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Review Article

# ACANTHOSIS NIGRICANS: AN EDIFYING REVIEW

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**ABSTRACT**

Acanthosis Nigricans (AN) is a skin condition characterized by hyperpigmentation and hyperkeratosis of the skin, particularly of skin fold regions, such as of the neck and groin and axillae. Various benign forms of AN have been identified in which the disorder may be inherited as a primary condition or associated with various underlying syndromes, obesity, or the use of certain medications.

**Keywords :-** Acanthosis Nigricans, Hyperpigmentation, Obesity, Metabolic disturbances.

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## INTRODUCTION

Acanthosis Nigricans (AN) is a skin disease that is characterized by hyper pigmented, thick, velvety plaque usually occurring in the body folds. It may involve other parts of the body [1]. The common sites are neck, armpit, popliteal fossa and groin region. It also sometimes occurs on the elbow, knee, knuckles and oral, gastrointestinal or anogenital mucosa [2-5] .The earliest changes of the face are usually dryness, pigmentation and roughness of the skin, which in affected area is gray-brown or black [6]. These usually occur symmetrically and are histopathologically characterized by papillomatosis and hyperkeratosis of the skin. The term AN was originally proposed by Unna. The first case was described by Pollitzer and Janovsky in 1891 [7].

### Epidemiology

Recently a high prevalence of AN has been observed which may be associated with rising prevalence of obesity and diabetes. There is no gender predilection. According to age, race, frequency of type, degree of obesity and concomitant endocrinopathy, the prevalence rate varies from 7% to 74%. It is commonly found in Native Americans. According to the American Academy of Dermatology, people of African, Caribbean, or Hispanic descent are also at an increased risk. All ethnic groups are equally at risk of acanthosis nigricans when body mass index (BMI) is well above normal. Hud et al. after conducting a research reported that AN is more predominant in black women when compared to white women. The malignant variant of AN is rare. The frequency of acanthosis nigricans varies between ethnic groups [8].

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**Etiopathogenesis**

Individuals affected with AN have shown increased levels of insulin or an abnormal response to exogenously administered insulin. It has been demonstrated that insulin crosses dermoepidermal junction (DEJ) to reach keratinocytes. Insulin regulates carbohydrate, lipid and protein metabolism and weakly promotes growth by binding to "classic" insulin receptors at low concentrations. However, insulin exerts more potent growth-promoting effects through binding to insulin-like growth factor 1 receptors (IGF-1Rs) that are similar in size and subunit structure to insulin receptors at higher concentrations. This stimulates proliferation of keratinocytes and fibroblasts, leading to AN [9]. Apart from direct toxic effects, hyperinsulinemia also acts indirectly by increasing free IGF-1 levels in circulation. The activity of IGF-1 is regulated by insulin-like growth binding proteins (IGFBPs), which increase IGF-1 half life, deliver IGFs to target tissues and regulate levels of metabolically active "free" IGF-1. IGFBP-1 and IGFBP-2 are both decreased in obese individuals with hyperinsulinemia, increasing plasma concentrations of free IGF-1, which promotes cell growth and differentiation. The etiopathogenesis has been summarized as a flow chart in Table 1.

The fact that insulin-dependent activation of IGF-1Rs can facilitate AN development can be justified by the following observations:

1. IGF receptors can be detected in cultured fibroblasts and keratinocytes.
2. Insulin has been demonstrated to cross dermoepidermal junction and at high concentrations it can stimulate growth and replication of fibroblasts.
3. Severity of AN in obesity correlates positively with fasting insulin concentration.

