Insulin Resistance and Acanthosis Nigricans

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Insulin resistance is related to impaired cell signal transduction, i.e. insulin receptor function and complex postreceptor events in the cells. To a certain extent, the defect is genetically determined. However, the role of external factors such as nutrition or lifestyle has been increasing.

Insulin resistance is considered to be a key feature present in the Metabolic syndrome.

Insulin resistance and related metabolic conditions are becoming increasingly frequent, and a substantial proportion of apparently healthy people are reported to be insulin resistant.

The Insulin resistance syndrome refers to the cluster of abnormalities and related physical outcomes that occur more commonly in insulin resistant individuals. Given tissue differences in insulin dependence and sensitivity, manifestations of the insulin resistance syndrome are likely to reflect the composite effects of excess insulin and variable resistance to its actions [1].

There are many causes of insulin resistance (see Table 8.1), however overweight and obesity are the most common.

The presentation of insulin resistance depends on the type and stage of the insulin-resistant state. Most patients have one or more clinical features of the insulin-resistant state. Many patients do not develop overt diabetes despite extreme insulin resistance.

Patients may present with the following:

- Metabolic syndrome—(see diagnostic criteria—Table 8.2) [2]
- Obesity (most common cause of insulin resistance) or history or excessive body weight

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E.N. Cohen Sabban et al. (eds.), *Dermatology and Diabetes*,
https://doi.org/10.1007/978-3-319-72475-1_8

Table 8.1 Causes of insulin resistance

1. Obesity/overweight (especially excess visceral adiposity)
2. Excess glucocorticoids (Cushing's syndrome or steroid therapy)
3. Excess growth hormone (acromegaly)
4. Pregnancy, gestational diabetes
5. Polycystic ovary disease
6. Lipodystrophy
7. Autoantibodies to the insulin receptor
8. Mutations of insulin receptor
9. Mutations of the peroxisome proliferators' activator receptor γ (PPAR- γ)
10. Mutations that cause genetic obesity
11. Hemochromatosis

Table 8.2 Metabolic syndrome diagnostic criteria

Central obesity (defined as waist circumference ≥94 cm for Europid men and ≥80 cm for Europid women, plus any two of the following four factors:
• Raised TG level: ≥150 mg/dL, or specific treatment for this lipid abnormality
• Reduced HDL cholesterol: <40 mg/dL in males and <50 mg/dL in females, or specific treatment for this lipid abnormality
• Raised blood pressure: systolic BP ≥130 or diastolic BP ≥85 mmHg, or treatment of previously diagnosed hypertension
• Raised fasting plasma glucose (FPG) ≥100 mg/dL, or previously diagnosed type 2 diabetes

TG triglycerides, *BP* blood pressure

- Type 2 diabetes mellitus, IGT (impaired glucose test) or IFG (impaired fasting glucose).
- History of biochemical abnormalities, such as dyslipidemia.
- History of hypertension.
- Symptoms related to macrovascular disease (e.g., stroke, coronary artery disease, peripheral vascular disease)
- History of Polycystic ovary syndrome (PCOS).

Numerous definitions of the metabolic syndrome have been suggested since the original described by Reaven in 1988. According to the current definition the metabolic syndrome is diagnosed if at least three of the following five Criteria are present: abdominal obesity measured by waist circumference, hypertension, hypertriglyceridemia, hyperglycemia and high LDL cholesterol.

Laboratory Studies

Routine laboratory measurements in the evaluation of patients with insulin resistance syndrome include the following:

- Plasma glucose level (fasting and oral glucose tolerance test)
- Hb A1c (Glycohemoglobin level), used to assess chronic hyperglycemia.

