pigmented surrounding epidermis. It is important to know that while sulci cutis and cristae cutis both exhibit pigmentation, but sulci may appear lightly pigmented because of the presence of basket weave stratum corneum filling the depressions of the epidermis. In long standing lesions, extensive papillomatosis leads to the formation of exophytic papillary structures.[116]

In a study by Shah VH et. al.[120] done to observe a clinical dermoscopic and histological correlation of AN lesions showed that lighter brown variants of facial AN had follicular obstruction, sulci patterns, irregular brown-globules, and perifollicular pigmentation. From a histopathological perspective, these instances showed modest acanthosis and papillomatosis together with little hyperkeratosis and increased melanization of the basal epidermis. On the other hand, under dermoscopy, the chronic forms (black and dark brown) showed bigger brown globules, noticeable sulci, and hyperpigmentation around the follicles. Histologically, these instances displayed papillomatosis and moderate to severe acanthosis together with hypermelanization and hyperkeratosis of the basal layer.

MATERIAL AND METHODS

MATERIALS AND METHODS

Source of Data: Patients attending Dermatology, Venereology and Leprosy OPD, KLE`S Dr Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Design: An open label randomized control trial.

Period: January 2023-December 2023

Sample Size: Sample size was calculated using the formula

$$n = \frac{2\left(Z\alpha_{/2} + Z_{\beta}\right)^2}{\left(\frac{|\mu_1 - \mu_2|}{\sigma}\right)^2}$$

$$d = \frac{|\mu_1 - \mu_2|}{\sigma}$$

Where μ1 is the average of the first category, μ2 is the mean of the second category and σ2 is the common error variance, for 95% confidence level, $Z\alpha\ 2/$value is 1.96 and for 80% power $Z\beta$ value is 0.84.

Difference in the reduction in severity of neck lesions was taken as effect size (d) and it's assumed as 0.75. From above inputs, sample size required was 29 patients for each group.

At 10% follow-up loss rate, final sample size required was 32 patients per each group.

Larger the sample better the precision.

Randomization table: Table 9

Randomization list was obtained from statistical software R version 4.1.2.

Table 9 – Randomization table

Group	**Patients number**
Piogliatazone	1, 2, 3, 4, 8, 9, 10, 11, 12, 18, 20, 21, 22, 24, 25, 28, 30, 31, 32, 35, 38, 42, 44, 45, 49, 52, 54, 55, 57, 58, 62, 64.
Metformin	5, 6, 7, 13, 14, 15, 16, 17, 19, 23, 26, 27, 29, 33, 34, 36, 37, 39, 40, 41, 43, 46, 47, 48, 50, 51, 53, 56, 59, 60, 61, 63.

Inclusion Criteria:

- Adult patients (≥18 years) having acanthosis nigricans attending the dermatology outpatient department (OPD) in KLE Prabhakar Kore Hospital
- Patients from whom written informed consent was obtained

Exclusion Criteria:

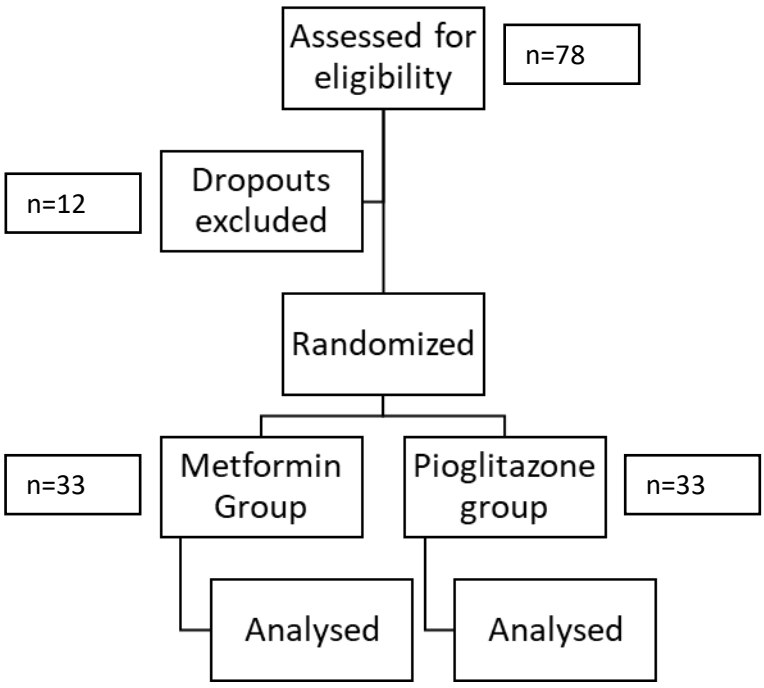
- Patients already taking any oral hypoglycaemic drug.
- Patient diagnosed as Type 1 Diabetes Mellitus
- Patient diagnosed as Drug induced AN
- Patients diagnosed as AN due to known malignancy
- Pregnant and lactating mothers
- Known allergic reaction to either Metformin or Pioglitazone
- Contraindicated for taking metformin or Pioglitazone

Study protocol:

A hospital based open label randomized controlled trial was done on patients visiting dermatology OPD of KLE Prabhakar Kore Hospital. After receiving Institutional Ethics Committee clearance (MDC/JNMCIEC/15) study was initiated. Written informed consent was taken from included patients. Trial was registered under Clinical Trial Registry - India (CTRI). (CTRI/2023/01/048858)

Participants received either metformin 500 mg BD or pioglitazone 7.5mg BD for 12 weeks. Study proforma in the form of a questionnaire was used to collect data including general patient information, history, anthropometric measurements, examination findings and investigations. Images of the skin lesions and dermoscopic images were stored.

Study flowchart



Visits

Baseline:

Consenting patients fulfilling inclusion were randomized equally into metformin and pioglitazone group according to a computer-generated random number table.

Patient details and baseline parameters were noted using a detailed proforma. AN lesions were scored and texture categorised using scoring by Burke et. al.[65] Waist-circumference, height, and body-weight was measured. Each participant was provided drugs as per randomization for one month and asked to collect the same monthly for three months, and asked to report for any adverse effects. They were asked to return for follow-up after completion of twelve weeks.

Follow-up:

Follow up was done at the end of three months. At follow-up, the variables noted at baseline were noted again and adverse effects were recorded.

Assessment of effectiveness

The primary outcome measure for effectiveness was betterment of neck lesions and neck texture given by Burke's grading.[9] The severity AN on neck lesions was graded from zero to four, where zero meant no lesions or not detectable on close inspection, one meaning lesions were visible on close observations, two for mild AN restricted to the base of the head but did not reach the side of neck (usually, less than three inches in width), three means moderate AN reaching side of neck (posterior border of sternocleidomastoid) (3–6 inches), and four means severe AN reaching anteriorly (>6 inches), visible whe participant is observed from the front.

Betterment of neck texture was evaluated by a four-point grading scale (0–3); 0 for neck texture means smooth to touch with no differentiation from normal skin on palpation, one means rough on palpation and visibly different from normal skin, two meaning coarseness could be seen with portions of the skin evidently raised above surrounding area and three meaning extremely coarse with "mountains and valleys" observed.

Obesity parameters, including body-weight, body mass index, and waist-circumference, were assessed at baseline and post treatment. Biochemical parameters, such as fasting insulin levels, glucose, serum triglycerides, and homeostatic model assessment of insulin resistance, were also measured at both baseline and follow-up.

Dermoscopic examination was done using hand held digital dermoscope connected to a laptop as a portable dermoscope. Dino-lite AM4113ZT digital microscope, 1280*1024 pixels at 50X and 200 X magnification.

The most common dermoscopic patterns (hyperpigmented dots/globules, Sulci cutis, crista cutis, white streaks, and crypts) were used to evaluate differences before and after treatment.

Polarized mode of video dermoscope was used to visualize hyperpigmented pigmented dots and globules, white streaks. Nonpolarized mode was used to see cristae cutis, papillary projections, crypts, and sulci cutis.

Dermocopic evaluation was done at fixed site (site was accurately anatomically defined by measuring shortest distance from nearest bony prominence, photographic record was taken) on baseline visit and follow-up visit.

For the ease of evaluation and absence of any preexisting dermoscopic scale for AN, a self-designed analytical method was used for dermoscopic evaluation mentioned in the proforma.

On dermoscopy; absence or presence of crista cutis, sulci cutis, hyperpigmented dots/globules crypts, white streaks and hyperpigmented blotches was noted at baseline and follow-up.

Change in morphology of papillary projections and sulci cutis and change in number of hyperpigmented dots/globules if any was noted at both visits.

Definition of dermoscopic terminologies used[117]

1. Sulci cutis – furrows/valleys or depressions. We have described Sulci cutis as
    i. Narrow
    ii. Wide
2. Crista Cuti - Elevated ridges

    Rhomboid formation - Rhomboid shaped islands that show significantly depressed sulci and prominent cristae.

3. Papillary projection – Exophytic projections present on crista cutis

    We considered 3 morphologies for papillary projections as noted on dermoscopy.

    i. Circular
    ii. Polygonal
    iii. Triangular
4. Crypts – Invaginations filled with Keratin which look larger than comedo like openings.

Statistical analysis

Statistical analysis was done using IBM SPSS v26 and Microsoft Excel. Continuous parameters were represented using mean ± SD/median. Categorical variables were represented using frequency(percentage). Categorical values were analysed using Chi-square test. To compare mean/distribution between two groups two sample t-test-Mann-Whitney test was used. Repeated measures of ANOVA-Friedman's test were used to compare variables over time and group. Normality of parameters was checked using Shapiro-Wilk's test/QQ plot was used. p-value <= 0.05 showed statistical significance.

RESULTS

RESULTS

In the current study, 78 patients were recruited, 12 were lost to follow-up and a total of sixty-six patients finished the 12-week follow-up and were included for analysis. Mean age was 35±14 years with maximum age being 67 years and minimum 18 years. The average age of onset of AN in patients was 28.76 years ranging from 13 years to 50.5 years. Average duration of AN at the time of presentation was 3.08 years ranging from 0.46 years to 5.7 years.

A. CLINICO-DERMOGRAPHIC DISTRIBUTION OF PATIENTS.

1. Age Distribution

Out of a total of 66 patients, majority (23/66, 34.8%) were less than 25 years followed by 25-34 years (15/66, 22.7%).

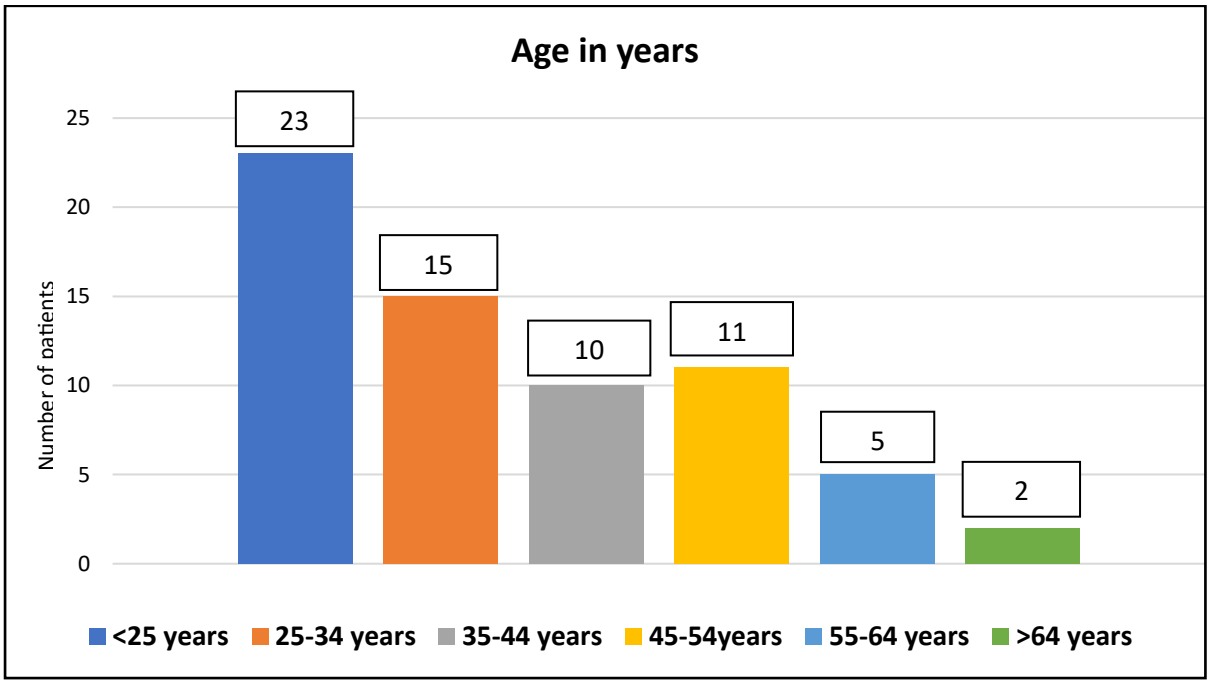


Figure 4 – Bar diagram showing the age distribution

2. Gender distribution:

Out of 66 patients, 47/66 were females and 19/66 were males which is 71.2% and 28.8% respectively; showing a female preponderance.

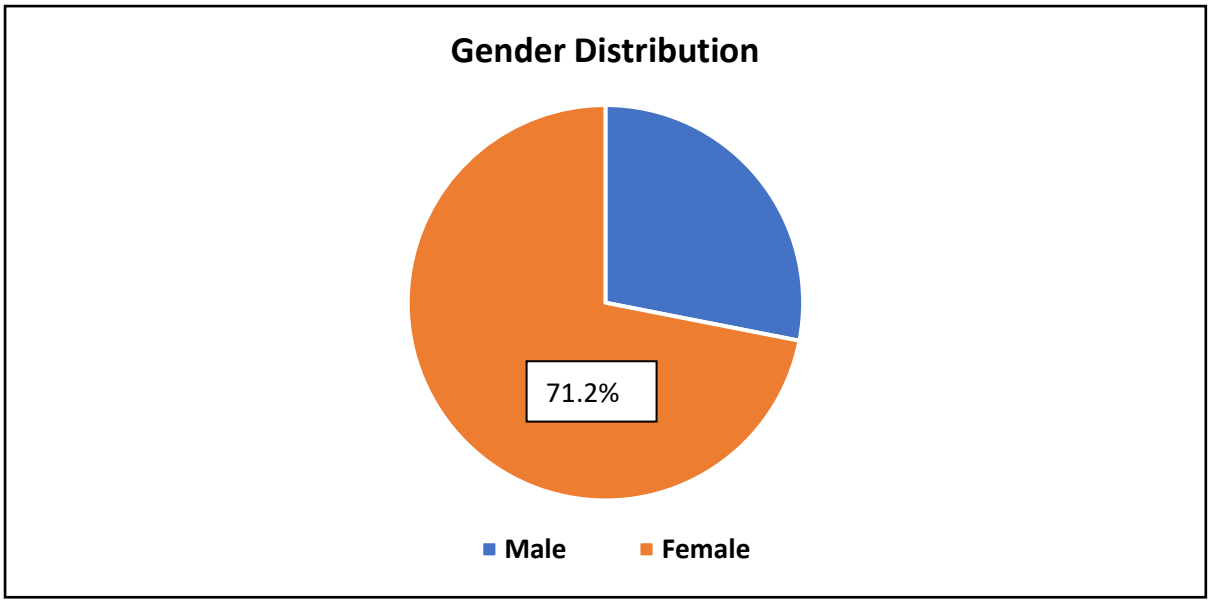


Figure 5 – Pie chart showing the gender distribution

3. Distribution of subjects based on residence

15.2% (10/66) belonged to rural area where as 84.8% (56/66) belonged to urban area.

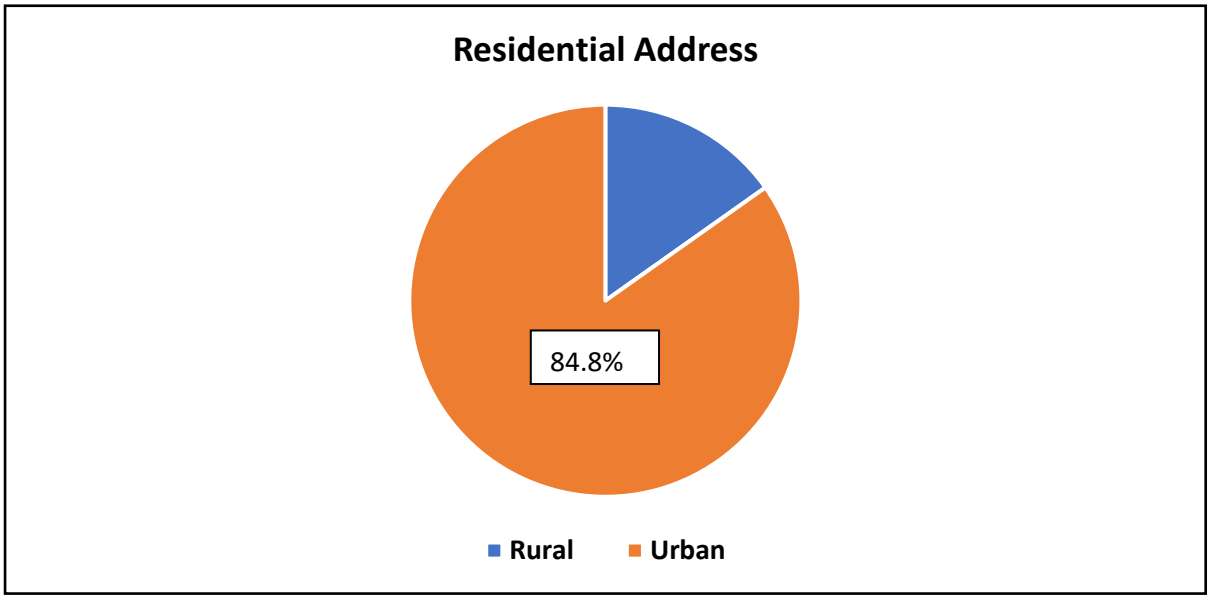


Figure 6 – Pie chart showing distribution of patients based of residence.

4. Patient distribution based upon marital status

Maximum were married i.e. 63.6% (42/66), and remaining 36.4% (24/66) were unmarried.

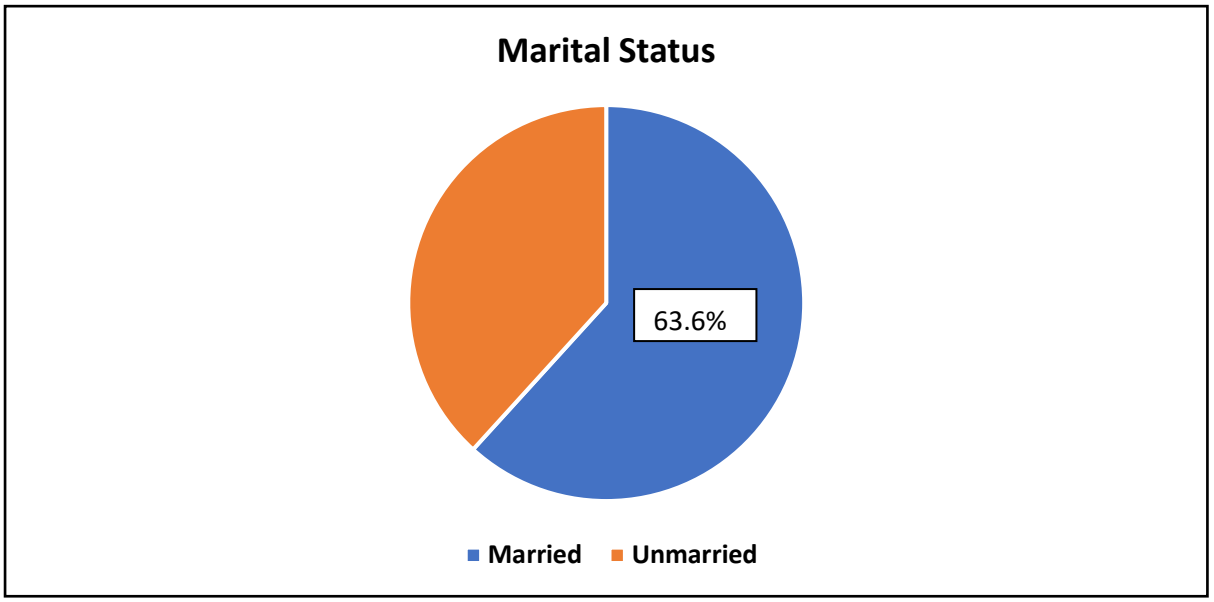


Figure 7 – Pie chart showing patient distribution based upon marital status.

5. Patient distribution based upon employment

Out of 66 patients, majority were unemployed i.e. 65.2% (43/66), and remaining 34.8% (23/66) were employed.

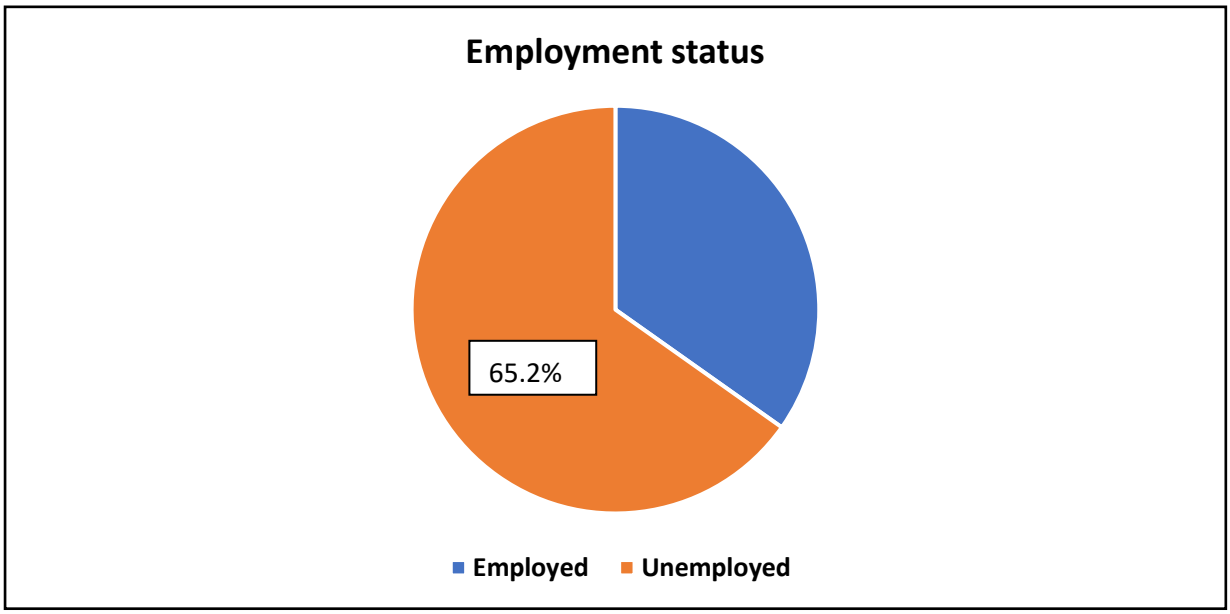


Figure 8 - Patient distribution based upon employment status

6. Patient distribution based upon number of sites involved.

Majority i.e 75.8% (50/66), had multiple site (neck/axilla/elbow/knee/facial) involvement and remaining 24.2% (16/66) had single site (neck or axilla) involved.

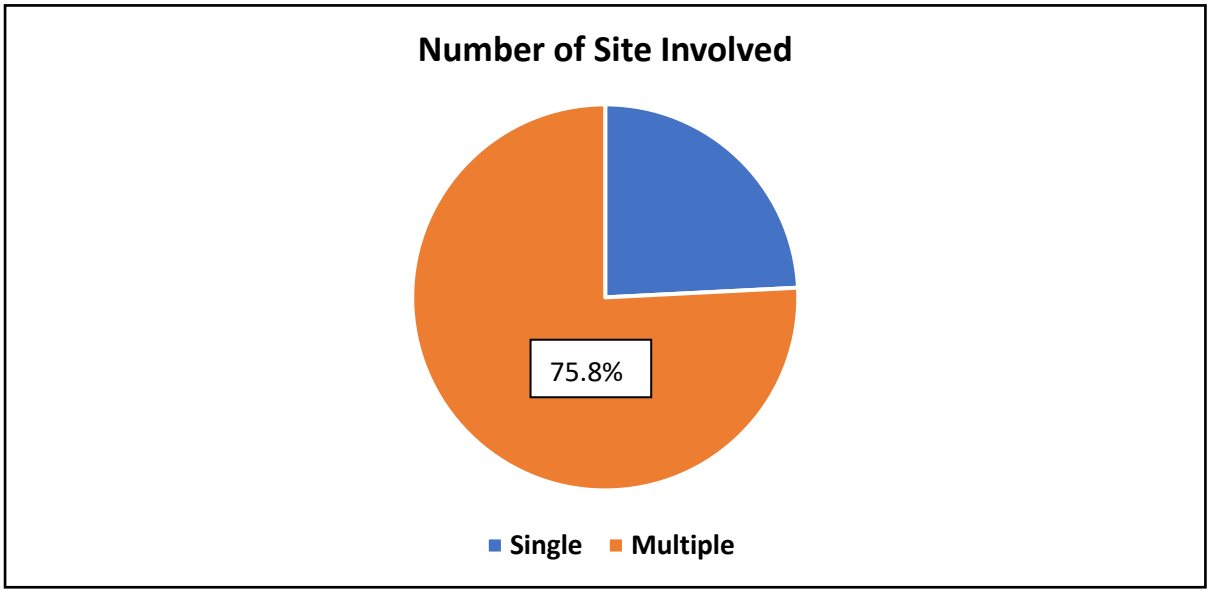


Figure 9 - Distribution of patients based on number of sites involved

7. Associated complains in the subjects

Out of 66 patients 93.9% (62/66) had a complain of weight gain, 30.3% (20/66) had patterned hair loss, and 56.1% (37/66) had skin tags.

