Excess Insulin Binding to Insulin-Like Growth Factor Receptors: Proposed Mechanism for Acanthosis Nigricans

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Clinical and epidemiologic evidence has shown acanthosis nigricans to be closely related to defective tissue utilization of insulin in a number of previously recognized (e.g., obesity, lipodystrophy, and leprechaunism) as well as recently characterized (e.g., type A and type B syndromes) disorders. This article reviews the relationship of acanthosis nigricans to these insulin-resistant states. It also focuses attention on the possibility that interaction between excessive amounts of circulating insulin with insulin-like growth factor receptors on keratinocytes and dermal fibroblasts leads to the development of acanthosis nigricans. *J Invest Dermatol 98:82S–85S, 1992*

Acanthosis nigricans (AN) has long been recognized as a cutaneous disorder with distinctive clinical and histologic features, and with diverse associations that run the gamut from benign conditions such as obesity to malignant states such as gastrointestinal adenocarcinoma [1]. Many authors have categorized these associations in a variety of ways, in an attempt to gain a better understanding of the mechanisms responsible for producing AN. In this paper, we trace the evolution of our current perspective of AN and review the different insulin-resistant states that are associated with AN. Finally, we propose a mechanism to account for the development of AN in the setting of insulin resistance.

THE TRADITIONAL VIEW OF AN

Early perspectives of AN were derived from observations made by Curth [2], who, in 1939, placed the greatest significance of AN in association with internal malignancy (Fig 1*A*). In addition, she acknowledged the existence of other forms of AN, including those that appeared to be of an autosomal dominant variety, AN in association with other genetic syndromes including leprechaunism and lipodystrophy, and an amorphous category termed psuedo AN, which included obesity [2]. Despite numerous modifications of this scheme, the principal implication remained the same: AN was thought to be the end-result of different unrelated disturbances.

AN AND INSULIN RESISTANT STATES

The real breakthrough in our current understanding of AN came in 1976, when Kahn and Flier and their colleagues [3] shifted the emphasis from AN associated with malignancy to AN associated with insulin-resistant states (Fig 1*B*). In their original report, they distinguished six cases of AN into type A and type B syndromes of insulin resistance [3]. Several disorders that feature the concurrent presence of AN and insulin resistance have since been recognized (Table I). In these disorders, AN is a visible marker of insulin resistance.

Important to distinguish are two different settings in which insulin resistance may be viewed [4]. One setting relates to patients with diabetes mellitus; here, insulin resistance is arbitrarily defined as a requirement of 200 or more units of insulin per day to control hyperglycemia and prevent ketosis. The second setting and relevant to this review is that of insulin resistance in association with AN, in which hyperinsulinemia occurs, usually in the presence of euglycemia and not hyperglycemia. Consequently, diabetes mellitus is not a prominent feature in most individuals with AN.

A useful classification of insulin resistance is one based on the pathogenic locus [5]. *Pre-receptor* resistance occurs in individuals with abnormal insulin or insulin antibodies; AN has not been reported in these cases. *Receptor* resistance results from decreased number of classic insulin receptors or diminished binding of insulin to these receptors. Finally, *post-receptor* resistance may arise from abnormal signal transduction, particularly due to failure to activate the receptor tyrosine kinase. Whereas the nature of the molecular defect is known in some syndromes, it remains undefined in many types of insulin resistance. As shown in Table I, a combination of defects, especially of the receptor and post-receptor types, can occur.

OBESITY

Obesity is the most common cause of AN (Table II) and of insulin resistance. Recently, we documented a 74% prevalence of AN in adult obese, but otherwise healthy, patients [6]. A high prevalence of AN (28%) was also observed by Stuart [7] in primary school children who were greater than 120% of ideal body weight (IBW). In studies that examined selected subsets of obese individuals, Dunaif [8] observed AN to be present in 50% of obese women with polycystic ovary syndrome, whereas Flier [9] reported AN in 5% of hyperandrogenic obese women. This latter phenotype of obese women with AN and masculinizing features has been designated the type C syndrome of insulin resistance [9].

There is a positive correlation between the development of AN and the severity of obesity. For instance, greater than 80% of adult patients who weighed 200% or more than their IBW had AN [6]. This finding closely parallels the observation that 66% of children who were in excess of this weight parameter also showed AN [7].

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Abbreviations:
AN: acanthosis nigricans
IBW: ideal body weight
IGF: insulin-like growth factor