- Fasting insulin level—A measure of the degree of insulin resistance in many patients with insulin resistance syndrome
- Lipid profile (fasting total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL], cholesterol, triglyceride)—Insulin resistance syndrome characterized by elevated LDL-B levels (small, dense, pattern B), high triglyceride levels, and reduced HDL-C levels
- Electrolyte levels (BUN [blood urea nitrogen], creatinine, and uric acid levels)—Hyperuricemia is common and is often considered a component of the metabolic syndrome.
- Microalbuminuria is a marker of endothelial dysfunction.
- Homocysteine (H[e])—An elevated level is a risk factor for atherosclerosis, which predicts macrovascular disease—levels are regulated by insulin.
- Plasminogen activator inhibitor (PAI)-1—An elevated level is associated with insulin resistance syndrome and is correlated with obesity, waist-to-hip ratio, hypertension, fasting and postprandial insulin levels, fasting glucose levels, and elevated triglyceride and LDL levels [3]. An increased PAI-1 level signifies impaired fibrinolysis.

Insulin sensitivity can be assessed through the following methods:

- Fasting insulin level—This provides an indirect assessment of insulin sensitivity, a useful measure in patients with insulin-resistance.
- Euglycemic insulin clamp technique—Plasma glucose levels are held constant, with variable glucose infusion. Biochemical responses that are surrogate estimates of insulin resistance, such as glucose disposal and anti-lipolysis, are determined. This method is considered the criterion standard.
- The latter tests are more accurate, but they are not routinely used in clinical practice.
- Homeostatic model assessment for insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI)—These are the most widely used simple indices for assessing insulin resistance in clinical research and practice. Both indices are based on fasting glucose and insulin measurements; they differ mainly in the log transformation of these variables in QUICKI [4].
- HOMA-IR is derived from the product of the insulin and glucose values divided by a constant, that is, calculated by using the following formula: fasting glucose (mg/dL) × fasting insulin (μU/mL)/405 (for SI units: fasting glucose (mmol/L) × fasting insulin (μU/L)/22.5). A value greater than 2.7 indicates insulin resistance.
- QUICKI is derived by calculating the inverse of the sum of the logarithmically expressed values of fasting insulin and glucose: 1/[log(fasting glucose) + log(fasting insulin)]. It measures insulin sensitivity, which is the inverse of insulin resistance. A value of less than 0.339 indicates insulin resistance.
- They both compensate for fasting hyperglycemia, and the results for the indices correlate reasonably well with the euglycemic clamp technique. Some investigators believe that QUICKI is superior to HOMA-IR, for instance in reproducibility, but the two indices correlate very well [5].
- A recent study suggests fasting insulin sensitivities are not better than routine clinical variables in predicting insulin sensitivity among black Africans [6].

Table 8.3 Comparison of acanthosis nigricans (AN) severity in terms of homeostatic model assessment insulin resistance (HOMA-IR)

	Insulin resistance	Metabolic syndrome		
Index	Cut-off value[a]	Cut-off value[b]	Sensibility (95%CI)	Sensibility (95%CI)
HOMA1-IR	2.7	2.3	76.8 (72.1–80.5)	66.7 (63.3–70.0)
HOMA2-IR	1.8	1.4	79.2 (74.7–82.8)	61.2 (57.6–64.6)

CI confidence interval
[a]The 90th percentile in the healthy group
[b]The optimal cut-off value verified in ROC analysis

The homeostatic model assessment (HOMA) is a validated method to measure insulin resistance from fasting glucose and insulin. The original model HOMA1-IR, first published by Mattews et al. in 1985 [4], has been widely used, especially in epidemiological and clinical studies. Recently, the model was updated with some physiological adjustments to a computer version (HOMA2-IR) [7].

Cut-off values of HOMA1-IR and HOMA2-IR indexes to identify insulin resistance and metabolic syndrome (Table 8.3).