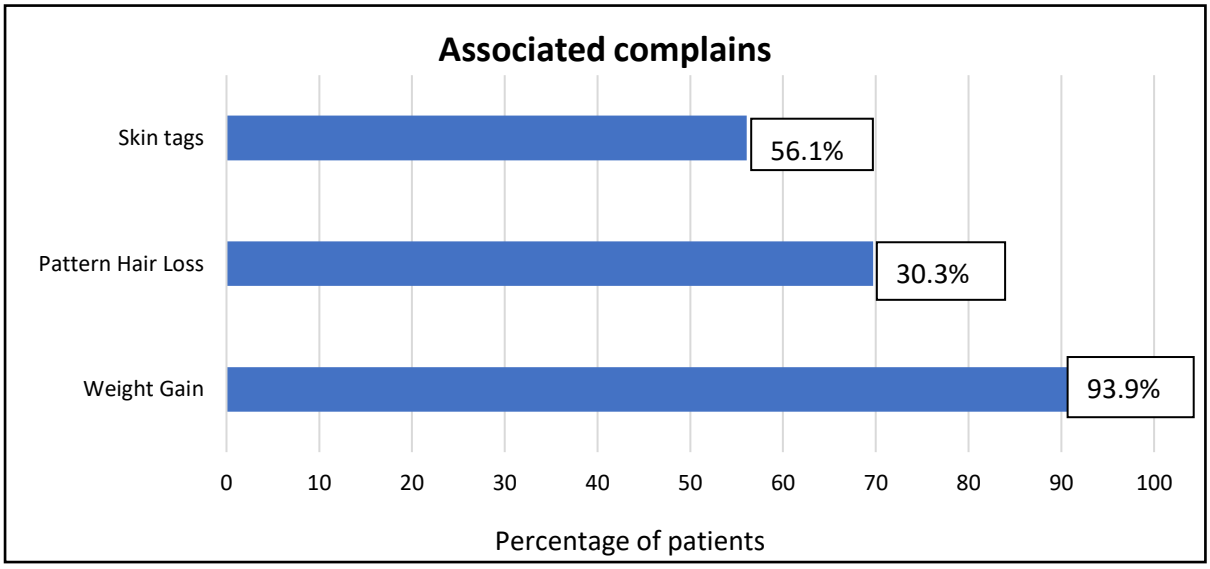


Figure 10 – Horizonal bar diagram showing prevalence of associated complains with AN.

8. Associated complains in female subjects.

Among 47 female subjects 18.2% (n=12) had hirsutism, and 40.9%(n=27) has history of irregular menstrual cycle.

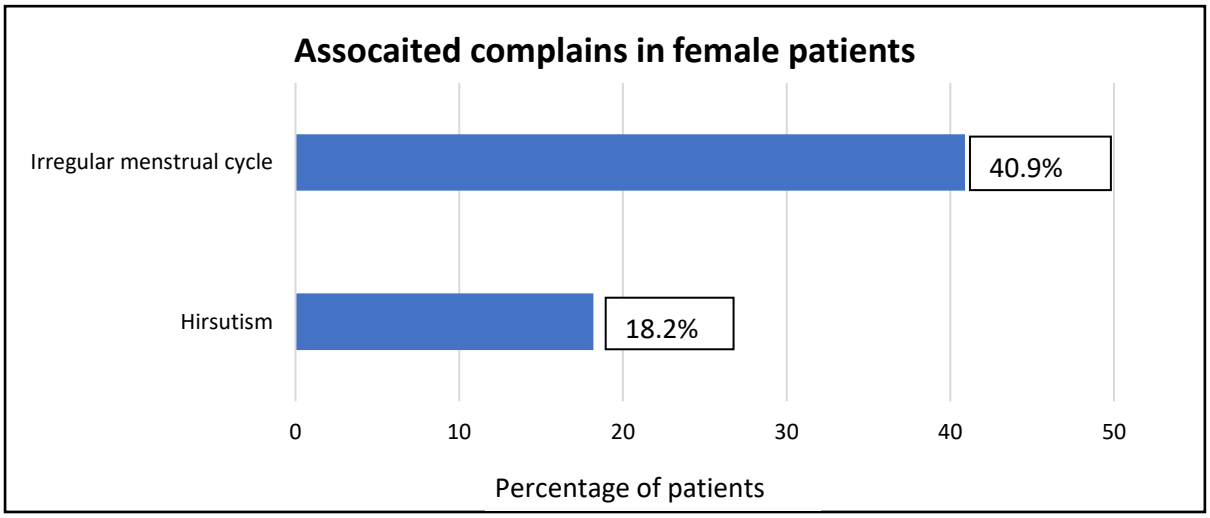


Figure 11 – Horizontal bar diagram showing prevalence of associated complains in female patients.

9. Presence of comorbidities

Out of 66 patients 6.1% (4/66) had hypertension (HTN), 3% (2/66) had diabetes (DM) (not taking any medication) and 6.1% (/66) were hypothyroid.

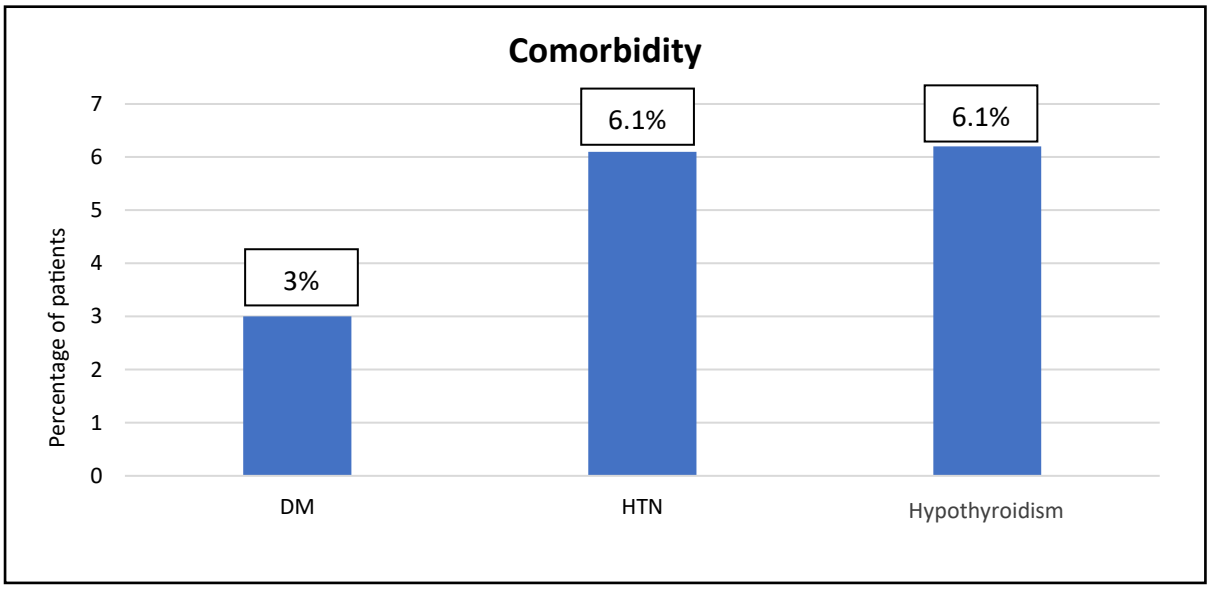


Figure 12 – Vertical Bar diagram showing prevalence of comorbidities in patients .

10. Presence of Habits

Out of the 66 patients 30.3% (20/66) patients consumed alcohol and 4.5% (3/66) patients smoked routinely.

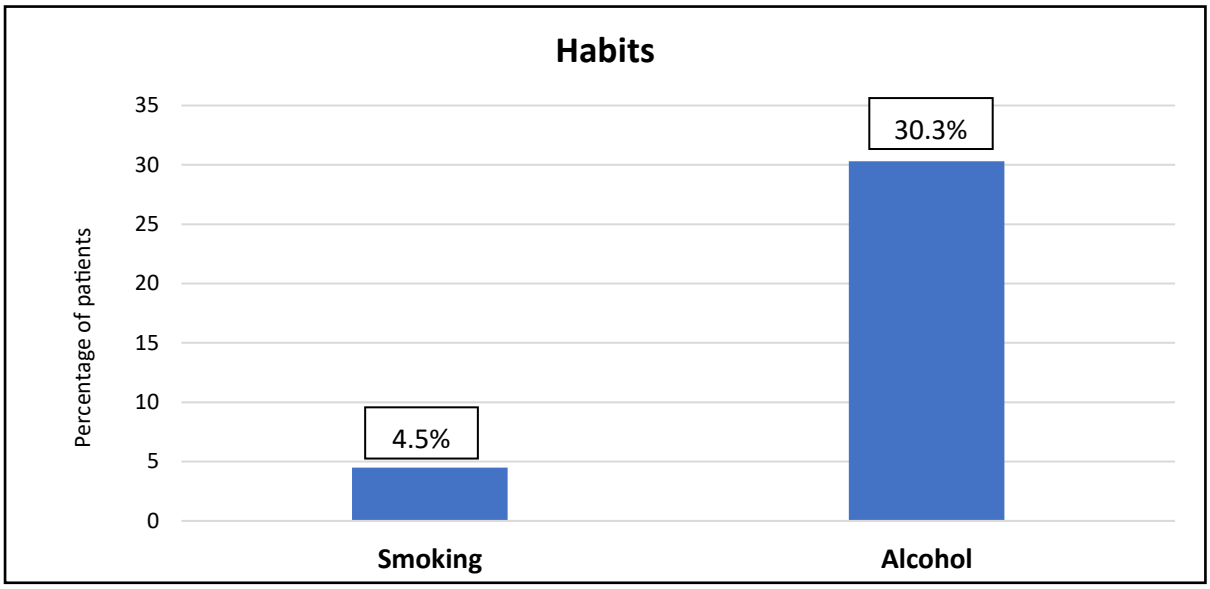


Figure 13 – Vertical bar diagram showing prevalence of habits in patient.

11. Family history of AN:

Out of 66 patients, 18.2% (12/66) patients had positive family history of AN

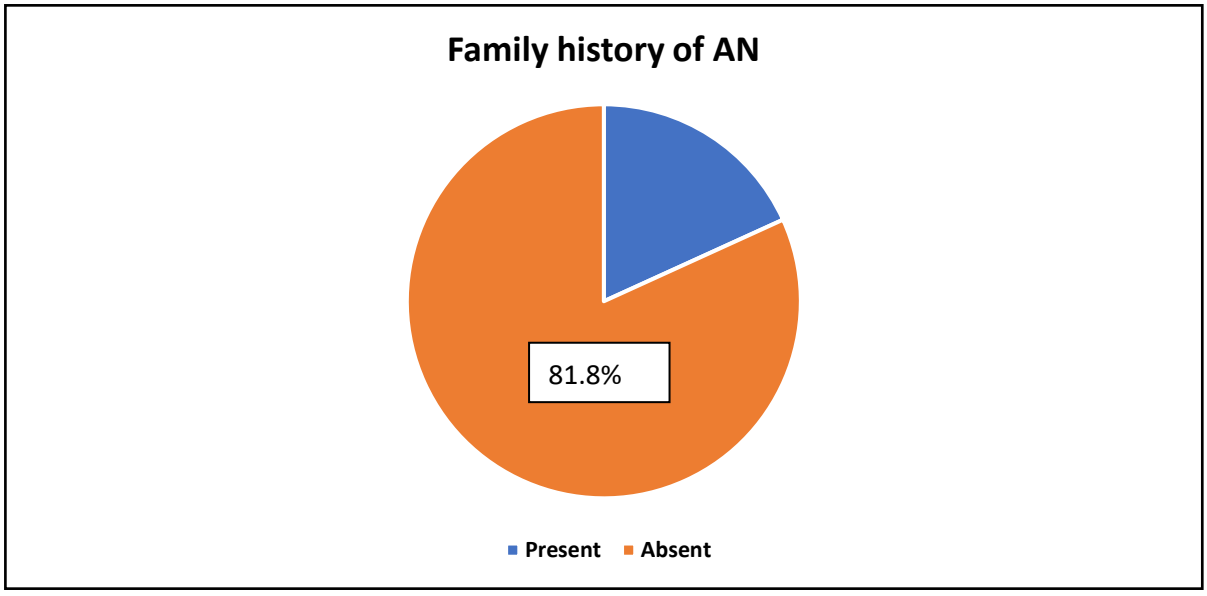


Figure 14 – Pie chart showing prevalence of presence family history in AN patients

12. Use of Oral Contraceptive Pills in female subjects.

Out of 47 female subjects 6 patients, 9.1% were using OCPs.

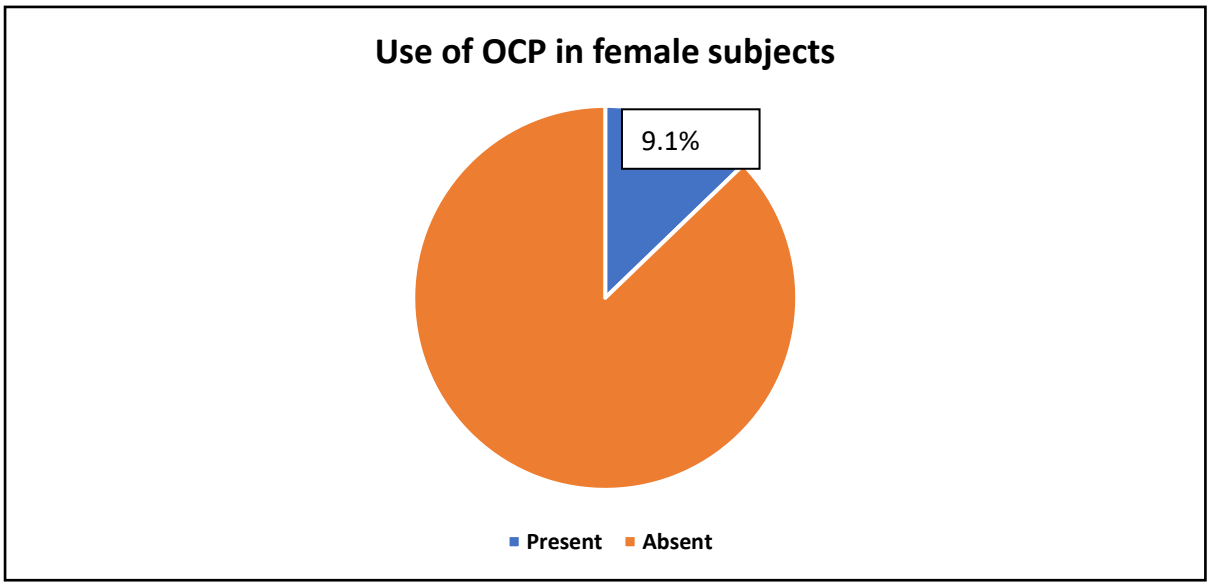


Figure 15 – Pie chart showing prevalence of use of OCPs in female participants.

B. PRE-TREATMENT AND POST-TREATMENT ANALYSIS IN METFORMIN GROUP.

A. Comparison of various Dermoscopic Parameters before and after administration of metformin at various sites

1. Neck

i. **Sulci Cutis**

Table 10 – Shows number of patients who had changes in dermoscopy of neck in sulci cutis pre- and post-administration of metformin.

		Post		P value
		Narrow	Wide	
Pre	Narrow	12 (42.90)	16 (57.10)	**< 0.001***
	Wide	1 (20)	4 (80)	

*Significant

ii. **Cristi Cutis - Rhomboid Formation**

Table 11- Shows number of patients who had changes in dermoscopy of neck in cristi cuti pre- and post-administration of metformin.

		Post		P value
		Absent	Present	
Pre	Absent	14 (100)	0 (0)	1
	Present	0 (0)	19 (100)	

iii. **Hyperpigmented Dots/Globules**

Table 12 - Shows number of patients who had changes in dermoscopy of neck in hyperpigmented dots/globules pre- and post-administration of metformin.

		Post			P value
		<50	>50	Absent	
Pre	<50	9 (81.80)	0	2 (18.20)	**0.011***
	>50	7 (87.50)	1 (12.50)	0	
	Absent	0	0	14 (100)	

*Significant

iv. Hyperpigmented Blotches

Table 13 - Shows number of patients who had changes in dermoscopy of neck in hyperpigmented blotches pre- and post-administration of metformin.

		Post		P value
		Absent	Present	
Pre	Absent	19 (100)	0	1
	Present	1 (7.10)	13 (92.90)	

v. Crypts

Table 14 - Shows number of patients who had changes in dermoscopy of neck in crypts pre- and post-administration of metformin.

		Post		P value
		Absent	Present	
Pre	Absent	24 (100)	0	0.125
	Present	4 (44.40)	5 (55.60)	

vi. White Streaks/Globules

Table 15 - Shows number of patients who had changes in dermoscopy of neck in white streaks and globules pre- and post-administration of metformin.

		Post		P value
		Absent	Present	
Pre	Absent	30 (100)	0	1
	Present	0	(100)	

The McNemar test was used to analyze the dermoscopic parameters before and after administering metformin. The results indicated that there were significant differences in the neck in context to **Sulci Cutis and Hyperpigmented Dots/Globules** between pre and post treatment. However, for the other variables (Cristi cutis - rhomboid formation, hyperpigmented blotches, crypts, white streaks/globules) no significant differences were found.

2. Right Axilla

i. Sulci Cutis

Table 16 - Shows number of patients who had changes in sulci cutis in right axilla pre- and post-administration of metformin.

		Post			P value
		Narrow	Wide	Absent	
Pre	Narrow	10 (41.70)	14 (58.30)	0	**< 0.001***
	Wide	0	2 (100)	0	
	Absent	0	0	1 (100)	

*Significant

ii. Cristae Cutis - Rhomboid Formation

Table 17 - Shows number of patients who had changes in cristae cutis in right axilla pre- and post-administration of metformin.

		Post		P value
		Absent	Present	
Pre	Absent	15 (100)	0	1
	Present	1 (8.30)	11 (91.70)	

iii. Hyperpigmented Dots/Globules

Table 18 - Shows number of patients who had changes in hyperpigmented dots/globules in right axilla pre- and post-administration of metformin.

		Post			P value
		<50	>50	Absent	
Pre	<50	3 (75)	0	1 (25)	**0.007***
	>50	9 (69.20)	4 (30.80)	0	
	Absent	0	0	10 (100)	

*Significant

iv. Hyperpigmented Blotches

Table 19 - Shows number of patients who had changes in hyperpigmented blotches in right axilla pre- and post-administration of metformin

		Post		P value
		Absent	Present	
Pre	Absent	18 (100)	0	0.5
	Present	2 (22.20)	7 (77.80)	

v. Crypts

Table 20 - Shows number of patients who had changes in crypts in right axilla pre- and post-administration of metformin

		Post		P value
		Absent	Present	
Pre	Absent	20 (100)	0	1
	Present	0	7 (100)	

vi. White Streaks/Globules

Table 21 - Shows number of patients who had changes in white streaks/globules in right axilla pre- and post-administration of metformin

		Post		P value
		Absent	Present	
Pre	Absent	26	0	1
	Present	0	1 (100)	

The McNemar test was used to analyse the dermoscopic parameters before and after administering metformin in the right axilla. The results showed that there were significant differences in the right axilla in context to **Sulci Cutis and Hyperpigmented Dots/Globules variables** between pre and post-treatment. However, for the other variables (Cristi cutis rhomboid formation, hyperpigmented blotches, crypts, white streaks/globules) no significant differences were found.

3. Left Axilla

i. Sulci Cutis

Table 22 - Shows number of patients who had changes in sulci cutis in left axilla pre- and post-administration of metformin

		Post			P value
		Narrow	Wide	Absent	
Pre	Narrow	8 (34.80)	15 (65.20)	0	**< 0.001***
	Wide	0	3 (100)	0	
	Absent	0	0	1 (100)	

*Significant

ii. Cristae Cutis - Rhomboid Formation

Table 23 - Shows number of patients who had changes in Cristae cutis in left axilla pre- and post-administration of metformin

Rhomboid formation		Post		P value
		Absent	Present	
Pre	Absent	18 (100)	0	1
	Present	0	9 (100)	

iii. Hyperpigmented Dots/Globules

Table 24 - Shows number of patients who had changes in hyperpigmented dots/globules in left axilla pre- and post-administration of metformin

		Post			P value
		<50	>50	Absent	
Pre	<50	3 (100)	0	0	**0.003***
	>50	9 (64.30)	5 (35.70)	0	
	Absent	0	0	10 (100)	

*Significant

iv. Hyperpigmented Blotches

Table 25 - Shows number of patients who had changes in hyperpigmented blotches in left axilla pre- and post-administration of metformin

		Post		P value
		Absent	Present	
Pre	Absent	17 (100)	0	1
	Present	1 (10)	9 (90)	

v. Crypts

Table 26 - Shows number of patients who had changes in crypts in left axilla pre- and post-administration of metformin

		Post		P value
		Absent	Present	
Pre	Absent	20 (100)	0	1
	Present	0	7 (100)	

vi. White Streaks/Globules

Table 27 - Shows number of patients who had changes in white streaks in left axilla pre- and post-administration of metformin

		Post		P value
		Absent	Present	
Pre	Absent	25 (100)	0	1
	Present	0	2 (100)	

The McNemar test was used to analyze the dermoscopic parameters at baseline and after metformin administration for 12 weeks. The results indicated that there were significant differences in the left axilla in context to **Sulci Cutis and Hyperpigmented Dots/Globules variables** between the pre and post data. However, for the other variables (Cristi cutis rhomboid formation, hyperpigmented blotches, crypts, white streaks/globules) no significant differences were found.

B. Comparison of anthropometric and metabolic parameters at baseline and after administration of metformin

Table 28 - Anthropometric and biochemical at first visit and at twelve weeks at follow-up in metformin group.

Baseline	Mean± SD	Post treatment	Mean ± SD	P Value
Weight (Kg)	76.5758 ± 10.21344	Weight (Kg)	74.6364 ± 10.29508	**< 0.001***
BMI	29.5464 ± 3.51105	BMI	28.9215 ± 3.44205	
Waist Circumference (Cm)	99.2879 ± 6.64388	Waist Circumference (Cm)	97.697 ± 5.99732	
Burke's Grade	8.64 ± 2.679	Burke's Grade	6.73 ± 2.081	
Fasting insulin	27.327 ± 5.9465	Fasting insulin	21.552 ± 5.3409	
Triglycerides	196.27 ± 45.076	Triglycerides	178.45 ± 47.889	
Fasting glucose	124.09 ± 39.575	Fasting glucose	106.3 ± 23.74	
HOMA-IR	7.94 ± 3.335	HOMA-IR	5.0909 ± 1.86017	

*Significant

The paired t-test was conducted to identify significant differences amongst the measurements at baseline and follow-up after giving metformin. The results of the paired t-test show significant difference between the pre- and post-intervention values for all the measured variables. The average values for weight, BMI, waist circumference, Burke's Grade, fasting levels of insulin, triglycerides, glucose, and Homeostatic Model Assessment of insulin resistance all exhibited a statistically significant decrease after the intervention with metformin, as indicated by p-values below 0.001.

C. PRE-TREATMENT AND POST-TREATMENT ANALYSIS IN PIOGLITAZONE GROUP.

I. Comparison of various Dermoscopic Parameters before and after administration of pioglitazone at various sites

1. Neck

i. Sulci Cutis

Table 29 - Shows number of patients who had alterations in morphology of sulci cutis at the neck pre- and post-administration of pioglitazone.

		Post		P value
		Narrow	Wide	
Pre	Narrow	9 (40.9)	13 (59.1)	**0.002***
	Wide	1 (10)	9 (90)	

ii. Cristi Cutis - Rhomboid Formation

Table 30 - Shows number of patients who had changes in cristae cutis at the neck pre- and post-administration of pioglitazone.

		Post		P value
		Absent	Present	
Pre	Absent	13 (100)	0	1
	Present	0	19 (100)	

iii. Hyperpigmented Dots/Globules

Table 31 - Shows number of patients who had changes in hyperpigmented dots/globules at the neck pre- and post-administration of pioglitazone

		Post			P value
		<50	>50	Absent	
Pre	<50	12 (100)	0	0	NA
	>50	7 (100)	0	0	
	Absent	0	0	13 (100)	

iv. Hyperpigmented Blotches

Table 32 - Shows number of patients who had changes in hyperpigmented blotches at the neck pre- and post-administration of pioglitazone

		Post		P value
		Absent	Present	
Pre	Absent	24 (100)	0	0.063
	Present	5 (62.5)	3 (37.5)	

v. Crypts

Table 33 - Shows number of patients who had changes in crypts at the neck pre- and post-administration of pioglitazone

		Post		P value
		Absent	Present	
Pre	Absent	24 (100)	0	0.25
	Present	3 (37.5)	5 (62.5)	

vi. White Streaks/Globules

Table 34 - Shows number of patients who had changes in white streaks/globules at the neck pre- and post-administration of pioglitazone

		Post		P value
		Absent	Present	
Pre	Absent	31 (96.9)	1 (3.1)	1
	Present	0	0	

The McNemar test was used to analyze the dermoscopic parameters before and after administering pioglitazone. The results indicated that there were significant differences in the neck in context to Sulci Cutis variable between pre and post treatment. However, for the other variables no significant differences were found.

2. Right Axilla

i. Sulci Cutis

Table 35 - Shows number of patients who had changes in sulci cutis in right axilla pre- and post-administration of pioglitazone.

		Post			P value
		Narrow	Wide	Absent	
Pre	Narrow	7 (36.8)	12 (63.2)	0	**0.001***
	Wide	0	4 (100)	0	
	Absent	0	0	1 (100)	

ii. Cristae Cutis - Rhomboid Formation

Table 36 - Shows number of patients who had changes in cristae cutis in right axilla pre- and post-administration of pioglitazone.

		Post		P value
		Absent	Present	
Pre	Absent	12 (92.3)	1 (7.7)	1
	Present	0	11 (100)	

iii. Hyperpigmented Dots/Globules

Table 37 - Shows number of patients who had changes in hyperpigmented dots/globules in right axilla pre- and post-administration of pioglitazone

		Post			P value
		<50	>50	Absent	
Pre	<50	6 (100)	0	0	**0.002***
	>50	10 (76.9)	3 (23.1)	0	
	Absent	0	0	5 (100)	

iv. Hyperpigmented Blotches

Table 38 - Shows number of patients who had changes in hyperpigmented blotches in right axilla pre- and post-administration of pioglitazone

		Post		P value
		Absent	Present	
Pre	Absent	15 (100)	0	0.125
	Present	4 (44.4)	5 (55.6)	

v. Crypts

Table 39 - Shows number of patients who had changes in crypts in right axilla pre- and post-administration of pioglitazone

		Post		P value
		Absent	Present	
Pre	Absent	17 (100)	0	1
	Present	1 (14.3)	6 (85.7)	

vi. White Streaks/Globules

Table 40 - Shows number of patients who had changes in white streaks/globules in right axilla pre- and post-administration of pioglitazone

		Post		P value
		Absent	Present	
Pre	Absent	21 (100)	0	1
	Present	0	3 (100)	

The McNemar test was used to analyse the dermoscopic parameters before and after administering pioglitazone. The results indicated that there were significant differences in the sulci cutis right axilla and hyperpigmented dots/globules right axilla variables between the pre and post data. However, for the other variables no significant differences were found.

3. Left Axilla

i. Sulci Cutis

Table 41- Shows number of patients who had changes in sulci cutis in left axilla pre- and post-administration of pioglitazone.

