"SERUM APELIN LEVELS IN ACANTHOSIS NIGRICANS: A CROSS-SECTIONAL COMPARATIVE STUDY"

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Abstract

Background

Acanthosis nigricans (AN) is a dermatosis that causes symmetrical, symptomless dimming in skin fold areas like axillary fossa, groins, sub-mammary region, and neckline. It is linked to obesity and insulin resistance. Due to lifestyle changes, the association of Acanthosis nigricans and obesity-related hyperinsulinaemia is gaining attention. Insulin resistance is connected to decreased apelin. Hence, this study compares apelin levels in Acanthosis nigricans patients and healthy people to discover if they are linked to metabolic issues and obesity.

Materials & Methods

This study was a cross-sectional comparative analysis carried out from April 2023 to November 2024 in RL Jalappa Hospital and Research Centre. The patient role was categorized into two distinct groups: Cluster A and Cluster B. Group A comprised patients diagnosed with AN, while Group B comprised healthy volunteers. Patients and healthy volunteers gave 2 ml of intravenous blood in a blood serum filter tube with a clot activator after 8-12 hours of fasting. After 10 min of centrifugation at 2000xg in a chilled bench-top centrifuge, serum was extracted from the tube and stored at -800C until analysis. The human Apelin 12 GENLISA ELISA KIT quantified serum Apelin 12. Data was imported into Excel for statistical analysis.

Results

100 study subjects were registered, with 50 in each group. The study comprised 74 males and 26 females. Group A displayed a mean BMI of 31.826, while group B had a mean BMI of 25.094. The mean HBA1C levels for groups A and B were recorded at 5.080 and 5.02, respectively. The mean HOMA-IR for group A was determined to be 9.372, whereas for group B, it was recorded at 2.05. The mean apelin levels in the cases were 0.28, while in the controls, it was 0.55.

Conclusion

Anti-inflammatory apelin was lower in Acanthosis nigricans patients than healthy controls. According to these findings, chronic inflammation in AN patients may produce adipokine dysregulation regardless of weight. Low apelin levels may be connected to AN's chronic inflammation and hypoxia. This condition may reduce anti-inflammatory adipokines by

causing adipose tissue dysfunction and fibrosis. Adipose tissue dysfunction and fibrosis might diminish apelin levels in AN patients. Supporting this claim requires larger population-based effect research.

Keywords: Serum Apelin levels, Acanthosis nigricans.

INTRODUCTION

Introduction

Acanthosis Nigricans (AN) is silky hyperpigmentation of coffee brown, dusky blue, or black. It typically affects the neck, axilla, knuckles, groin, umbilicus, and perianal areas. After Unna proposed it, Pollitzer and Janovsky verified the first circumstance of AN in 1891. [1-7] AN is symmetrically distributed in the inframammary region, antecubital, and popliteal fossae. A single patient can develop AN in diverse patterns at different places over time. [8-11]

In certain instances, AN can affect eyelids, lips, vulva, and flexural ranges in the groin, knees, and thighs. It is presumed that women develop lesions on the nipple, and in children, the posterior neck is the frequent site of AN. Infrequently, the scratches may become generalised and involve the mucosa. [12]

AN is generally asymptomatic, yet it can be pruritic. Categories of AN comprise benign, overweightness-related, syndromic, malicious, acral, one-sided, drug-induced, and varied types. The strictness of AN rises with growing body mass, waist-hip ratio, and fat proportion.[13-15]

Insidious AN onset. Even newborns can see AN lesions. Malignant acanthosis nigricans affects the elderly. Patients and families sometimes overlook it or mistake it for filth. Its tone makes the affected skin appear light brown to black. Margins and skin marks give it a rough, velvety touch. Lesion progression may cause papillomatosis or verrucous plaque. [16]

Mucosal involvement is frequently observed in cases of AN linked to malignancy, although it is uncommon in cases linked to obesity.[17] Because acanthosis nigricans can indicate some conditions, from endocrinological issues to cancer, clinicians should be aware of it. Early documentation of these syndromes helps in the appropriate diagnosis of the underlying sickness and proper care management. [18]

AN severity is directly related to fast insulin levels, and high insulin levels binding to IGF-1Rs on keratinocytes and fibroblasts may cause it. Acanthosis nigricans involves insulin and its receptors. IGF1 is equivalent to skin-produced insulin. IGF1 binds to the IGF1 receptor with the highest affinity, enhancing mitogenic effects, while insulin attaches to the insulin receptor, affecting metabolism. However, metabolic glitches can cause papillomatosis, hyperkeratosis, and acanthosis when high insulin levels unswervingly activate the IGF1 receptor on keratinocytes and dermal fibroblasts. [19]

Several adipocyte-derived regulating hormones called adipokines have been studied recently. In 1998, apelin was found among these adipokines. After 13 years, apelin was revealed to have numerous biological effects in many organs. High insulin resistance in Acanthosis nigricans is linked to low apelin levels.[20]

This study seeks to examine apelin levels in patients with Acanthosis nigricans and healthy individuals to regulate the connotation of these levels with underlying metabolic problems and obesity

AIMS & OBJECTIVES

Aims & Objectives

- To estimate the alteration in serum apelin levels in Acanthosis nigricans and healthy subjects

REVIEW OF LITERATURE

Review of Literature

Background

While Addison might have encountered an instance of AN earlier in 1885 and erroneously labelled it as Addison's sickness. This primary recognized case was chronicled in 1889 in Germany. It is also known as black lentigines, dystrophia papillary pigmentosa. [21]

Definition

Clinically expressive term for Gray-brown papillomatosis-hyperkeratosis, chiefly asymptomatic, polyetiological, widespread skin developments, frequently happening intertriginously, and less regularly in acral areas (nose, ears, palmoplantar skin, and oral cavity). It is a standardized dermal answer wherein the skin responds to diverse endogenous "growth" stimuli with nonspecific expansion. [22,23]

Acanthosis nigricans can be idiopathic or responsive in persons who are overweight, as a symbol of genetic anomalies, paraneoplastic (when frequently called "acanthosis nigricans maligna") regarding adenocarcinomas, or in association with endocrinological ailments or gravidity (in this instance, gestational diabetes should be thoroughly eliminated). [24]

Classification [25]

Curth's classified AN as

- Malignant
- Benign hereditary and
- Pseudo-associated with overweightness

Hernandez-Perez categorised as

- Modest (naevoid/obese/drug interacted/syndromic)
- Paraneoplastic

Schwartz described AN as eight types

- Benign
- Overweightness associated
- Systematic
- Hostile
- Distal
- Independent
- Medication-moved and
- Assorted type when two varieties exist

Prevalence

AN is presently on the upsurge due to the improved frequency of obesity and diabetes mellitus in the human population. It is more common in obese individuals. Its prevalence in the general population is unknown. It is most common in Native Americans, tracked by African Americans, Hispanics, and Caucasians prevalence of AN ranges between 7% to 75% in the human population, depending on age, race and type, grade of obesity, and associated endocrine issues. AN typically occurs in Americans, African Americans, Hispanics, and Caucasians. [14]

Pathogenesis

To a large extent, the consequences of AN seem linked to the explosion of cuticular keratin cells and cutaneous mesenchymal cells in various situations that are not completely unwritten. It is highly difficult to understand the biochemical mechanisms that are responsible for the development of the lesions. These mechanisms include numerous cytokines and signalling trail crosstalk. A few of these courses have been identified, but there are still a great deal of them that have not been uncovered.[24]

AN can be induced by hyperinsulinemia in many different ways, including a direct influence as well as an indirect effect. The straight action is demonstrated by the activation of the IGF-1 receptor by insulin, brought about by the high concentration of the element. The nature of the unintended result is more multifaceted: it circuitously advances the total of permitted IGF-1 that is circulating in the bloodstream, which accounts for the vigorous percentage.[25]

In the AN, insulin or an IGF has remained recommended as a supporter of improved cuticular cell spread. Other intermediaries appear to be tangled as well, counting fibroblast growth factor (FGF) and tyrosine kinase receptors [25]

To reach Keratinocytes, insulin is shown to traverse the dermo-epidermal junction (DEJ). Simple carbohydrate and lipid metabolism is controlled by minimal insulin absorption, which can promote progress by connecting to classic insulin receptors. Insulin at utmost concentration can show even extra strong growth-enhancing properties by threading to (IGF-1Rs) that are identical in dimensions to insulin but can connect with 100-1000-fold better attraction to insulin. This kind of connecting arouses the division of keratinocytes and fibroblasts, leading to AN. [26]

Both permitted and in combination with IGFBPs are present in the flow at levels of insulin-like growth factor-1 (IGF-1). IGFBPs are accountable for transporting IGF-1 to the target, and regulating the IGF-1 portion, which is the component that is accountable for its activity in the metabolic process. It is hypothesized that hyperinsulinemia leads to a reduction in the circulating concentration of IGFBP-1 and 2, which in turn principals to an upsurge in the amounts of unrestricted IGF-1 in muscles, which in turn promotes cell proliferation and inflammation. In addition, high quantities of insulin may be responsible for the displacement of IGF-1 from IGFBPs, which consequences in an increase in the proportion of free IGF-1 in plasma and may also be responsible for determining the development and differentiation of cells.[27]