Physical Examination

1. Central obesity, is a strong marker of insulin resistance syndrome. Waist or waist-to-hip ratio, height, weight, and body mass index (BMI) may indicate insulin resistance syndrome. This notion was supported by an Argentinian study that found waist circumference and BMI to be the anthropometric indexes that best correlate with the presence of insulin resistance [8].
2. Varying degrees of hirsutism or virilization may be present in women with Polycystic ovary syndrome (PCOS).
3. Others findings:
   Premature arcus cornealis—Deposits of cholesterol and phospholipids
   Xanthelasma—Indicates that lipid status should be investigated
   Lipemia retinalis—Retinal vessels with milky, chylomicron-rich plasma commonly observed in acute, uncontrolled diabetes
   Skin xanthomata—Eruptive xanthomas found most commonly on the buttocks
   Tendon xanthomata—Usually over the patellar and Achilles tendon
4. Acanthosis nigricans (AN) is common in patients with insulin resistance syndrome; it has been reported in nearly one tenth of women evaluated for PCOS.

In the benign form of AN, the factor is probably insulin or an insulin like growth factor (IGF) that incites the epidermal cell proliferation due to the effect of high circulating levels of insulin on insulin like growth factor (IGF) receptors in the skin. Other proposed mediators include other tyrosine kinase receptors (epidermal growth factor receptor [EGFR] or fibroblast growth factor receptor [FGFR]).

At high concentrations, insulin may exert potent proliferative effects via high-affinity binding to IGF-1 receptors. In addition, free IGF-1 levels may be elevated in obese patients with hyperinsulinemia, leading to accelerated cell growth and differentiation [9].

Table 8.4 The neck severity of Acanthosis Nigricans

Neck severity description
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 <7.62 cm in breadth)
3 Moderate: extending to the lateral margins of the neck (posterior border of the sternocleidomastoid) (usually 7.62–15.24 cm), should not be visible when the participant is viewed from the front
4 Severe: extending anteriorly (>15.24 cm), visible when the participant is viewed from the front

Insulin and IGF-1 levels are affected by hepatitis C infection and both of them may be implicated in the pathogenesis of acrochordons and AN through their proliferative and differentiating properties [10].

This skin disorder is characterized by brown hyperpigmentation, hyperkeratosis, and papillomatosis and it is a clinical marker that has been linked to surrogate markers of insulin resistance in adults [11].

It can develop in various parts of the body, including the neck, axillae, knees, elbows, and inguinal folds.

AN severity was evaluated based on the neck severity scale (Table 8.4) designed by Burke et al. [12].

The Fig. 8.1 shows the relation between AN and obesity/metabolic syndrome in the childhood [13].

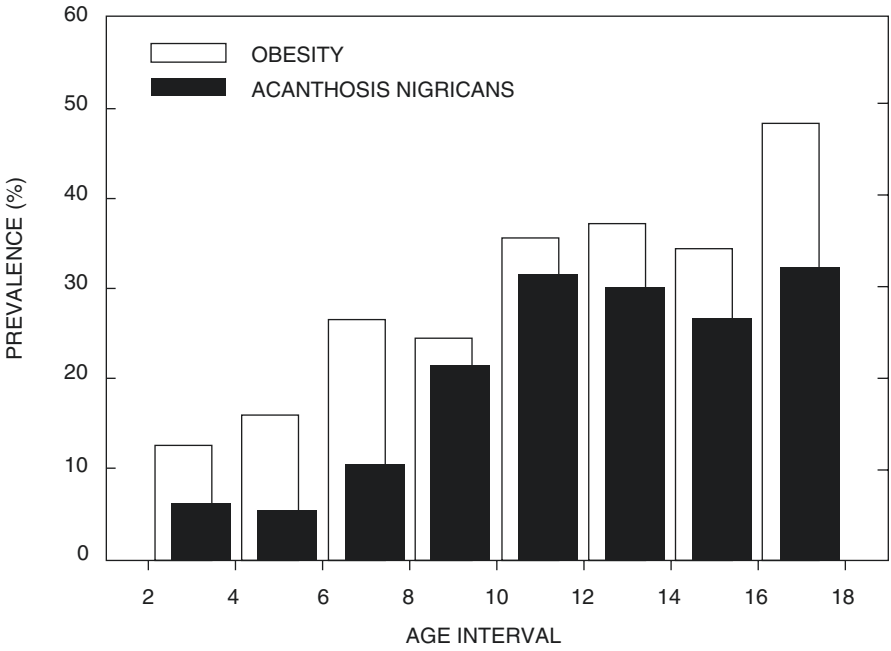
Others Forms of Acanthosis Nigricans

Despite the acanthosis related to insulin resistance and obesity, there are other eight types of acanthosis nigricans described.