		Post			P value
		Narrow	Wide	Absent	
Pre	Narrow	11 (55)	8 (40)	1 (5)	**0.011***
	Wide	0	3 (100)	0	
	Absent	0	0	1 (100)	

ii. Cristi Cutis - Rhomboid Formation

Table 42 - Shows number of patients who had changes in cristae cutis in left axilla pre- and post-administration of pioglitazone.

		Post		P value
		Absent	Present	
Pre	Absent	12 (92.3)	1 (7.7)	1
	Present	0	11 (100)	

iii. Hyperpigmented Dots/Globules

Table 43 - Shows number of patients who had changes in hyperpigmented dots/globules in left axilla pre- and post-administration of pioglitazone.

		Post			P value
		<50	>50	Absent	
Pre	<50	7 (100)	0	0	**0.002***
	>50	10 (83.3)	2 (16.7)	0	
	Absent	0	0	5 (100)	

iv. Hyperpigmented Blotches

Table 44 - Shows number of patients who had changes in hyperpigmented blotches in left axilla pre- and post-administration of pioglitazone.

		Post		P value
		Absent	Present	
Pre	Absent	14 (100)	0	1
	Present	1 (10)	9 (90)	

v. Crypts

Table 45 - Shows number of patients who had changes in crypts in left axilla pre- and post-administration of pioglitazone.

		Post		P value
		Absent	Present	
Pre	Absent	15 (100)	0	1
	Present	0	9 (100)	

vi. White Streaks/Globules

Table 46 - Shows number of patients who had changes in white streaks/globules in left axilla pre- and post-administration of pioglitazone.

		Post		P value
		Absent	Present	
Pre	Absent	21 (100)	0	1
	Present	0	3 (100)	

The McNemar test was used to analyse the dermoscopic parameters at baseline and post pioglitazone administration. The results indicated that there were significant differences in the left axilla in context to Sulci Cutis and Hyperpigmented Dots/Globules variables between pre and post treatment. However, for the other variables no significant differences were found.

II. Comparison of Anthropometric and Biochemical Parameters baseline and post pioglitazone administration.

Table 47 - Anthropometric and biochemical at baseline and at 12 weeks of follow-up in pioglitazone group.

Baseline	Mean± SD	Post treatment	Mean ± SD	P Value
Weight (Kg)	74.9697 ± 8.10665	Weight (Kg)	74.9394 ± 7.43278	0.933
BMI	30.0061 ± 2.88064	BMI	30.0012 ± 2.55048	0.974
Waist Circumference (Cm)	101.1818 ± 6.88047	Waist Circumference (Cm)	99.9697 ± 6.81214	**< 0.001***
Burke's Grade	7.48 ± 3.134	Burke's Grade	5.79 ± 2.534	**< 0.001***
Fasting insulin	22.245 ± 6.3646	Fasting insulin	17.818 ± 5.4969	**< 0.001***
Triglycerides	164.7 ± 44.677	Triglycerides	148.06 ± 35.142	**< 0.001***
Fasting glucose	121.09 ± 33.441	Fasting glucose	107.64 ± 24.847	**< 0.001***
HOMA-IR	6.15 ± 2.526	HOMA-IR	4.3933 ± 1.8199	**< 0.001***

*Significant

The paired t-test was used to compare the differences between baseline and follow-up measurements after administering Pioglitazone drug. The results indicate significant changes in several variables. Waist circumference, Burke's Grade, fasting insulin levels, triglyceride levels, fasting glucose levels and Homa-IR all showed statistically significant decreases post-intervention, as demonstrated by p-values less than 0.001. However, there were no significant differences observed in weight and BMI between the pre and post measurements.

D. PRE-TREATMENT AND POST-TREATMENT ANALYSIS BETWEEN METFORMIN AND PIOGLITAZONE.

A. Dermoscopic parameters

1. Neck

Table 48 – Comparison of changes in dermoscopic parameters observed at neck in metformin group and pioglitazone group.

		Drug		P Value
		Metformin (%)	Pioglitazone (%)	
Sulci Cutis	No Change	16 (47.10)	18 (52.90)	0.531
	Change	17 (54.80)	14 (45.20)	
Cristi Cutis - Rhomboid Formation	No Change	33 (50.80)	32 (49.20)	1
	Change	0	0	
Hyperpigmented Dots/Globules	No Change	24 (49)	25 (51)	0.614
	Change	9 (56.30)	7 (43.80)	
Hyperpigmented Blotches	No Change	32 (54.20)	27 (45.80)	0.105
	Change	1 (16.70)	5 (83.30)	
Crypts	No Change	29 (50)	29 (50)	1
	Change	4 (57.10)	3 (42.90)	
White Streaks/Globules	No Change	33 (51.60)	31 (48.40)	0.492
	Change	0	1 (100)	
Papillary Projections	No Change	12 (57.10)	9 (42.90)	0.478
	Change	21 (47.70)	23 (52.30)	

The chi-square test was used to examine the relationship between dermoscopic parameters for neck and type of drug used. However, the results did not show a significant association between dermoscopic parameters for the neck and the type of drug.

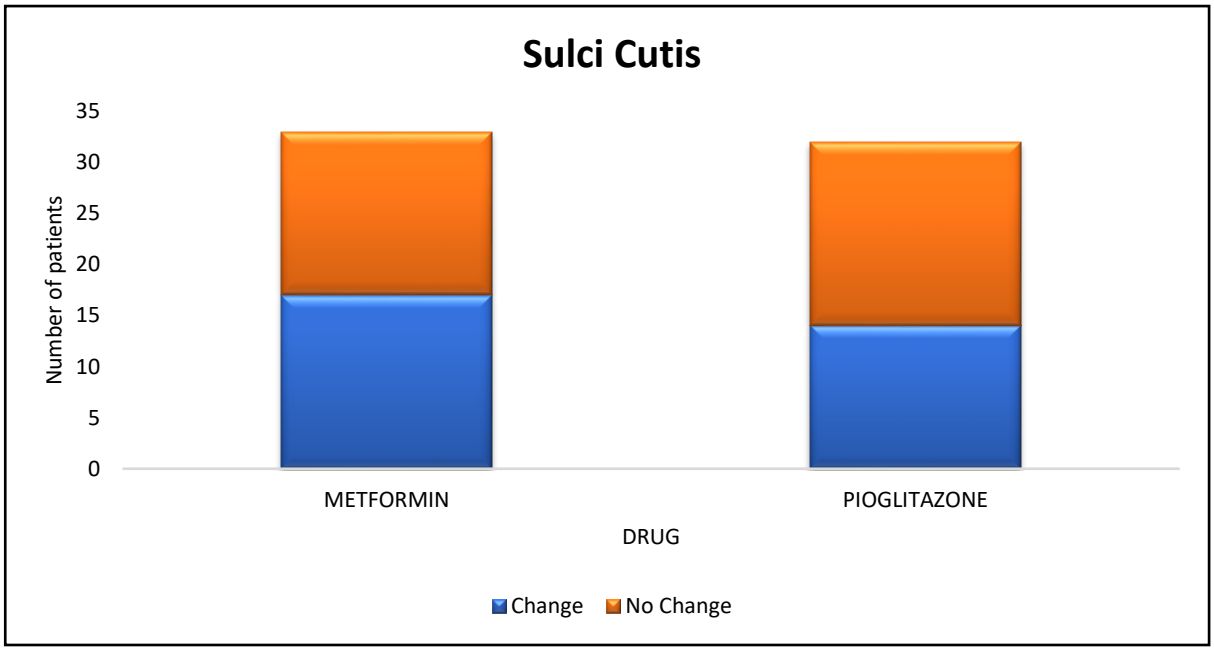


Figure 16 – Bar diagram showing number of patients who had changes in sulci cutis on neck dermoscopy.

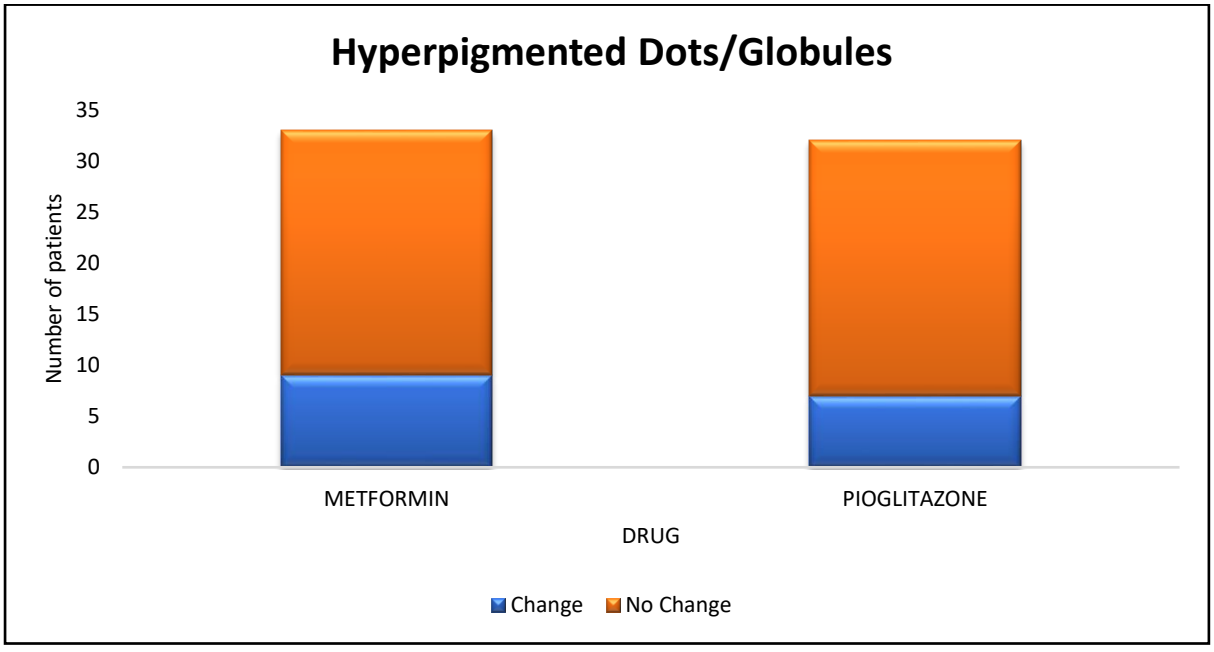


Figure 17 - Bar diagram showing number of patients who had changes in hyperpigmented dots on neck dermoscopy.

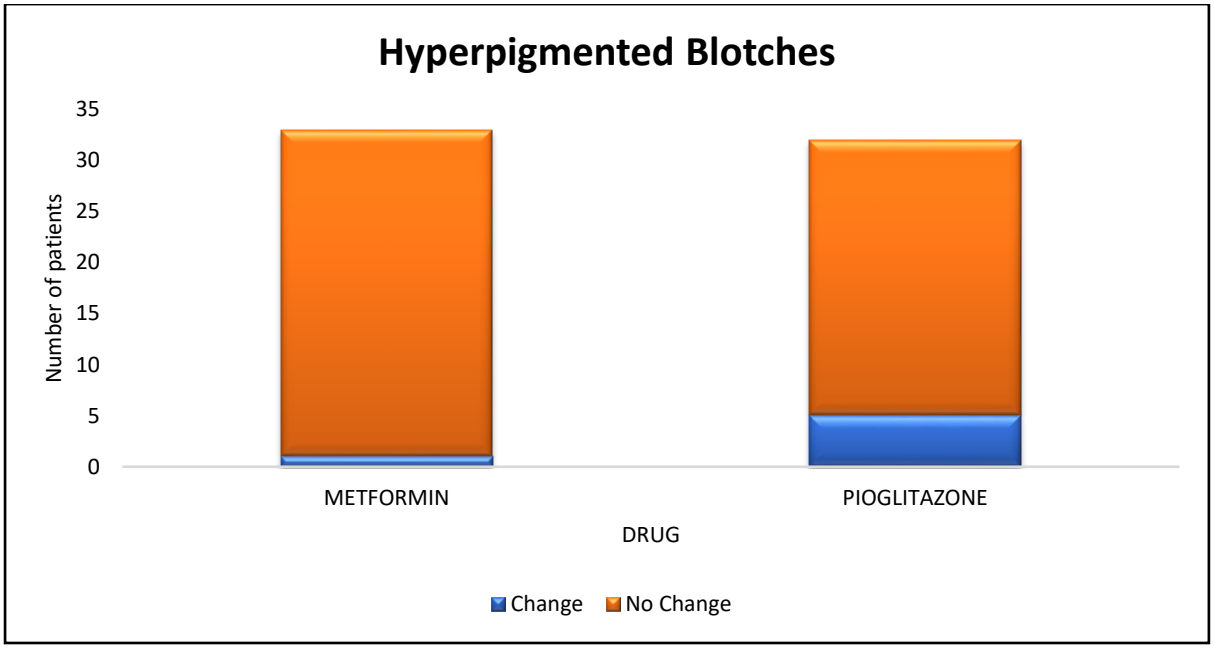


Figure 18 - Bar diagram showing number of patients who had changes in hyperpigmented blotches on neck dermoscopy.

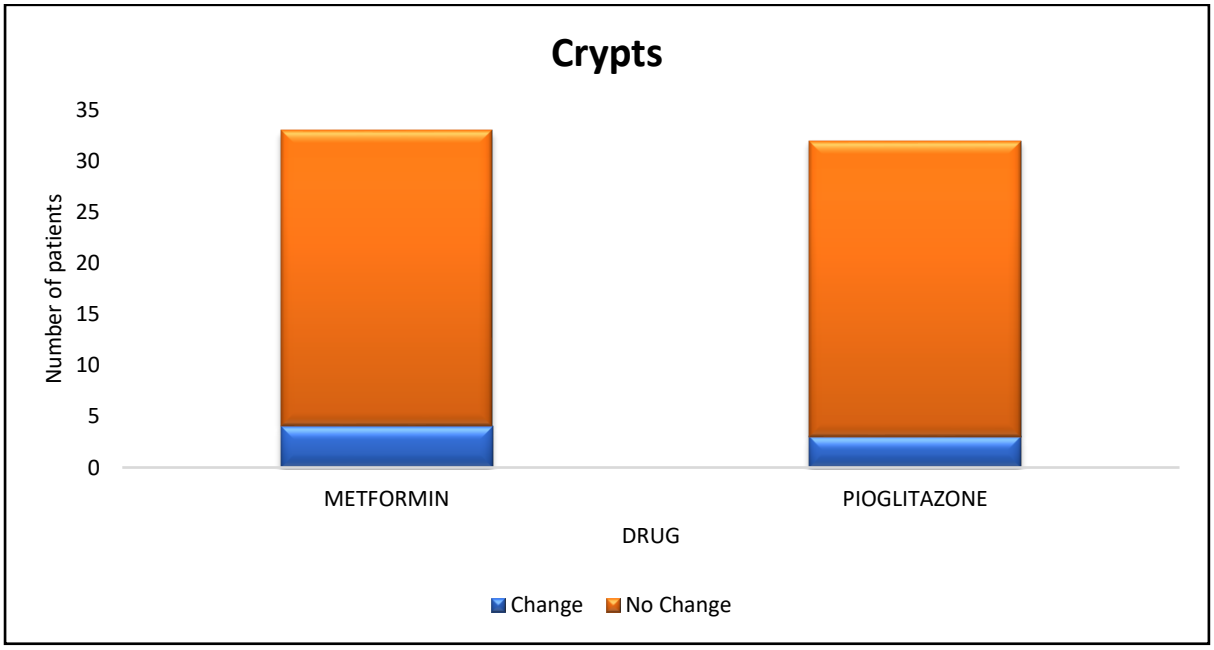


Figure 19 - Bar diagram showing number of patients who had changes in crypts dots on neck dermoscopy.

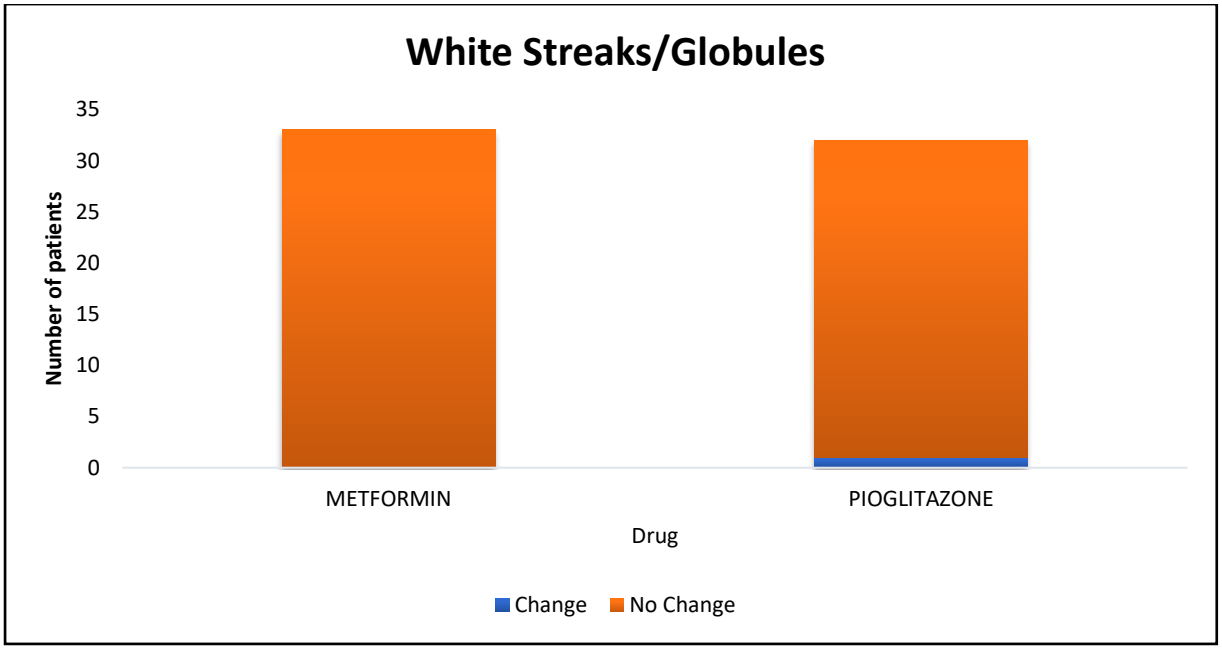


Figure 20 - Bar diagram showing number of patients who had changes in white streaks/ globules on neck dermoscopy.

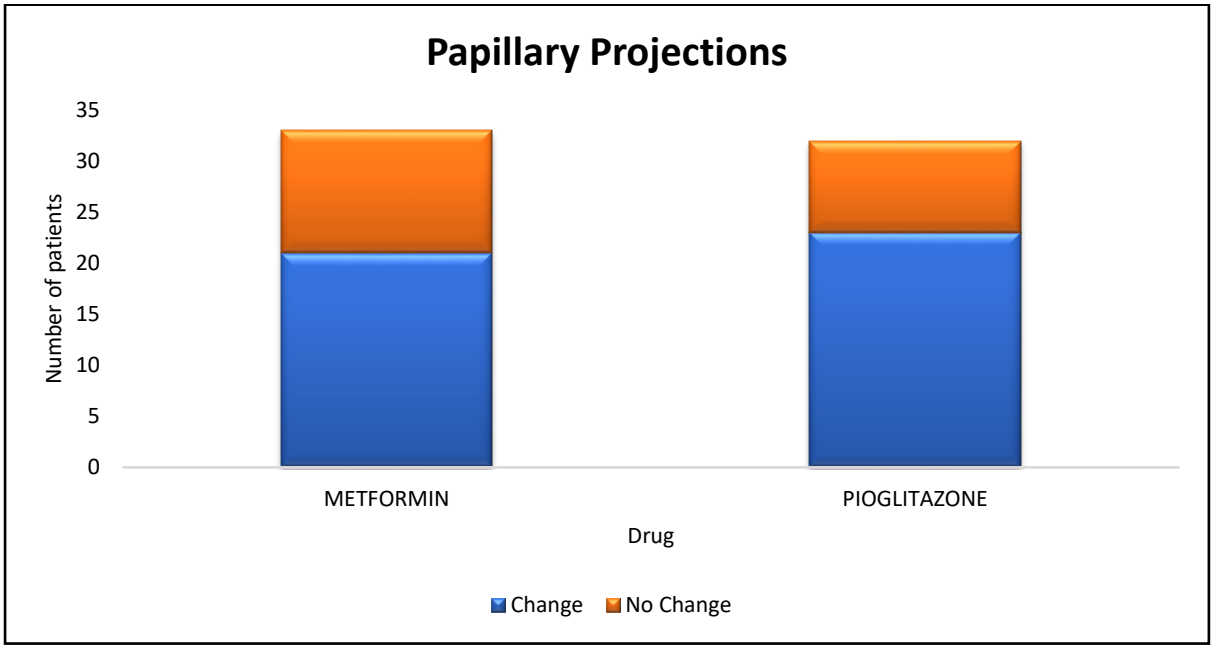


Figure 21 - Bar diagram showing number of patients who had changes in papilaary projections on neck dermoscopy.

2. **Right Axilla**

Table 49 - Comparison of changes in dermoscopic parameters observed in right axilla in metformin group and pioglitazone group.

Dermoscopic parameter		DRUG		P Value
		Metformin (%)	Pioglitazone (%)	
Sulci Cutis Right Axilla	No Change	13 (52)	12 (48)	0.895
	Change	14 (53.80)	12 (46.20)	
Cristi Cutis - Rhomboid Formation Right Axilla	No Change	26 (53.10)	23 (46.90)	1
	Change	1 (50)	1 (50)	
Hyperpigmented Dots/Globules Right Axilla	No Change	17 (54.80)	14 (45.20)	0.735
	Change	10 (50)	10 (50)	
Hyperpigmented Blotches Right Axilla	No Change	25 (55.60)	20 (44.40)	0.402
	Change	2 (33.30)	4 (66.70)	
Crypts Right Axilla	No Change	27 (54)	23 (46)	0.471
	Change	0	1 (100)	
White Streaks/Globules Right Axilla	No Change	27 (52.90)	24 (47.10)	1
	Change	0	0	
Papillary Projections Right Axilla	No Change	8 (53.3)	7 (46.7)	0.971
	Change	19 (52.8)	17 (47.2)	

The chi-square test was used to evaluate the relationship between dermoscopic parameters for right Axilla and the type of drug used. However, the results did not show a significant association between dermoscopic parameters for the Right Axilla and the type of drug.

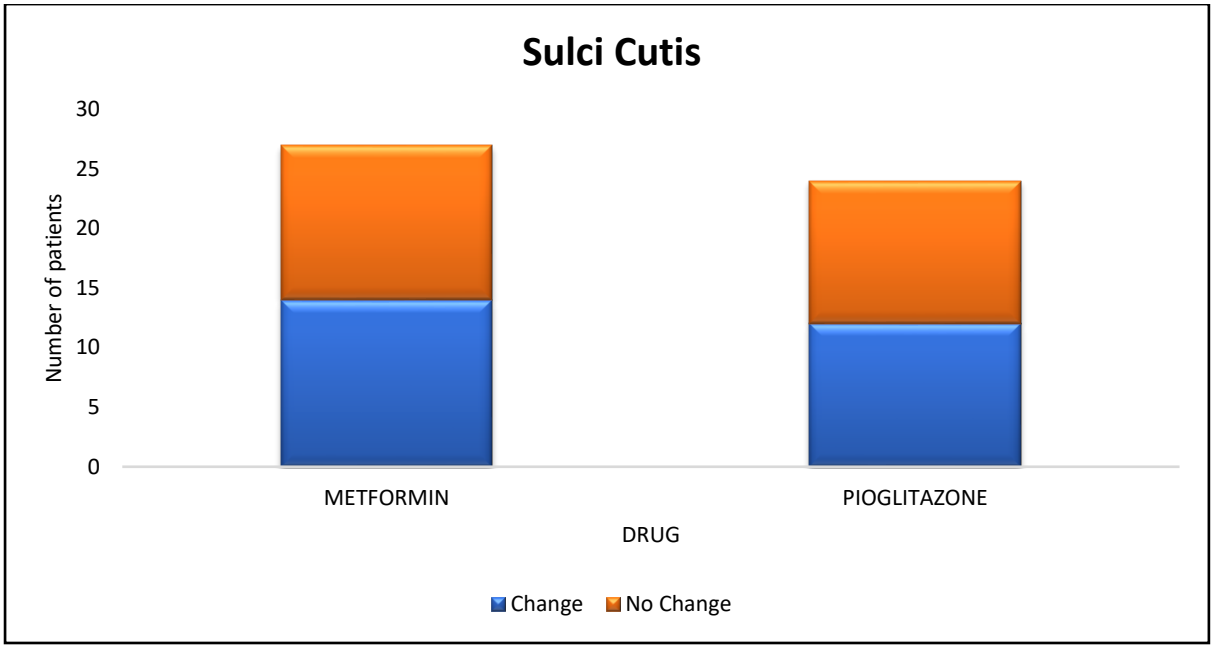


Figure 22 - Bar diagram showing number of patients who had changes on dermoscopy of right axilla in sulci cutis after treatment.