Thus, insulin may promote AN through direct activation of the IGF-1 signaling pathway[10]. The fact that AN is more common in areas such as neck and axillae suggests that perspiration and/or friction may be predisposing factors. For AN, other than insulin-receptor antibody, unknown autoantibodies have been implicated. This could explain the effectiveness of cyclosporine in treating AN with autoimmune manifestations [11]. Insulin and IGF-1 levels are affected by hepatitis C infection and both of them may be implicated in etiopathogenesis of acrochordons and AN through their proliferative and differentiating properties. Acanthosis nigricans maligna (ANM) might be explained by elevated levels of transforming growth factor (TGF-α), exerting effects on epidermal tissue through epidermal growth factor (EGF) receptor. IGF-1, fibroblast growth factor, and melanocyte stimulating hormone α that regulates melanocyte pigmentation and stimulates growth of keratinocytes, can play a role in the pathogenesis of hyperplasia and hyperpigmentation. It can occur with endocrine diseases such as Cushing disease and diabetes mellitus, from tumors of the pituitary gland, underlying malignancies, certain drugs, and as a genetic disorder[12]. Various other causes or syndromes associated with AN are given in Table 2.

**Types**

According to Shwartz RA [1], acanthosis nigricans can be classified as: Benign, Pseudo AN associated with obesity, Syndromic, Malignant, Acral, Unilateral, Drug Induced, and Mixed.

A more simplified classification had been proposed by Hernandez-Perez [13]. He classified AN as simple AN (not related to malignancy) and paraneoplastic AN. Burke et al. used a scale of 0-4 based on how many areas are affected to classify AN [7].This scale correlates with fasting insulin and body mass index (BMI). Hence it is easy to use and has a high inter-observer reliability.

**Clinical Features**

The characteristic feature of AN is dark, coarse, thickening of the skin with a velvety texture which are usually symmetrically distributed [14]. The initial change evident is grey-brown/black pigmentation with dryness and roughness of the skin. The affected areas are palpably thickened and covered by small papillomatous eruptions, giving it a characteristic velvety texture. With time the thickening increases and the skin lines are further accentuated. The surface becomes mammilated and wrinkled, with the development of larger warty out growths [15]. AN is usually asymptomatic, but occasionally, it can be itchy. The lesions affect back and sides of neck, axillae, groin, and ante-cubital and popliteal areas [14, 15]. Neck is the most common site affected (99%) in children when compared with axillae (73%). Face, eyelids, flexor and extensor surface of elbows and knees, dorsa of joints of hands, umbilicus, external genitalia, inner aspects of thighs and anus are also involved.With extensive involvement, lesions can be found over the areolae, conjunctiva, and lips [15].

**Oral Manifestations**

Involvement of mucous membranes is relatively rare for AN. But oral mucous membrane may have a delicate velvety wrinkled appearance in affected individuals. There may be extensive papillomatosis of the lips, palate, gingiva and tongue in some cases[16].

**Malignant An**

Rarely generalized involvement can be found in AN, mostly in adults with underlying malignancy. 'Acanthosis nigricans maligna' (ANM) is the term used for the malignant variety of AN. In most cases (70-90%), it occurs in the course of adenocarcinomas of abdominal organs, particularly gastric cancer followed by adenocarcinoma of pancreas, ovary, kidneys, bladder, bronchi, thyroid, bile duct, breast, and esophagus [14]. ANM is clinically indistinguishable from benign forms, but usually the appearance is sudden and profuse. Frequently

the oral, nasal and laryngeal mucosa, esophagus and areola of nipple are involved. Papillomatous lesions may be seen on the eyelids and conjunctiva. Leukonychia and hyperkeratosis of nails has also been reported. Acrochordons are often found in affected areas [16]. Warning signs for malignancy in AN patients include age >40 years, not having any previous endocrine disorder or any genetically determined disease, unexplained weight loss, rapid onset of extensive AN, symptomatic lesions, atypical sites, tripe palms, florid cutaneous papillomatosis, and sign of Leser–Trélat. Regression of AN occurs with treatment of the malignancy. Reappearance may suggest recurrence or metastasis of the primary tumor [17].

**Diagnosis**

It is based on clinical examination followed by histopathology if needed for confirmation. Histological findings of AN include papillomatosis, hyperkeratosis and hyperpigmentation of the basal layer**.** There may be finger-like dermal papillary projections. The papillae reveal mild acanthosis and are filled with keratotic material. Clinically observed hyperpigmentation is due to hyperkeratosis and clinical thickening [18, 19]. In ANM proliferation of keratinocytes with hyperkeratosis dominates and with minimal hyperpigmentation. Spectroscopic and colorimetric measurements combined with chemo metric analysis methods provide sensitive and specific diagnosis of AN [20].