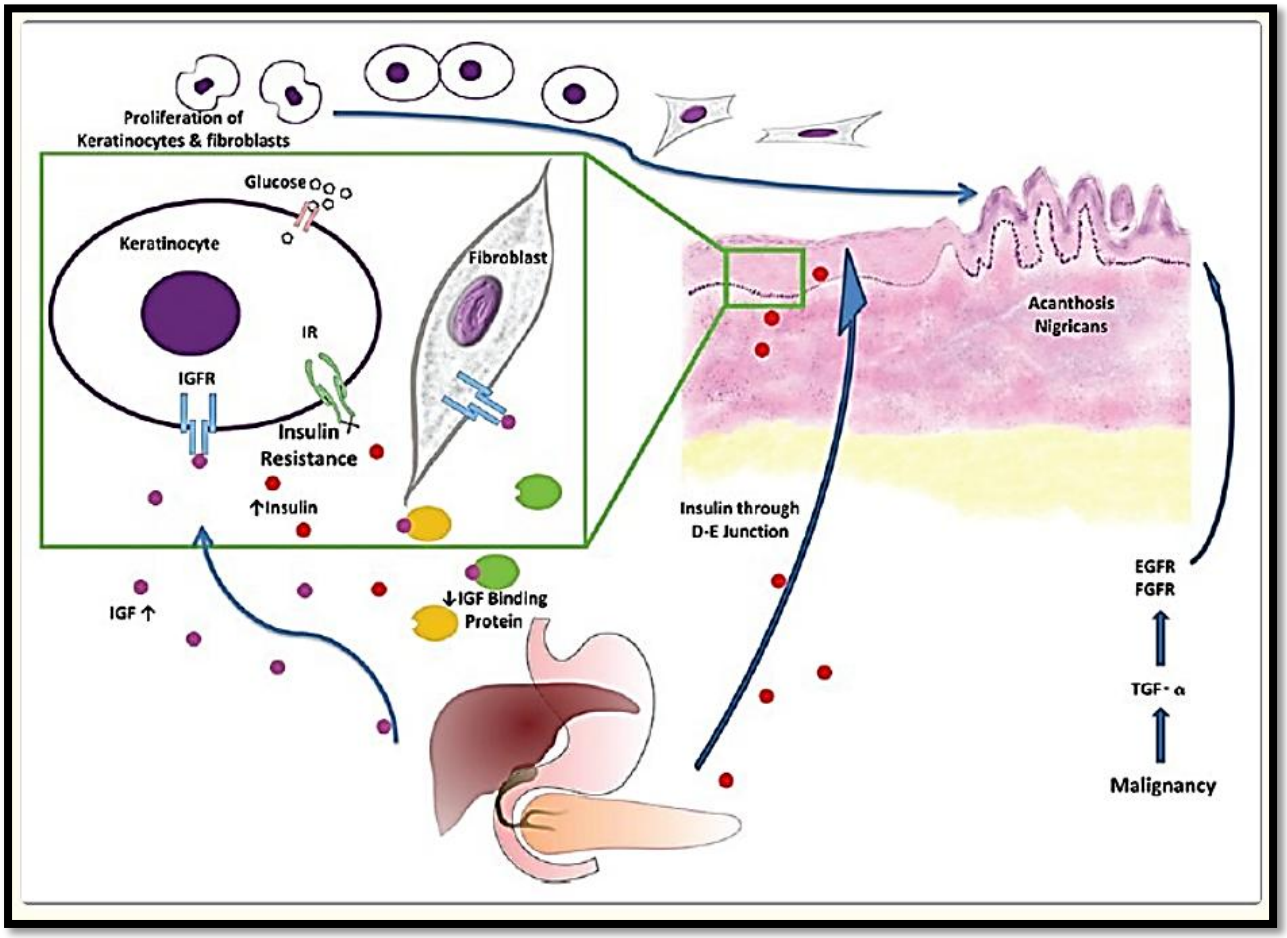

Figure 1: Development of Acanthosis Nigricans

Hyperinsulinemia promotes AN directly and indirectly by increasing free IGF-1 levels. Insulin-like growth factor binding proteins (IGFBPs) extend the half-life of growth factor 1, distribute it to target sites, and control metabolically active free IGF-1 levels. In hefty people with hyperinsulinemia, IGFBP-1 and 2 decrease, increasing plasma levels and cell proliferation and differentiation. (Figure 2)

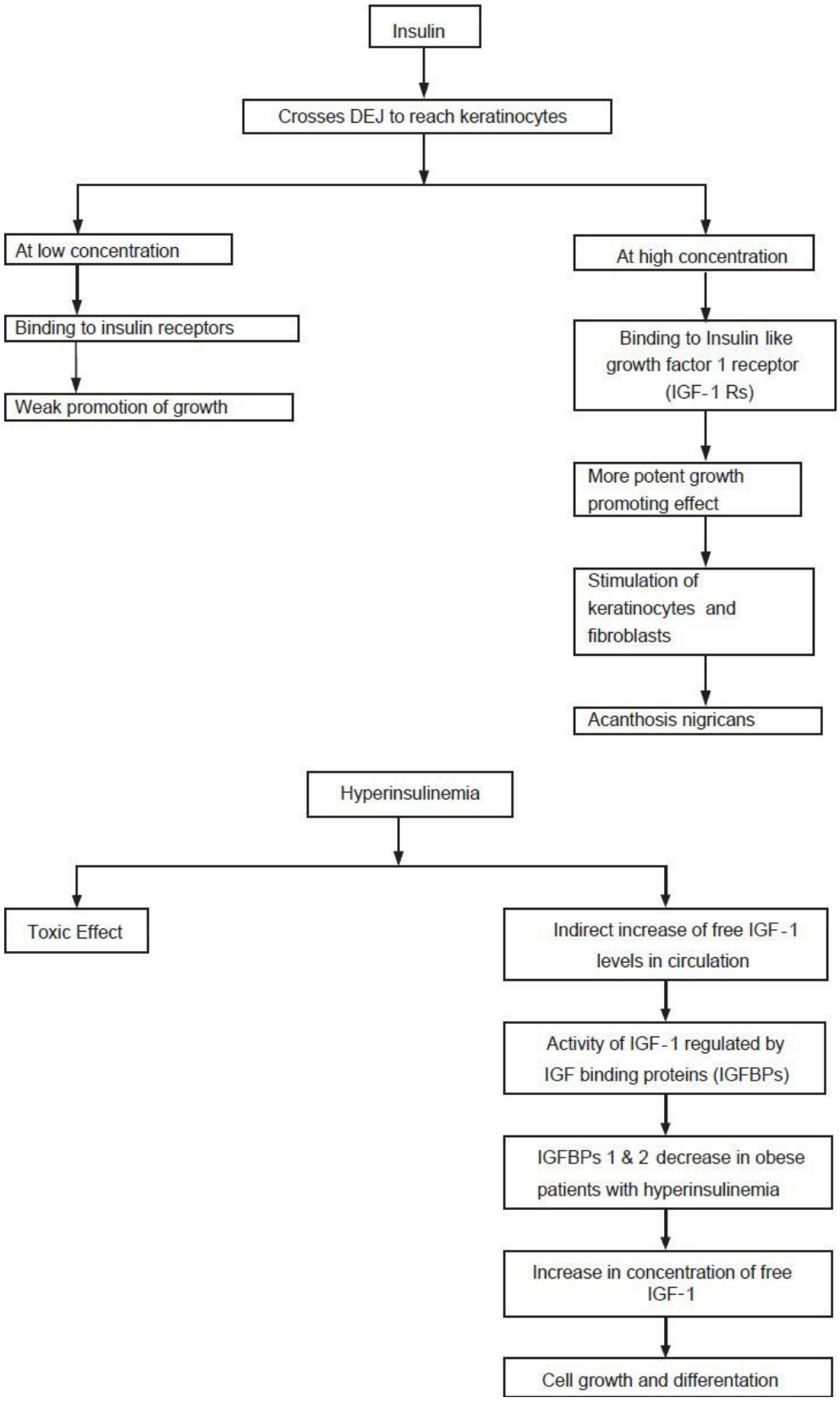

Figure 2: Highlighting role of IGF on signal pathways and keratinocytes and melanocytes

Insulin-dependent IGF-1Rs can expand AN due to two factors:

(1) IGF sensory receptors can be formed in refined fibroblasts and keratinocytes, and

(2) High amounts of insulin can drive fibroblast development and proliferation. (3) Avoiding insulin absorption improves obesity-related AN severity. Insulin directly activates the IGF-1 signaling pathway to cause AN. The neck and axillae are prone to AN, suggesting sweat or abrasion are cofactors. [27]

Malignancy connected with Acanthosis Nigricans

Enhanced TGF-alpha phases can illuminate Acanthosis nigricans maligna (ANM) by affecting cuticular tissue via EGF receptors. IGF-1, and melanocyte-stimulating hormone normalize melanocyte skin color, causing hyperpigmentation and hyperplasia. [28]

Clinical features

AN is characterised by dim, coarse, shortened skin with a silky texture. The early amendment is grey-brown/black skin-color connected with dryness and bumpiness, enclosed by small papillomatosis increases that give rise to a velvety surface. AN is asymptomatic but can be pruritic. The neck can be a more commonly affected site than the axillae. [29]

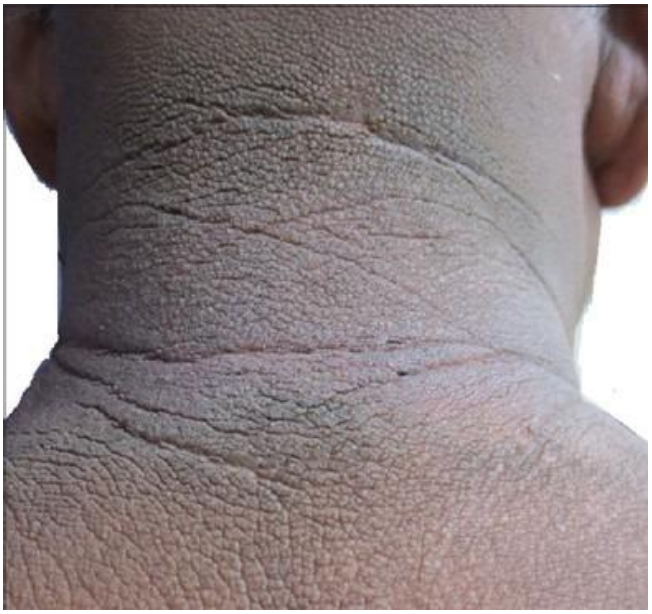

Figure 3: AN of the neck

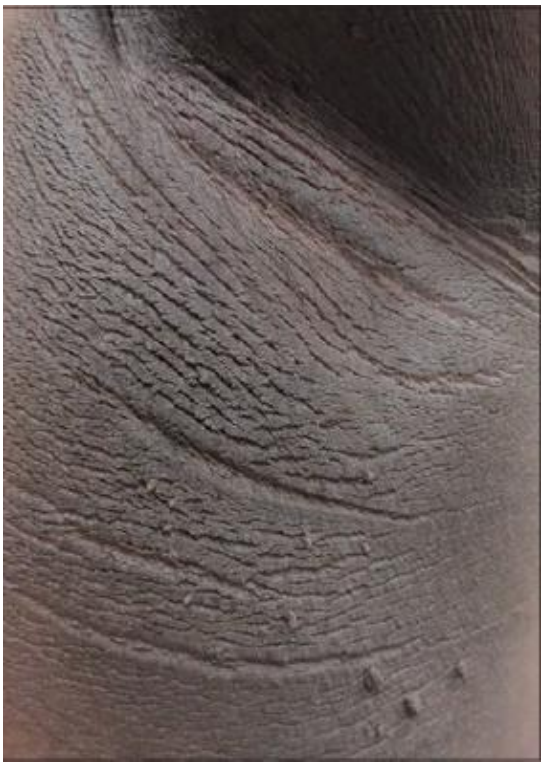

Figure 4: AN of the axillae

Types of Acanthosis Nigricans

Slenderness-associated Pseudo-acanthosis nigricans

Utmost cases are AN obesity-related with severity correlated with weight. Post-weight-loss lesions often recede slowly. Obese insulin-resistant patients have it more. Two kinds of syndromic AN have been labelled: type A has hyperandrogenaemia (HA), insulin confrontation, and AN, while type B has diabetes and ovarian hyperandrogenaemia

Obesity stands as a predominant cause of AN. Pigmentation might seem to seem at any age, but is mutual in the elderly. Persons weighing >200% of the body mass are supposed to constitute AN. The colour of the skin is dependent on weight, with regression followed by a reduction in weight. Resistant to insulin is more common in this kind of patient. [30]

Medication-associated AN

Nicotinic acid, combination oral contraceptive, and growth hormone therapy can cause AN. Skin lesions are reversible when treatment is stopped, however, the severity of the condition should determine the decision. Erickson et al. found that insulin injections can cause AN lesions in rare circumstances. AN can appear as a side effect to several medications and promote hyperinsulinemia, and can be prevented with proper insulin type prescription and delivery. [31]