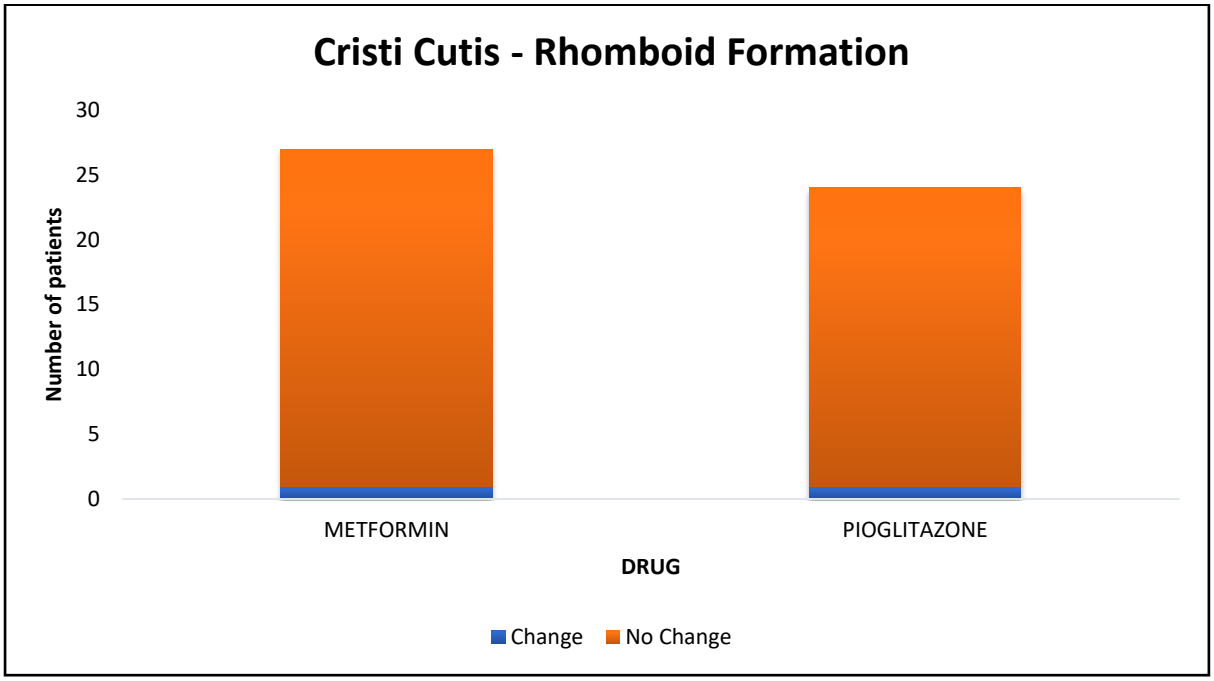


Figure 23 - Bar diagram showing number of patients who had changes on dermoscopy of right axilla in cristi cutis after treatment

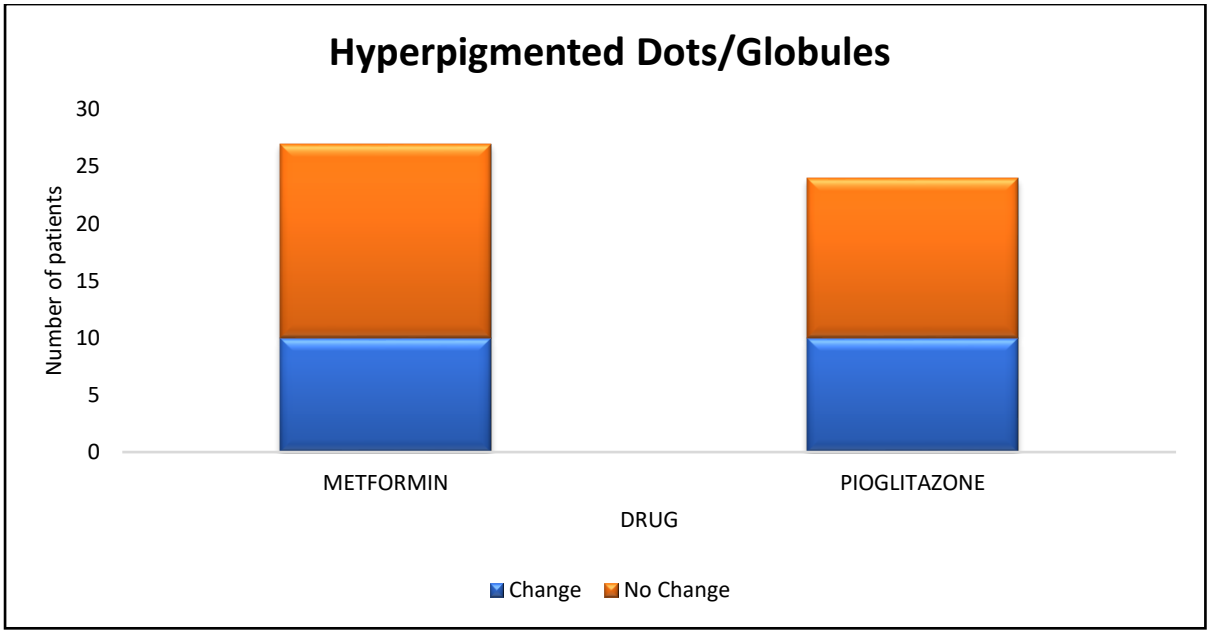


Figure 24- Bar diagram showing number of patients who had changes on dermoscopy of right axilla in hyperpigmented dots after treatment

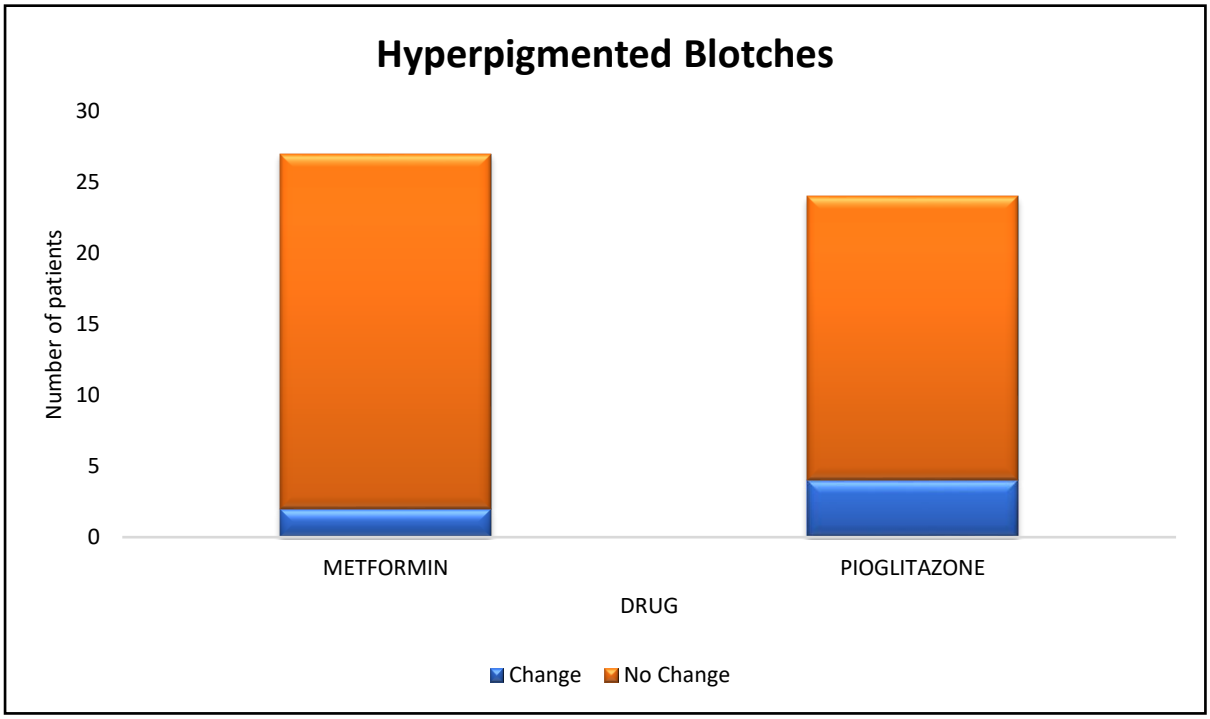


Figure 25- Bar diagram showing number of patients who had changes on dermoscopy of right axilla in hyperpigmented blotches after treatment.

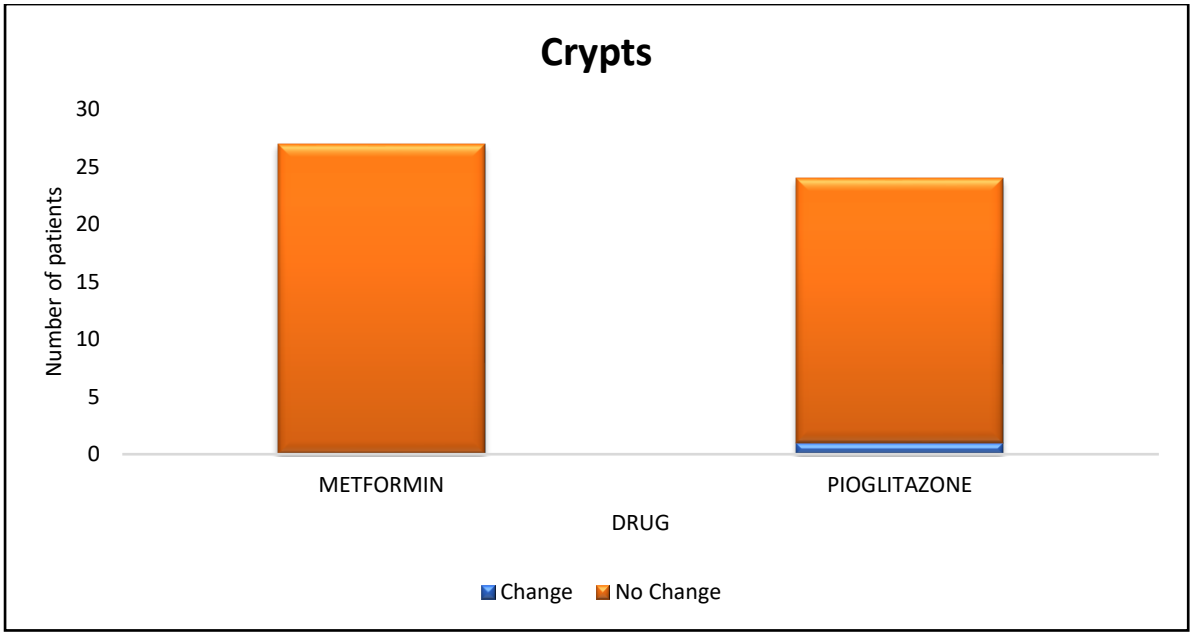


Figure 26 - Bar diagram showing number of patients who had changes on dermoscopy of right axilla in crypts after treatment.

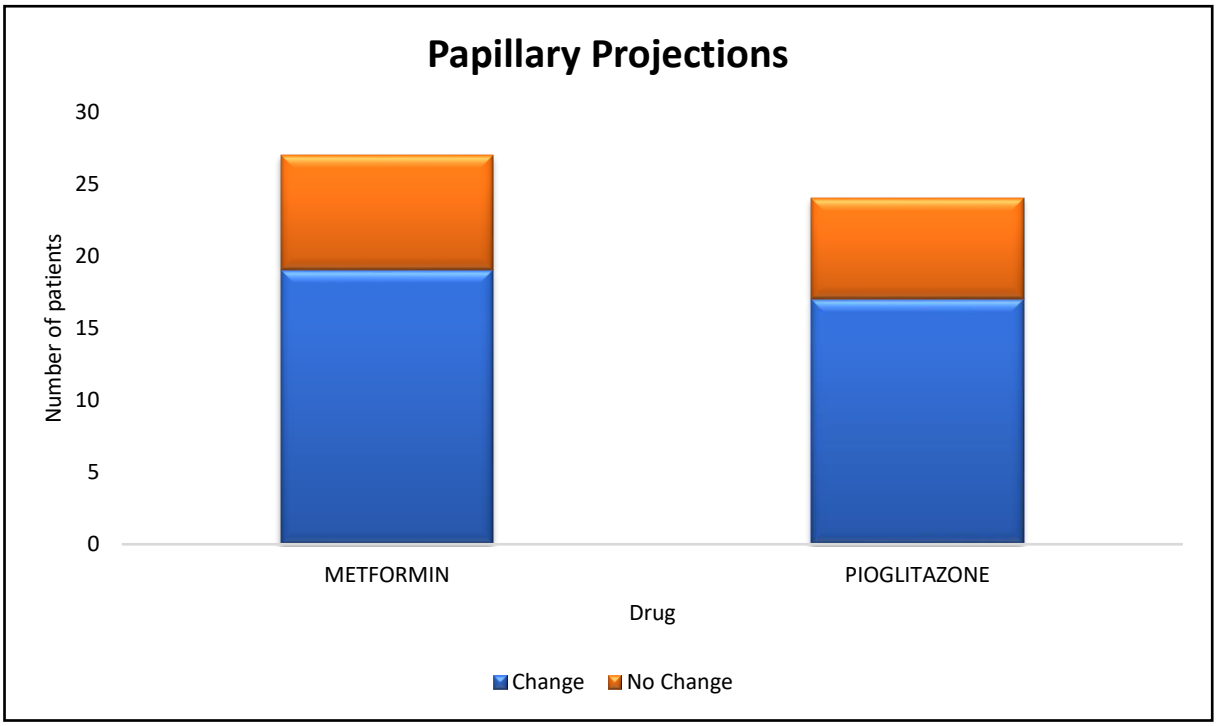


Figure 27 - Bar diagram showing number of patients who had changes on dermoscopy of right axilla in papillary projections after treatment.

3. Left Axilla

Table 50 - Comparison of changes in dermoscopic parameters observed in left axilla in metformin group and pioglitazone group.

		DRUG		P Value
		Metformin (%)	Pioglitazone (%)	
Sulci Cutis Left Axilla	No Change	12 (44.40)	15 (55.60)	0.197
	Change	15 (62.50)	9 (37.50)	
Cristi Cutis - Rhomboid Formation Left Axilla	No Change	27 (54)	23 (46)	0.471
	Change	0	1 (100)	
Hyperpigmented Dots/Globules Left Axilla	No Change	18 (56.30)	14 (43.80)	0.539
	Change	9 (47.40)	10 (52.60)	
Hyperpigmented Blotches Left Axilla	No Change	26 (53.10)	23 (46.90)	1
	Change	1 (50)	1 (50)	
Crypts Left Axilla	No Change	27 (52.90)	24 (47.10)	1
	Change	0	0	
White Streaks/Globules Left Axilla	No Change	27 (52.90)	24 (47.10)	1
	Change	0	0	
Papillary Projections Left Axilla	No Change	8 (57.1)	6 (42.9)	0.712
	Change	19 (51.4)	18 (48.6)	

The chi-square test was used to evaluate the relationship between dermoscopic parameters for left Axilla and the type of drug used. However, the results did not show a significant association between dermoscopic parameters for the Left Axilla and the type of drug.

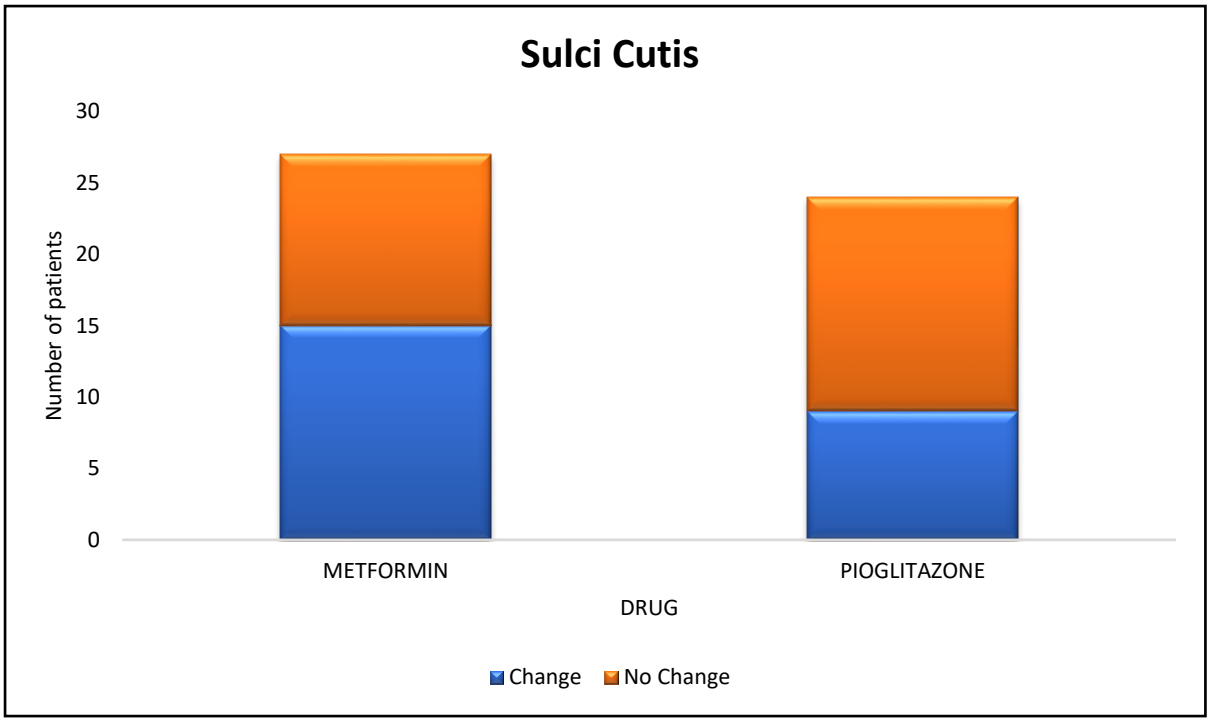


Figure 28 - Bar diagram showing number of patients who had changes on dermoscopy of left axilla in sulci cutis after treatment.

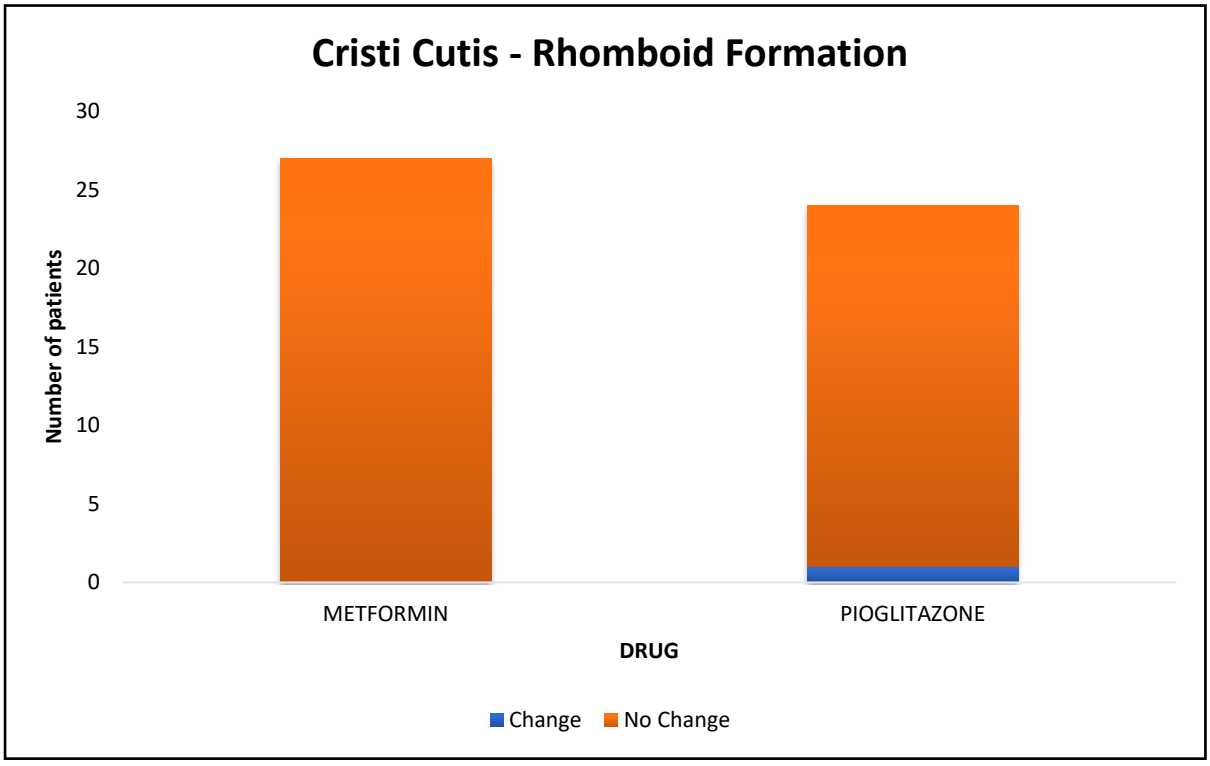


Figure 29 - Bar diagram showing number of patients who had changes on dermoscopy of left axilla in crista cutis after treatment

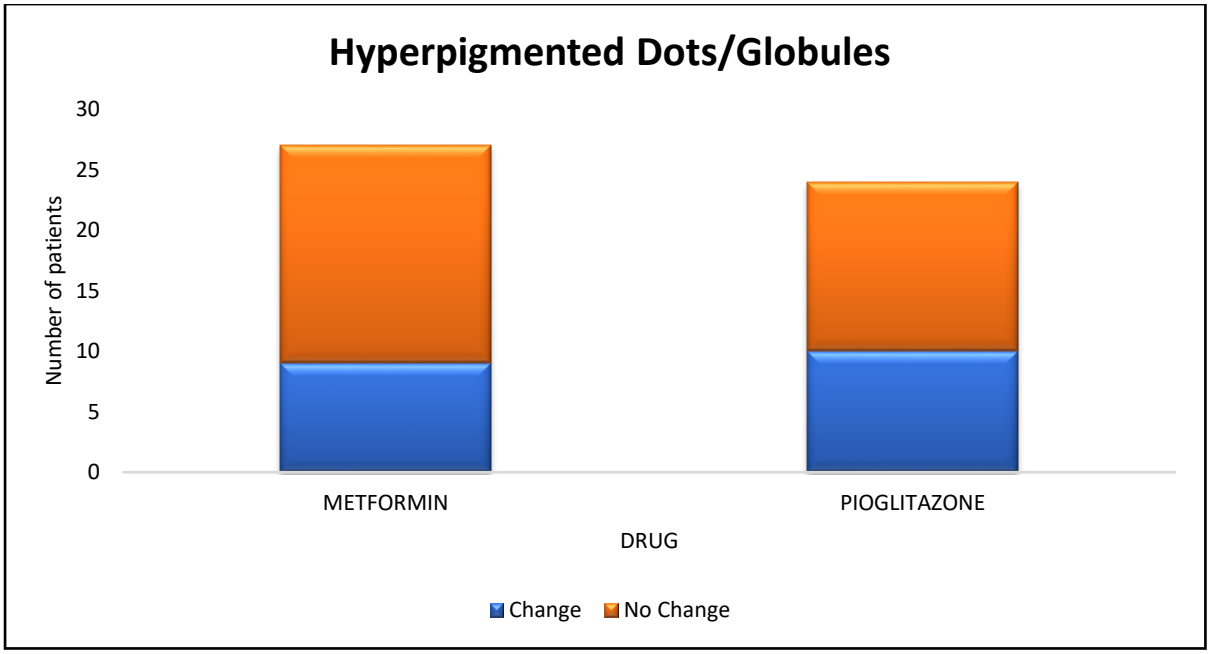


Figure 30 - Bar diagram showing number of patients who had changes on dermoscopy of left axilla in hyperpigmented dots after treatment

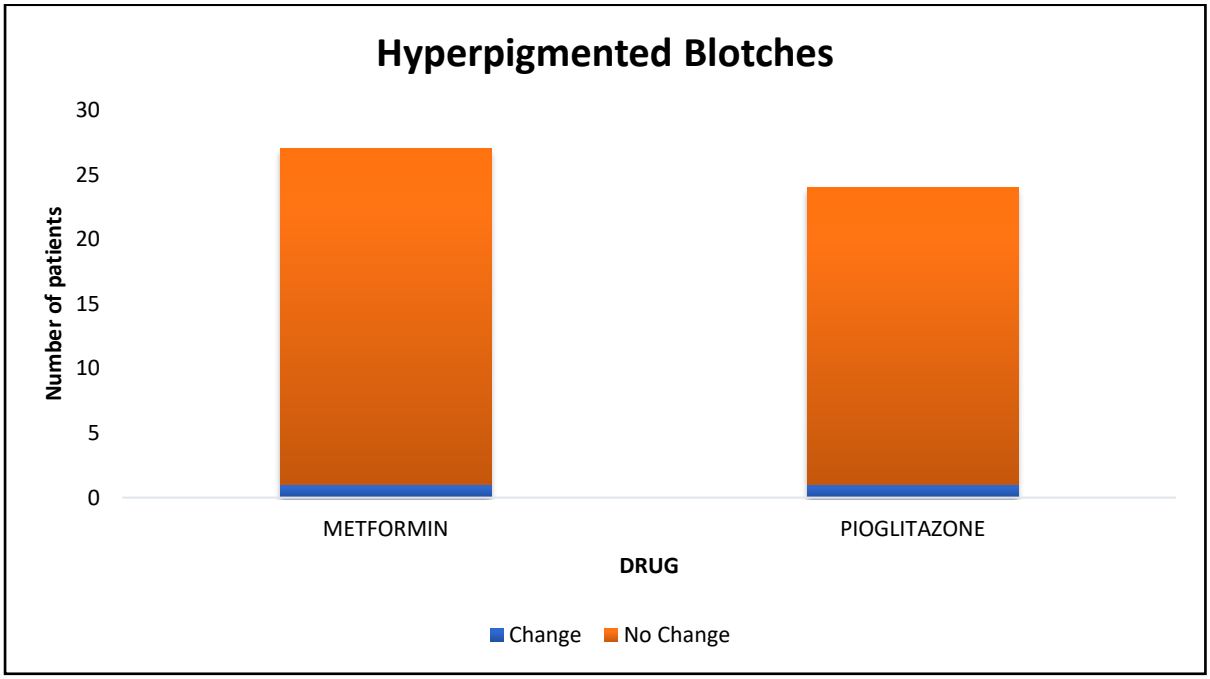


Figure 31 - Bar diagram showing number of patients who had changes on dermoscopy of right axilla in hyperpigmented blotches after treatment.

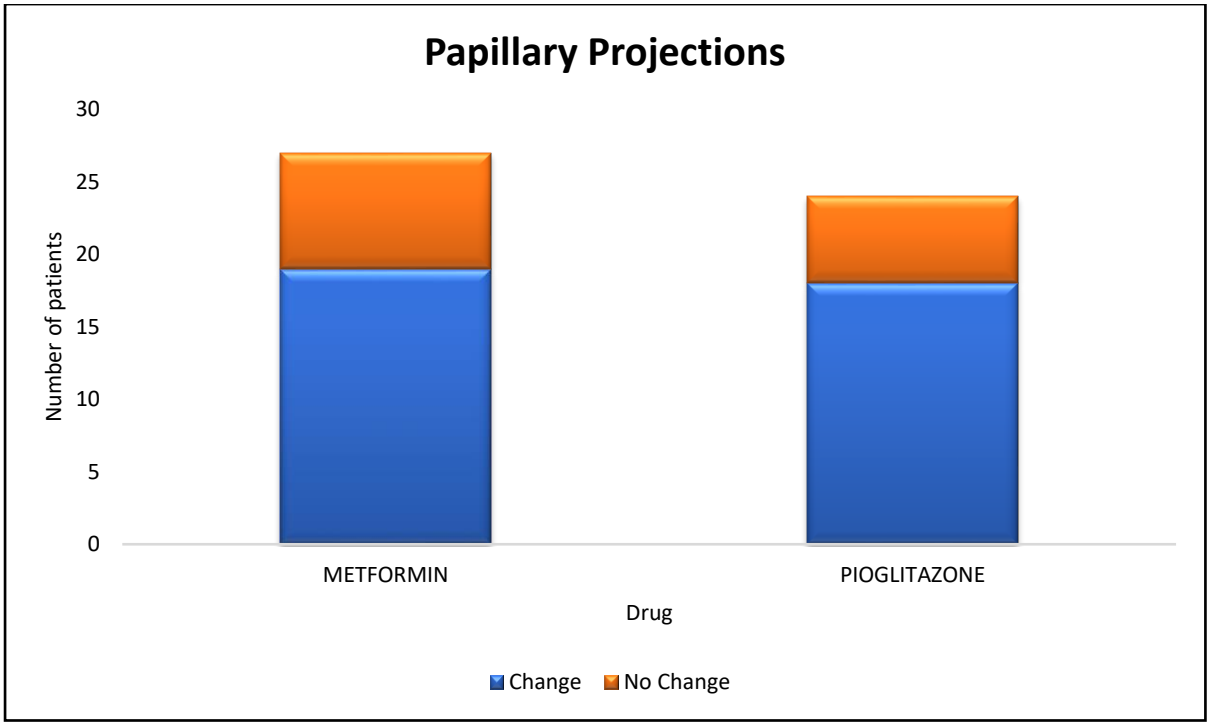


Figure 32 - Bar diagram showing number of patients who had changes on dermoscopy of right axilla in papillary projections after treatment.