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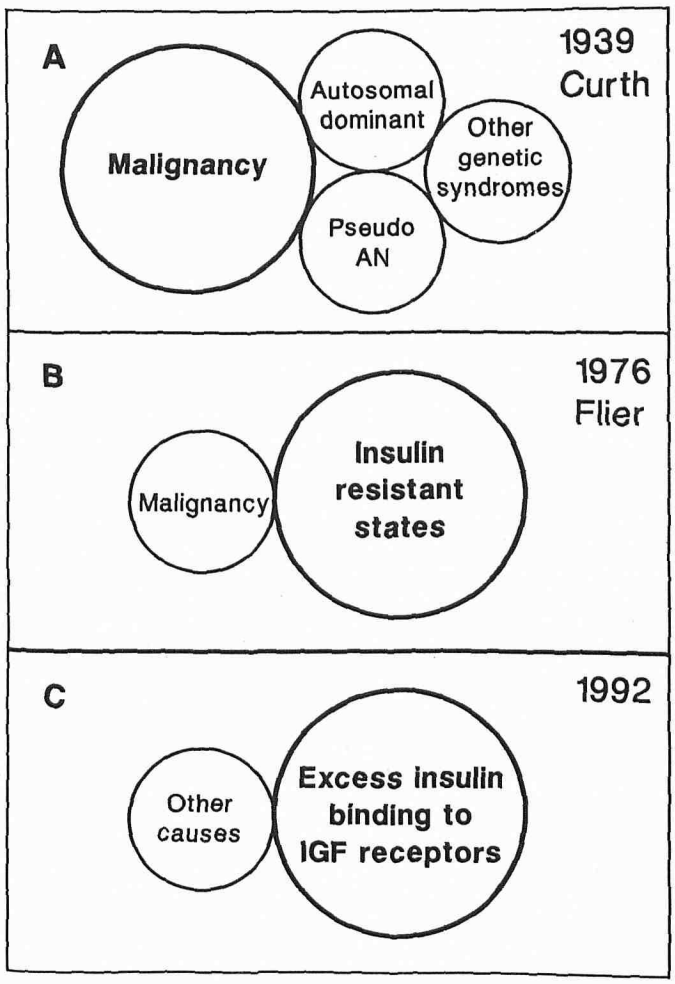

Figure 1. Evolution of our perspective in viewing acanthosis nigricans and its associations.

Quite interestingly, we have witnessed the disappearance of AN in obese patients following reduction to more IBW.

AN is a reliable predictor of hyperinsulinemia in obese individuals [6,7]. In addition, the severity of AN in these individuals appears to depend upon the duration and magnitude of hyperinsulinemia. Insulin resistance in obesity is probably due to a combination of receptor and post-receptor defects. Diminution in insulin action in obese patients with mild hyperinsulinemia and insulin resistance is thought to be due principally to a reduced number of functional receptors. However, as the metabolic defect worsens in these patients, a post-receptor defect may emerge and become the predominant abnormality, leading to severe insulin resistance.

Table I. Disorders that Exhibit Acanthosis Nigricans and Insulin Resistance

Disorder	Apparent Cause of Insulin Resistance
Obesity	Reduced number of functional insulin receptors combined with post-receptor failure to activate tyrosine kinase
Type A syndrome	Absent or dysfunctional insulin receptor
Type B syndrome	Anti-insulin receptor autoantibodies compete with insulin for binding to receptor
Lipodystrophy	Reduced number of receptors, decreased affinity of receptor for insulin, or post-receptor defect
Leprechaunism	Dysfunctional receptor or post-receptor pathway
Rabson-Mendenhall syndrome	Defective receptor

Table II. Prevalence of Acanthosis Nigricans in Obese Populations

Study	Prevalence	Obese Population Studied
Hud (1991)	74%	Adult obese (otherwise healthy) patients from a county hospital obesity clinic
Stuart (1989)	28%	Obese children enrolled in primary school
Dunaif (1987)	50%	Adult obese women with polycystic ovary disease
Flier (1985)	5%	Adult obese women with hyperandrogenic manifestations

TYPE A SYNDROME

Twenty cases of the type A syndrome of insulin resistance have been reported (Table III) [10–23]. These cases were predominantly black girls or young women who present with abnormal signs and symptoms as early as infancy or childhood. Most patients exhibited severe, even generalized, AN in association with hyperandrogenic manifestations, such as hirsutism, clitormegaly, masculine habitus, and increased somatic growth. Polycystic ovarian syndrome has been diagnosed in many of these cases, based in part on profiles of elevated plasma androgens.

Type A patients have genetic defects of the insulin receptor. Most patients have a decrease in the number of insulin receptors, whereas in some patients there is a normal number of dysfunctional receptors. At the molecular level, defects range from decreased mRNA for the receptor to mutations that alter receptor processing or incorporation into the cell membrane. Type A patients exhibit high plasma insulin concentrations.

TYPE B SYNDROME

By comparison, 19 cases of the type B syndrome of insulin resistance have been reported (Table III) [24–36]. The majority of type B cases were also of the female sex and of black ethnicity. Unlike type A patients, however, type B patients manifested AN at a later age (mean of 39 years), and their AN was both less extensive and less severe. In addition, in contrast to the progressive nature of AN in the type A syndrome, patients with the type B syndrome may exhibit waxing and waning of AN that parallel worsening and im-

Table III. Clinical Features of Type A and Type B Syndromes of Insulin Resistance