Syndromic acanthosis nigricans

It is of two types

- Type A includes IR grants connecting hyperandrogenaemia, IR, and AN.
- Type B has uncontrolled diabetes mellitus, ovarian HA, and autoimmune disease. [32]

Autoimmune acanthosis nigricans

Anti-insulin receptor antibodies in autoimmune infections like complete lupus erythematosus regulate autoimmune AN. AN with autoimmune signs but no type B insulin fighting responded to systemic immunosuppression. AN mucocutaneous lesions may be caused by autoantibodies other than the insulin-receptor antibody. Positive antinuclear antibodies (ANA), antimitochondrial antibodies (AMA), or elevated immune globulin stages may indicate aberrant immunoreactivity without clinical symptoms. [33]

Acral acanthosis nigricans

Acral AN arises in nearly healthy, dusky persons. It is inadequate for the abaxial exteriors of the body parts. It might be activated by yet unidentified genetic features that will ultimately place it in the cluster of inherent disorders. It takes place in healthy patients and commonly in dark skinned individuals. [33]

Genetic

Independent AN is an autosomal type that can emerge at any point of age without endocrinopathy. Unilateral abrasions occur in the back, thighs, and periumbilical area. Family AN is a rare autosomal dominant condition that evolves self-limitingly. It usually starts in early

childhood and stabilizes or recedes by adolescence, but it can appear at any age. Rare autosomal dominant benign genetic AN occurs from genetic or primary childhood.[34]

Malignant AN

Internal malignancies cause clinically indistinguishable lesions from benign types but often cause significant pruritus. They frequently start quickly before, with, or after internal malignancy. Paraneoplastic AN arises in abdominal and genitourinary adenocarcinomas. Cancers such as lung, thyroid, and lymphoma are infrequent with AN. Effective therapy causes AN remission, but recrudescence may indicate recurrence.[34]

Unilateral acanthosis nigricans

It is not a common formula of AN and is genetic as a dominant trait. It is commonly noted on the face, crown, trunk, belly, and thigh. [34]

Familial acanthosis nigricans

It begins in early childhood and can manifest at any age. This can progress till adolescence, after which it calms. [35]

Benign genetic acanthosis nigricans

It is a infrequent autosomal condition. AN can occur during adenocarcinomas of abdominal organs, followed by the ovary, kidneys, thyroid, bile duct, breast, and oesophagus. [35]

Mixed-type acanthosis nigricans

It arises from either of the above two types of AN develops. Conditions that are evident in AN are as follows. Metabolic diseases like Addison's disease, Hirsutism, Gigantism, and Leprechaunism. Syndromes like Cushing's syndrome, Down, Bloom syndrome, Marfan, rub, and Alstrom syndrome. [36]

Acanthosis nigricans and cardiovascular disease

Cardiac dysfunction is caused by insulin resistance, and a higher prevalence is seen in the nonischaemic heart disease populace. It antedates the expansion of circulatory illness and autonomously describes a worse prediction. The minimization of endothelial occupation might be an assembly among IR and a failure in cardiovascular function. IR might be associated with systemic disorders by many instruments, such as trouble in the subcellular signalling path and the PI-3-kinase /Akt path. [37]

Acanthosis Nigricans and Adipokines

Cases with hyperglycemia are higher risk of atherosclerotic cardiovascular illness. The frequent root of IR is surplus intestinal adipose muscle that proclaims an augmented amount of free blubbery acids that unswervingly release fatty acids next to insulin signalling and enhance gluconeogenesis in the liver. Interlukin-6 and tumor necrosis factor alpha are some factors that play a role in IR. [38]

Metabolic syndrome, Insulin resistance, and Adipokines

Slenderness is frequently connected with type 2 diabetes, vein sickness, and high blood pressure. IR deceits are at the core of the anabolic disorder. Increased serum triglycerides are normally connected with IR and signify an appreciated marker of metabolic pattern.

White adipose tissue serves as a primary location for Vigor storage and is gradually acknowledged as a significant endocrine organ. It stows various physically active substances known as "adipokines," including leptin, adiponectin, and resistin. Notably, certain adipokines, particularly resistin and adiponectin, have been demonstrated to influence sugar hormone sensitivity, either directly or indirectly, by modulating insulin flagging and the associated components tangled in glucose and fat metabolism.

The enduring state of insulin resistance is linked to minor alterations in adipokine stages, characterized by reduced blood serum adiponectin, hightened serum fighting, and reduced adiponectin gene expression. Inherited and ecological factors that reduce adiponectin levels play a role in the development of metabolic syndrome. Adiponectin plays a crucial role due to its antidiabetic and antiatherogenic properties, suggesting its potential as a novel calming agent for metabolic patterns. The thiazolidinedione (TZD) period of antidiabetic drugs exerts pleiotropic properties on cardiac ailments and wax absorption, in part by increasing adiponectin levels. Rosiglitazone upregulates adiponectin expression and circulating levels. [39,40]

Apelin

Apelin is a newly exposed protein chain that has gathered substantial attention in recent years. It was first isolated from bovine intestinal cuttings in a treatment screening for endogenous bite angle for a beforehand bereaved G protein-coupled receptor called Astral 1 or APJ. APJ bears significant sequence homology to the type 1 angiotensin receptor and is known to associate with heterotrimeric G protein G1 and GQ. APJ is the only identified sensory site for apelin. [41]

Apelin is situated on chromosome Xq25-26.1. It is a 77-acid prepropeptide that is diverged post-translationally into many lively procedures of varied lengths. Among these, the 36 is most extensively spoken in various organs, including adipocytes and endothelia of minor veins.[42,43]

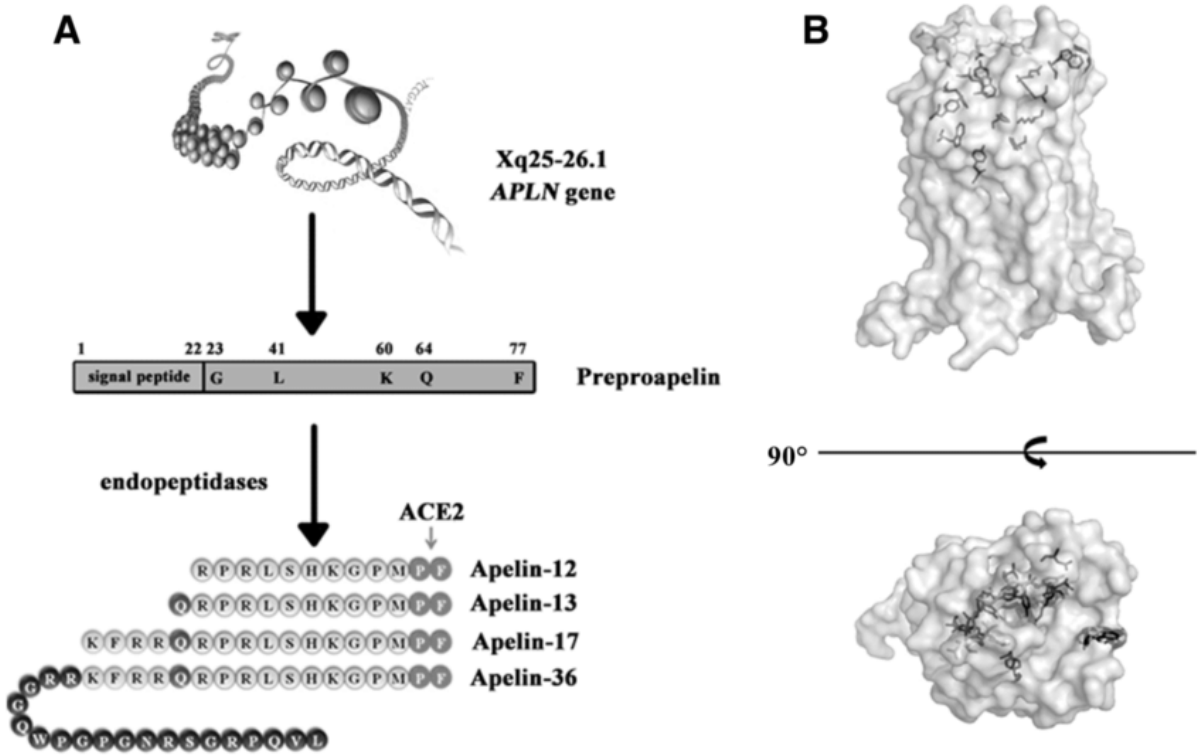

Figure 5: Position of Apelin

Apelin has been revealed to have various things in various structures and materials that include various body parts. In distinction to APJ, apelin is concealed in a few endothelial cells. This tissue supply has diversified to the theory that displays activities in a paracrine way. Newly, both are present in adipocytes. [44,45]

The connotation between apelin and insulin fight

Reliable with its reputed character, apelin has been allied to positions of insulin confrontation in recent years. Innumerable lessons have demonstrated that apelin absorption is amplified in insulin-resistant and obese subjects than in healthy controls. Apelin was also correlated with haemoglobin A1c. (Hba1c). Remarkably, some updated rumours have exposed

that clot apelin contents were chiefly reduced in a newly branded patient role with diabetes mellitus. [46,47]

To date, most recognised SNPS remain recognised to associate with stroke and systemic high blood pressure.

A few studies quantified that male patients resonant the C allele of SNP Rs 2235306 in the APLN genetic factor are found to have increased fasting glucose levels corresponding to the T allele. These findings were not noted in females. However, notice in classifying and assessing the implications of hereditary alternatives in apelin and APJ. [48,49]

Apelin and insulin signalling: mechanical insights

The understandings added since discovering apelin's role in insulin glucose homeostasis have reinforced to examination of the causal mechanism responsible for these properties. To date, Gi-, GQ-, and AMPK connected lanes have been allied with the recommendation of sugar arrangement by apelin.