**Differential Diagnosis**

The differential diagnosis of AN is based on the clinical appearances. Various differential diagnoses are as follows:

**Confluent and reticulated papillomatosis**

It manifests in the mammary region and upper lateral trunk as scaly macules which may be normal in colour or erythematous or hyper pigmented.

**Intertriginous granular parakeratosis**

It presents as erythematous to brownish hyperkeratotic papules and plaques in the intertriginous regions. It is prevalent in middle aged women and mostly affects the axillary region. Inguinal and sub mammary folds may also be involved.

**Acropigmentation reticularis of Kitamura**

It manifests as freckle like areas of pigmentation on the dorsal aspects of hands. It may involve other areas of body. Palmar pits and breakage of epidermal ridge pattern are also present.

**Haber syndrome**

It appears as acne like facial dermatoses and multiple verrucous lesions on non-sun-exposed areas of the body surface.

**Dowling-Degos disease**

It presents as a progressive brown black hyperpigmentation of the flexures withsoft fibromas and follicular hyperkeratosis [18].

**MANAGEMENT**

The management of AN involves multiple aspects including treatment of underlying disease or tumor, cessation/avoidance of the inciting agent in drug-induced AN, use of topical/oral agents and cosmetic surgery [21]. Maintaining a healthy lifestyle can usually prevent AN. Aerobic exercise can help one in managing weight and is one of the best natural ways to get rid of this entity fast. Losing weight, controlling diet and adjusting any medications that are contributing to the condition are all crucial steps. Reduction of insulin resistance is one important aspect of management of AN. Weight reduction and exercises have shown to increase insulin sensitivity and reduce insulin levels causing improvement in obesity associated AN [22]. Correction of hyperinsulinemia reduces hyperkeratotic lesions. Other treatments to improve skin appearance include retinoid such as tretinoin, tazarotene, or adapalene, 20% urea, alpha hydroxyacids, topical vitamin D and salicylic acid prescriptions [23]. These are only minimally effective, however. For more severe, stubborn AN, oral treatments may include: dietary fish oils. Dermabrasion, a mechanical process of controlled, surgical scraping of the skin [24]. It is important to be patient when using this natural treatment for acanthosis. Coconut oil is antifungal, antibacterial and antiviral. Melt pure fractionated coconut oil on the stove and add a camphor pellet to it. Remove the oil from heat and let the pellet dissolve completely. Cool this blend and apply it to the plaques on the skin. This natural acanthosis remedy can also counter itchiness and hyperpigmentation. Tea tree oil, neem oil, almond oil, olive oil, chamomile oil, eucalyptus oil, rose oil & jojoba oil can also be massaged on the affected areas of the skin. This remedy has helped people get rid of dark patches on the thighs and restore natural skin color. Lemon is a common household ingredient that can do wonders for blackened skin due to its amazing bleaching property and natural citric acid. Rose water reduces the acidic nature of the lemon to prevent irritation. Lemon, turmeric and honey is always considered as an excellent combination for treating various skin ailments. Oats are good for overall health including treating a dark neck. It acts as a natural exfoliate that helps to remove the dead skin cells in the applied area. Yogurt is considered as good natural cleanser for the skin due to its acidic property. Lime juice has a bleaching effect, so the two are a good combination. Cucumber has a cooling, exfoliating and soothing effect that naturally brightens the dark neck. Papaya contains an enzyme called papain, helps to remove dead skin cells. Strawberries have antioxidants that repair damaged skin very quickly. This combination will give the essential vitamins and minerals that will nourish the skin

