Review Article

Acanthosis nigricans in the pediatric population: a narrative review of the current approach to management in primary care

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Background and Objective: Acanthosis nigricans (AN) is frequently seen in obese and overweight children and adolescents. Current research suggests an association with insulin resistance, type 2 diabetes mellitus, and obesity, and often primary care physicians are the first point of contact for individuals with this dermatologic condition. However, identifying the condition at an early stage may be difficult. This narrative review aims to provide readers with a comprehensive overview of the current literature of AN in the pediatric and adolescent population, including best practices for identifying the condition, with a focus on the recommended management in the primary care setting to enable early and enhanced intervention.

Methods: We identified case and cross-sectional studies, clinical trials, and literature reviews of pediatric AN for ages 0 to 18 years in the United States and internationally. We considered publications for background from 1994 to 2007 and publications for approach to management from 2007 to 2020.

Key Content and Findings: The literature review contains information on the recommended work up of a patient with AN, with a special focus on insulin resistance. AN may be present prior to diabetes, and the severity of AN can be used as a clinical predictor of metabolic disorders and the underlying nutritional status of normal, overweight, and obese children and adolescents. Early metabolic screening with focus on insulin sensitivity, liver function, lipid panel, and glucose tolerance is recommended.

Conclusions: AN in the pediatric population can be a harbinger for underlying metabolic syndrome and insulin resistance. A thorough investigation and appropriate screening of children at risk, with a focus on early identification of the dermatologic condition and its associated comorbidities in the primary care setting, and early treatment is recommended to prevent long term consequences and decrease the risk of cardiovascular complications.

Keywords: Acanthosis nigricans (AN); insulin resistance; obesity; multidisciplinary care

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Introduction

The skin often provides clues as to the health of an individual, showing outwardly visible manifestations of health or lack thereof. In particular, the now common skin condition, acanthosis nigricans (AN), was known for its association with malignancy in the adult population (1), and in 2000, the American Diabetes Association (ADA) established AN as a formal risk factor for the development of

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type 2 diabetes mellitus (2). Over the years, the prevalence of AN among the pediatric population has increased in parallel with the incidence of obesity (3). This review aims to provide readers with a comprehensive overview of the current literature of AN in the pediatric population. We discuss the best practices for identifying the condition, with a focus on the recommended management in the primary care setting to enable early and enhanced intervention. We present the following article in accordance with the Narrative Review reporting checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-21-70/rc). The studies included in this review are listed in *Table 1*.

Methods

In this narrative review, a literature search in English language was conducted across multiple databases including PubMed, MEDLINE, and Cochrane. MeSH and non-MeSH terms such as "acanthosis nigricans", "diagnosis", "treatment", "topical", "systemic therapy", "insulin resistance", "obesity", "metabolic syndrome", "diabetes mellitus", "lasers", were considered. We identified cross-sectional and case studies, clinical trials, and literature reviews of pediatric AN for ages 0 to 18 years in the United States and internationally. Publications considered for background information were identified from the years 1994 to 2007, and we considered publications for the approach to management from years 2007 to 2020 (*Table 2*).

Dermatologic presentation

AN is characterized by symmetrical distribution of thickened, velvety, brown to black hyperpigmented plaques most seen on the body's intertriginous sites, such as the neck, axillae, groin, and anogenital areas (1) (*Figure 1*). The inframammary, abdominal, antecubital and popliteal fossae, face, eyelids, nasal creases, and nipples are less frequently affected. The condition may occasionally involve mucosal surfaces; however, hyperpigmentation is less common in these areas (3,4). An acral form of AN is characterized by hyperpigmented plaques on the knuckles, elbows, knees, palms, and soles.

In the early stages, AN may reveal a "dirty" and dry appearance that may appear differently on different skin phototypes; those with lighter skin may notice a yellowish-tan to red appearance in early stages, while those with deeper skin tones notice a darker brown (4). However, as the lesions progress, the skin becomes thicker, demonstrating accentuation of skin lines with ill-defined margins, and may show papillomatous surface change (*Figure 1*). Acrochordons (skin tags) may also be present within or around the affected areas (*Figure 2*). The acrochordons are usually asymptomatic though rarely may be associated with pruritus and inflammation due to excessive friction of affected skin folds (1).