Apelin directly promotes glucose uptake through a mechanism that includes AMPK and Enos. Apelin inhibits lipolysis through the phosphorylate of HSL, which tortuously enhances insulin sensitivity by decreasing the statement of free fatty acids into the flow. [50]

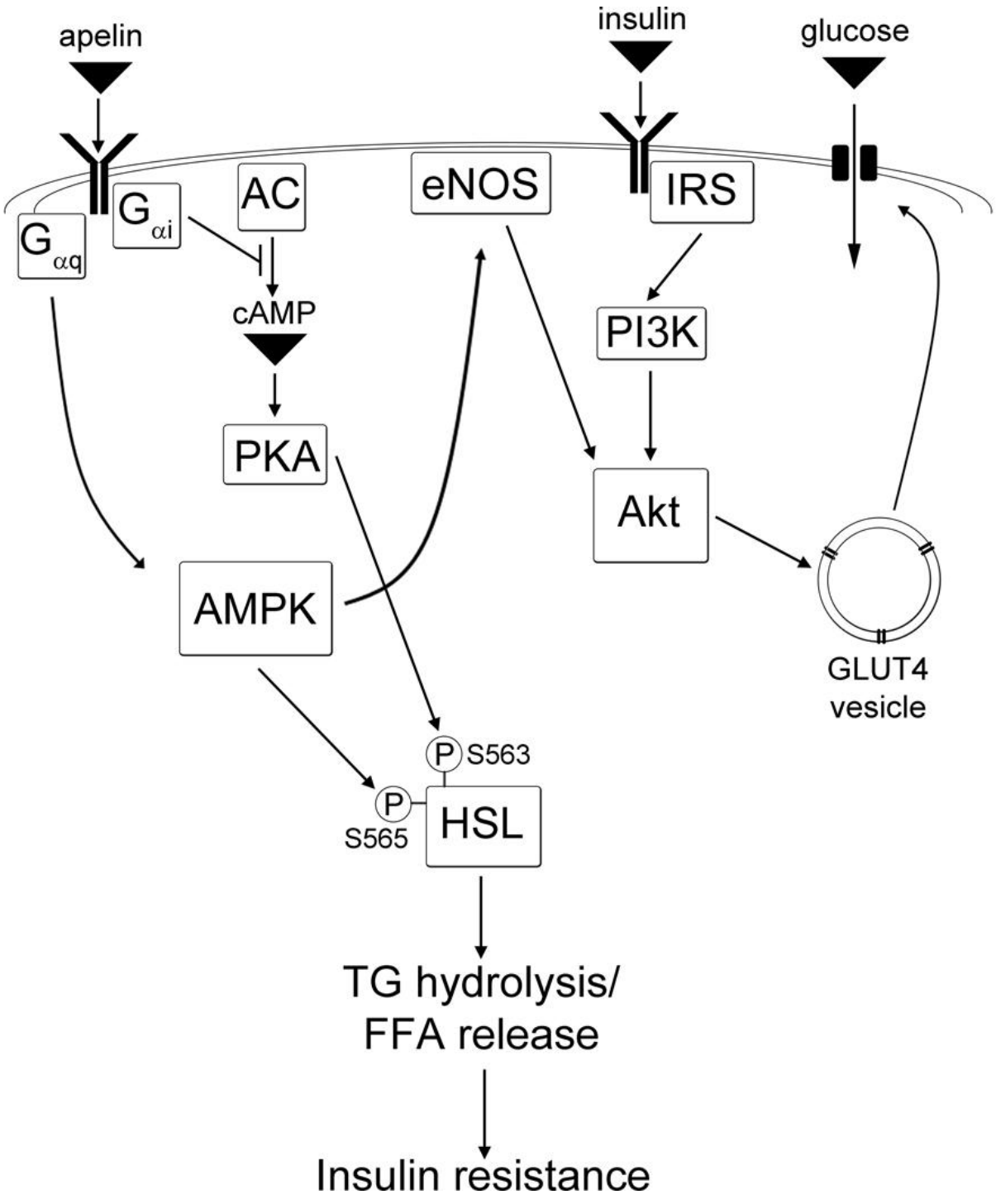

Figure 6: Putative signalling devices for apelin's regulation of insulin sensitivity.

Apelin interacts with APJ, which is a G protein-coupled receptor. Following its discovery, APJ was identified as a coupling partner for the heterotrimeric G protein Gi10. Research indicates that whooping cough toxin, a Gi inhibitor, impedes apelin-restoring fructose approval and Akt phosphorylation, thereby corroborating the involvement of a Gi-mediated pathway in apelin's regulation of glucose uptake. While downstream signalling actions of Gi remain poorly characterised, it is well identified that Gi has a predetermined a role in the control of glucose uptake. For instance, the deletion of Gi specifically in hepatocytes and adipocytes leads to insulin resistance, while its overexpression in hepatocytes, adipocytes, and myocytes enhances insulin sensitivity. [51]

Moreover, it is posited that APJ interacts with GQ. Apelin has been shown to enhance the accretion of inositol triphosphate (IP3). Furthermore, the reserve of GQ-dependent components, including phospholipase C, and the sarcolemma and Ca2+, has been shown to obstruct apelin-regulated tightening in inaccessible hearts. Three-D modelling of APJ utilising a concealed algorithm indicates a significant probability of connection to GQ. The data collectively indicate that apelin triggers GQ through its collaboration with APJ. The dependence of glucose uptake on GQ remains unclear [52]

Apelin influences glucose uptake through the energy-sensing enzyme AMP-activated protein kinase (AMPK), which is recognised for its role in mediating the metabolic response to intracellular ATP depletion (for review see 48). Apelin triggers AMPK, and the inhibition of AMPK action, whether through pharmacologic or molecular means, leads to the cessation of

apelin-regulated glucose absorption. The signalling measures linking APJ to AMPK remain incompletely understood; however, the probability of a Gi-controlled mechanism is diminished by the established Gas/camp/PKA-mediated instigation of AMPK. A signalling force involving phospholipase C, IP3, and Ca2+ release, characteristic of a GQ response, has recently been implicated in adiponectin-mediated AMPK activation. Furthermore, similar to the signalling mechanisms associated with AMPK, the distal trails related to apelin/APJ remain inadequately unspoken. Deactivation of AMPK inhibits Akt phosphorylation, indicating the participation of the final.[53]

Apelin regulates various devices of the insulin lane that include phosphoinositide 3-kinase (P13K) and Akt. It is shown that apelin enhances sugar uptake in the adipose tissue. Apelin is renowned for minimising the making of seditious intermediaries other than NF-kb, having sensitive oxygen classes, IL-6, and monocyte chemoattractant protein-1 (MCP1). [54,55]

Outcome of apelin on adiposity and fatty acid management

Apelin is connected to obesity, linked with body mass index (BMI). Mice were identified to have bigger belly adipose and stout bulk fluctuations.

Obesity is connected with improved free fatty acids, which in turn normalise insulin function and reduce insulin sensitivity.

On the source cross, many investigative groups have looked into carbohydrate intake. Inappropriately, apelin's impression on this limitation is controversial, as detectives have

distinctly testified to an upsurge, a decline, or no alteration in food eating in numerous settings. The motives of contrary fallouts may lie in the model selected, the model of management, and the management, all of which were dissimilar among the revisions. Apelin's properties on lipolysis have also been explored. [56,57]

Recent literature on Apelin

Maged A EI Wakeel and his co-investigators considered serum apelin and obesity correlated difficulties in the Egyptian population. The study aims to find the connection sandwiched between serum apelin and infantile obesity. All individuals had their biochemical parameters tested, HOMA-IR, and serum apelin measured. The outcomes showed that Heavy children exhibited elevated levels of Hba1c. Linear regression examination indicated that fasting blood glucose was the greatest significant forecaster of apelin levels (P = 0.04). These findings provide evidence that apelin may have an important role in the expansion of strength issues associated with obesity in broods, like insulin fighting, hypertension, and an amplified danger of metabolic conditions [58]

Florian Gourge and his coworkers studied slenderness and triple adverse breast cancer: Is apelin a new key marker? The writers hypothesise that apelin, an adipokine, is raised in obesity and may significantly contribute to tumour growth and metastasis in patients with triple-negative breast cancer (TNBC) who are obese. The growth of overweightness under a more cholesterol diet in TNBC tumour-conducting mice pointedly enlarged tumour evolution. Our findings indicate that high-fat diets do not influence mice that are obese resistant,

highlighting the need to establish obesity and other syndromes to promote tumour growth. Apelin mRNA expression was elevated in the hypodermic tissue and obese mice. The replica of obesity-associated apelin stages in weak mice was associated with augmented growth of triple-negative breast cancer (TNBC) and the formation of brain metastases. Inoculations of the antagonist in obese mice reduced TNBC growth, indicating that targeting the apelinergic system may represent a promising therapeutic strategy for obesity-related TNBC.[59]

Florian Gourge et al. explored whether apelin and overweightness are related to abridged response to chemotherapy in breast carcinoma participants. In addition to obesity-related dysregulations, elevated apelin adipokine levels have been connected to breast tumour progression. Obesity and tumoral apelin countenance exaggerated neoadjuvant chemotherapy response in 62 breast cancer patients in this retrospective cohort. In the statistical analysis, obesity and apelin countenance lowered NAC responsiveness in our people, signifying they may be distinctly linked with lower NAC response. Autonomous cohorts should confirm these findings.[60]

Moriah P. Bellissimo and colleagues found that apelin and nectin are connected to obesity, body shape, and fitness in salaried persons. In a cross-sectional secondary survey, 64% of 177 working adults (mean age 49.6 years (± 9.9)) were women. NWO women and men have body fat above 30% and 23%, respectively. The overweight-obesity group had greater plasma adiponectin levels ($P < 0.05$) than to lean groups ($P > 0.05$). Apelin levels were similar across all three body arrangement groups ($P < 0.05$), with no significant correlation with body shape.

Negative correlation found between apelin levels and VO2 maximum. Lean and NWO groups had similar ApoE and adiponectin levels. Since leg fat mass and adiponectin are positively correlated, body conformation and fat delivery should be considered when pursuing adipokines and cardiometabolic ailments. More research is required on apelin production, body composition, and activity [61]

Chinmaya Mund et al. examined serum apelin and insulin fighting in obese and non-obese diabetic patients. This study included 180 participants: 90 T2DM sufferers and 90 healthy controls. Case and control groups were confidentially classified as non-obese and obese per the Asia Pacific BMI categorization. Obese diabetes patients had significantly greater Apelin levels compared to non-obese persons (206.44±83.0 pg/mL). BMI is positively linked with serum Apelin ($r=0.367$, $p=0.003$). In obese patients, HOMA-IR is higher than in controls. BMI and HOMA-IR and Apelin and IR were positively correlated. This study suggests Apelin improves T2DM insulin sensitivity. To determine Apelin's T2DM therapeutic role, larger, multicentric trials are needed. [62]

Soheir Yahia, along with his team, directed research on blood serum apelin-12 and obesity-associated markers in Egyptian offspring with Down syndrome. The current investigation shows that apelin-12 is linked to clinical and biochemical markers of obesity and metabolic syndrome in obese-DS and control groups. Apelin-12 may be a promising MetS marker, with better presentation in obese-DS than obese-control, improving its clinical and therapeutic potential.[63]

Treatment of Acanthosis Nigricans

In and of itself, AN is not a disease; rather, it is a symptom of several other reasons, and it cannot be treated. Because the progression of the skin condition is dependent on the progression of the causal ailment, the handling of AN tries to address the problem that is producing the condition.

Treatment of AN includes topical/oral and cosmetic.