cells and lighten it. Baking soda is a natural exfoliant that effectively helps to remove dark patchy skin that was caused due to hyper pigmentation. Potato is a bleaching agent that helps to treat a dark neck very effectively. It contains an enzyme called catecholase that helps to lighten the skin color. Orange Peel Mask: Oranges contain vitamin C and anti – oxidants, as well as a bleaching property that effectively lightens the skin. Milk used in this process will work as natural cleanser that makes skin glow. Dry fruits also will act as a great remedy in preventing the dark neck problem. Dry fruits like almonds and walnuts can lighten up the skin tone by clearing the dead skin cells with its natural exfoliate property. Almonds are rich in vitamins which gives a new life to the skin. The oil in it acts as a moisturizer & provides soft, supple skin without any dark patches. Aloe vera is a great cleanser that not only diminishes the skin spots but also lightens the skin tone of the neck. It is rich in anti-oxidants and other natural compounds that greatly assists in repairing and reproducing new skin cells to clear the dark pigmentation of the neck. This rice starch reduces the dark spots on the neck as this one of the inexpensive and health method for the skin in treating the black neck problem. Sandalwood powder has soothing effect on the skin and helps to regain skin glow. Cocoa butter moisturizes the skin to reduce the dark appearance of the neck. It can be mixed with milk and applied on the affected site [25]. Various treatment modalities of AN are given in Table 3.