Syndromic Acanthosis Nigricans

Syndromic acanthosis nigricans is the name given to AN that is associated with a syndrome. In addition to the widely recognized association of AN with insulin resistance, acanthosis nigricans has been associated with numerous syndromes (see the Table in Pathophysiology). The type A syndrome and type B syndrome are special examples.

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



IMAGES OF ACANTOSIS NIGRICANS

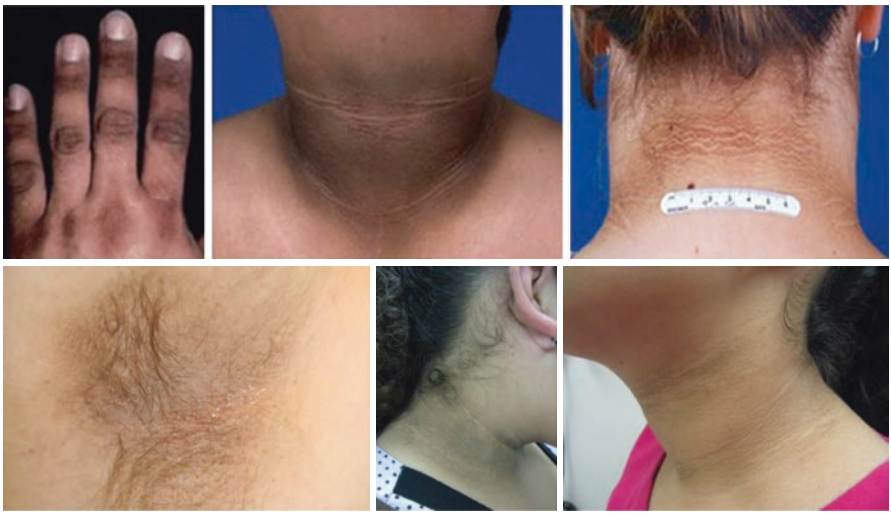


Fig. 8.1 Relation between acanthosis nigricans (AN) and obesity in children

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

Acral Acanthosis Nigricans (Acralacanthotic Anomaly)

It occurs in otherwise healthy patients. It is most common in dark-skinned individuals (African American descent), lesions being prominent over the dorsal aspects of hands and feet.

Unilateral Acanthosis Nigricans

It is a rare form of AN, inherited as an autosomal dominant trait. Lesions are unilateral along lines of Blaschko and may become evident during infancy, childhood, or adulthood. Lesions occur over the face, scalp, chest, abdomen, especially periumbilical area, back and thigh. Lesions can enlarge gradually before stabilizing or regressing. Unilateral nevoid AN is not related to endocrinopathy.

Generalized Acanthosis Nigricans

Generalized AN is rare and has been reported in pediatric patients without underlying systemic disease or malignancy [14].

Familial Acanthosis Nigricans

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

Drug-Induced Acanthosis Nigricans

Drug-induced AN, although uncommon, may be due to several medications, including nicotinic acid, insulin, systemic corticosteroids, fusidic acid, protease inhibitors, estrogens and methyltestosterone. Nicotinic acid has been most widely associated with AN, developing on abdomen and flexor surfaces and resolving within 4–10 weeks of discontinuation [15]. Fibroblast growth factor receptor ligands such as palifermin may cause drug-induced AN [16].

The lesions of AN may regress following discontinuation of the offending medication.