B. Anthropometric and metabolic parameters.

Table 51 - Comparison of changes in anthropometric and metabolic parameters in metformin group and pioglitazone group

Variable	Group	N	Sum of Ranks	P value
Weight	Metformin	33	**1508.5**	**< 0.001***
	Pioglitazone	33	**702.5**	
BMI	Metformin	33	**1395.5**	**< 0.001***
	Pioglitazone	33	**815.5**	
Waist Circumference	Metformin	33	1177.5	0.328
	Pioglitazone	33	1033.5	
Total Score	Metformin	33	1161	0.463
	Pioglitazone	33	1050	
Fasting Insulin	Metformin	33	1252	0.06
	Pioglitazone	33	959	
Triglycerides	Metformin	33	1122.5	0.827
	Pioglitazone	33	1088.5	
Fasting Glucose	Metformin	33	1167.5	0.426
	Pioglitazone	33	1043.5	
HOMA-IR	Metformin	33	**955.5**	**0.048***
	Pioglitazone	33	**1255.5**	

*Significant

Mann Whitney U Test was conducted to compare anthropometric and metabolic parameters between metformin and pioglitazone. The results showed that there was a significant difference in weight ($p < 0.001$), body mass index ($p < 0.001$) and Homeostatic Model Assessment of insulin resistance ($p=0.048$) between the metformin and pioglitazone drugs. Specifically, metformin showed higher sum or ranks for weight and BMI and significantly decreased BMI and weight from baseline to a greater extend as compared to pioglitazone. However, pioglitazone showed higher sum of ranks for HOMA-IR and decreased HOMA-IR to a greater extend from baseline as compared to metformin.

E. Correlation of Burke's Grading with morphology of sulci cutis.

Table 52- Shows correlation between Burke's grading with morphology sulci cutis

Variable	Group	N	Sum of Ranks	P value
Total Grade	Narrow	50	1992	< 0.001*
	Wide	15	153	

*Significant

The Mann-Whitney U Test was used to compare the Burke's Grade and the narrow and wide morphologies in sulcus cutis. The results showed that there is a significant difference in Burke's Grade ($p < 0.001$) between the narrow sulci cutis and wide sulci cutis. Specifically, the narrow morphology category exhibited a significantly higher sum of ranks compared to the wide morphology, indicating that narrow sulci cutis are associated with higher scores of Burke's grading while wide morphology is associated with lower scores of burkes grading.

F. Correlation of Burke's Grading with morphology of papillary projection and hyperpigmented dots.

Table 53 - Shows correlation between Burke's grading with morphology of papillary projection and hyperpigmented dots.

Variable	Group	N	Mean Rank	P value	Pair wise Comparison	P Value
Burke's Grade vs Hyperpigmented Dots	<50	23	33.04	< 0.126	NA	
	>50	15	40.90			
	Absent	27	28.57			
Burke's Grade vs Papillary Projections	Absent	2	16	< 0.001*	Triangular vs Absent	1
	Circular	25	50.64		Triangular vs Polygonal	**0.002***
	Polygonal	24	30.71		Triangular vs Circular	**<0.001***
	Triangular	14	7.86		Absent vs Polygonal	1
					Absent vs Circular	0.73
					Polygonal vs Circular	**<0.001***

*Significant

The Kruskal Wallis Test was conducted to compare the Burke's Grade across different morphologies of papillary projections. The results revealed a significant difference in Burke's grade between different morphologies of papillary projections ($p < 0.001$). Post hoc analysis using Bonferroni correction revealed triangular papillary projections had significantly lower Burke's grades than polygonal variant ($p = 0.002$) and circular variant ($p < 0.001$). Additionally, polygonal variant also had significantly lower Burke's grades as compared to circular variant ($p < 0.001$). Implying that triangular papillary projections were associated with lower grades, polygonal papillary projections with intermediate grades and circular papillary projections with higher grades of Burke's grading.

Table 54 – Changes in Burke's grading vs changes in papillary projections after treatment.

Number of patients who had changes after treatment		
Neck severity	Neck texture	Papillary projections
38/66	37/66	44/22

38 patients showed changes in neck severity with treatment, 37 showed changes in neck texture and 44 showed changes in morphology of papillary projection.

DISCUSSION

DISCUSSION

Hospital-based randomized control open-label research was conducted to assess the effect of metformin versus pioglitazone on acanthosis nigricans clinically and dermoscopically. A unique feature of the current study is that, it is an original research aimed at comparing metformin and pioglitazone across a broad range of dermoscopic, metabolic, and clinical characteristics in a group of individuals with acanthosis nigricans. Since our goal was to evaluate the effectiveness of these drugs without changing dietary practices, we did not control patients' caloric intake and food choices.

There were a total of 66 participants in the study, 33 in each study arm. Participants were similar in terms of their age, sex, and rural or urban status in both the study arms.

In the present research, the overall average age was 35 years , with the metformin group averaging 32 years and the pioglitazone group averaging 36 years. Female predominance was observed across both study arms, possibly indicative of greater cosmetic concerns among women. Similarly, Sett et. al. found a predominance of female patients, especially in their early twenties, in their study comparing metformin with Canthex^{TM} in patients with AN.[121] Conversely, in a Mexican study by Rojas et al [122]. comparing metformin with rosiglitazone in acanthosis nigricans, both treatment groups had lower mean ages than in the current study, with the metformin group averaging 30.0±6.3 years and the rosiglitazone group averaging 24.4±7.2 years.[122] In research done by Petersen K.F. et. al., variations in average age of individuals with insulin resistance across different ethnic groups were observed. Notably, the mean age for Asian Indians was 28.7 ± 8.3 years, while for African descent population, it stood at 23.8 ± 7.0 years. Caucasians and Hispanics exhibited mean ages of 26.0 ± 7.0 years and 26.5 ± 6.4 years, respectively.

These results imply that different ethnic groups have different age distributions, with Asian Indians having a little higher mean age than the other study cohort groups.[123] Regarding comorbidities, in the current study, 4 patients (6.1%) had hypertension, 2 (3%) had diabetes (not on any medication), and 4 patients (6.1%) had hypothyroidism, whereas Sett et. al. reported only two participants (11.7%) with DM as a comorbidity.[121]

Clinical Severity and metabolic parameters.

Specifically, the metformin group in our study had an average BMI of 29.5 ± 3.5 kg/m^2, while the pioglitazone group averaged 30.0 ± 2.8 kg/m^2. This contrasts with findings of Rojas et al.[122] of 33.9 ± 6.3 kg/m^2 and 31.2 ± 3.4 kg/m^2 in metformin and rosiglitazone groups respectively. Furthermore, our findings showed only a minor difference from those reported by Sett et. al.[121], where the baseline mean BMI for the metformin group was 25.77 ± 5.10 and 26.73 ± 3.59 for the Canthex^{TM} group. These differences and similarities in the various studies can be attributed to variations in the demographic features of the population, like ethnicity, age, and geographical location, that can influence BMI level.

There was a significant difference in weight (2.5%) and BMI (2.1%) between the pre- and post-treatment values in the metformin group in our study. Our results are compatible with those reported by Haber R et al.[124], indicating that metformin exhibited a notable impact on BMI reduction compared to a placebo. Specifically, metformin was related with a significant reduction in body mass index, with an average reduction of 0.56 kg/m^2. leading to a significant change in body mass index of 2.53%, suggesting that metformin induces weight decrement in non-diabetic obese patients.[124]

Similarly, Rojas et. al.[122] also reported significant differences in baseline and post-treatment in BMI by 2.06% following metformin administration.

Sett A et. al.[121] showed that weight and BMI reduced significantly from baseline by 3.12% and 3.25% respectively with metformin and 2.2% reduction in both parameters from baseline with Canthex™.[121]

No statistically significant variation in weight or body mass index at baseline and post-treatment periods in the pioglitazone group of our study. Among the patients taking pioglitazone, 11 out of 33 experienced weight gain, while 15 maintained constant weight, and 7 exhibited weight loss compared to baseline, with an average weight gain of 1.6 kg. Various hypotheses have been suggested to justify the weight gain associated with thiazolidinediones, such as; increased appetite, increased subcutaneous fat deposition, and fluid retention. Ghosh S et. al. [80] observed similar results in their investigation of pioglitazone-induced weight alterations in type 2 diabetics. After taking pioglitazone for three months, there was a 1.68 ± 1.3 kg mean weight gain.[80] Our results also align with a meta-analysis examining how pioglitazone medication affects weight and BMI in people with type 2 diabetes mellitus (T2DM). Fifteen trials were included in the meta-analysis that showed pioglitazone medication increased weight and BMI in T2DM patients significantly.[125]

In our study a significant disparity in weight and BMI was seen amongst metformin and pioglitazone groups, with metformin demonstrating a substantial reduction in these parameters from baseline after 12 weeks of treatment. This indicates that metformin may be given preference over pioglitazone in participants with higher BMI.

A significant variation in waist circumference from baseline in both groups was noted 1.6% decrease in patients taking metformin and 1.2% in patients taking pioglitazone was seen in the current study. However, there was no significant variation for waist circumference for both cohorts. Sett A et. al[121] found that waist circumference reduced

significantly from starting point in metformin and Canthex^{TM} groups by 3.1 % and 2.9% respectively.[121]

Rojas et. al.[122] showed that waist circumference reduced by 2.6% with metformin and by 1.99% with rosiglitazone.[122]

Metformin was found to significantly lower weight, waist-circumference, BMI, total body fat, and blood glucose levels in a 6-month trial in women with PCOS.[126]

Jensterle et. al.[127] conducted a comparative study where they evaluated the impact of liraglutide along with metformin versus only liraglutide. They observed significant weight loss with both treatment approaches; however, liraglutide alone demonstrated more pronounced impact on BMI and waist-circumference.[127]

A significant decrease was observed in the severity of AN in the Burke's grading in both groups in our study, however, no significant difference was noted in the 2 medications in our research.

Similarly, Sett et. al.[121] stated that starting with the first follow-up, both the metformin and Canthex^{TM} groups had significantly less severe neck lesions. Both treatment groups showed a significant betterment in neck texture from the first visit, and no significant intergroup differences were found over the follow-up period.[121]

Rojas PB et. al.[122] noted that roughly half of the patients receiving either metformin or rosiglitazone in their research did not experience any improvement in their skin lesions, neither in terms of severity.[122]

Our study diverges from that of Rojas PB et. al.[122], probably due to our utilization of extended Burke's grading encompassing all affected sites to evaluate AN severity, while Rojas PB et. al.[122] solely assessed AN at the neck. Consequently, alterations at any site may influence the total Burke's grading score. All subjects in our study displayed insulin resistance, as evidenced by HOMA-IR, intricately linked to AN's primary pathogenesis.

However, Rojas et. al.[122] noted that hyperinsulinemia and/or insulin resistance was not the only predominant pathogenic factors in all the patients they included, implicating role of other contributing causes. Thus, treatment with drugs which reduce insulin resistance did not uniformly yield improvement in their study. They suggested that hyperinsulinemia only plays pathogenic role in a subset of patients, consistent with our findings of significant clinical improvement with metformin or pioglitazone in those with confirmed insulin-resistance. Petersen K.F. et. al.'s[123] study revealed a 3- to 4-fold higher prevalence of insulin resistance in young, lean, healthy Asian-Indian men compared to men of other ethnicities.[123] Insulin resistance might be the main cause of AN in our patients, which explains why they responded better to treatment than patients in other studies.

Biochemical Parameters

In the metformin group, a significant difference was observed between baseline and post-treatment values for fasting insulin, triglycerides, fasting glucose, and HOMA-IR. A 19.9% decrease in fasting insulin level, 14.3% decrease in fasting glucose levels, 9% decrease in triglycerides level and a 28.56% decrease in HOMA-IR was seen from baseline. For the pioglitazone group, significant differences were noted in baseline and post-treatment values for fasting insulin, triglycerides, fasting glucose, and HOMA-IR. A 20.86% decrease in fasting insulin level, 11% decrease in fasting glucose levels, 10% decrease in triglycerides level and a 35.8% decrease in HOMA-IR was seen from baseline.

Rojas et. al.[122] found no significant difference in baseline and post-treatment measurements of fasting levels of glucose, insulin and serum triglycerides levels in patients taking metformin.[122]

Higher plasma insulin is a baseline predictor of clinical response to metformin.[128]

In a study by Moghetti P et. al.[128], fasting plasma insulin levels dropped after metformin treatment. They studied the impact of metformin taken for six months on menstrual abnormalities in 23 patients with PCOS and normal glucose tolerance.[128]

Sett et. al. [121] noted a slightly elevated levels of in serum triglycerides patients taking metformin, however, these levels were not in the abnormal range.[121]

Pioglitazone significantly reduced HOMA-IR readings when compared to metformin (35.8% vs. 28.56%). This finding aligns with Kazuo Eguchi et al [129], where pioglitazone significantly reduced fasting glucose and HOMA-IR, while metformin decreased levels of cholesterol. Pioglitazone's ability to enhance insulin sensitivity is further supported by its positive impact on adiponectin levels.[129]

Similarly, Imre Pavo et al.[8] demonstrated that pioglitazone outperformed metformin monotherapy in improving insulin sensitivity indicators in recently diagnosed type 2 diabetic patients who had not previously received oral antihyperglycemic medicine.[8]

Rojas et al[122]. also found a significant decrease in baseline and post-treatment fasting insulin and HOMA-IR levels. A reduction of 44% ($p<.05$) in mean insulin levels was observed in the rosiglitazone group, whereas those who received metformin reduced insulin by only 9%.[122]

Dermoscopic Parameters

For ease of evaluation and absence of any existing methods to evaluate dermoscopic changes seen in AN we used a self-designed method to evaluate the dermoscopic parameters.

In SS Pardeshi et. al.'s study[117], sulcus cutis and crista cutis were predominant dermoscopic findings, observed in all patients (100% and 99%, respectively). In addition, hyperpigmented blotches, white streaks/globules, and papillary projections,

hyperpigmented dots, and crypts were seen and analyzed, hence these parameters were used for analysis.

1. Sulci cutis

Both treatment groups exhibited a notable change in morphology of sulci cutis on dermoscopy of neck and bilateral axilla lesions from baseline to post-treatment at 12 weeks.

Specifically, 17 out of 33 patients demonstrated a change in morphology of sulci cutis from narrow to wide with metformin, and 14 out of 33 patients showed changes with pioglitazone. However, there was no significant difference in the two medications' ability to reduce sulci cutis.

2. Hyperpigmented dots/globules

Changes in number of hyperpigmented dots on dermoscopy of neck and left axilla with metformin.

Specifically, 6 out of 33 patients on metformin and 7 out of 33 patients on pioglitazone showed changes in the number of hyperpigmented dots/globules. Nevertheless, there was no significant disparity between the efficacy of the two drugs.

3. Crista Cutis

No significant change was observed in crista cutis with metformin on dermoscopy of neck and bilateral axilla. Similarly, no significant changes were seen with pioglitazone on dermoscopy of neck, and bilateral axilla.

4. Hyperpigmented blotches

No significant change was observed in hyperpigmented blotches with metformin on dermoscopy of neck, bilateral axilla. Similarly, no significant changes were seen with pioglitazone on dermoscopy of neck and bilateral axilla.

5. Crypts

No significant change was observed in crypts with metformin on dermoscopy of neck and bilateral axilla. Similarly, no significant changes were seen with pioglitazone on dermoscopy of neck and bilateral axilla.

6. White streaks/globules.

No significant change was observed in white streaks/globules with metformin on dermoscopy of neck and bilateral axilla. Similarly, no significant changes were seen with pioglitazone on dermoscopy of neck and bilateral axilla.

This suggests that sulci cutis and hyperpigmented dots/globules may exhibit an early response to treatment, while longer treatment durations might be necessary to observe changes in other parameters. Unfortunately, no studies were identified in the literature search to corroborate or expand upon these dermoscopic findings.

Correlation of dermoscopic parameters with severity

On dermoscopy we observed 3 morphologies of papillary projections. The most predominant type was considered for evaluation.

The morphology of papillary projections was significantly associated with the severity of Burke's grading. Triangular papillary projections were associated with lower total score of Burke's grading followed by polygonal papillary projections and circular papillary

projections were associated with higher total score of Burke's grading. Shah et al.[120] highlighted the presence of exophytic papillary structures because of extreme papillomatosis observed in chronic and severe cases.[120] Normal skin dermoscopy typically reveals intersecting skin markings forming triangles. With treatment, the circular projections tend to flatten, transitioning into polygonal and eventually triangular papillary projections, resembling the texture of normal skin.

Another interesting observation noted was that narrow sulci cutis are associated with higher scores of Burke's grading while wide morphology was associated with lower scores of Burke's grading as shown in Table 52. Flattening of papillary projections and crista cutis can cause the surrounding narrow and markedly depressed sulci cutis to appear wider.

Dermoscopic changes in morphology of papillary projections were seen without any change in neck texture and severity in 8 and 9 patients respectively as shown in Table 54, indicating that dermoscopic changes in papillary projections may precede clinical improvement and can be used as an early marker to asses response to treatment, Further studies are required to validate these findings.

Adverse Effects

Four patients receiving metformin and eleven patients receiving pioglitazone reported adverse events deemed to be related with the study treatments. Among those taking metformin, the most prevalent adverse events were mild and transient nausea, along with headaches. Meanwhile, eleven patients receiving pioglitazone experienced weight gain, which was noted at the end of the study period. Rojas et. al.[122] noted that eight patients prescribed metformin and two patients administered rosiglitazone reported adverse events suspected to be linked to the study treatments. Among those treated with metformin, mild

and transient nausea, flatulence, and diarrhea were the predominant adverse events reported. Additionally, two patients in the rosiglitazone group experienced severe headaches leading to their withdrawal from their study.

Strengths

1. Comprehensive evaluation of acanthosis nigricans, involving various parameters including clinical severity, metabolic markers, and dermoscopic features.
2. First study to observe pre- and post-treatment dermoscopic changes in acanthosis nigricans (AN), leading to identification of parameters to monitor response to treatment.
3. First study of its kind to demonstrate a correlation between dermoscopic parameters and Burke's grading, providing new insights into AN characterization.

Limitations

1. Limitation of our study is the relatively short duration of the study period. A study with longer duration of treatment and follow up would have provided a more comprehensive understanding of the effects of the both drugs on various dermoscopic variables.
2. Interpretation of dermoscopy can be altered by hair removal techniques like waxing, shaving and epilation.

SUMMARY

SUMMARY

- The present randomised control trial was conducted among the patients attending the Dermatology OPD, during January 2023 to December 2023.
- All clinically diagnosed patients of Benign acquired AN more than 18 years were considered for evaluation.
- The average age of 66 patients who met the inclusion criteria in the current study was 35±14. Majority were less than 25 years (34.8%) followed by 25-34 years (15/66, 22.7%).
- There were 71.2% women and 18.8% men among them.
- Among the included patients, 15.2% belonged to rural location and 84.8% belonged to urban location.
- 63.6% were married and 36.4% unmarried.
- By occupation 65.2% were unemployed and 34.8% employed.
- Average age of onset was 28.76 years, whereas average duration of AN was 3.08±2.62 years.
- 93.9% patients gave history of gaining weight prior.
- Menstrual history was found to be irregular in 40.9%, with hirsutism in 18.2% of the female patients and 9.1% gave history of OCP usage.
- Associated skin tags were seen in 56.1% and pattern hair loss was noted in 30.3% of the patients.
- Positive family history of AN seen in 18.2%.
- In present study, comorbidities noted were; diabetes (3%), hypertension (6.1%) and hypothyroidism (6.1%).

- 30.3% patients consumed alcohol on a routine basis and 4.5% were smokers.
- In the metformin and pioglitazone group significant difference was seen on dermoscopy of neck and bilateral axilla in sulci cutis and hyperpigmented dots/globules from baseline and at follow up.
- There was no significant difference among both categories in any dermoscopic parameter.
- In the metformin group significant difference was seen in weight, BMI, waist circumference, Burke's Grade, fasting insulin, triglycerides, fasting glucose, and HOMA-IR after treatment for 3 months.
- In the pioglitazone group significant difference was seen in waist circumference, Burke's Grade, fasting insulin, triglycerides, fasting glucose, and Homa-IR after treatment for 3 months.
- As compared to pioglitazone, metformin decreased weight and BMI significantly at 12 weeks. However, pioglitazone led to more significant decrease than metformin in HOMA-IR at 12 weeks.
- Pioglitazone led to weight gain in 11 patients, adverse effects associated with metformin were mild nausea and headache.
- In this study a significant correlation was seen between morphology of papillary projections and Burke's grading. Triangular type was associated with lower grades followed by polygonal and circular type was associated in higher grades.
- We also observed a significant association between morphology of sulci cuti and Burke's grading. Narrow sulci cuti were associated with higher grades and wide sulci cuti with lower grades.

- In 8/66 patients and 9/66 patients with neck lesions changes in papillary projections were present without any change in neck severity or neck texture according to Burke's grading.

CONCLUSION

CONCLUSION

1. Metformin and pioglitazone both lead to improvement in acanthosis nigricans lesions.
2. Metformin decreased weight and BMI more significantly than pioglitazone and should be preferred in overweight patients.
3. Pioglitazone leads to more significant decrease in HOMA-IR as compared to metformin and can be preferred in non-obese patients with underlying insulin resistance as a cause of AN.
4. Pioglitazone might be a good choice for the patients with AN who are intolerant or not responding to metformin.
5. Dermoscopic parameters like number hyperpigmented dots/globules, morphology of sulci cutis and morphology or papillary projections can be used to identify response to treatment before clinical improvement is seen.
6. Morphology of sulci cutis and papillary projections are associated with severity of Burke's grading.

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ANNEXURE I – CONSENT FORM

KAHERs JNMC, BELAGAVI

INFORMED CONSENT FORM

"Clinical and Dermoscopic Evaluation to study the Effectiveness of Metformin vs Pioglitazone in Acanthosis Nigricans – A Randomized Control Trial."

Objective: This study aims to compare the clinical efficacy of metformin vs pioglitazone on skin lesions of and insulin resistance profile in patients of acanthosis nigricans.

Introduction: Acanthosis Nigricans (AN) defined by hyperpigmented, coarse, thickened skin with a velvety texture is a mirror to several systemic diseases like metabolic syndrome, endocrine disorders, polycystic ovarian disease, drug side effects, malignancy, and genetic disorders. Escalation in the prevalence of AN has been observed recently due to the increasing prevalence of metabolic syndrome, analogous to the expanding epidemic of type-2 diabetes, hypertension, and obesity. The main aim of treating AN is correction of the primary pathology. Hence identifying and treating AN will indirectly help in reducing the burden of diseases caused by hyperinsulinemic states.

Explanation of procedure: After screening, eligible study participants details and baseline parameters will be noted using a detailed proforma. Acanthosis lesions will be graded and texture will be defined according to gradation by Burke et al. Waist circumference, height, and weight will be measured as well as blood collected for routine investigations and fasting insulin level, serum triglyceride levels, HOMA-IR will be calculated. Each study patient will be provided with medications for 4 weeks as per randomization and will be explained

regarding dosage - for 3 months. The study participants will be asked to come back for follow-up after completion of 3 months.

Withdrawal from participation in the study: Participation in this study is voluntary. You will be free to decide whether to participate in this study or continue participation once enrolled. In case you decide to withdraw your participation, you are free to do so. However, please convey the decision to the principal investigator.

Possible benefits from participating in the study: You will/will not have nor get any benefits by participating in this study. The data gathered will help the population at large.

Possible risks from participating in the study: There are no risks involved in participating in this study.

Privacy and confidentiality: The information collected from you will be coded, to prevent any person from identifying you. Your identity will never be revealed. The data collected from you will be kept confidential and only processed or aggregated data will be used for publication.

Financial incentives: You will not receive any payment for participating in this study.

Authorization for publication of aggregated data: Results obtained after processing of the aggregated data will be published for scientific purposes and or presented to scientific groups. However, your identity will never be revealed.

Questions: In case of any questions regarding this study, you are free to contact: "Name of student/PI, mobile number, email ID" If you have any question or complaints regarding your right as study participant you may contact Dr Harsha Hegde, Chairperson, Ethical committee of JNMC, 0831-2473777 Extension 4052.

Legal rights: By signing this consent form, we are not waving any of your legal rights.

CONSENT STATEMENT

I am making a voluntary decision to participate in the study "**Clinical and Dermoscopic Evaluation to study the Effectiveness of Metformin vs Pioglitazone in Acanthosis Nigricans – A Randomized Control Trial.**" My signature below indicates that I have decided to participate and I have read the information provided above or the information provided above has been read to me in the language that I understand best. I was given the opportunity to ask questions and that they have been answered to my satisfaction.