Topical treatment

Retinoids

Retinoids are the foremost choice for unilateral naevus AN and are effective in correcting hyperkeratosis. [64]

Ammonium lactate and tretinoin

It is an hydroxy acid that acts as a flaking agent and also loosens desmogleins, representing the breakdown of desmosomes.[65]

Peels

Trichloroacetic acid (TCA) exfoliates and rejuvenates while destroying the epidermis. Safe, inexpensive, readily available, and easy to make. [66]

Oral treatment

Oral retinoids

Isotretinoin, acitretin were found to be active, and they work by normalising epithelial growth and differentiation. It works effectively with syndromic and benign AN. [67]

Metformin and rosiglitazone

These drugs are used for AN characterised by IR. Metformin works by minimizing glucose manufacture by enhancing insulin responsiveness, decreasing hyperinsulinemia, and fat mass, and rallying insulin warmth. [68]

Cosmetic treatment

As AN often causes darkening. Alan Rosenbach examined a long-pulsed alexandrite laser that targets hair melanin to enhance the condition. 95% clearance of AN is possible with axillae treatment. [69,70]

MATERIALS & METHODS

Materials & Methods

Study type: Cross-sectional comparative study

Study duration: April 2023 to November 2024

Study Setting: The Clinic of Dermatology, Venereology, and Leprosy at RL Jalappa Hospital and Research Centre, Sri Devaraj Urs Medical College, Tamaka, Kolar, did the study.

Study Participants: Patients with a history of Acanthosis nigricans appearing in the section of Dermatology of our hospital, diagnosed with Acanthosis nigricans, were evaluated based on fasting serum apelin levels. The patients were grouped based on the diagnosis into Group A and Group B.

Group A includes patients with AN

Group B consists of Healthy volunteers

Sample size: It was calculated based on the variants estimated on Apelin level as per the study of J Turk, considering a power of 95% with 99% confidence intervals to detect a difference of

0.024. The required sample size per group is 41. Expecting a non-compiliance rate of 20% during the study, the final sample size is expected to be 41+9, a total of 50 per group.

Inclusion criteria

Patients with Acanthosis nigricans over the posterior of the neck, armpit, and groin are coming to R.L. Jalappa Hospital.

Excusion criteria

Patients who are not willing to give consent.

Procedure

2 ml of blood was pooled in a sieve tube with a clot activator from the patients and healthy volunteers after 8-12 hours of fasting. Blood tasters were centrifuged at 2000xg for 10 minutes with a chilled extractor, and the serum was collected from the tube and stored at -80^0C till analysis.

The human Apelin 12 GENLISA ELISA KIT was cast off as an analytical tool for the quantitative determination of Human Apelin 12 in serum. Data was collected and entered into Excel for statistical analysis.

Statistical analysis

The entered data in the Excel sheet was analysed by SPSS 22 version software. Definite data was presented in frequency and proportion. A chi-square test was hand-me-down to find the significance. Continuous data was accessible as mean and standard deviation. p-value <0.05 was measured as significant.

RESULTS

Results

This was a cross-sectional comparative study with a total population of 100 subjects. They were grouped into Group A with Acanthosis nigricans and Group B with heathy volunteers.

In Group A, there were 41 males and 9 females.

In Group B, 33 men and 17 women.

The age distribution of patients is depicted in the figure below.

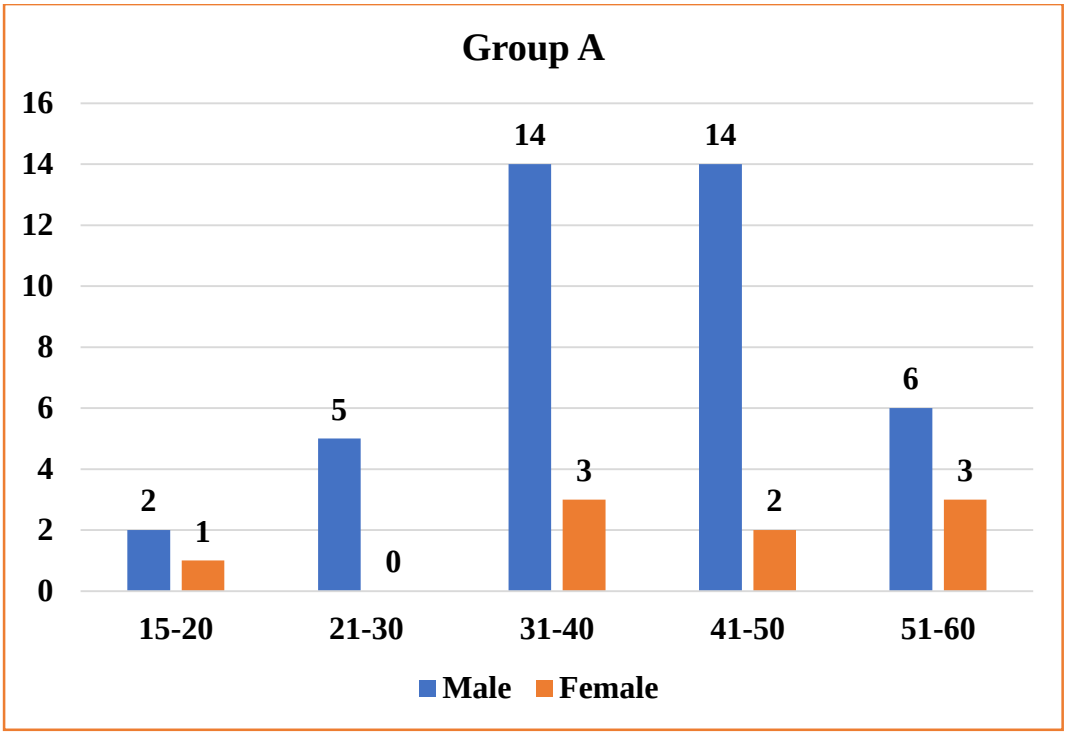

Figure 7: Age-wise distribution of Group A subjects

The majority of participants were in the phase of 31-40 and 41-50 years**.**

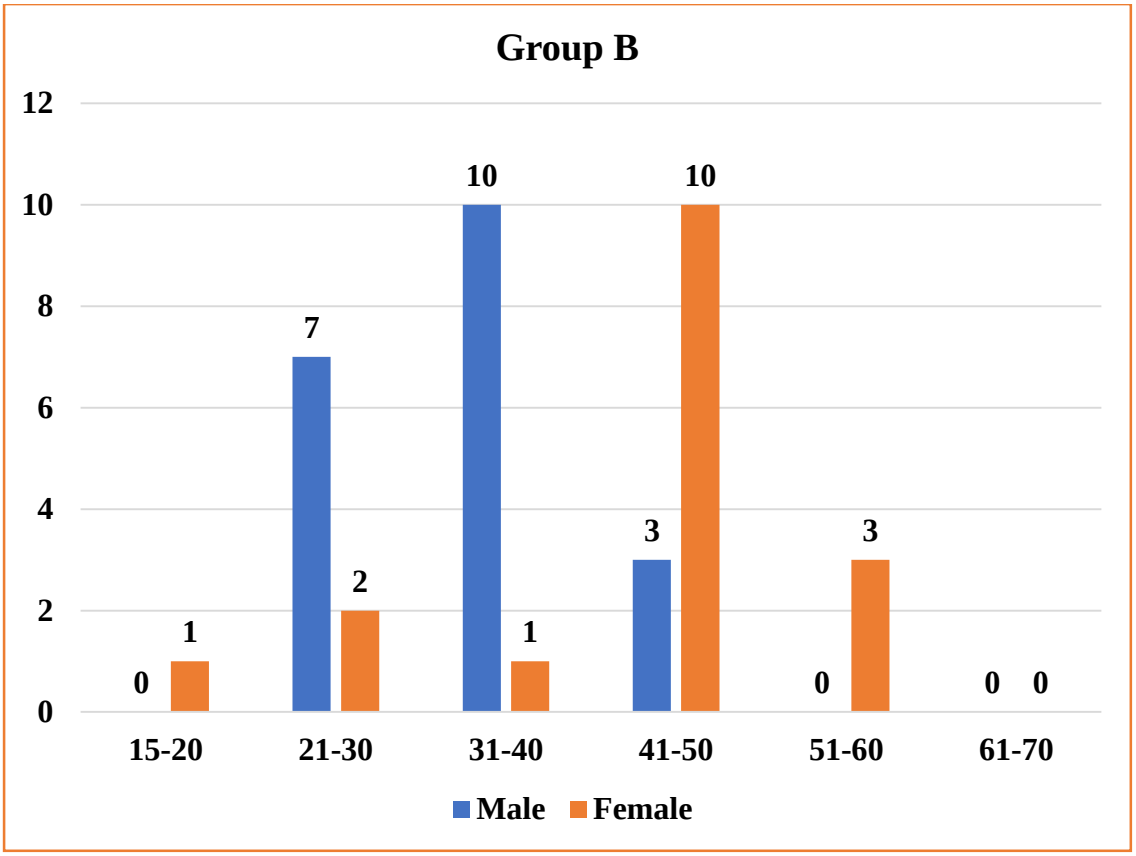

Figure 8: Age-wise distribution of Group B participants

In Group B, more cases fall under 31-40 and 41-50 years.