Malignant Acanthosis Nigricans

Malignant AN, which is associated with internal malignancy, is the most worrisome AN variant, because the underlying neoplasm is often an aggressive cancer (see the Table in Pathophysiology).

Acanthosis nigricans has been reported with many kinds of cancer, but, by far, the most common underlying malignancy is an adenocarcinoma of gastrointestinal origin, usually a gastric adenocarcinoma. In an early study of 191 patients with malignant AN, 92% had an underlying abdominal cancer, of which 69% were gastric. Another study reported 94 cases of malignant AN, of which 61% were secondary to a gastric neoplasm.

Malignant AN in pediatric patients has been described with gastric adenocarcinoma, Wilms tumor, and osteogenic sarcoma.

In 25–50% of cases of malignant AN, the oral cavity is involved. The tongue and the lips most commonly are affected, with elongation of the filiform papillae on the dorsal and lateral surfaces of the tongue and multiple papillary lesions appearing on the commissures of the lips. Oral lesions of AN seldom are pigmented.

Tripe palms may show altered dermatoglyphs due to alteration of epidermal rete ridges.

Malignant AN is clinically indistinguishable from the benign forms; however, one must be more suspicious if the lesions arise rapidly, are more extensive, are symptomatic, or are in atypical locations.

Regression of AN has been seen with treatment of the underlying malignancy, and reappearance may suggest recurrence or metastasis of the primary tumor.

Mixed-Type Acanthosis Nigricans

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

Differential Diagnoses

- Epidermal naevus
- Confluent and reticulated papillomatosis of Gougerot-Carteaud
- Dowling-Degos disease (reticular pigmented flexural anomaly)
- Atopic Dermatitis
- Becker Melanosis
- Candidiasis
- Dermatologic aspects of Addison disease
- Dermatologic manifestations of Hemochromatosis
- Dermatologic manifestations of Pellagra
- Erythrasma
- Giant melanocytic nevi
- Ichthyosis hystrix
- Linear epidermal nevus
- Lichen simplex chronicus

- Mycosis fungoides
- Plaque Parapsoriasis
- Pemphigus vegetans

Another marker of insulin resistance are the acrochordons. An association with type 2 diabetes mellitus has been observed [17].

A study of 118 research subjects with acrochordon reported an incidence of 40.6% of either overt type 2 diabetes mellitus or impaired glucose tolerance. Reports exist suggesting that the mechanism is through the effect of insulin and glucose starvation [18]. The previous study showed no correlation between the location, size, color, or number of acrochordons with impairment of glucose tolerance.

They are smalls, softs, commons, benign usually pedunculated neoplasm, that are found particularly in persons who are obese. They are also a marker of increased risk of atherosclerosis and cardiovascular disease [19].

It is usually skin colored or hyperpigmented, and it may appear as surface nodules or papillomas on healthy skin. Most acrochordons vary in size from 2 to 5 mm in diameter, although larger acrochordons up to 5 cm in diameter are sometimes evident. The most frequent localizations are the neck and the axillae, but any skin fold, including the groin, may be affected.

Acrochordons are frequently present in patients with metabolic alteration as the Fig. 8.2 shows [20].

METABOLIC ALTERATION	PERCENTAGE
INSULIN RESISTANCE	71,3
DIABETES MELLITUS	49,3
OBESITY	51,3
PRE DIABETES	18

IMAGES OF ACROCHORDONS

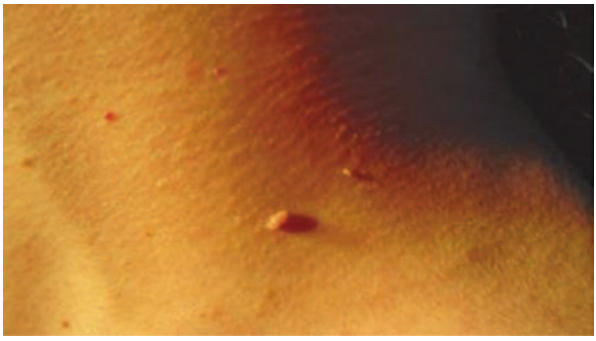


Fig. 8.2 Acrochordon: skin colored, soft, usually pedunculated benign neoplasm

Differential Diagnoses

Also, consider the following:

- Pedunculated seborrheic keratosis
- Nodular exophytic (polypoid) melanoma
- Pseudosarcomatous polyp

References

1. Reaven G. The metabolic syndrome or the insulin resistance syndrome? Different names, different concepts, and different goals. Endocrinol Metab Clin North Am. 2004;33:283–303.
2. Anderson PJ, Critchley JAJH, Chan JCN, et al. Factor analysis of the metabolic syndrome: obesity vs insulin resistance as the central abnormality. Int J Obes. 2001;25:1782.
3. De Taeye B, Smith LH, Vaughan DE. Plasminogen activator inhibitor-1: a common denominator in obesity, diabetes and cardiovascular disease. Curr Opin Pharmacol. 2005;5(2):149–54.
4. Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. Am J Physiol Endocrinol Metab. 2008;294(1):E15–26.
5. Antuna-Puente B, Faraj M, Karelis AD, et al. HOMA or QUICKI: is it useful to test the reproducibility of formulas? Diabetes Metab. 2008;34(3):294–6.
6. Sobngwi E, Kengne AP, Echouffo-Tcheugui JB, Choukem S, Sobngwi-Tambekou J, Balti EV, et al. Fasting insulin sensitivity indices are not better than routine clinical variables at predicting insulin sensitivity among Black Africans: a clamp study in sub-Saharan Africans. BMC Endocr Disord. 2014;14:65.
7. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model 5.assessment (HOMA) evaluation uses the computer program. Diabetes Care. 1998;21(12):2191–2.
8. Hirschler V, Ruiz A, Romero T, Dalamon R, Molinari C. Comparison of different anthropometric indices for identifying insulin resistance in schoolchildren. Diabetes Technol Ther. 2009;11(9):615–2.
9. Higgins SP, Freemark M, Prose NS. Acanthosis nigricans: a practical approach to evaluation and management. Dermatol Online J. 2008;14(9):2.
10. El Safoury OS, Shaker OG, Fawzy MM. 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. 2012;57:102–6.
11. Burke JP, Hale DE, Hazuda HP, Stern MP. A quantitative scale of acanthosis nigricans. Diabetes Care. 1999;22:1655–9.
12. Burke JP, Hale DE, Hazuda HP, Stern MP. A quantitative scale of acantosis nigricans. Diabetes Care. 1999;22:1655–9.
13. Ice CL, Murphy E, Minor VE, Neal WA. Metabolic syndrome in fifth grade children with acanthosis nigricans: results from the CARDIAC project. World J Pediatr. 2009;5(1):23–30.
14. Gönül M, Kiliç A, Cakmak SK, Gül U, Ekiz OD, Ergül G. Juvenile generalized acanthosis nigricans without any systemic disease. Pediatr Int. 2009;51(4):595–7.
15. Sinha S, Schwartz RA. Juvenile acanthosis nigricans. J Am Acad Dermatol. 2007;57(3):502–8.
16. Lane SW, Manoharan S, Mollee PN. Palifermin-induced acanthosis nigricans. Intern Med J. 2007;37(6):417–8.
17. Goyal A, Raina S, Kaushal SS, Mahajan V, Sharma NL. Pattern of cutaneous manifestations in diabetes mellitus. Indian J Dermatol. 2010;55(1):39–41.

18. Mathur SK, Bhargava P. Insulin resistance and skin tags. Dermatology. 1997;195(2):184.
19. Sari R, Akman A, Alpsoy E, Balci MK. The metabolic profile in patients with skin tags. Clin Exp Med. 2009;10(3):193–7.
20. Guerra C, et al. Metabolic diseases associated with acrochordons. Folia Dermatol Peru. 2006;17(2):60–4.