AN is thought to be caused by factors that stimulate epidermal keratinocyte and dermal fibroblast proliferation. At high concentrations, insulin may exert proliferative effects via insulin growth factor (IGF) and IGF-1 receptors on keratinocytes and fibroblasts, leading to proliferation and progressive pigmentation of the skin, and development of papillomatous plaques of AN (5). Other proposed mediators include epidermal growth factor receptor (EGFR) or fibroblast growth factor receptor (FGFR). The predilection for body folds, such as neck and axillae, suggests that perspiration or friction may play a contributory role (6,7).

There are many cutaneous disorders that may share features with AN. Careful attention should be paid to the location and pattern, the alleviating or aggravating factors, and the skin texture itself to help determine the underlying condition. *Table 3* highlights the most common disorders that may be confused with AN.

Recommended workup

Several causes have been described for AN, resulting in various classifications. It may be divided into benign and paraneoplastic, or into benign, malignant, and syndromic AN (4). Several complex classifications have been proposed, further dividing AN into etiological criteria to better understand the underlying pathology (7,9) (*Tables 4,5*).

AN occurs frequently in adolescents, with prevalence ranging from 49.2% to 58.2% in studies involving children or adolescents with obesity (3). With rates of obesity and type 2 diabetes rapidly increasing in the pediatric population, it is imperative that pediatric providers utilize the primary care setting as an opportunity to identify those at risk for obesity and type 2 diabetes, and provide early intervention for this at-risk group.

Many factors contribute to the development of metabolic abnormalities, including family history and obesity (8). Literature identifies race and ethnicity as risk factors, however this categorization may be a simplification (8). In an analysis of food insecurity trends from 2001 to 2016, both non-Hispanic black and Hispanic households were two times as likely to have food insecurity than that of non-Hispanic white households (15). Furthermore, recent

Table 1 Review of studies of acanthosis nigricans

Authors & year	Purpose of study	Design	Sample	Variables measured	Results
Stuart CA, Smith MM, Gilkison CR, Shaheb S, Stahn [1994]	Evaluate the validity of AN among Native Americans as an indicator of high diabetes risk	Cross-sectional study	1,217 children 3 to 19 years of age	AN on neck, fasting insulin level, BMI	Prevalence of AN increased with BMI. AN group had significantly higher level of insulin. AN (on neck) is a visible marker of hyperinsulinemia and for developing T2DM
Mukhtar Q, Cleverley G, Voorhees RE, McGrath [2001]	Determine the association of AN with hyperinsulinemia is independent of obesity and other variables	Survey Questionnaire Data analyzed by descriptive analytic methods	675 sixth, seventh & eighth grade students in New Mexico	AN screening on neck, Fasting Insulin, & glucose, age, gender, ethnicity, family history of DM nutrition status, and physical activity data	AN group has higher fasting insulin, AN prevalence varied with ethnicity: Native Americans 38.6%, Hispanic 19.7%, non-Hispanic White 4.7%. AN is a positive predictor for hyperinsulinemia
Nguyen TT, Keil MF, Russell DL [2001]	To examine the relationship between AN, hyperinsulinemia and body adiposity	Cross sectional study	139 overweight children in US aged 6 to 10 years	AN, BMI, fasting insulin	Children with race, sex, age specific high BMI scores should be screened for hyperinsulinemia, whether or not they have AN
Stoddart ML, Blevins KS, Lee ET, Wang W, Blackett PR [2002]	To determine the prevalence of AN to hyperinsulinemia compared with other risk factors for T2DM in American Indian children	A cross-sectional study using a random sample, correlation analysis	2,205 Cherokee Indian children and adults from 5 to 40 years	Visual screening for AN, BMI, BP, Fasting insulin level, lipids, FBS	AN is an independent marker for hyperinsulinemia and a predictor of T2DM. Prevalence increased with age and degree of Indian heritage and higher in female. AN increased with BMI and family history of T2DM
Hirschler V, Aranda C, Oneto A, Gonzalez C, Jadzinsky [2002]	To evaluate the significance of AN as a marker of IR in obese children	Randomized cross-sectional study, multivariate analysis	1,250 Hispanic students. Mean age 12.4 years	Birth weight, family history of obesity and T2DM, BMI, AN, BP, and Tanner stage. OGTT, Insulin level, lipid profile	Presence of AN has positive correlation with BMI. Higher fasting insulin and IR indices in those with AN
Yamazaki H, Ito S, Yoshida [2003]	To determine whether AN is a reliable cutaneous marker of IR and T2DM in obese Japanese children	Retrospective comparative study	439 obese Japanese children. Mean age 10.1 years	Visual screening for AN, fasting plasma insulin, FBS, OGTT	AN is a reliable marker of IR and T2DM. Children with AN showed more impaired glucose tolerance and T2DM compared with those without AN. Mean insulin concentration correlated with AN presence
Kobaissi H, Marc J. Weigensberg, Geoff D.C. Ball, Martha L. Cruz, Gabriel Q. Shaibi, Michael I. Goran [2004]	To investigate the relationship between AN and severity of AN and insulin sensitivity, independent of obesity	Longitudinal study, multivariate linear regression analysis	131 Hispanic overweight children between 8 and 13 years	Visual scoring of AN (0–4 scale), BMI, glucose tolerance testing	AN is an independent risk factor for IR, in overweight Hispanic children at risk for T2DM. Body adiposity is primary determinant of insulin sensitivity