Name of the participant:

Signature or left thumb impression of the participant:

Name of the witness:

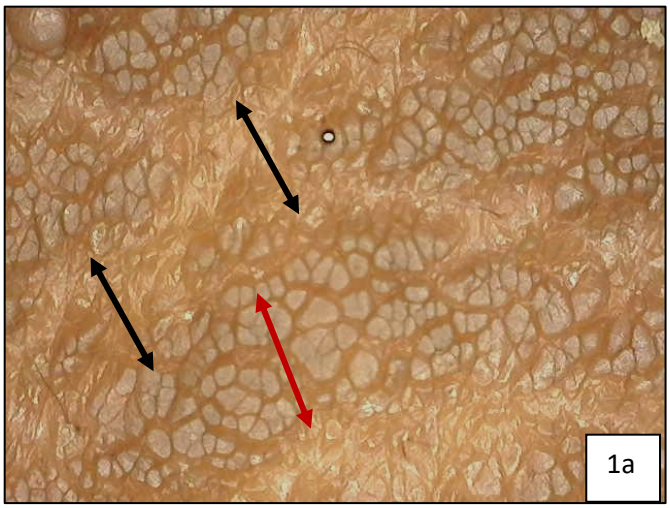
Signature or left thumb impression of the witness:

Name of the investigator:

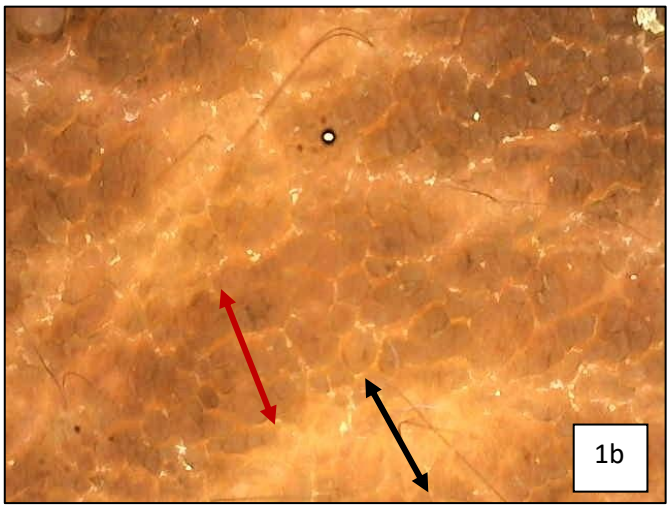
Signature of the investigator:

ANNEXURE II – PATIENT IMAGES

Image 1 - Clinically patient had Burke's Grade neck severity– 4, neck texture - 3.

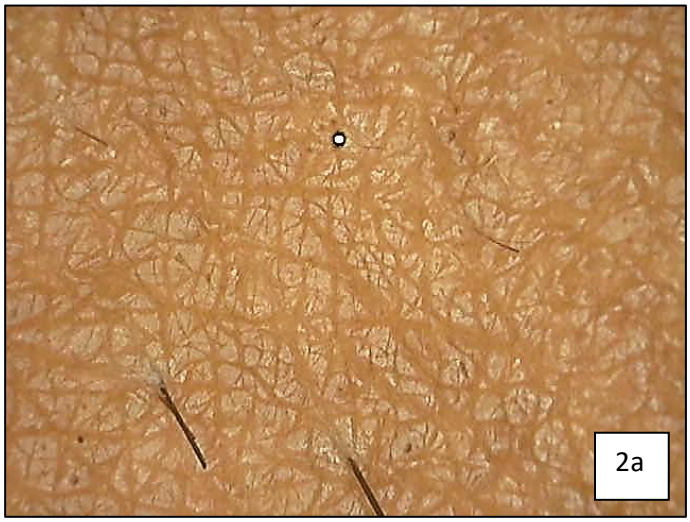


1a- Sulci cutis (marked with double headed black arrow) and cristae cutis (marked with double headed red arrow). Predominantly polygonal papillary projections present on the crista cuti seen on non-polarized mode.

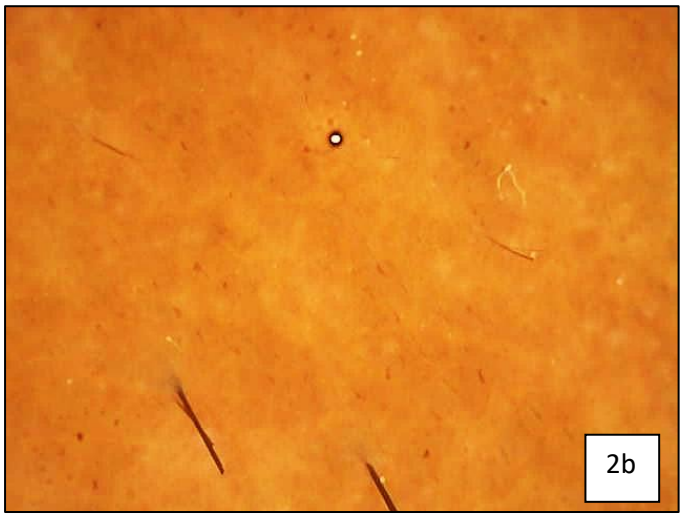


1b – Same site as 1a seen in polarized mode. Sulci cutis seen as light-coloured areas (double headed black arrow) and cristae cuti as brown globules(double headed red arrow)

Image 2 - Clinically patient had Burke's Grade neck severity -1, neck texture - 1



2a-Predonimantly Triangular Papillary Projections seen in non-polarized mode



2b - Same site as 2a seen in polarized mode, showing disperse faint hyperpigmented dots.

Images capture using Dinolite digital dermoscope at 100x on the neck

Image 3 – Dermoscopic images capture using Dinolite digital dermoscope at 100x on the neck.

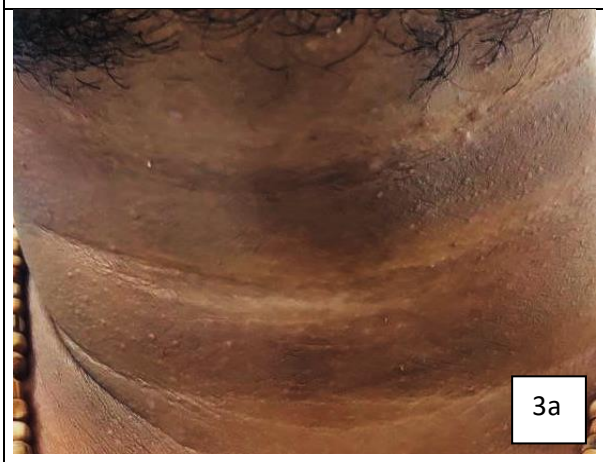
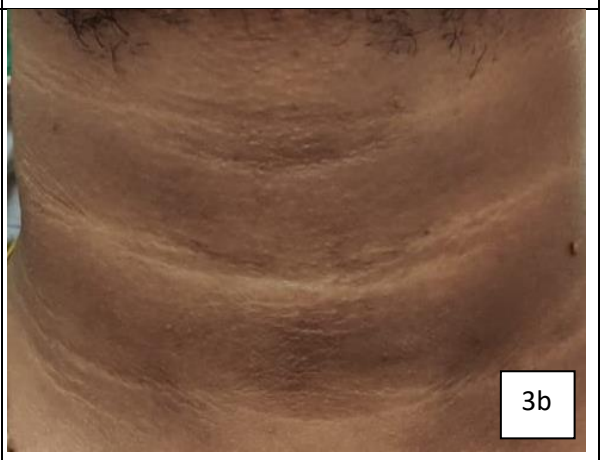
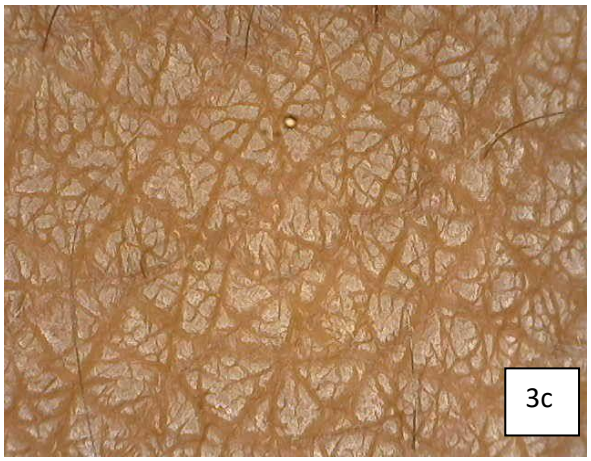
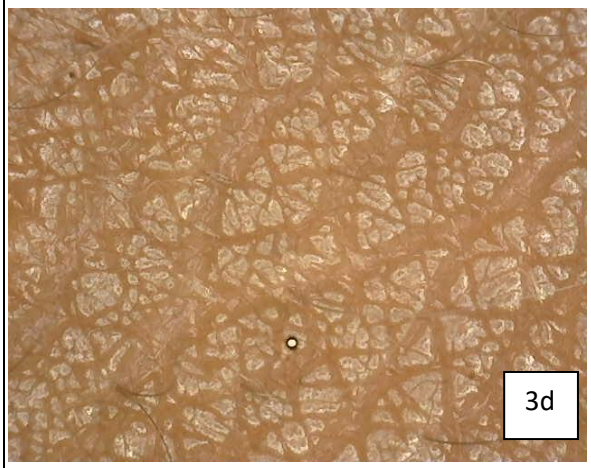
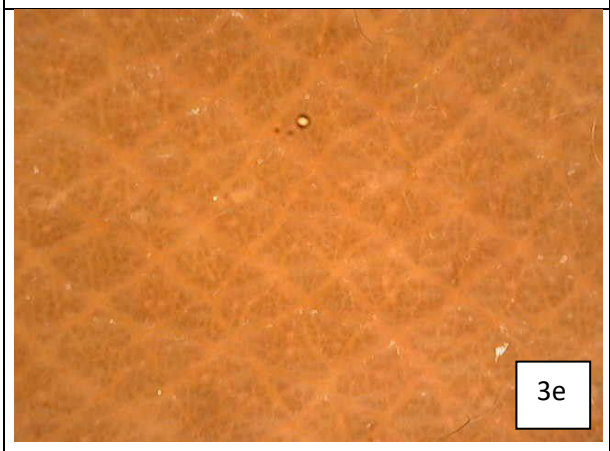
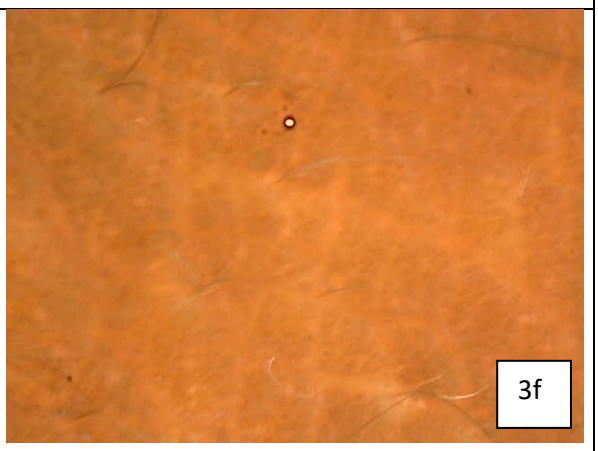
Baseline	**Follow up (12 weeks)**
	
3a-Clinically Burke's grade 4, Neck texture - 1	3b-Clinically Burke's grade 4. Neck texture - 1
	
3c-Non polarised dermoscopy showing narrow sulci cutis with cristae cutis with predominantly polygonal papillary projections.	3d-Non polarised dermoscopy showing wide sulci cutis with cristae cutis with predominantly triangular papillary projections.
	
3e-Polarised dermoscopy showing light coloured narrow sulci cutis with brown well defined rhomboid shaped cristae cutis.	3f-Polarised dermoscopy showing light coloured wide sulci cutis with brown ill-defined cristae cutis.

Image 4 – Dermoscopic images captured using Dinolite digital dermoscope at 100x on the neck.

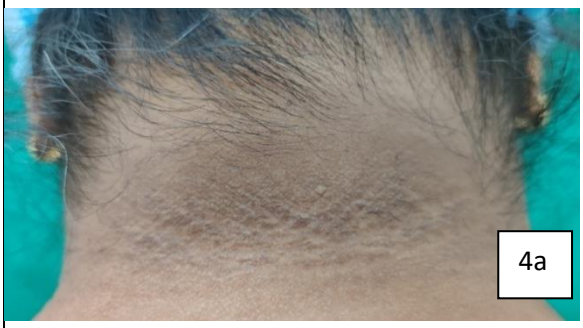
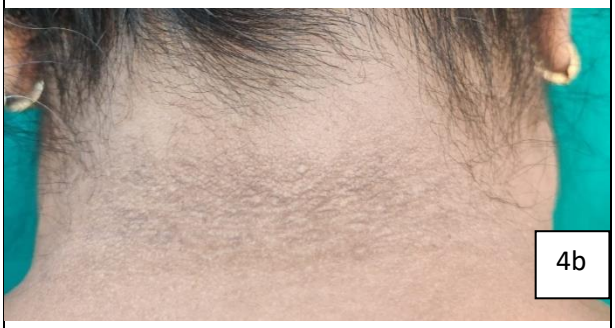
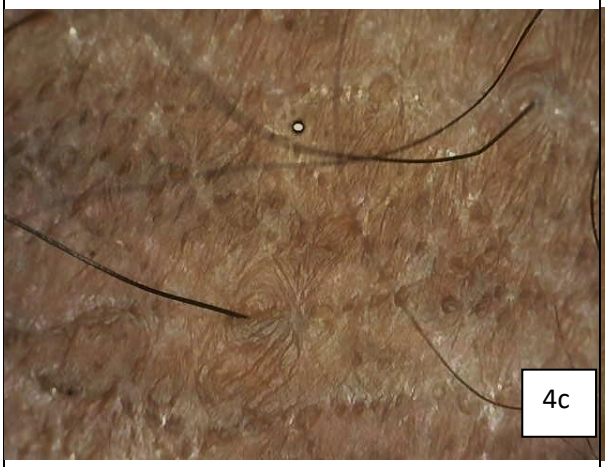
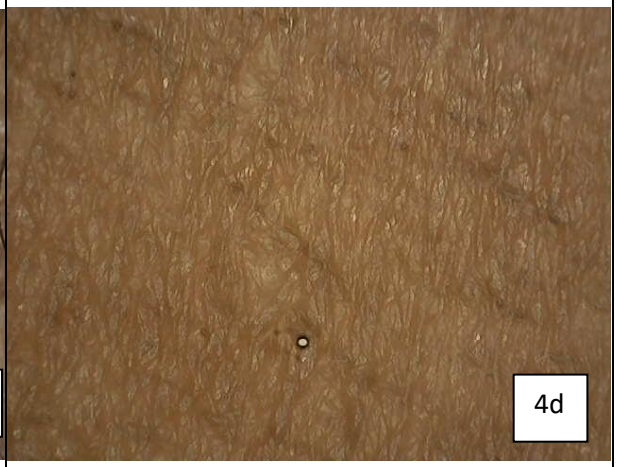
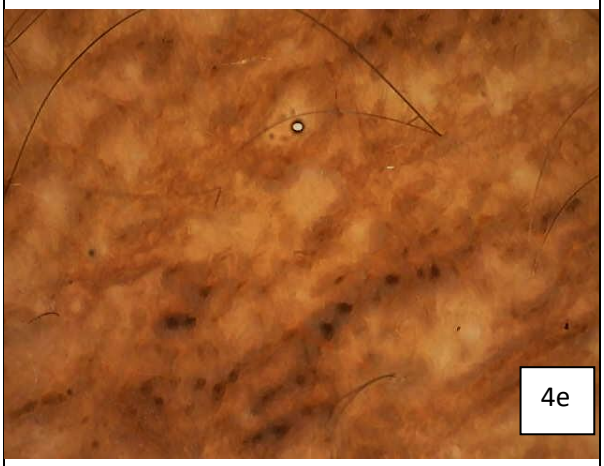
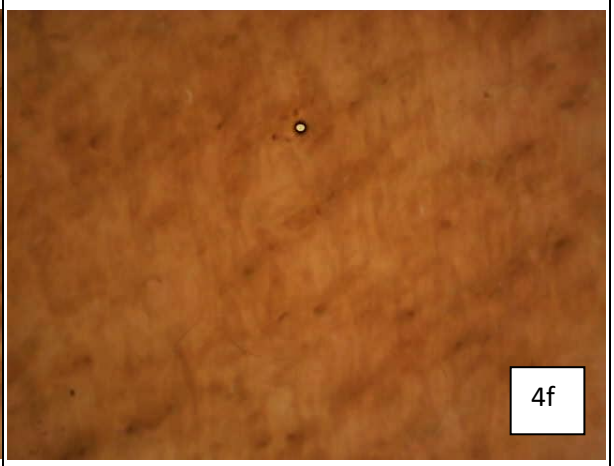
Baseline	**Follow up (12 weeks)**
	
4a-Clinically Burke's grade 4, Neck texture - 2	4b-Clinically Burke's grade 3, Neck texture - 1
	
4c-Non polarised mode of dermoscopy showing hyperpigmented dots and globules.	4d-Non polarised mode of dermoscopy showing decreased hyperpigmented dots.
	
4e-Polarised mode of dermoscopy showing hyperpigmented dots and globules	4f-Polarised mode of dermoscopy showing decreased hyperpigmented dots and globules

Image 5 - Dermoscopic images captured using Dinolite digital dermoscope at 100x on the neck.

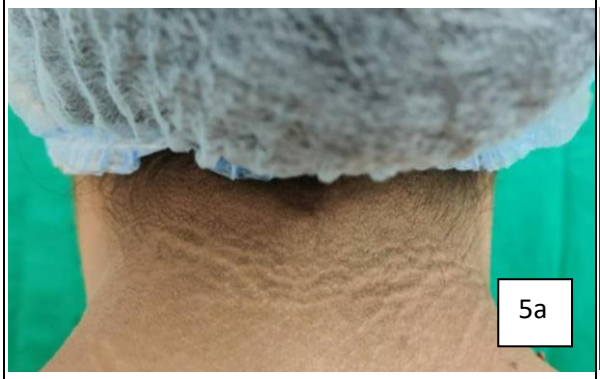
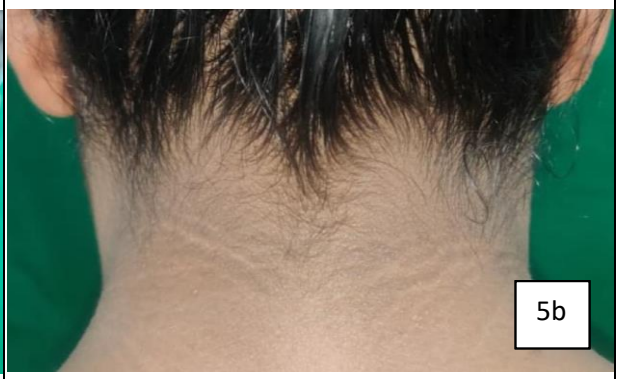
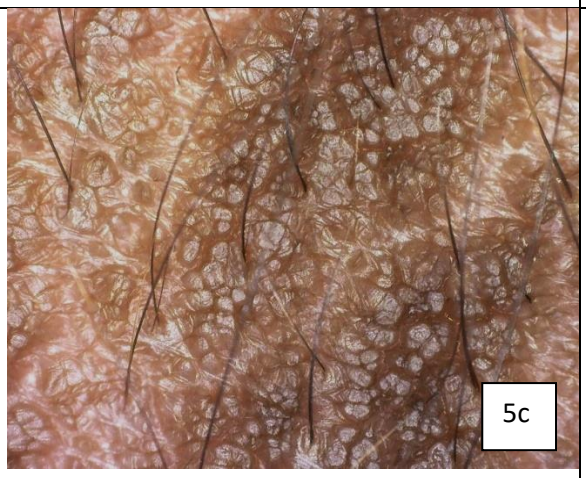
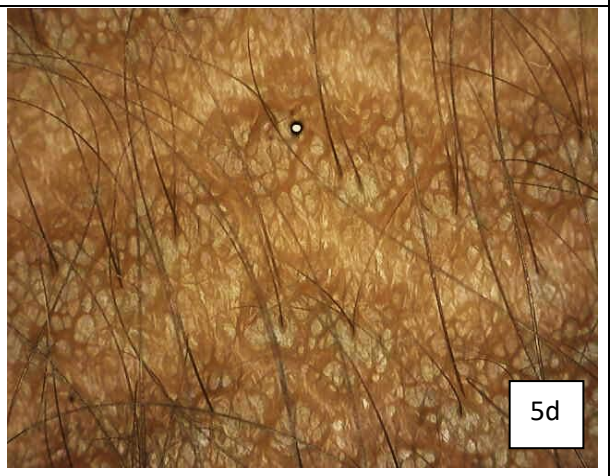
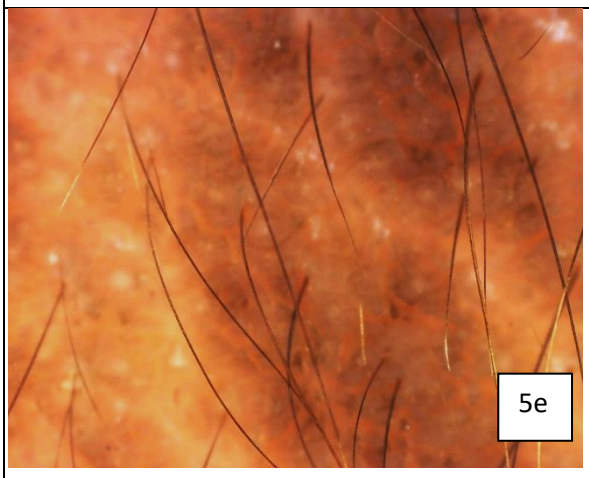
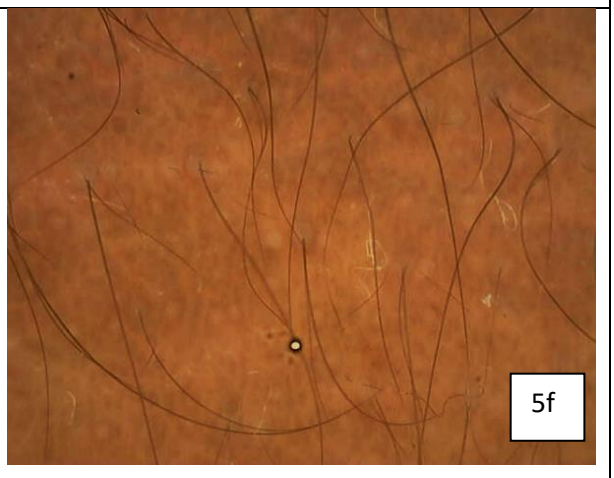
Baseline	**Follow up (12 weeks)**
	
5a-Clinically Burke's grade 4, Neck texture - 3	5b-Clinically Burke's grade 3, Neck texture - 2
	
5c-Non polarised dermoscopy showing narrow sulci cutis with pigmented cristae cutis with predominantly circular papillary projections.	5d-Non polarised dermoscopy showing wide sulci cutis with cristae cutis with predominantly circular papillary projections.
	
5e-Polarised dermoscopy showing sulci cutis with hyperpigmented cristae cutis.	5f-Polarised dermoscopy showing diffuse hyperpigmented globules present.

Image 6 - Dermoscopic images captured using Dinolite digital dermoscope at 100x in the left axilla