**Table 1. Etiopathogenesis of Acanthosis Nigricans**

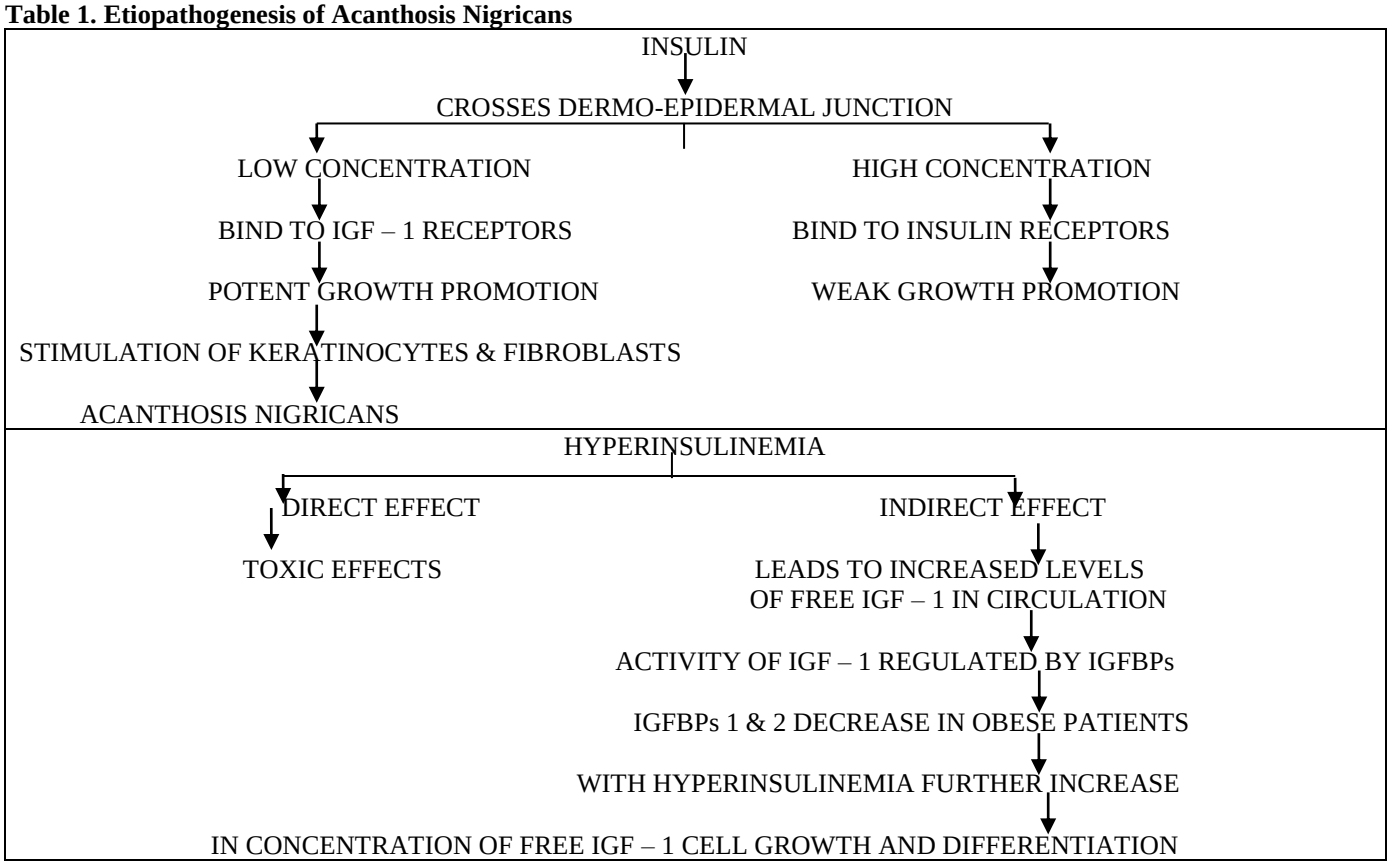


**Table 2. Conditions or syndromes associated with Acanthosis Nigricans**

| | **Metabolic Conditions** | | **Syndromes** |
|---|---|---|---|
| 1 | Lipoatrophic Diabetes | 1 | Down Syndrome |
| 2 | Hypothyroidism | 2 | Marfan Syndrome |
| 3 | Acromegaly | 3 | Prader-Willi Syndrome |
| 4 | Pseudoacromegaly | 4 | Crouzon Syndrome |
| 5 | Gigantism | 5 | Polycystic Ovarian Syndrome |
| 6 | Addison's Disease | 6 | Cushing Syndrome |
| 7 | Hirsutism | 7 | Hypogonadal Syndrome |
| 8 | Primary Biliary Cirrhosis | 8 | Bloom Syndrome |

**Table 3. Management modalities of Acanthosis Nigricans**

| | |
|---|---|
| In obese | Weight reduction, exercise |
| In insulin resistance | Pharmacological treatment of insulin resistance |
| Unilateral and syndromic patients | Topical or oral retinoids |
| Drug induced AN | Suspension of drug |
| Mixed AN | Calcipotriol |
| ANM | Treat underlying malignancy |

## CONCLUSION

Although AN is mostly an aesthetic concern for the affected individuals, it could be a sign of major underlying metabolic disorder or even malignancy. A thorough investigation is mandatory and extremely essential to detect the cause as early as possible to institute a proper treatment thereby preventing any untoward complication.

## ACKNOWLEDGEMENT

Nil

## CONFLICT OF INTEREST

None

## STATEMENT OF HUMAN AND ANIMAL RIGHTS

All procedures performed in human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethicalstandards. This article does not contain any studies with animals performedby any of the authors.