Table 1 (*continued*)

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Authors & year	Purpose of study	Design	Sample	Variables measured	Results
Copeland K, Pankratz K, Cathey V [2006]	To evaluate whether IR is associated with AN, Native American heritage, BMI, fasting insulin, and plasma lipids in children and adolescents	Retrospective chart review	Native American children aged 3.6 to 17.8 years in 4 tribal or Indian Health Service clinics	Family history of type 2 DM, AN, BMI, lipid profile, fasting insulin	Severe AN associated with higher BMI and fasting insulin levels and lower HDL. Among Native American children at risk for T2DM, AN is an independent marker of IR
Kong AS, Williams RL, Smith M [2007]	To determine the association of AN with T2DM risk factors and metabolic disease in children	Cross-sectional study. Data collected by chart review and interview	96 children aged 7–19 years (total population 483 adults and children)	Visual scoring of AN, graded using photographs, BMI, Family history in first- or second-degree relatives	AN associated with increased risk for T2DM, and is independent risk factor for development of T2DM. AN presence can identify patients with multiple risk for T2DM
Guran, Turan, Akcay [2008]	To determine the clinical and laboratory difference in obese children with AN and without AN	A cross-sectional study	160 obese children, mean age 10.4 years	Visual scoring of AN, BMI, fasting glucose, fasting and PM insulin level, HOMA-IR	AN is a useful clinical indicator for T2DM and IR. Obese children with AN show hyperinsulinemia, and IR. Prevalence of AN increases with increases in weight
Brickman WJ, MD, Huang J, ScD, Silverman BL, MD, Metzger BE, MD [2010]	To determine whether AN identifies youth at risk for metabolic abnormalities including IR	Descriptive, cross-sectional study, using survey questions prevalence study	287 children, mean age 11.7 years	AN, BMI, BP, OGTT	AN is an indicator of significant IR and evidence of abnormal glucose homeostasis that is supportive of development of T2DM
Brown B, Noonan C, Bentley B, Conway K, Corcoran M, FourStar K, Gress S, Wagner S. [2010]	To present prospective data on AN prevalence in the context of risk factors for diabetes	Cross sectional study, prospective analysis	2,520 Northern Plains American Indian children in K through 12th grade	AN, BMI, BP, family history of diabetes, physical activity	Relative risk for obesity and incident AN was 9.8 compared to normal weight. Sports participation inversely associated with AN. Utility in AN as marker for IR in at-risk population
Rafalson L, Eysaman J, Quattrin [2011]	To determine the prevalence of AN and other diabetes risk factors in urban school health clinics	Prospective observational study	854 students, mean age 11.4 years	AN, glucose, BMI	AN can be identified by trained health care professionals in busy school-based clinic settings. Females and minorities were more likely to have AN. Children with AN were twice as likely to have elevated glucose
Santoro N, Amato A, Grandone [2013]	Verify in obese children whether high WHR, family history of T2DM, AN, predicts occurrence of metabolic syndrome or prediabetes	Cohort study, calculation of odds ratios	1,080 Italian obese children (567 females) age 4 to 17 years	Blood pressure, fasting glucose, insulin, lipid, OGTT, presence of AN	AN and WHR clinical signs linked to higher risk for metabolic syndrome. Odds ratio raised when occurring simultaneously