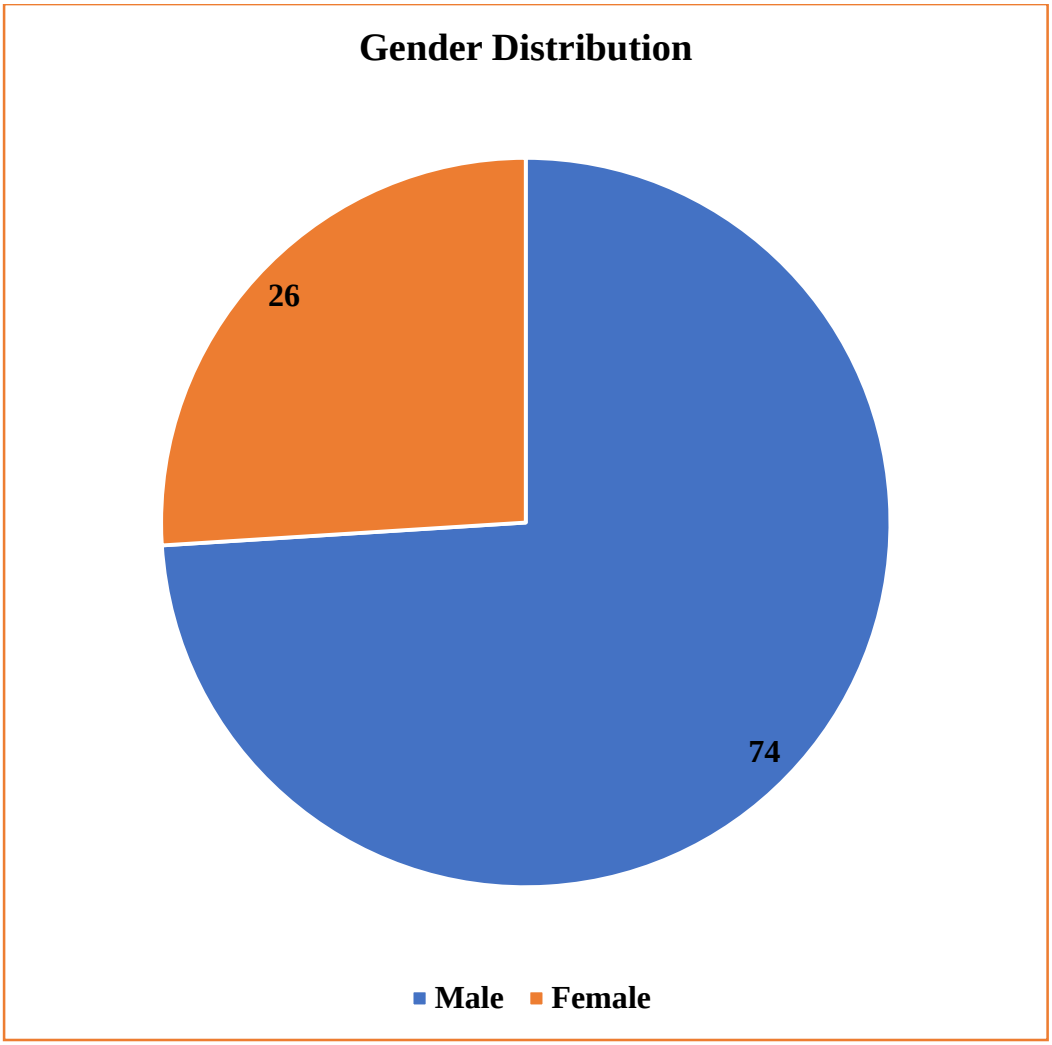

Figure 9: Gender distribution of study participants

In the present study, a total of 74 males and 26 females were included

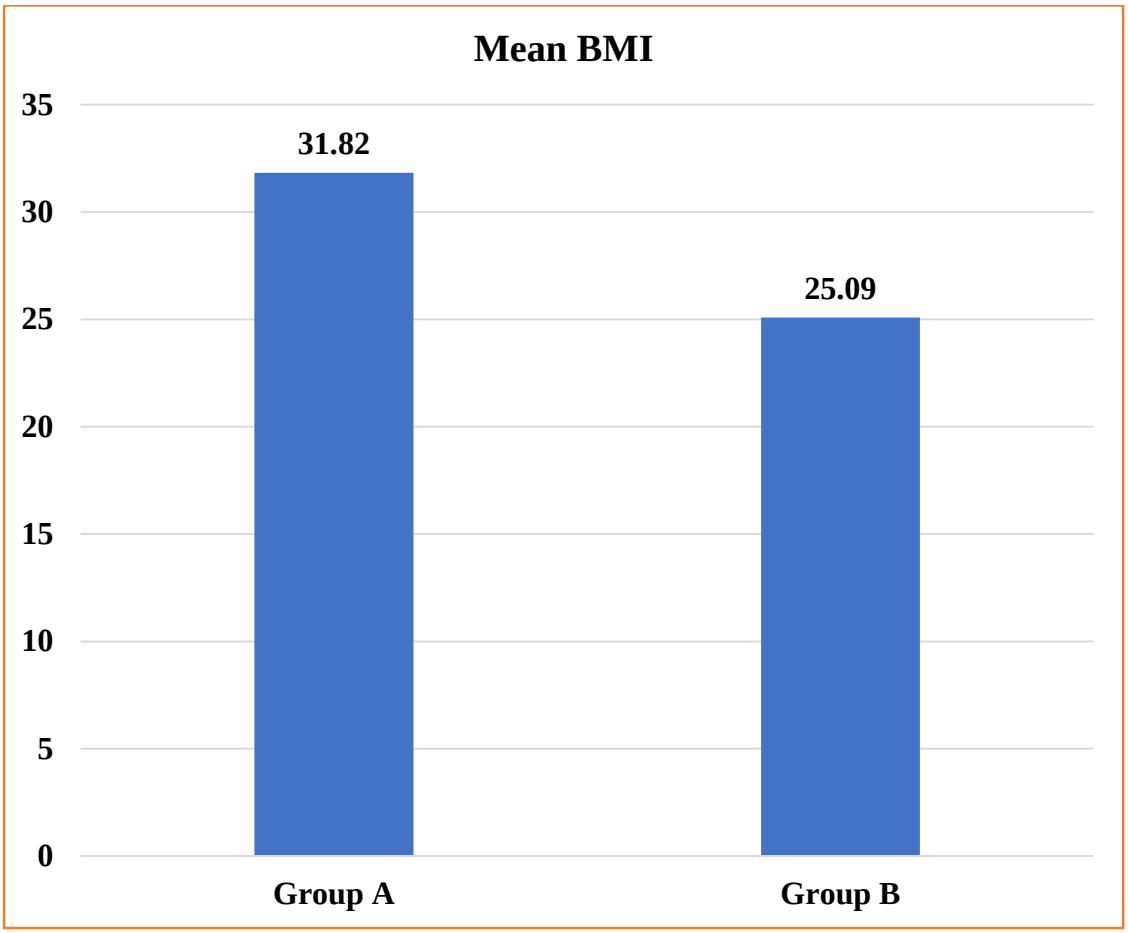

Figure 10: BMI of the study participants

The BMI of group A patients was 31.82, while group B's was 25.09.

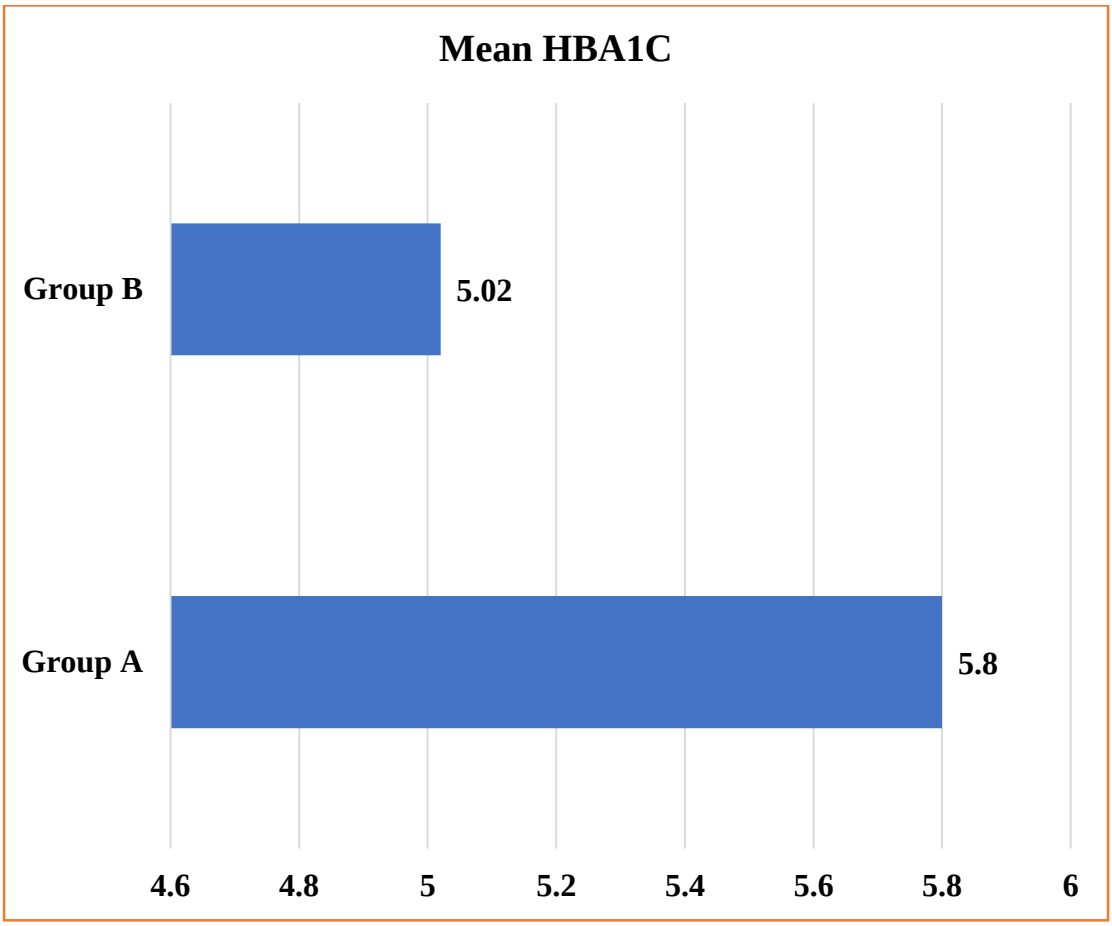

Figure 11: Mean HBA1C levels

The mean HBA1C levels of the study group are as follows.

Group A:5.8 mmol/mol

Group B: 5.02 mmol/mol

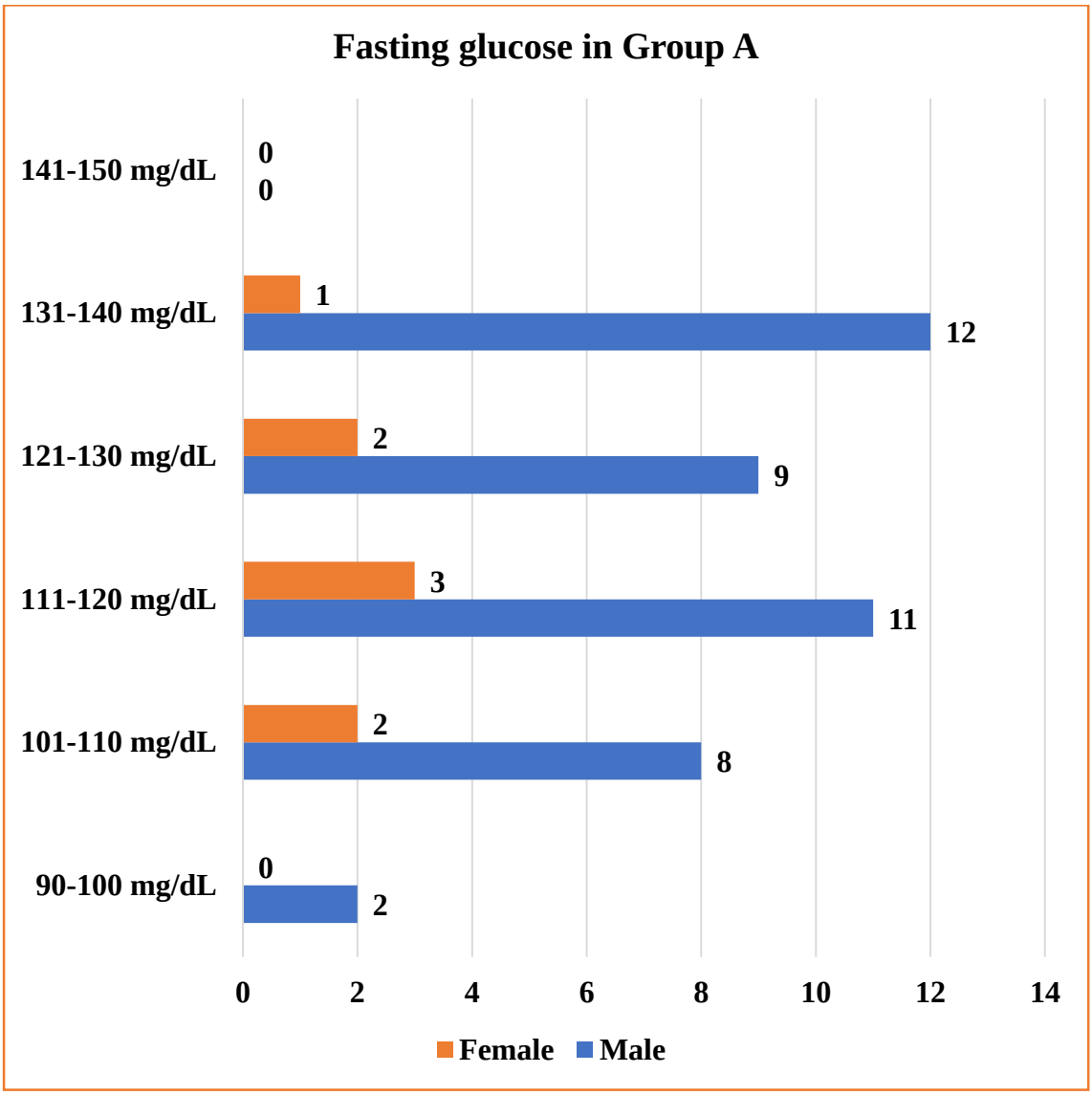

Figure 12: Fasting glucose in Group A

- 12 male patients had fasting glucose 131-140 mg/dL
- 11 male patients had fasting glucose 111-120 mg/dL
- 9 male patients had fasting glucose 121-130 mg/dL