## REFERENCES

1. Schwartz RA. (1994). Acanthosis nigricans. *J Am Acad Dermatol*, 31, 1-19.
2. Sharquie KE, Noaimi AA and Al-Ogaily SM. (2015). Acanthosis Nigricans as a Cause of Facial Melanosis (Clinical and Histopathological Study). *IOSR Journal of Dental and Medical Science*, 14, 84-90.
3. Burke JP, Hale DE, Hazuola HP and Stern MP. (1992). A quantitative scale of acanthosis nigricans. *Diabetes care*, 22, 1655 – 1658.
4. Stuart CA, Driscoll MS, Lundquist KF, Gilkison CR, Shaheb S and Smith MM. (1998). Acanthosis nigricans. *J. Basic Clin Physiol Pharmacol*, 9, 407 – 418.
5. Stuart CA, Gilkison CR and Smith MM. (1998). Acanthosis nigricans as a risk factor for non-insulin dependent diabetes mellitus. *Clin Pediatr (Phila)*, 37, 73 – 79.
6. Houp KR and Crus PD. (1999). Acanthosis Nigricans. Fitzpatrick's Dermatology in General Medicine, 5th Edition, McGraw-Hill Book Company, New York, 40, 244-252.
7. Burke JP, Hale DE, Hazuda HP, Stern MP. (1999). A quantitative scale of acanthosis nigricans. *Diabetes Care*, 22(10), 1655-9.
8. Hud JA, Cohen JB, Wagner JM, Cruz PD. (1992). Prevalence and significance of acanthosis nigricans in an adult obese population. *Arch Dermatol*, 128(7), 941-4.
9. Neville BW, Damm DD, Allen CM, Bouquot JE. Dermatological Diseases: Oral and Maxillofacial Pathology. 3rd Edition. Elsevier, 2010, 803-04.
10. Kondo Y, Umegaki N, Terao M, Murota H, Kimura T, Katayama I. (2012). A case of generalized acanthosis nigricans with positive lupus erythematosus-related autoantibodies and antimicrosomal antibody: Autoimmune acanthosis nigricans? *Case Rep Dermatol*, 4, 85-91.
11. Safoury OS, Shaker OG, Fawzy MM. (2012). Skin tags and acanthosis nigricans in patients with hepatitis C infection in relation to insulin resistance and insulin like growth factor-1 levels. *Indian J Dermatol*, 57,102-6.
12. Jakubovic BD, Sawires HF, Adam DN. (2012). Occult cause of paraneoplastic acanthosis nigricans in a patient with known breast dcis: Case and review. *CurrOncol*, 19, e299-302.
13. Hernández PE. (1984). On the classification of acanthosis nigricans. *Int J Dermatol*, 23(9), 605-6.
14. Endocrine diseases. In: James WD, Elston DM, Berger TG, editors. Andrews' Diseases of the Skin: Clinical Dermatology. 11th ed. Elsevier; 2011. p. 494-5.
15. Judge MR, McLean WH, Munro CS. Disorders of keratinization. In: Burns T, Breathnach S, Cox N, Griffiths C, editors. Rook's Textbook of Dermatology. 8th ed. UK: Blackwell Publishing, 2010, 119-21.
16. Cairo F, Rubino I, Rotundo R, Pini Prato G, Ficarra G. (2001). Oral Acanthosis nigricans as a Marker of Internal Malignancy. A Case Report. *J Periodont*, 72, 1271-5.
17. Higgins SP, Freemark M, Prose NS. (2008). Acanthosis nigricans: a practical approach to evaluation and management. *Dermatol OnlineJ*, 14, 2.

18. Ramirez AV, Esquivel PL, Caballero ME, Berumen CJ, Orozco TR, Angeles AA. (1999). Oral manifestations as a hallmark of malignant acanthosis nigricans. *J Oral Pathol Med*, 28, 278-81.
19. Pavithran K, Karunakaran M, Palit A. (2008). Disorders of keratinization. In: Valia RG, Ameet RV, editors. IADVL Textbook of Dermatology. 3rd ed. Mumbai: Bhalani Publishing House, 1009-11.
20. Devpura S, Pattamadilok B, Syed ZU, Vemulapalli P, Henderson M, Rehse SJ, *et al.* (2011). Critical comparison of diffuse reflectance spectroscopy and colorimetry as dermatological diagnostic tools for acanthosis nigricans: A chemometric approach. *Biomed Opt Express*, 2, 1664-73.
21. Roy N, Das T, Kundu AK, Maity A. (2012). Atypical presentation of acanthosis nigricans. *Indian J Endocrinol Metab*, 16, 1058-9.
22. Bellot RP, Posadas SR, Caracas PN, Zamora GJ, Cardoso SG, Jurado SF, *et al.* (2006). Comparison of metformin versus rosiglitazone in patients with acanthosis nigricans: A pilot study. *J Drugs Dermatol*, 5, 884-9.
23. Katz RA. Treatment of acanthosis nigricans with oral isotretinoin. (1980). *Arch Dermatol*, 116, 110–1.
24. Rosenbach A and Ram R. (2004). Treatment of Acanthosis nigricans of the axillae using a long-pulsed (5-msec) alexandrite laser. *DermatolSurg*, 30, 1158–60.
25. Abraham C and Rozmus CL. (2012). Is acanthosis nigricans a reliable indicator for risk of type 2 diabetes in obese children and adolescents? A systematic review. *J Sch Nurs*, 28(3), 195-205.

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