Table 1 (*continued*)

Table 1 (*continued*)

Authors & year	Purpose of study	Design	Sample	Variables measured	Results
Saki, Karamizadeh [2014]	Investigate prevalence of fatty liver in Iranian children and its' association with metabolic syndrome and IR	Cross-sectional study	102 obese Iranian children	BMI, WHR, lipid profile, glucose, insulin, AN	Presence of fatty liver is high in obese children, associated with metabolic syndrome and IR. Severity of fatty liver had close relationship with AN and IR
Ng HY, Young JHM, Huen KF, Chan [2014]	Investigate demographic characteristics and IR in overweight/obese Chinese children with and without AN, and associations of AN with IR	Case series with cross-sectional analyses	Chinese overweight and obese children aged 5 to 18 years	AN, BP, OGTT, insulin levels, triglycerides, ALT, lipid profile	Obese children and adolescents with AN more likely to have IR and cardiometabolic comorbidities. Those with AN more likely to have IR, hypertension, fatty liver, abnormal glucose homeostasis
Verma R, Jorwal P, Keshwani [2014]	Determine the association between presence of AN with biochemical parameters and anthropometric variables	Analytical cross-sectional study	Young males age 18 to 25 in North India	BMI, WHR, glucose, insulin, cholesterol triglycerides, blood pressure	Individuals with AN have lower HDL, higher BMI, fasting blood glucose, insulin, total cholesterol, triglycerides, LDL, and BP
Krishnakanth, Anandan, Gayathri, Adikrishnan, Murugan, Sudha, Mahalakshmi [2015]	Compare serum insulin levels and insulin sensitivity between obese and non-obese individuals with AN and association between epidermal thickness and serum insulin levels	Case-control study design with cross-sectional analyses	30 patients with AN, 10 patients as control	Epidermal thickness, WHR, BMI, insulin levels	Significant positive correlation of epidermal thickness and serum insulin levels in obese patients with AN
Huang, Yang, Li [2016]	Relationship between FGF21 and obesity-related AN	Analytical cross-sectional study, using multivariable logistic regression analyses	40 obese patients without AN, 40 obese patients with AN, 40 healthy volunteers	Weight, BMI, lipid profile, FFA, UA, CRP, OGTT, HOMA-IR	AN patients had hyperinsulinemia but better serum glucose levels than obese patients without AN. Increased FGF21 associated with AN, may be compensatory response to decreased insulin sensitivity
Bhagyanathan M, Dhayanithy D, Parambath VA, Bijayraj [2017]	To determine whether presence of AN can be used to screen for IR in children and detect this risk factor for Type 2 DM	Cross sectional, observational study	507 children aged 10 to 18 years in India	AN, height/weight, WHR, fasting glucose, insulin, lipid profile	Presence of AN positively correlated with high IR, and when combined with increased BMI, incidence rate of IR is 80%

Table 1 (*continued*)