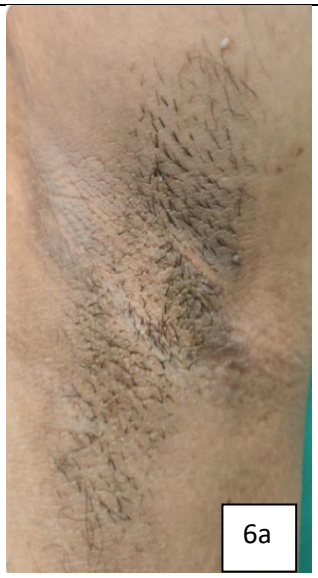
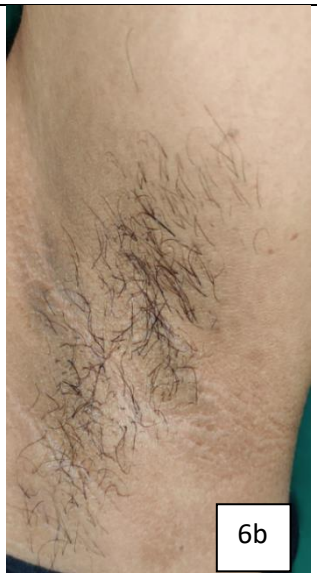
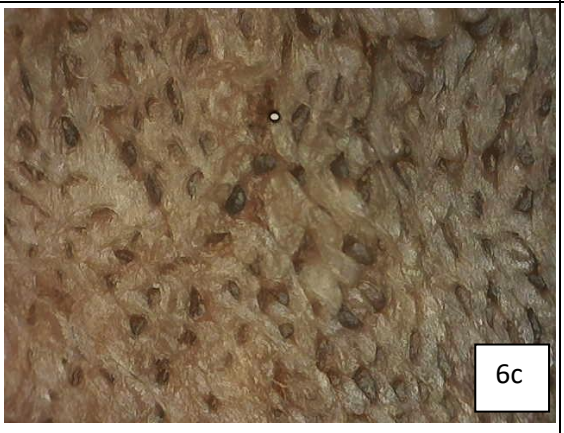
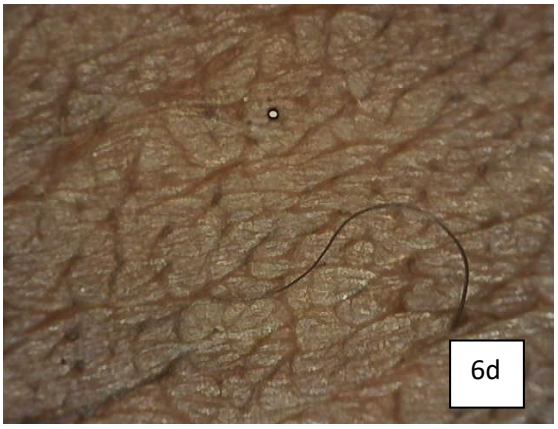
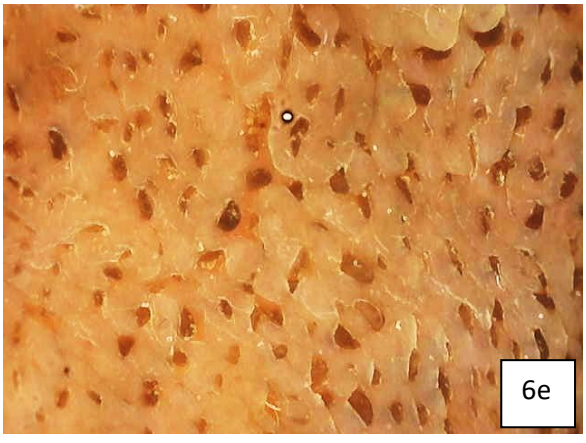
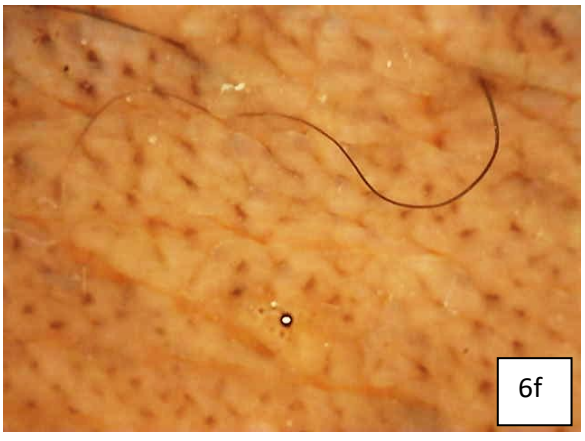
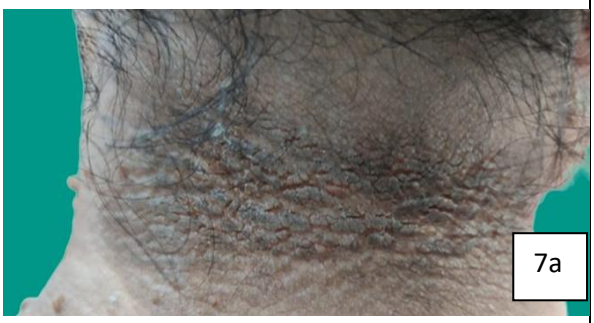
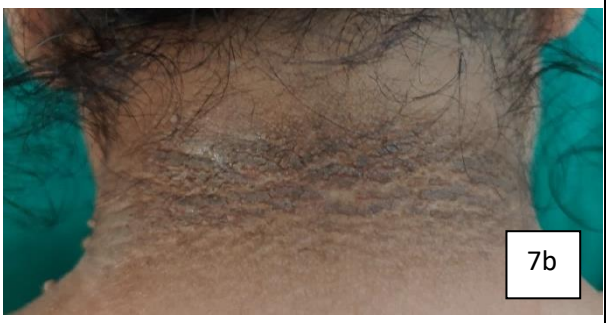
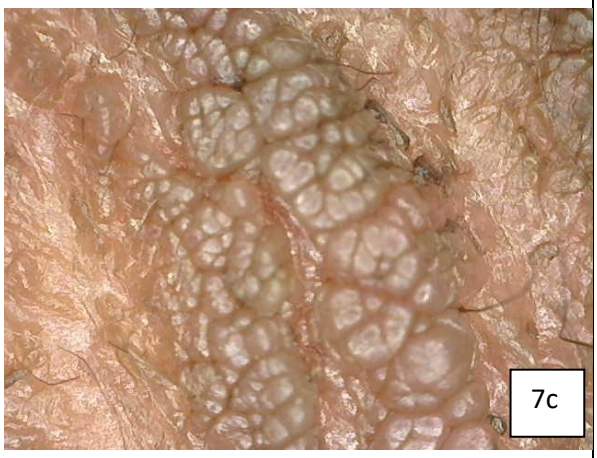
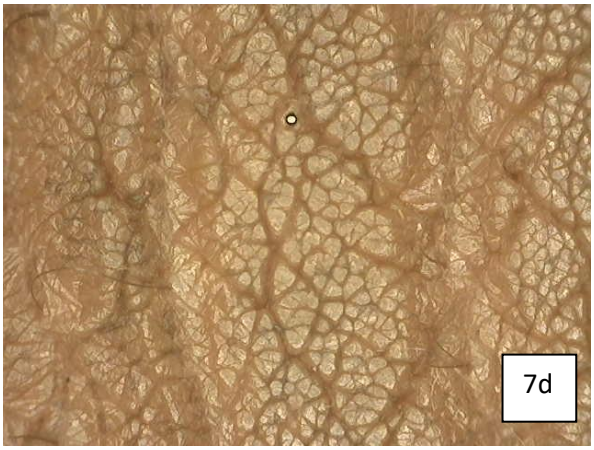
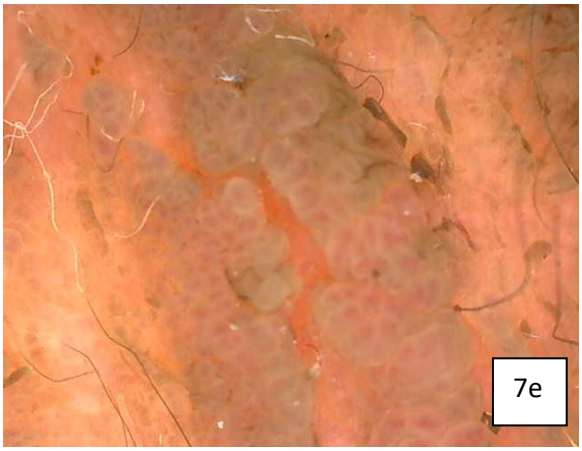
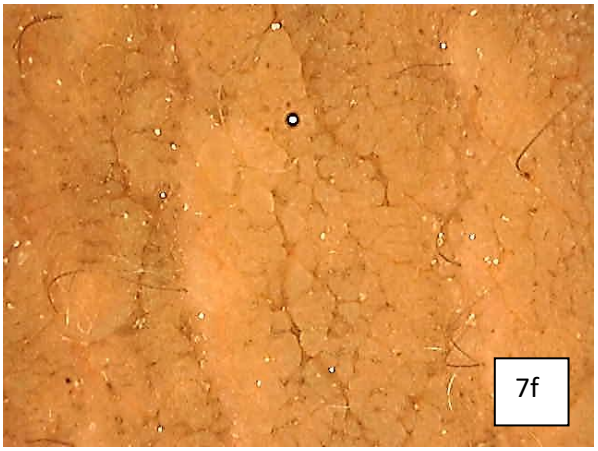
Baseline	**Follow up (12 weeks)**
 6a-Burke's grade Axilla - 3	 6b-Burke's grade Axilla - 2
 6c-Non polarised dermoscopy showing sulci gyri pattern with papillary projections with numerous hyperpigmented dots.	 6d-Non polarised dermoscopy showing sulci gyri pattern with papillary projections with scanty hyperpigmented dots.
 6e-Polarised dermoscopy showing numerous hyperpigmented dots.	 6f-Polarised dermoscopy showing scanty hyperpigmented dots.

Image 7 - Dermoscopic images captured using Dinolite digital dermoscope at 100x on the neck.

Baseline	**Follow up (12 weeks)**
 7a-Clinically Burke's grade 4, Neck texture -3	 7b-Clinically Burke's grade 4, Neck texture - 3
 7c-Non polarised dermoscopy showing sulci cutis with cristae cutis with predominantly circular papillary projections.	 7d-Non polarised dermoscopy showing sulci cutis with rhomboid cristae cutis with predominantly polygonal papillary projections.
 7e-Polarised dermoscopy showing sulci cutis with cristae cutis with hyperpigmented globules.	 7f-Polarised dermoscopy showing sulci cutis with cristae cutis

ANNEXURE III PROFORMA

Patient number_____ study group_____

Demographic details						
Name			Marital status	M/u/d/w		
Age			Gender	Male/female		
Occupation	Employed/unemployed		Case number			
Address	Urban	Rural	Op number			
Contact no.			Ip number			
Pregnant	Yes	No	Lactation	Yes	No	
Symptoms			Yes	No		
Itching			Yes	No		
Others please specify						
Associated symptoms						
Weight gain			Yes	No		
Weight loss			Yes	No		
Increased appetite			Yes	No		
Increased frequency of micturition			Yes	No		
Menstrual complaints						
Periods			Regular	Irregular		
Hirsutism			Yes	No		
Number of sites involved	Single		Multiple			
Site	Neck	Axilla	Face	Groin	Acral	Others
Age of onset						
Onset	Gradual		Sudden			
Duration						
Progression	Progressive		Stationary	Regressive		
Similar complains in family			Yes	No		
Drug intake	Yes			No		

Antidiabetic drug	Yes		No
Antioxidant drug	Yes		No
Ayurvedic medicines	Yes		No
Others	Yes	**Kindly specify**	

Past history		
Dm	Yes	No
Htn	Yes	No
Hypercholestrolenemia	Yes	No
Malignancy	Yes	No
Pcos		

Personal history		
Smoking	Yes	No
Alcohol	Yes	No

Anthropometric measurements	**Pre**	**Post**
Height		**N/a**
Weight		
Bmi		
Waist circumference		

Burke grading for acanthosis nigricans

Neck severity		**Pre**	**Post**
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 base 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 the front		
4	Severe: extending anteriorly (.6 inches), visible when the participant is viewed from the front		
Axilla			
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: 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 from normal skin to palpation.		
1	Rough to touch: clearly differentiated from normal skin		
2	Coarseness can be observed visually, portions of the skin clearly raised above other areas		
3	Extremely coarse: “hills and valleys” observable on visual examination		
Knuckle			
Present			
Absent			
Elbow			
Present			
Absent			
Knee			
Present			
Absent			

Total grade			

Metabolic parameters	**Pre**		**Post**	
Fasting insulin level				
Fasting glucose level				
Triglyceride levels				
Homa-ir				
Dermoscopy **Site 1**	**Pre**		**Post**	
	Crista cutis	Absent/present	**Crista cutis**	Absent/present
	Sulci cutis	Wide/narrow	**Sulci cutis**	Wide/narrow
	Papillary projections	Triangular Polygonal Circular	**Papillary projections**	Triangular Polygonal Circular
	Hyperpigmented dots	**<50 or >50**	**Hyperpigmented dots**	**<50 or >50**
	Hyperpigmented blocthes	Absent/present	**Hyperpigmented blocthes**	Absent/present
	Crypts	Absent/present	**Crypts**	Absent/present

Associated Findings	
Acrochordons	
Pattern Hair Loss	
Hirsutism	

ANNEXURE IV – MASTER CHART

Key to Master Chart

CODE	DESCRIPTION
OP NO.	OPD PATIENT NUMBER
F	FEMALE
M	MALE
Ma	MARRIED
UM	UNMARRIED
E	EMPLOYED
UE	UNEMPLOYED
U	URBAN
R	RURAL
Y	YES
N	NO
R	REGULAR
IR	IRREGULAR
MPS	MENOPAUSE
NA	NOT APPLICABLE
PHL	PATTERN HAIR LOSS
G	GRADE
Mu	MULTIPLE
S	SINGLE
HT	HEIGHT
WT	WEIGHT
BMI	BODY MASS INDEX
WC	WAIST CIRCUMFERENCE

BG NS	BURKE'S GRADING NECK SEVERITY
AX	AXILLA
NT	NECK TEXTURE
E	ELBOW
KNU	KNUCKLES
KNE	KNEES
T GRADE	TOTAL GRADE
FI	FASTING INSULIN
FG	FASTING GLUCOSE
TG	TRIGLYCERIDE
D'SCOPY	DERMOSCOPY
SC	SULCI CUTIS
Nr	NARROW
W	WIDE
CC	CRISTA CUTIS
A	ABSENT
P	PRESENT
PP	PAPPILLARY PROJECTION
T	TRIANGULAR
PO	POLYGONAL
C	CIRCULAR
MT	MIXED-TRIANGULAR
MP	MIXED-POLYGONAL
MC	MIXED-CIRCULAR
HD/G	HYPERPIGMENTED DOTS/GLOBULES
HB	HYPERPIGMENTED BLOTCHES
C	CRYPTS

WS/G	WHITE STREAKS/GLOBULES
PARAMETER	UNIT
AGE	YEARS
DURATION	YEARS
HEIGHT	METERS (m)
WEIGHT	KILOGRAMS (kg)
WAIST CIRCUMFERENCE	CENTIMETERS (cm)
BMI	kg/m^2

ANNEXURE V - MASTERCHART

SR. NO	OP NO	AGE	SEX	MARITAL STATUS	OCCUPATION	ADDRESS	WT GAIN	WT LOSS	PERIODS	H'TISM	PHL	SKIN TAGS	SITES INVOLVED	AGE OF ONSET	DURATION	FH	OCP
1	6762619	56	F	Ma	UE	U	Y	N	IR	N	N	N	M	54	2	N	N
2	5087652	22	F	UM	UE	U	Y	N	IR	Y	G 3	N	M	16	6	Y	Y
3	4035983	43	F	Ma	UE	U	Y	N	R	N	N	<5	S	40	3	N	N
4	6205973	19	F	UM	UE	U	Y	N	IR	Y	N	<5	M	17	2	Y	N
5	6550934	23	M	UM	UE	U	Y	N	NA	NA	N	N	M	22.5	0.5	N	NA
6	4099042	26	F	Ma	UE	U	Y	N	R	Y	G 2	>5	M	24	2	N	Y
7	6468743	50	M	Ma	E	R	Y	N	NA	NA	N	<5	M	25	1	N	NA
8	6719268	46	F	Ma	UE	U	Y	N	IR	N	Y	>5	S	43	3	N	N
9	6827897	32	M	Ma	E	U	Y	N	NA	NA	N	>5	M	25	7	N	N
10	6268893	22	F	UM	UE	U	Y	N	IR	Y	G 3	N	M	16	6	N	N
11	6532417	47	F	Ma	UE	U	Y	N	R	Y	G 2	>5	M	41	6	N	N
12	6980265	45	M	Ma	E	U	Y	N	NA	NA	G 2	>5	M	41	4	N	NA
13	6733242	18	F	UM	UE	U	Y	N	IR	Y	G 1	>5	M	13	5	N	N
14	6410356	27	F	Ma	UE	U	Y	N	R	N	N	<5	M	23	4	N	N
15	6567490	38	M	Ma	E	R	Y	N	NA	NA	N	Y	M	35	3	N	NA
16	5184653	24	F	UM	UE	U	Y	N	IR	Y	G 1	N	M	18	6	Y	Y
17	6880395	43	M	Ma	E	U	N	N	NA	NA	N	<5	M	35	5	N	NA
18	6328973	21	F	UM	UE	U	Y	N	IR	Y	N	<5	M	19	2	Y	N
19	6576898	38	M	Ma	E	R	Y	N	NA	NA	N	Y	M	35	3	N	NA
20	5875631	24	F	UM	UE	U	Y	N	IR	Y	G 1	N	M	18	6	Y	Y
21	4035983	41	F	Ma	E	U	Y	N	R	N	N	<5	S	38	3	N	N
22	6786904	25	F	UM	UE	U	Y	N	R	N	N	N	M	21	4	Y	N
23	6567893	52	M	Ma	E	R	Y	N	NA	NA	N	<5	M	51	1	N	NA
24	6879170	26	F	UM	UE	U	Y	N	R	N	N	N	M	25	1	N	N
25	6692357	49	F	Ma	E	U	Y	N	IR	N	Y	>5	S	46	3	N	N
26	3871235	24	F	Ma	UE	U	Y	N	IR	N	N	N	M	22	2	N	N
27	6976546	30	M	Ma	E	U	Y	N	NA	NA	N	>5	M	23	7	N	N
28	6623412	20	M	Ma	UE	U	Y	N	IR	N	G 2	N	M	18	2	N	NA
29	5234918	20	F	UM	UE	U	Y	N	R	N	G 1	N	M	18	2	N	N
30	6533618	46	F	Ma	UE	R	Y	N	R	N	N	<5	S	44	2	N	N
31	6472413	43	F	Ma	UE	U	Y	N	R	N	G 2	>5	M	37	6	N	N
32	6881984	22	F	UM	UE	U	Y	N	IR	N	G 2	<5	M	17	5	N	N
33	6733242	21	F	UM	UE	U	Y	N	IR	Y	G 1	>5	M	16	5	N	N
34	6783456	55	F	Ma	UE	R	Y	N	MPS	Y	Y	N	S	54	1	Y	N
35	6510916	29	F	Ma	UE	U	Y	N	R	N	N	<5	M	25	4	N	N
36	6768639	21	F	Um	UE	U	N	N	IR	N	N	>5	S	18	3	N	N
37	6566498	35	M	Ma	E	R	Y	N	NA	NA	N	Y	M	32	3	N	NA
38	6281052	21	F	UM	UE	U	Y	N	IR	N	N	N	M	16	5	N	Y
39	6679674	18	F	UM	UE	U	Y	N	R	N	N	N	M	14	4	Y	N
40	6999481	28	M	Ma	E	U	Y	N	NA	NA	N	N	M	25	3	N	NA
41	6995345	32	M	Ma	E	R	Y	N	NA	NA	N	N	S	29	3	Y	NA
42	6980265	45	M	Ma	E	U	N	N	NA	NA	N	<5	M	40	5	N	NA
43	6758119	24	F	UM	UE	U	Y	N	R	N	N	N	M	23	1	N	N
44	6815350	32	F	Ma	E	U	Y	N	IR	N	N	N	S	29	3	N	N
45	3941906	27	F	Ma	UE	U	Y	N	IR	N	N	N	M	25	2	N	N
46	6689884	65	F	Ma	UE	U	Y	N	MPS	N	N	>5	M	63	2	N	N
47	6817650	61	F	Ma	UE	U	Y	N	MPS	N	N	N	S	58	2	N	N
48	6544417	44	F	Ma	UE	R	Y	N	R	N	N	<5	S	42	2	N	N
49	854846	38	F	Ma	E	U	Y	N	R	N	N	<5	S	36	2	N	N
50	6886272	18	F	UM	UE	U	Y	N	IR	N	N	N	M	13	5	N	N
51	2983727	54	M	Ma	E	U	Y	N	NA	NA	N	>5	M	51	3	N	NA
52	6759019	22	F	UM	UE	U	N	N	IR	N	N	>5	M	19	3	N	N
53	6213244	20	F	UM	UE	U	Y	N	IR	N	G 2	Y	M	16	4	Y	N
54	5661649	25	F	UM	UE	U	Y	N	IR	N	G 3	>5	M	23	2	Y	N
55	6754389	60	F	Ma	UE	U	Y	N	IR	N	N	N	M	58	2	N	N
56	6276547	24	F	UM	UE	U	Y	N	IR	N	N	N	M	19	5	N	Y
57	6776941	31	M	Ma	E	U	Y	N	NA	NA	N	N	M	28	3	N	NA
58	6976814	34	M	Ma	E	R	Y	N	NA	NA	N	N	S	31	3	Y	NA
59	6895641	34	F	Ma	E	U	Y	N	IR	N	N	N	S	31	3	N	N
60	6782775	67	F	Ma	UE	U	Y	N	MPS	N	N	>5	M	65	2	N	N
61	6983451	63	F	Ma	UE	U	Y	N	MPS	N	N	N	S	61	2	N	N
62	6349814	24	F	UM	UE	U	Y	N	IR	Y	G 2	N	M	18	6	N	N
63	8446217	36	F	Ma	E	U	Y	N	R	N	N	<5	S	34	2	N	N
64	6997563	21	F	UM	UE	U	Y	N	IR	N	N	N	M	16	5	N	N
65	6893424	47	M	Ma	E	U	Y	N	NA	NA	G 2	>5	M	43	4	N	NA
66	2890128	51	M	Ma	E	U	Y	N	NA	NA	N	>5	M	48	3	N	NA

SR. NO	DM	HTN	HC	SMOKING	ALCOHOL	HT	WT	BMI	WC	BGNS	AX	NT	E	KNU	KNE	TGRADE	FI	FG	TG	HOMA-IR
1	N	N	N	N	N	1.61	78	30.1	97	3	1	2	0	0	0	6	13	99	150	3
2	N	N	N	N	N	1.56	66	27.1	92	3	3	3	0	0	0	9	27	100	180	6
3	N	Y	N	N	N	1.57	92	38	106	2	1	1	0	0	0	4	15	89	130	3
4	N	N	N	N	N	1.57	63	25.6	98	3	3	3	0	0	0	9	25.2	88	189	5
5	N	N	N	N	N	1.75	90	29.4	93	1	0	1	0	0	0	2	20	110	190	5
6	N	N	N	N	N	1.54	70	29.53	88	4	3	2	1	1	0	11	12	145	220	4
7	N	N	N	N	N	1.75	75	24.5	88	3	3	2	0	0	0	8	24	135	221	8
8	N	Y	N	N	N	1.57	65	26	89	3	0	3	0	0	0	6	23	100	150	5
9	N	N	N	N	N	1.65	90	33.1	106	4	4	3	1	1	1	14	28	178	245	12
10	N	N	N	N	N	1.6	80	31.2	100	3	4	3	0	0	0	10	26.8	101	201	6
11	N	N	N	N	N	1.6	80	31.2	104	4	4	3	0	0	0	11	19.8	111	219	5
12	N	N	N	N	N	1.71	82	28	101	3	4	3	1	1	0	12	18.2	170	246	7
13	N	N	N	N	N	1.67	86	30.8	101	3	3	3	0	0	0	9	16.8	129	209	5
14	N	N	N	N	N	1.49	70	29.1	98	3	3	3	0	0	0	9	18	99	165	4
15	N	N	N	N	N	1.68	87	29.8	102	4	3	1	0	1	1	10	15	190	98	7
16	N	N	N	N	N	1.56	66	27.1	102	3	3	3	1	1	1	12	20	92	256	4
17	N	N	N	N	N	1.67	90	32.3	103	4	4	3	0	0	0	11	18.1	87	199	3
18	N	N	N	N	N	1.57	63	25.6	90	3	3	3	0	0	0	9	29	98	231	7
19	N	N	N	N	N	1.7	90	29.8	102	4	3	1	0	1	1	10	19	167	178	7
20	N	N	N	N	N	1.56	66	27.1	101	3	3	3	0	0	0	9	32.9	91	254	7
21	N	N	N	N	N	1.57	92	38	114	2	1	1	0	0	0	4	27	90	134	6
22	N	N	N	N	N	1.58	70	28	100	4	3	3	0	0	0	10	25	100	208	6
23	N	N	N	N	N	1.75	75	24.5	98	3	3	2	0	0	0	8	23	178	178	10
24	N	N	N	N	N	1.57	64	26	99	3	2	2	0	0	0	7	25	90	190	5
25	N	N	N	N	N	1.57	65	26	90	3	0	3	0	0	0	6	10	134	222	3
26	N	N	N	N	N	1.54	70	29.5	111	3	2	2	0	0	0	7	24	178	190	10
27	N	N	N	N	N	1.65	90	33.1	105.5	4	4	3	0	0	0	11	22.2	90	300	4
28	N	N	N	N	N	1.6	70	27.3	104	3	3	2	0	0	0	8	23.4	123	156	7
29	N	N	N	N	N	1.54	80	33.7	99	3	3	2	0	0	0	8	28	167	183	11
30	N	Y	N	N	N	1.52	61	26.4	88	2	0	2	0	0	0	4	17	134	109	5
31	N	N	N	N	N	1.6	80	31.2	99	4	4	3	0	0	0	11	18.1	87	209	3
32	N	N	N	N	N	1.46	75	35.2	108	3	3	3	0	1	1	11	39.4	101	265	9
33	N	N	N	N	N	1.67	86	30.8	100	3	3	3	0	0	0	9	31.2	145	202	11
34	N	N	N	N	N	1.57	73	29.6	102	0	2	0	0	0	0	2	23	101	104	5
35	N	N	N	N	N	1.55	70	29.1	100	3	3	3	1	1	0	11	31.3	95	170	7
36	N	N	N	Y	N	1.57	63	25.6	92	0	3	0	0	0	0	3	22.4	89	109	4
37	N	N	N	N	N	1.7	90	29.8	96	4	3	1	0	0	0	8	28	146	101	10
38	N	N	N	N	N	1.61	87	33.1	99	4	1	3	0	0	0	8	14	90	100	3
39	N	N	N	N	N	1.58	70	28	99	4	3	3	0	0	0	10	29.8	94	134	6
40	N	N	N	N	Y	1.6	75	29.3	92	3	3	2	0	0	0	8	27.2	109	120	7
41	N	N	N	N	Y	1.62	75	28.6	93	2	0	1	0	0	0	3	22.1	102	140	5
42	N	N	N	N	N	1.67	90	32.3	96	4	4	3	0	0	0	11	33.9	98	128	8
43	N	N	N	N	N	1.57	64	26	89	3	2	2	0	0	0	7	30.1	127	190	9
44	Y	N	N	N	N	1.48	74	35	104	3	0	3	0	0	0	6	30.4	162	119	12
45	N	N	N	N	N	1.54	70	29.5	100	3	2	2	0	0	0	7	39.4	101	156	9
46	N	N	N	N	N	1.6	81	31.6	114	3	2	2	0	0	0	7	30	90	189	6
47	N	N	N	N	N	1.51	72	32	101	3	0	2	0	0	0	5	26.5	190	156	12
48	N	Y	N	N	N	1.52	61	26.4	88	2	0	2	0	0	0	4	25.2	88	143	5
49	N	N	N	Y	N	1.47	75	34.7	108	2	0	2	0	0	0	4	31.3	95	121	7
50	N	N	N	N	N	1.67	80	28.7	112	4	4	3	0	1	1	13	29.8	98	111	7
51	N	N	N	N	N	1.6	80	31.2	104	4	3	3	0	0	0	10	29	101	198	7
52	N	N	N	N	N	1.57	65	25.6	100	2	3	1	0	0	0	6	25.2	88	189	5
53	N	N	N	N	N	1.54	60	25.3	94	4	4	3	0	1	1	13	31.3	95	200	7
54	N	N	N	N	N	1.54	60	25.3	100	3	3	3	0	0	0	9	10	120	190	2
55	N	N	N	N	N	1.61	78	30.1	105	3	1	2	0	0	0	6	28	190	150	13
56	N	N	N	N	N	1.61	87	33.1	102	4	1	3	0	0	0	8	28.7	201	231	14
57	N	N	N	N	Y	1.6	75	29.3	100	3	3	2	0	0	0	8	28	230	202	15
58	N	N	N	Y	Y	1.62	75	28.6	99	2	0	1	0	0	0	3	25	123	148	7
59	Y	N	N	N	N	1.48	74	35	113	3	0	3	0	0	0	6	23	123	145	6
60	N	N	N	N	N	1.6	81	31.6	114	3	2	2	0	0	0	7	33.9	98	234	8
61	N	N	N	N	N	1.51	72	32	102	3	0	2	0	0	0	5	29.8	178	189	13
62	N	N	N	N	N	1.6	80	31.2	100	3	4	3	0	0	0	10	26	114	190	7
63	N	N	N	N	N	1.47	75	34.7	108	2	0	2	0	0	0	4	15	135	190	5
64	N	N	N	N	N	1.67	80	28.7	112	4	4	3	0	0	1	12	33	179	189	14
65	N	N	N	N	N	1.71	82	28	101	3	4	3	1	1	1	13	33.2	89	290	7
66	N	N	N	N	N	1.6	80	31.2	100	4	3	3	0	0	0	10	28.3	156	209	10