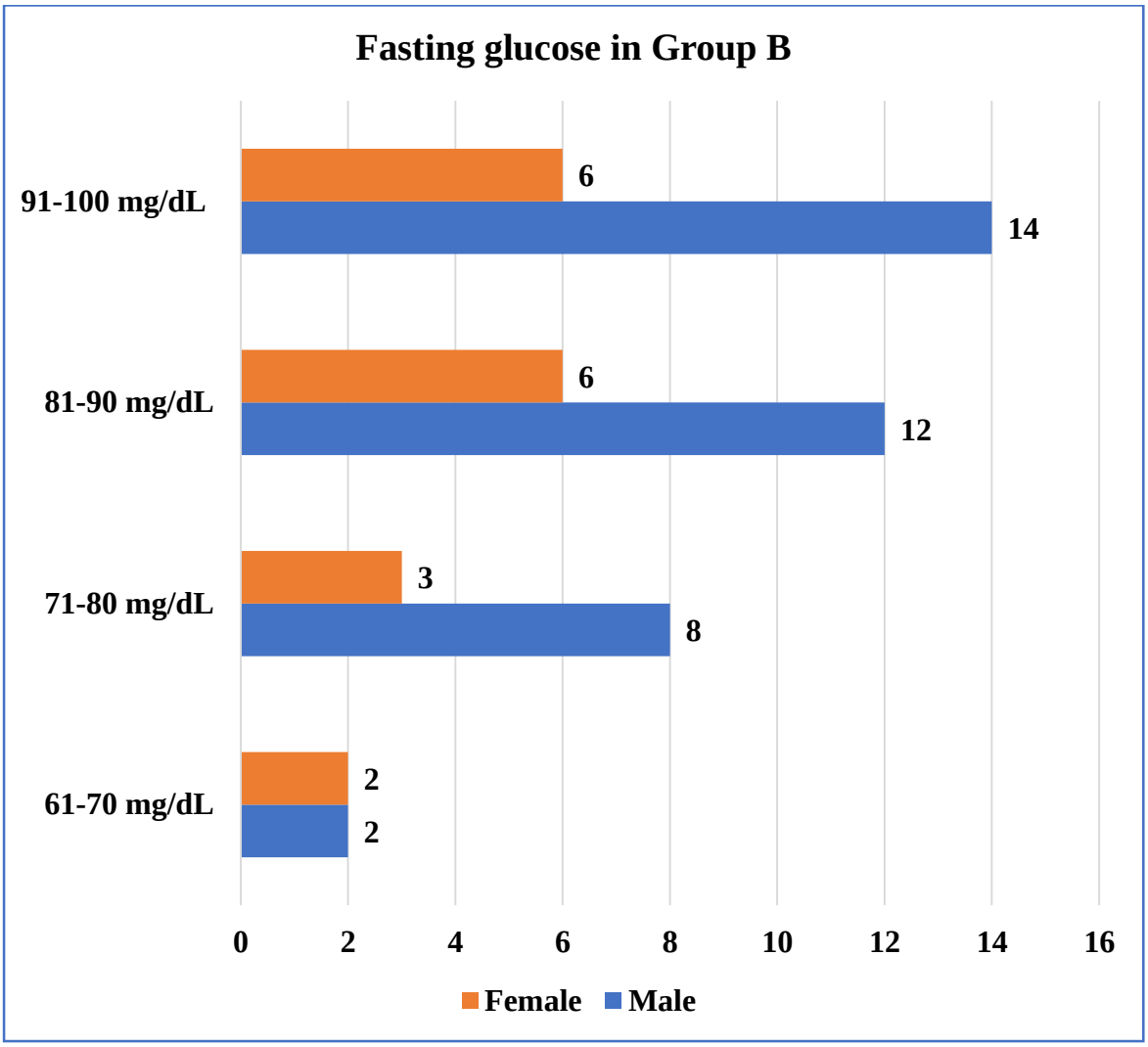

Figure 13: Fasting glucose in Group B

14 male patients had 91-100 mg/dL

12 male patients had 81-90 mg/dL

8 male patients had 71-80 mg/dL

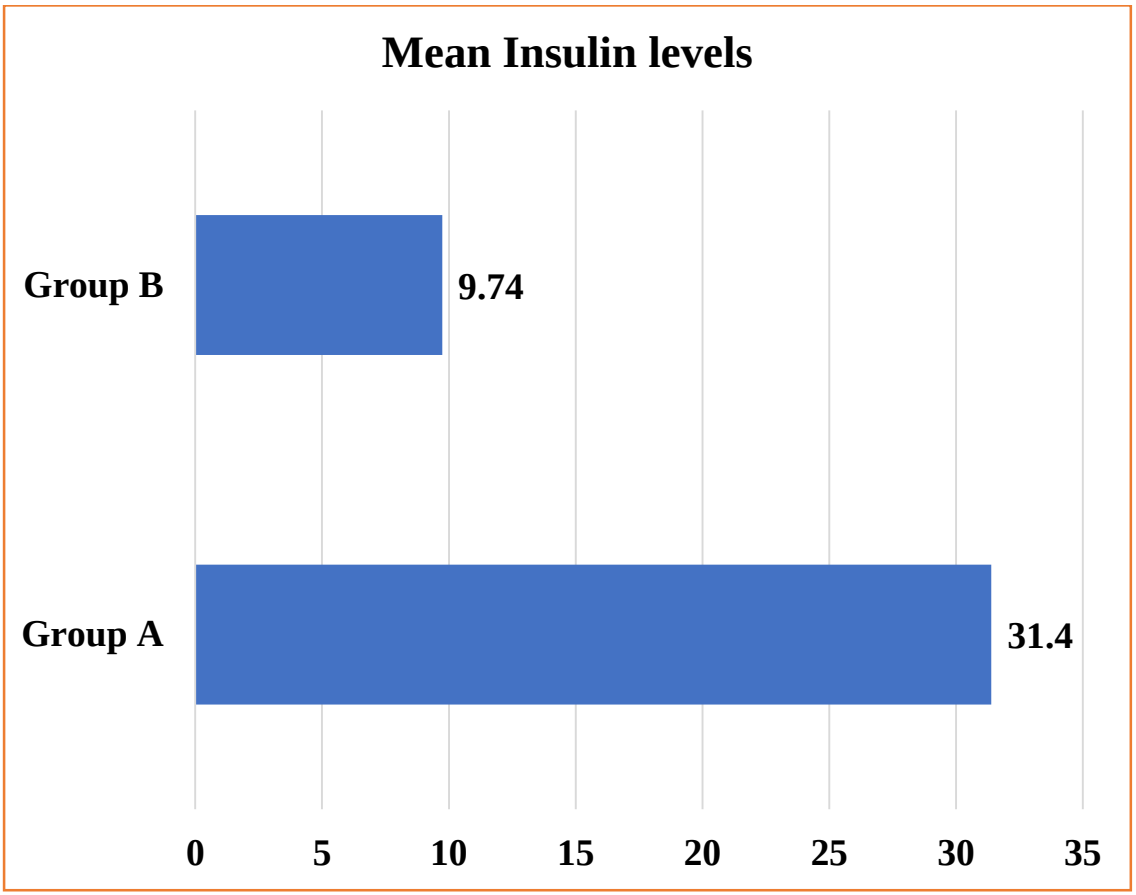

Figure 14: Mean Fasting insulin levels in Groups A and B

The mean fasting glucose in Group A was 31.4 µU/ml and in Group B was 9.74 µU/ml

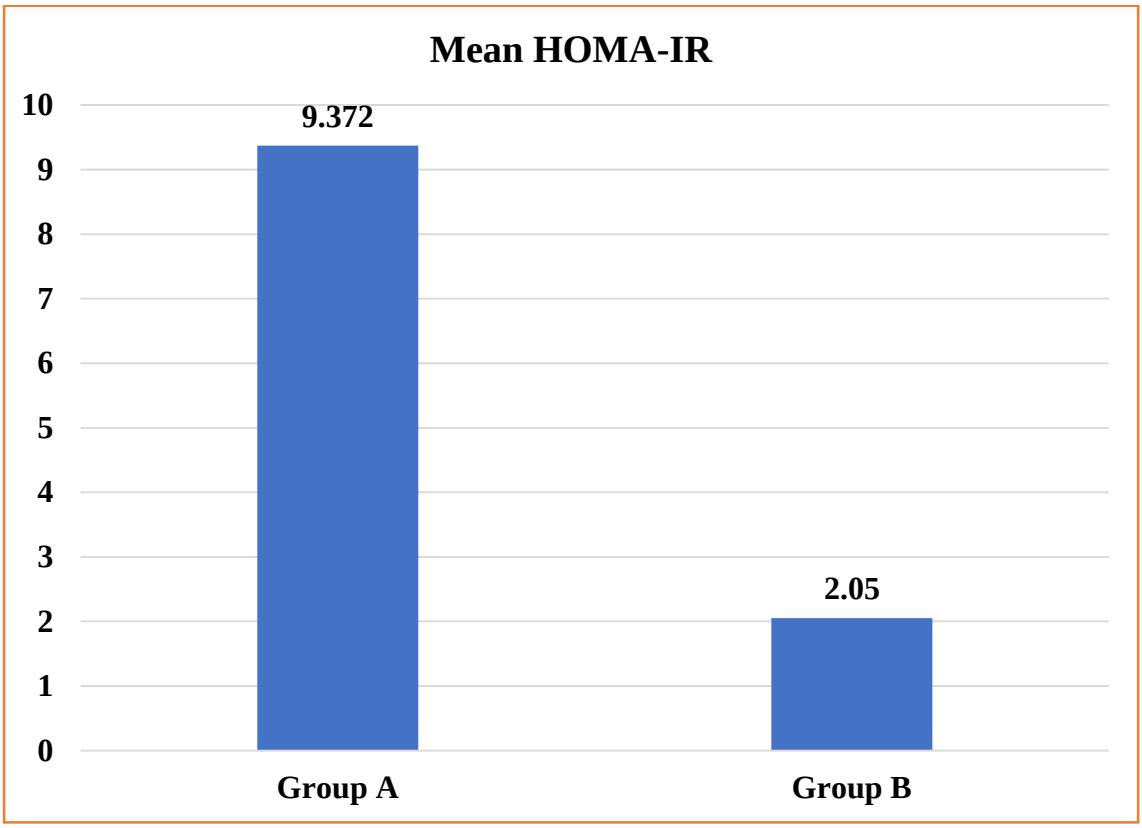

Figure 15: Mean HOMA-IR of the study participants

Group A has 9.372 and B has 2.05

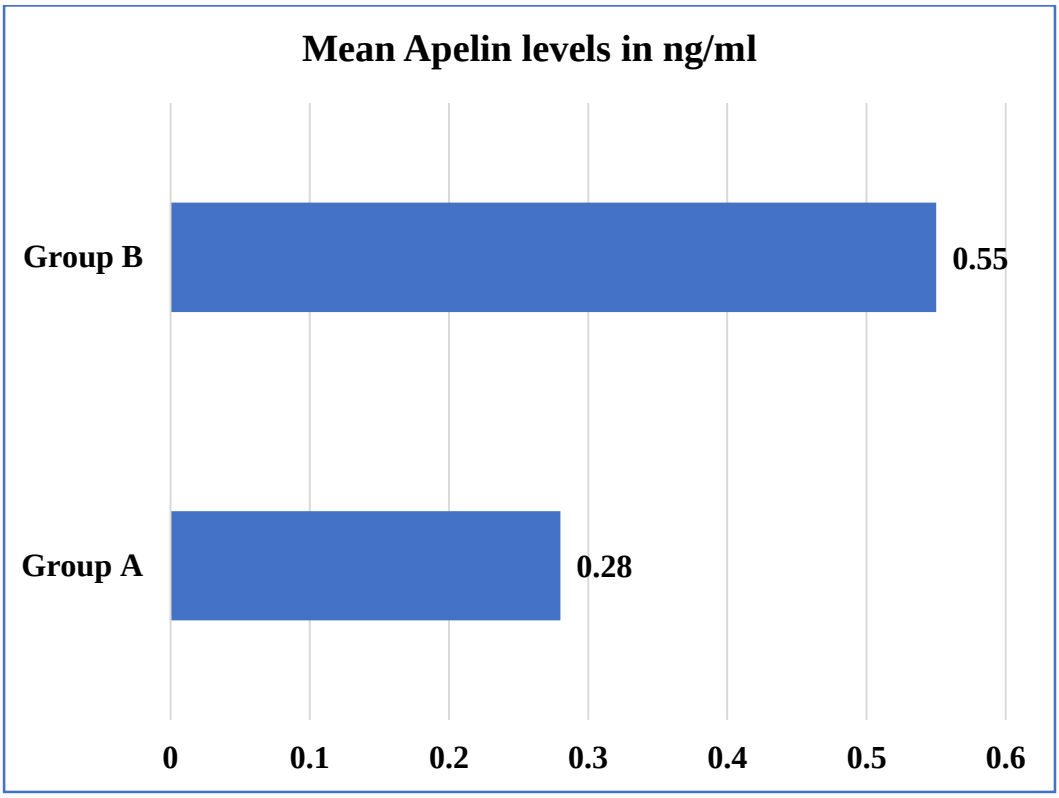

Figure 16: Mean Apelin levels in ng/ml

Mean Serum apelin levels in Group A is 0.28 and Group B is 0.55

Table 1: Serum apelin levels between groups

Groups	**N**	**Serum Apelin levels in ng/ml**	**P value**
Group A	50	0.28	0.042*
Group B	50	0.55	

Serum apelin levels were significantly lower in Acanthosis nigricans patients of group A and were higher in the control group. The chi-square test was initiated to be noteworthy with $p < 0.05$.

Table 2: Serum Insulin levels between groups

Groups	**N**	**Serum Insulin levels in µU/ml**	**P value**
Group A	50	31.4	<0.002*
Group B	50	9.74	

Serum insulin levels were meaningfully higher in Group A with the AN participant than in B.

Table 3: Serum HOMA-IR between groups

Groups	N	Serum HOMA- IR	P value
Group A	50	9.3	<0.001*
Group B	50	2.05	

Serum HOMA-IR was suggestively advanced in group A than in B with p<0.001.

Table 4: Serum HBA1C levels

Groups	N	Serum HBA1C levels	P value
Group A	50	5.8	<0.003*
Group B	50	5.02	

Serum HBA1C levels were significantly higher in group A than in group B.

DISCUSSION

Discussion

This cross-sectional learning was conducted in our Hospital's Venereology and Leprosy Department. The study compares serum apelin levels in Acanthosis nigricans patients and healthy people.

To our knowledge, we validated for the first time in the current education that serum apelin levels were decreased in AN patients.

Over the past three periods, there has been a substantial rise in the level of obesity. Severe thinness is a contributing factor in the progression of metabolic syndromes like insulin resistance, high blood pressure, fatty liver disease, ovarian disease, and some different types of carcinomas.[71] The hormones that are found in adipose tissue and are known as adipokines, such as apelin, play a significant part in the problems that result from obesity. [72] There is a correlation between adiposity and high plasma apelin levels, which a variety of authors have documented in cases of extreme obesity. [73] Besides, a positive relationship exists between leptin and insulin resistance, regardless of the body weight or adiposity of the separate, in both usual and diabetic patients, instantaneously. [74] It has been found that there is a strong connection between obesity and differences in insulin sensitivity status that are brought about by apelin release by adipocytes. It was observed that apelin decreases the amount of insulin that is secreted by the pancreatic beta cells. [75-80]

In our study, the levels of insulin were higher in the Acanthosis nigricans group than in healthy controls.

It was confirmed in a study that the levels of apelin in the serum plasma were favourably connected with BMI. The findings of this investigation are comparable to those of another study, which suggests that apelin might have an impact on the development of obesity. According to the findings of other research, apelin levels are much greater in hefty individuals in comparison to control participants, and they have a positive correlation with body mass index. There was a substantial constructive correlation between the increase in hypodermic fat and apelin levels in obese females who participated in the current research, as demonstrated by the regression analysis. It would suggest that obesity is a significant issue that plays a role in influencing the concentration of apelin in plasma [80-81].

In our study, apelin is found to be lower in Group A patients with Acanthosis nigricans, individuals who have a higher BMI than control levels with lower BMI. It clearly states that Obesity is the real player in the development of Acanthosis nigricans. [82]

A large positive link between Apelin and insulin resistance was exposed in our research, which is also long-established by the results of Boucher et al., who proposed that a disturbance. [83] Apelin homeostasis may result from higher insulin absorption, which eventually results in higher Apelin levels. [84] In addition, there is a strong connotation amid HOMA-IR and BMI, that is at odds with the findings of the examination carried out by Li et al. Several inquiries have verified that Apelin inhibits the emission of insulin plasma. Furthermore, Apelin has been