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Authors & year	Purpose of study	Design	Sample	Variables measured	Results
Sayarifard F, Sayarifard A, Allahverdi B, Ipakchi S, Moghtaderi M, Yaghmaei B [2017]	Estimate the prevalence of AN and related laboratory factors in Iranian obese children	Cross-sectional study	71 obese children age 4 to 13 years with BMI >95th percentile for age and gender specific BMI	AN, BMI, fasting glucose, total cholesterol, triglycerides, AST < ALT, Alkaline phosphatase, LDL, HDL, TSH, Ca, Phos, Vit D	Mean BMI, insulin, TG, AST higher in cases with AN. Obese children with AN are at risk of developing diabetes
Novotny, Davis, Butel [2018]	To prevent young child overweight and obesity and improve health in US Affiliated Pacific region	Randomized clinical trial	4042 children aged 2 to 8 years in 27 communities from 2012 to 2015	Body size measurements, AN, sleep quality and duration, dietary intake, physical activity	Interventions including messaging, training, target behaviors (sleep, physical activity, nutrition) reduced prevalence of overweight and obesity, and AN
Palhares HMDC, Zaidan PC, Dib FCM, Silva APD, Resende DCS, Borges MF [2018]	To evaluate presence or absence of AN and its association with metabolic changes in overweight and obese children and adolescents	Cross sectional study	161 overweight children and adolescents aged 5 to 19 years in Brazil	AN, BMI, skinfolds, WHR, BP, glucose, insulin, lipid profile, uric acid, transaminases	AN in overweight/obese children and adolescents is associated with elevated of body fat, BP, insulin and a clinical marker for metabolic syndrome
Thiagarajan, Arun, Manivel [2020]	To investigate relationship between AN with BMI, WHR, metabolic risk factors among obese children in India	Cross-sectional study, logistic regression analysis	Children aged 5 to 15 years with BMI equivalent to adults more than 23 kg/m^2	AN, BP, WHR, lipid profile	Severity of AN is associated with higher BMI, higher waist circumference, high systolic BP, high triglycerides and VLDL in overweight and obese children

AN, acanthosis nigricans; BMI, body mass index; T2DM, type 2 diabetes mellitus; DM, diabetes mellitus; IR, insulin resistance; WHR, waist hip ratio; BP, blood pressure; FBS, fasting blood sugar; LDL, low density lipoprotein; TG, triglycerides; AST, aspartate transaminase; ALT, alanine transaminase; OGTT, oral glucose tolerance test; HDL, high-density lipoprotein; TSH, thyroid stimulating hormone; FFA, free fatty acid; UA, urinalysis; CRP, C-reactive protein; HOMA-IR, homeostatic model assessment insulin resistance; FGF21, fibroblast growth factor-21.

Table 2 The search strategy summary

Items	Specification
Date of search	July 1 2021–August 30 2021
Databases and other sources searched	PubMed, MEDLINE, Cochrane Library
Search terms used	Acanthosis nigricans, diagnosis, treatment, topical, systemic therapy, diabetes mellitus, insulin resistance, obesity, metabolic syndrome, lasers
Timeframe	1994–2020
Inclusion and exclusion criteria	Inclusion: cross-sectional, case-studies, clinical trial, systematic review, age 0 to 18 years, English language
	Exclusion: case reports, case series, studies involving participants older than 18 years of age, full text not available in English
Selection process	Pollock, Swamy conducted selection, approved by senior author Shen