SR. NO	D'SCOPY SITE 1	SC	CC	PP	HD/G	HB	C	WS/G	D'SCOPY SITE 2	SC	CC	PP	HD/G	HB	C	WS/G
1	NECK	Nr	A	A	> 50	A	A	A	RA	Nr	A	MT	<50	A	A	A
2	NECK	Nr	A	MT	>50	P	A	A	RA	Nr	P	T	>50	A	A	A
3	NECK	W	A	MT	<50	A	A	A	RA	NA	NA	NA	NA	NA	NA	NA
4	NECK	Nr	P	MC	A	P	P	A	RA	Nr	P	MC	>50	P	P	A
5	NECK	W	A	T	A	A	A	A	RA	NA	NA	NA	NA	NA	NA	NA
6	NECK	Nr	P	MC	A	A	A	P	RA	W	P	C	A	A	A	A
7	NECK	Nr	P	MT	A	A	A	P	RA	Nr	A	A	A	A	A	A
8	NECK	Nr	A	MP	<50	P	A	A	RA	NA	NA	NA	NA	NA	NA	NA
9	NECK	Nr	P	C	<50	A	P	A	RA	Nr	P	C	>50	A	P	A
10	NECK	Nr	P	MC	<50	P	P	A	RA	Nr	A	A	>50	P	P	A
11	NECK	Nr	P	C	<50	P	P	A	RA	Nr	A	A	A	P	A	A
12	NECK	Nr	P	MC	<50	P	A	A	RA	Nr	A	C	>50	P	A	A
13	NECK	Nr	P	MC	A	P	P	A	RA	Nr	A	MC	A	P	A	A
14	NECK	Nr	P	T	> 50	A	A	A	RA	Nr	P	C	>50	A	A	A
15	NECK	Nr	A	MC	A	A	A	A	RA	Nr	A	A	<50	A	A	A
16	NECK	Nr	A	T	>50	P	A	A	RA	Nr	P	C	>50	A	A	A
17	NECK	Nr	P	C	>50	P	A	A	RA	Nr	P	C	>50	A	P	P
18	NECK	Nr	P	C	A	P	P	A	RA	Nr	P	C	>50	P	P	A
19	NECK	Nr	A	MC	A	A	A	A	RA	Nr	A	A	<50	A	A	A
20	NECK	Nr	A	MP	>50	P	A	A	RA	Nr	P	T	>50	A	A	A
21	NECK	W	A	MP	<50	A	A	A	RA	NA	NA	NA	NA	NA	NA	NA
22	NECK	Nr	P	C	>50	A	A	A	RA	Nr	P	C	>50	A	P	A
23	NECK	Nr	P	MT	A	A	A	P	RA	Nr	A	A	A	A	A	A
24	NECK	Nr	A	MP	A	A	A	A	RA	A	A	MP	A	A	A	A
25	NECK	Nr	A	PO	<50	P	A	A	RA	NA	NA	NA	NA	NA	NA	NA
26	NECK	Nr	P	MC	A	A	A	A	RA	W	A	A	A	A	A	A
27	NECK	Nr	P	MC	<50	A	P	A	RA	Nr	P	MC	>50	A	P	A
28	NECK	Nr	P	MC	<50	A	A	A	RA	Nr	A	A	A	P	A	A
29	NECK	W	A	PO	A	A	A	A	RA	Nr	A	MC	>50	A	A	A
30	NECK	W	A	MT	A	A	A	A	RA	NA	NA	NA	NA	NA	NA	NA
31	NECK	Nr	P	MC	<50	P	P	A	RA	Nr	A	A	A	P	A	A
32	NECK	Nr	P	C	>50	A	A	A	RA	Nr	P	C	<50	A	A	A
33	NECK	Nr	P	MC	A	P	P	A	RA	Nr	A	C	A	P	A	A
34	NECK	W	P	T	<50	P	P	A	RA	W	A	A	>50	P	A	A
35	NECK	Nr	P	MC	> 50	A	A	A	RA	Nr	P	MC	>50	A	A	P
36	NECK	NA	NA	NA	NA	NA	NA	NA	RA	Nr	A	T	<50	A	A	A
37	NECK	Nr	A	MP	A	A	A	A	RA	Nr	A	MP	<50	A	A	A
38	NECK	Nr	P	MP	A	A	A	A	RA	Nr	P	C	>50	A	A	A
39	NECK	Nr	P	MC	>50	A	A	A	RA	Nr	P	MC	>50	A	P	A
40	NECK	Nr	P	MP	<50	A	A	A	RA	Nr	P	MP	>50	A	A	A
41	NECK	W	A	T	A	A	A	A	RA	NA	NA	NA	NA	NA	NA	NA
42	NECK	Nr	P	MC	>50	P	A	A	RA	Nr	P	MC	>50	A	P	P
43	NECK	Nr	A	T	A	A	A	A	RA	A	A	C	A	A	A	A
44	NECK	Nr	P	MP	>50	A	A	A	RA	NA	NA	NA	NA	NA	NA	NA
45	NECK	Nr	P	MC	A	A	A	A	RA	W	A	A	A	A	A	A
46	NECK	W	A	MP	A	A	A	A	RA	W	A	A	A	A	A	A
47	NECK	W	A	MT	<50	A	A	A	RA	NA	NA	NA	NA	NA	NA	NA
48	NECK	W	A	MT	A	A	A	A	RA	NA	NA	NA	NA	NA	NA	NA
49	NECK	W	A	MT	<50	A	A	A	RA	NA	NA	NA	NA	NA	NA	NA
50	NECK	Nr	P	MP	<50	A	P	A	RA	Nr	P	C	>50	P	P	A
51	NECK	Nr	P	MC	A	P	P	A	RA	Nr	A	A	<50	P	A	A
52	NECK	Nr	A	MP	<50	A	A	A	RA	Nr	A	MP	<50	A	A	A
53	NECK	Nr	P	C	>50	P	P	A	RA	Nr	P	C	>50	P	P	P
54	NECK	Nr	P	C	A	P	P	A	RA	Nr	P	C	A	P	P	A
55	NECK	Nr	A	A	> 50	A	A	A	RA	Nr	A	MP	<50	A	A	A
56	NECK	Nr	P	MP	A	A	A	A	RA	Nr	P	C	>50	A	A	A
57	NECK	Nr	P	MP	<50	A	A	A	RA	Nr	P	PO	>50	A	A	A
58	NECK	W	A	T	A	A	A	A	RA	NA	NA	NA	NA	NA	NA	NA
59	NECK	Nr	P	MP	>50	A	A	A	RA	NA	NA	NA	NA	NA	NA	NA
60	NECK	W	A	T	A	A	A	A	RA	W	A	A	A	A	A	A
61	NECK	W	A	MT	<50	A	A	A	RA	NA	NA	NA	NA	NA	NA	NA
62	NECK	Nr	P	MC	<50	P	P	A	RA	Nr	A	A	>50	P	P	A
63	NECK	W	A	MP	<50	A	A	A	RA	NA	NA	NA	NA	NA	NA	NA
64	NECK	Nr	P	MP	<50	A	P	A	RA	Nr	P	C	>50	P	P	A
65	NECK	Nr	P	MP	<50	P	A	A	RA	Nr	A	C	>50	P	A	A
66	NECK	Nr	P	C	A	P	P	A	RA	Nr	A	A	<50	P	A	A

SR. NO	D'SCOPY SITE 3	SC	CC	PP	HD/G	HB	C	WS/G	DRUG	HT	WT	BMI	WC	BG NS	AX	NT	E	KNU	KNE	TOTAL G
1	LA	Nr	A	MT	<50	A	A	A	MET	1.61	75	28.9	95	3	1	1	0	0	0	5
2	LA	Nr	P	C	>50	A	A	A	MET	1.56	64	26.2	90	2	2	2	0	0	0	6
3	NA	NA	NA	NA	NA	NA	NA	NA	MET	1.57	90	36.5	102	2	1	1	0	0	0	4
4	LA	Nr	P	MC	>50	P	P	A	MET	1.57	60	24.3	95	3	2	2	0	0	0	7
5	NA	NA	NA	NA	NA	NA	NA	NA	MET	1.75	87	28.4	93	1	0	1	0	0	0	2
6	LA	W	A	A	A	A	A	A	MET	1.54	68	28.6	86	3	2	2	1	0	0	8
7	LA	Nr	A	A	A	A	A	A	MET	1.75	73	23.8	88	2	2	1	0	0	0	5
8	NA	NA	NA	NA	NA	NA	NA	NA	MET	1.57	66	26.7	88	2	0	3	0	0	0	5
9	LA	Nr	A	C	>50	A	P	A	MET	1.65	88	32.3	1021	3	3	2	1	0	1	10
10	LA	Nr	A	A	>50	P	P	A	MET	1.6	77	30	97	2	3	2	0	0	0	7
11	LA	Nr	A	A	A	P	A	A	MET	1.6	78	30.4	102	3	3	2	0	0	0	8
12	LA	Nr	A	C	>50	P	A	A	MET	1.71	82	28	100	3	3	2	1	1	0	10
13	LA	Nr	A	MC	A	P	A	A	MET	1.67	86	30.8	101	2	2	3	0	0	0	7
14	LA	Nr	P	C	>50	A	A	A	MET	1.49	68	30.6	98	2	2	2	0	0	0	6
15	LA	Nr	A	A	<50	A	A	A	MET	1.68	85	30.1	98	3	3	1	0	1	1	9
16	LA	Nr	P	C	>50	A	A	A	MET	1.56	65	26.7	102	3	2	3	1	0	1	10
17	LA	Nr	P	C	>50	P	P	P	MET	1.67	89	31.9	103	3	3	2	0	0	0	8
18	LA	Nr	P	C	>50	P	P	A	MET	1.57	60	24.3	90	3	3	3	0	0	0	9
19	LA	Nr	A	A	<50	A	A	A	MET	1.7	88	30.4	100	3	2	1	0	1	1	8
20	LA	Nr	P	C	>50	A	A	A	MET	1.56	64	26.2	101	2	2	2	0	0	0	6
21	NA	NA	NA	NA	NA	NA	NA	NA	MET	1.57	90	36.5	109	2	1	1	0	0	0	4
22	LA	Nr	P	C	>50	A	P	A	MET	1.58	67	26.8	98	3	2	2	0	0	0	7
23	LA	Nr	A	A	A	A	A	A	MET	1.75	72	23.5	98	2	2	2	0	0	0	6
24	LA	A	A	MP	A	A	A	A	MET	1.57	62	25.1	95	3	2	2	0	0	0	7
25	NA	NA	NA	NA	NA	NA	NA	NA	MET	1.57	64	25.9	90	2	0	2	0	0	0	4
26	LA	W	A	A	A	A	A	A	MET	1.54	68	28.6	109	2	2	2	0	0	0	6
27	LA	Nr	P	MC	>50	A	P	A	MET	1.65	88	32.3	103	3	3	2	0	0	0	8
28	LA	Nr	A	A	A	P	A	A	MET	1.6	67	26.1	102	3	2	1	0	0	0	6
29	LA	W	A	MC	>50	A	A	A	MET	1.54	77	32.4	99	3	3	1	0	0	0	7
30	NA	NA	NA	NA	NA	NA	NA	NA	MET	1.52	59	25.5	88	1	0	1	0	0	0	2
31	LA	Nr	A	A	A	P	A	A	MET	1.6	77	30	99	3	3	2	0	0	0	8
32	LA	Nr	P	C	>50	A	A	P	MET	1.46	74	34.7	106	3	2	2	0	1	1	9
33	LA	Nr	A	C	A	P	A	A	MET	1.67	85	30.4	97	3	2	3	0	0	0	8
34	LA	Nr	A	A	>50	P	A	A	PIO	1.57	73	29.6	100	0	1	1	0	0	0	1
35	LA	Nr	P	MC	>50	A	A	P	PIO	1.55	72	29.9	98	2	2	2	1	1	0	8
36	LA	Nr	A	T	<50	A	A	A	PIO	1.57	63	25.5	92	0	2	0	0	0	0	2
37	LA	Nr	A	MP	<50	A	A	A	PIO	1.7	89	30.7	94	3	3	1	0	0	0	7
38	LA	Nr	P	C	>50	A	A	A	PIO	1.61	78	30	99	2	1	2	0	0	0	5
39	LA	Nr	P	MC	>50	A	P	A	PIO	1.58	73	29.2	97	3	2	2	0	0	0	7
40	LA	Nr	P	MP	>50	A	A	A	PIO	1.6	75	29.2	92	3	3	2	0	0	0	8
41	NA	NA	NA	NA	NA	NA	NA	NA	PIO	1.62	76	28.9	90	2	0	1	0	0	0	3
42	LA	Nr	P	MC	>50	P	P	P	PIO	1.67	90	32.2	96	3	2	2	0	0	0	7
43	LA	A	A	C	A	A	A	A	PIO	1.57	66	27.7	87	2	1	1	0	0	0	4
44	NA	NA	NA	NA	NA	NA	NA	NA	PIO	1.48	74	33.3	102	2	0	2	0	0	0	4
45	LA	W	A	A	A	A	A	A	PIO	1.54	69	29	100	2	1	1	0	0	0	4
46	LA	W	A	A	A	A	A	A	PIO	1.6	78	30.4	114	3	2	2	0	0	0	7
47	NA	NA	NA	NA	NA	NA	NA	NA	PIO	1.51	72	31.5	100	2	0	1	0	0	0	3
48	NA	NA	NA	NA	NA	NA	NA	NA	PIO	1.52	61	26.4	88	2	0	1	0	0	0	3
49	NA	NA	NA	NA	NA	NA	NA	NA	PIO	1.47	73	33.7	108	2	0	2	0	0	0	4
50	LA	Nr	P	C	>50	P	P	A	PIO	1.67	81	29	109	3	3	2	0	1	1	10
51	LA	Nr	A	A	<50	P	P	A	PIO	1.6	81	31.6	100	3	2	2	0	0	0	7
52	LA	Nr	A	MP	<50	A	A	A	PIO	1.57	68	27.5	98	2	2	1	0	0	0	5
53	LA	Nr	P	C	<50	P	P	P	PIO	1.54	60	25.2	94	3	3	2	0	1	0	9
54	LA	Nr	P	C	A	P	P	A	PIO	1.54	61	25.7	98	3	3	3	0	0	0	9
55	LA	Nr	P	MP	<50	A	A	A	PIO	1.61	78	30	103	3	1	2	0	0	0	6
56	LA	Nr	P	C	>50	A	A	A	PIO	1.61	87	33.5	100	3	1	2	0	0	0	6
57	LA	Nr	P	PO	>50	A	A	A	PIO	1.6	76	29.6	100	3	2	2	0	0	0	7
58	NA	NA	NA	NA	NA	NA	NA	NA	PIO	1.62	75	28.5	99	1	0	1	0	0	0	2
59	NA	NA	NA	NA	NA	NA	NA	NA	PIO	1.48	76	34.6	111	3	0	2	0	0	0	5
60	LA	W	A	A	A	A	A	A	PIO	1.6	80	31.2	112	3	1	2	0	0	0	6
61	NA	NA	NA	NA	NA	NA	NA	NA	PIO	1.51	72	31.5	98	2	0	1	0	0	0	3
62	LA	Nr	A	A	>50	P	P	A	PIO	1.6	80	31.2	99	2	3	2	0	0	0	7
63	NA	NA	NA	NA	NA	NA	NA	NA	PIO	1.47	76	35.1	108	2	0	2	0	0	0	4
64	LA	Nr	P	C	>50	P	P	A	PIO	1.67	80	28.6	112	4	3	3	0	0	0	10
65	LA	Nr	A	C	>50	P	A	A	PIO	1.71	82	28	101	2	4	2	1	1	1	11
66	LA	Nr	A	A	<50	P	P	A	PIO	1.6	78	30.4	100	3	2	2	0	0	0	7

SR. NO	FI	FG	TG	HOMA IR	D'COPY SITE 1	SC	CC	PP	HD/G	HB	C	WS/G	D'SCOPY SITE 2	SC	CC	PP	HD/G	HB	C	WD/G
1	9	89	140	1.9	NECK	Nr	A	A	<50	A	A	A	RA	Nr	A	MT	A	A	A	A
2	24	92	150	5	NECK	Nr	A	MT	<50	A	A	A	RA	Nr	A	T	<50	A	A	A
3	10	90	123	2	NECK	Nr	A	T	<50	A	A	A	NA	NA	NA	NA	NA	NA	NA	NA
4	20	90	170	4	NECK	Nr	P	MP	A	P	P	A	RA	W	P	MP	>50	P	P	A
5	16	110	190	4	NECK	W	A	T	A	A	A	A	NA	NA	NA	NA	NA	NA	NA	NA
6	10	99	200	2	NECK	W	P	MP	A	A	A	P	RA	W	P	MP	A	A	A	A
7	24	135	229	8	NECK	W	P	T	A	A	A	P	RA	W	A	A	A	A	A	A
8	20	96	140	4	NECK	W	A	MT	A	P	A	A	RA	NA	NA	NA	NA	NA	NA	NA
9	20	154	224	7	NECK	Nr	P	MP	<50	A	P	A	RA	W	P	MP	<50	A	P	A
10	21	100	200	5	NECK	W	P	MP	<50	P	P	A	RA	W	A	A	<50	P	P	A
11	13	102	200	3	NECK	W	P	MP	A	P	A	A	RA	Nr	A	A	A	P	A	A
12	15	154	240	5	NECK	W	P	MP	<50	P	A	A	RA	W	A	MP	<50	P	A	A
13	13	101	200	3	NECK	Nr	P	MP	A	P	A	A	RA	W	A	MT	A	P	A	A
14	13	99	140	3	NECK	Nr	P	T	<50	A	A	A	RA	Nr	P	PO	<50	A	A	A
15	12	170	89	5	NECK	Nr	A	A	A	A	A	A	RA	Nr	A	A	<50	A	A	A
16	14	90	250	3	NECK	Nr	A	T	<50	P	A	A	RA	Nr	P	MC	<50	A	A	A
17	15	82	150	3	NECK	W	P	MP	<50	P	A	A	RA	W	P	MP	>50	A	P	P
18	20	88	200	4	NECK	Nr	P	PO	A	P	P	A	RA	Nr	P	PO	<50	P	P	A
19	14	130	150	4	NECK	W	A	MP	A	A	A	A	RA	Nr	A	A	<50	A	A	A
20	24	90	250	5	NECK	Nr	A	T	>50	P	A	A	RA	W	P	T	<50	A	A	A
21	17	80	130	3	NECK	W	A	T	<50	A	A	A	RA	NA	NA	NA	NA	NA	NA	NA
22	19	89	200	4	NECK	W	P	MP	<50	A	A	A	RA	W	P	PO	<50	A	P	A
23	20	150	120	7	NECK	W	P	T	A	A	A	P	RA	Nr	A	A	A	A	A	A
24	29	90	167	6	NECK	W	A	MT	A	A	A	A	RA	A	A	MT	A	A	A	A
25	10	100	125	2	NECK	W	A	T	<50	P	A	A	RA	NA	NA	NA	NA	NA	NA	NA
26	22	150	150	8	NECK	W	P	MP	A	A	A	A	RA	W	A	A	A	A	A	A
27	20	89	278	4	NECK	W	P	MP	<50	A	A	A	RA	W	P	MP	>50	A	P	A
28	18	120	150	5	NECK	Nr	P	MP	<50	A	A	A	RA	W	A	A	A	A	A	A
29	22	111	178	6	NECK	W	A	MT	A	A	A	A	RA	W	A	MT	>50	A	A	A
30	13	120	101	3	NECK	W	A	T	A	A	A	A	RA	NA	NA	NA	NA	NA	NA	NA
31	15	80	206	2	NECK	Nr	P	MP	<50	P	P	A	RA	Nr	A	A	A	P	A	A
32	28	90	260	6	NECK	W	P	PO	<50	A	A	A	RA	W	P	MP	<50	A	A	A
33	28	122	189	8	NECK	W	P	PO	A	P	A	A	RA	W	A	PO	A	A	A	A
34	20	96	100	4.2	NECK	W	T	<50	A	A	A	RA	RA	A	A	<50	P	A	A	LA
35	24	90	150	4	NECK	N	P	MP	<50	A	A	P	RA	W	P	MP	>50	A	A	P
36	17	80	100	5	NA	NA	NA	NA	NA	NA	NA	NA	RA	W	P	MT	<50	A	A	A
37	28	130	100	3	NECK	N	A	MP	A	A	A	A	RA	Nr	A	MP	<50	A	A	A
38	10	90	100	8	NECK	N	P	MT	A	A	A	A	RA	Nr	P	MP	<50	A	A	A
39	25	90	120	2	NECK	W	P	MP	<50	A	A	A	RA	W	P	MP	<50	A	P	A
40	22	100	120	5	NECK	W	P	MP	<50	A	A	A	RA	W	P	MP	<50	A	A	A
41	18.2	100	130	5	NECK	W	A	T	A	A	A	A	NA	NA	NA	NA	NA	NA	NA	NA
42	26	89	120	4	NECK	N	P	MP	<50	P	A	A	RA	W	P	MP	<50	A	P	P
43	23	85	100	5	NECK	W	A	T	A	A	A	A	RA	A	A	MP	A	A	A	A
44	19	120	118	4	NECK	W	P	MT	<50	A	A	A	RA	NA	NA	NA	NA	NA	NA	NA
45	29	90	145	5	NECK	W	P	MC	A	A	A	A	RA	W	A	A	A	A	A	A
46	23	90	176	6	NECK	N	A	MP	A	A	A	A	RA	W	A	A	A	A	A	A
47	20	150	150	5	NECK	W	A	T	<50	A	A	A	NA	NA	NA	NA	NA	NA	NA	NA
48	20	100	134	7	NECK	W	A	T	A	A	A	A	RA	NA	NA	NA	NA	NA	NA	NA
49	27	100	120	4	NECK	W	A	MT	<50	A	A	A	RA	NA	NA	NA	NA	NA	NA	NA
50	26	90	110	6	NECK	W	P	MT	<50	A	P	A	RA	Nr	P	PO	<50	P	P	A
51	13	90	189	5	NECK	W	P	MT	A	A	P	A	RA	W	A	A	<50	P	A	A
52	20	88	130	2	NECK	N	A	MT	<50	A	A	A	RA	Nr	A	MT	<50	A	A	A
53	23	95	160	4	NECK	N	P	MC	<50	A	P	A	RA	W	P	MP	<50	P	P	P
54	10	101	149	5	NECK	W	P	MP	A	A	P	A	RA	Nr	P	PO	A	P	P	A
55	25	150	140	2	NECK	W	A	A	<50	A	A	A	RA	W	A	MT	<50	A	A	A
56	22	150	200	9	NECK	W	P	T	A	A	A	A	RA	W	P	PO	<50	A	A	A
57	20	160	150	8	NECK	N	P	MP	<50	A	A	A	RA	Nr	P	MT	>50	A	A	A
58	17	100	140	7	NECK	W	A	T	A	A	A	A	RA	NA	NA	NA	NA	NA	NA	NA
59	23	100	140	4	NECK	N	P	MT	<50	A	A	A	RA	NA	NA	NA	NA	NA	NA	NA
60	28	79	230	5	NECK	W	A	T	A	A	A	A	RA	W	A	A	A	A	A	A
61	26	150	167	5	NECK	W	A	T	<50	A	A	A	RA	NA	NA	NA	NA	NA	NA	NA
62	20	100	189	9	NECK	W	P	MT	<50	A	A	A	RA	W	A	A	>50	A	P	A
63	10	133	178	4	NECK	W	A	MT	<50	A	A	A	RA	NA	NA	NA	NA	NA	NA	NA
64	29	122	167	3	NECK	W	P	T	<50	A	A	A	RA	W	P	PO	<50	A	A	A
65	28	80	234	8	NECK	W	P	MP	<50	P	A	A	RA	W	A	C	>50	A	A	A
66	20	120	180	5	NECK	N	P	MC	A	P	P	A	RA	Nr	A	A	<50	A	A	A

SR. NO	D'SCOPY SITE 3	SC	CC	PP	HD/G	HB	C	WS/G
1	LA	W	A	MT	<50	A	A	A
2	LA	Nr	P	C	>50	A	A	A
3	NA	NA	NA	NA	NA	NA	NA	NA
4	LA	W	P	MP	>50	P	P	A
5	NA	NA	NA	NA	NA	NA	NA	NA
6	LA	W	A	A	A	A	A	A
7	LA	W	A	A	A	A	A	A
8	NA	NA	NA	NA	NA	NA	NA	NA
9	LA	W	A	MP	<50	A	P	A
10	LA	W	A	A	<50	P	P	A
11	LA	W	A	A	A	P	A	A
12	LA	W	A	MP	>50	A	A	A
13	LA	W	A	MT	A	P	A	A
14	LA	W	P	PO	<50	A	A	A
15	LA	W	A	A	<50	A	A	A
16	LA	W	P	PO	>50	A	A	A
17	LA	Nr	P	PO	<50	P	P	P
18	LA	Nr	P	PO	<50	P	P	A
19	LA	Nr	A	T	<50	A	A	A
20	LA	W	P	PO	<50	A	A	A
21	NA	NA	NA	NA	NA	NA	NA	NA
22	LA	W	P	PO	<50	A	P	A
23	LA	Nr	A	A	A	A	A	A
24	LA	A	A	MT	A	A	A	A
25	NA	NA	NA	NA	NA	NA	NA	NA
26	LA	W	A	A	A	A	A	A
27	LA	Nr	A	PO	>50	A	P	A
28	LA	N	A	A	A	P	A	A
29	LA	W	A	MT	<50	A	A	A
30	NA	NA	NA	NA	NA	NA	NA	NA
31	LA	Nr	A	A	A	P	A	A
32	LA	W	P	MP	<50	A	A	P
33	LA	W	A	PO	A	P	A	A
34	A	A	A	<50	P	A	A	A
35	LA	W	P	MT	<50	A	A	P
36	LA	W	P	MT	<50	A	A	A
37	LA	W	A	MP	<50	A	A	A
38	LA	Nr	P	MP	>50	A	A	A
39	LA	Nr	P	MP	<50	A	P	A
40	LA	Nr	P	MP	<50	A	A	A
41	NA	NA	NA	NA	NA	NA	NA	NA
42	LA	Nr	P	MP	<50	P	P	P
43	LA	A	A	MC	A	A	A	A
44	NA	NA	NA	NA	NA	NA	NA	NA
45	LA	W	A	A	A	A	A	A
46	LA	W	A	A	A	A	A	A
47	NA	NA	NA	NA	NA	NA	NA	NA
48	NA	NA	NA	NA	NA	NA	NA	NA
49	NA	NA	NA	NA	NA	NA	NA	NA
50	LA	Nr	P	MP	<50	P	P	A
51	LA	W	A	A	<50	A	P	A
52	LA	W	A	MT	<50	A	A	A
53	LA	Nr	P	PO	<50	P	P	P
54	LA	Nr	P	MP	A	P	P	A
55	LA	W	A	MP	<50	A	A	A
56	LA	W	P	MP	<50	A	A	A
57	LA	Nr	P	MT	<50	A	A	A
58	NA	NA	NA	NA	NA	NA	NA	NA
59	NA	NA	NA	NA	NA	NA	NA	NA
60	LA	W	A	A	A	A	A	A
61	NA	NA	NA	NA	NA	NA	NA	NA
62	LA	Nr	A	MP	<50	P	P	A
63	NA	NA	NA	NA	NA	NA	NA	NA
64	LA	W	P	PO	>50	P	P	A
65	LA	Nr	A	MP	<50	P	A	A
66	LA	Nr	A	C	<50	P	P	A