proven to stimulate lipolysis and fatty acid oxidation, as well as to boost glucose metabolism and improve insulin sensitivity. [85] The management of apelin is a possible conduct option for the problems linked to diabetes. Therefore, diabetes and the matters that are allied with it could be achieved by focusing on the apelin-APJ system at the same time. Studies exposed that the direction of exogenous apelin led to an enhancement in glucose metabolism. In addition to this, apelin-induced glucose absorption was seen in remote adipocytes from both type 2 diabetic and normal subject groups. [86] Based on these discoveries, apelin may be able to achieve the role of an exogenous insulin sensitizer when circumstances of high insulinemia are extant. The pancreatic mass and insulin stages of diabetic individuals are suggestively improved by the administration of apelin over an extended period. As a result of its ability to enhance insulin sensitivity, numerous writers have also hypothesized that Apelin might function as an influential insulin-sensitizing factor and might be a real marker for control. These findings are in correlation with the present study. [87-89]

Apelin is a recently known adipokine that exhibits anti-inflammatory, antiatherogenic, and cardioprotective properties. This peptide, which is inducible by hypoxia, is shaped and concealed by adipocytes, stromal vascular structures, and cardiovascular matters. In addition to hypoxia, TNF-alpha and insulin influence this peptide's release. Some metabolic disease studies show elevated apelin. [90-93]

In cardiovascular syndromes, preeclamptic females, and polycystic ovary syndrome, apelin levels are low and serve as novel biomarkers. These revisions stress positive inotropic, antiatherogenic, and cardioprotective characteristics. [94]

Several revisions in the works have testified to the part of apelin in skin disorders. [95-97]Dertlioglu et al., pragmatic elevated levels of apelin in patients with psoriasis; though, their study did not exclude individuals with metabolic syndrome. [98] Bigger planes of apelin have been practical in patients with general scleroderma, although the conclusions are unpredictable. [99,100] Kovacs et al. examined the appearance of key adipokines in the sebaceous glands of strong skin trials, verdict no evidence of apelin appearance in sebocytes.[101]

Apelin levels were also recognized as abnormal in cases of psoriasis. Nevertheless, certain lessons present combative data representing that the alterations in adipokine levels resemble those experimental in obesity, yet are self-reliantly connected to Psoriasis. Adipose tissue produces anti-inflammatory adipokines like adiponectin, CTRPs, omentin, and SFRP5.

. Numerous studies have indicated that psoriatic patients exhibit reduced levels of these substances. Furthermore, various studies have reported elevated heights of proinflammatory adipokines, including leptin, chemerin, and resistin, in patients with psoriasis. [102-104]

In our study, the levels of apelin were decreased in AN patients and were found be elevated in healthy subjects.

Limitations

A smaller sample size is the major limitation of the study

Summary

- This was a cross-sectional comparative study

- The study participants were 100. Divided into two groups of 50 each, denoted as Assembly A and Assembly B
- Set A encloses AN individual, and Set B had controls
- There were 74 males and 26 females in the study
- The mean BMI was 31.826 in group A and 25.094 in group B
- The mean HBA1C in groups A and B is 5.080 and 5.02
- The mean HOMA-IR in group A was found to be 9.372, and in group B, it was 2.05.
- Mean apelin levels in cases were 0.28, and in controls, it is 0.55

CONCLUSION

Conclusion

Our study revealed lower levels of apelin, known for its anti-inflammatory properties, in Acanthosis nigricans patients compared to healthy individuals. Based on these findings, we assert that in patients with AN, chronic swelling may contribute to the dysregulation of adipokines independent of obesity. It is observed that reduced levels of apelin appear to be associated with the chronic inflammation seen in AN, which induces hypoxia. This condition may lead to dysfunction and fibrosis of adipose tissue, potentially resulting in a diminished release of anti-inflammatory adipokines. Lower levels of apelin in patients with AN may be linked to the mechanisms of adipose tissue dysfunction and fibrosis, which lead to a reduced release of apelin. Further effect studies involving a larger population are necessary to substantiate this claim.

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