Parameters	Type A Syndrome	Type B Syndrome
Female to male ratio	19:1	6:1
Ethnic background	Mostly black	Mostly black
Clinical onset	Infancy or childhood	15–64 years; mean of 39 years
Acanthosis nigricans	Usually severe and generalized	Varying and even fluctuating severity
Associated disorders	Hyperandrogenic manifestations, such as hirsutism, clitormegaly, and masculine habitus	Autoimmune disease, particularly systemic lupus erythematosus; also scleroderma, Sjogren's syndrome, rheumatoid arthritis, Grave's disease, and Hashimoto's thyroiditis
Laboratory features	Hyperinsulinemia Hyperandrogenemia	Hyperinsulinemia Positive ANA Hypergammaglobulinemia Hypocomplementemia

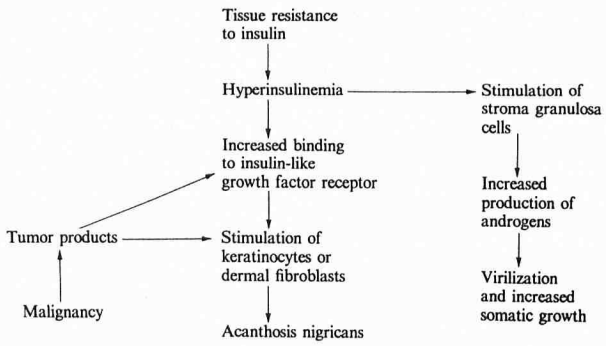

Figure 2. Postulated pathomechanism for the development of acanthosis nigricans.

provement of their underlying immunologic disease, the most common of which has been systemic lupus erythematosus [1].

Insulin resistance in type B patients is due to blocking autoantibodies to the insulin receptor (not to insulin itself). Of interest is the observation that these anti-receptor antibodies can also cause hypoglycemia. Type B patients demonstrate high plasma insulin concentrations that can fluctuate in parallel with the level of anti-receptor antibodies.

LIPODYSTROPHY

The lipodystrophies are acquired or congenital syndromes of fat depletion that differ in the extent of fat atrophy [4,5]. The generalized form has been equated with lipoatrophic diabetes and is characterized by an almost complete absence of body fat. By contrast, the more common partial form exhibits atrophy of fat in the head and upper trunk and extremities, with normal or even increased adiposity in the lower trunk and extremities. Patients of either form may develop hyperglycemia, but ketosis does not occur. Marked hypertriglyceridemia with eruptive xanthomas is a prominent feature. In addition, affected individuals may display hepatomegaly, splenomegaly, cardiomegaly, lymphadenopathy, and (in the congenital forms) muscle hypertrophy. Hirsutism and hypertrophied external genitalia may be present, mental retardation is common, and renal disease may develop.

Insulin resistance is due to decreased number of receptors, diminished affinity of receptor for insulin, or a post-receptor defect. All patients have elevated plasma insulin levels.

LEPRECHAUNISM

Leprechaunism is characterized by an elfin appearance of the face, thickened skin, absence of subcutaneous fat, and hirsutism [4,5]. Insulin resistance is probably due to abnormal insulin receptor function.

RABSON-MENDENHALL SYNDROME

Rabson-Mendenhall syndrome consists of dental dysplasia, dystrophic nails, premature puberty, and acanthosis nigricans [4,5]. Insulin resistance in these patients is probably also due to an insulin receptor abnormality.

PROPOSED MECHANISM FOR PATHOGENESIS OF AN

How might our knowledge of the frequent development of AN in insulin-resistant states provide insight into the pathogenesis of this cutaneous disorder? Figure 2 outlines a postulated mechanism. Regardless of the underlying cause, tissue resistance to insulin causes the pancreatic islet B cells to compensate by producing more insulin, resulting in hyperinsulinemia. At relatively low concentrations, insulin is believed to bind preferentially to its classic receptor, which is thought to be primarily responsible for mediating the effects of insulin in glucose metabolism [37]. By contrast, at higher concentrations, insulin acquires relatively greater affinity for insulin-like growth factor (IGF) receptors, which are thought to be responsible for mediating the effects of insulin on the proliferation of cells [38–43]. Both classic insulin receptors and IGF receptors have been identified in cultured human fibroblasts and keratinocytes [40–43]. Furthermore, insulin has been shown to cross the dermal-epidermal junction to reach keratinocytes [43].

Virilization and increased somatic growth observed in certain patients, such as those with the type A syndrome, may be due to stimulation by insulin of stroma granulosa cells, which in turn produce androgens [44]. It is also possible that particular tumors, such as gastric adenocarcinomas, may secrete tumor products (maybe insulin itself) that can serve as ligands for IGF receptors on fibroblasts and keratinocytes, thereby explaining the rare instances of AN in association with malignancy.

OUR PRESENT VIEW OF AN

Half a century since Curth proposed a clinical categorization of AN, our present view of AN, based primarily on its metabolic association, is far different (Fig 1*C*). Insulin resistance and consequent hyperinsulinemia are unifying attributes, which link several of the seemingly disparate types of AN. In this respect, we propose AN in the setting of insulin resistance to be a consequence of excessive signaling transduced in skin cells such as keratinocytes and fibroblasts by the ligation of putative receptors on these cells with a factor present in abnormally high quantities. Circumstantial evidence indicate IGF receptors and insulin, respectively, to be the prime candidates for the roles of collaborator-receptor and of instigator-ligand in the pathogenesis of AN.

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