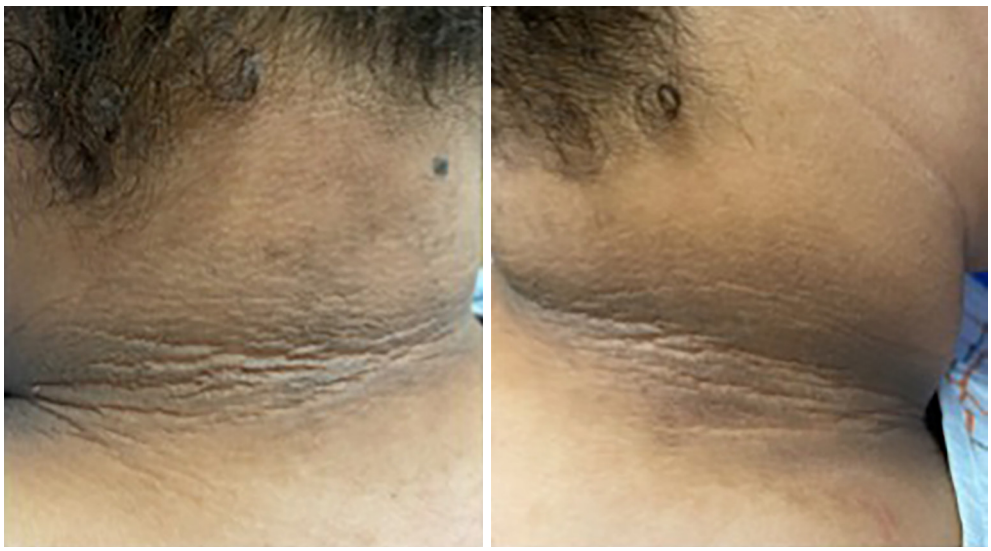

Figure 1 Acanthosis nigricans on the neck of a pediatric patient. Note the accentuation of skin lines and papillomatous surface change of the hyperpigmented plaque.

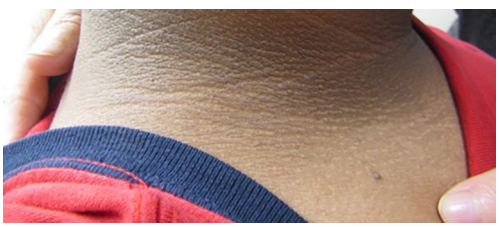

Figure 2 Acrochordon in affected area of acanthosis nigricans.

studies demonstrate that regions with racial inequalities in poverty and employment are positively correlated with higher obesity rates (16). Independent of obesity, several studies suggest AN is associated with hyperinsulinemia and development of insulin resistance, and may be an early marker for such chronic illness (8). Given this independent association, only evaluating children who are already overweight may in fact overlook some cases of hyperinsulinemia.

When a pediatric patient is noted to have AN, physicians must utilize this warning sign to search for underlying associated disease and metabolic abnormalities. It is important to recognize that apart from the metabolic association, the skin lesions have a profound impact on the quality of life of patients. During a phase where physical changes and appearance occupy an important part of the development of an individual's self-image, visible skin conditions and obesity may lead to psychosocial consequences. Studies have indicated that obese adolescents with AN may experience increased social anxiety and low self-esteem than the general population (17). Therefore, early intervention, and early identification of modifiable risk factors, not only for metabolic syndrome and AN, but for low-self-esteem in adolescents, is important to help prevent cardiovascular and psychosocial consequences and allow for a positive transition to adulthood. The following section highlights the recommended workup for such cases.

Fasting insulin levels and homeostasis model of insulin resistance

Most patients with AN have either clinical or sub-clinical insulin resistance, with higher levels of insulin than patients without AN (18). However, insulin resistance does not develop concurrently with development of AN, and in fact, may not be present until many years after the initial onset of the dermatosis. Insulin is most often implicated as the cause of AN, stimulating fibroblast proliferation through IGF-1 receptors as described previously (5). As such, the presence of AN can serve as a proxy physical marker for biochemical elevation in insulin.

In a sample of United States (US) middle school students, AN was found to be an independent predictor of hyperinsulinemia in adolescents; its presence increased the likelihood of hyperinsulinemia to four times the baseline, after adjusting for variables including body

Table 3 Differential diagnosis

Condition	Location	Course	Associated symptoms/ syndromes	Clinical characteristics	Key distinction from AN	Histology/diagnostic tests
Acanthosis nigricans	Intertriginous sites with symmetric distribution	Dry, "dirty" appearance in early stages; thickens over time	Skin tags, pruritus, inflammation	Thickened, velvety, corrugated hyperpigmented plaques	N/A	Papillomatosis, hyperkeratosis, minimal hyperpigmentation; dermal papillae have upward projection with thinning of the epidermis
CARP of Gougerot and Carteaud (1,7)	Neck, chest, upper back	Spreads over weeks–months to breasts, abdomen, flanks, groin	Mild pruritus	Hyperpigmented scaly macules, thin papules coalescing into confluent patches or plaques	Peripheral and heterogenous reticular pattern (*vs.* homogenous reticulation of AN)	Hyperkeratosis, papillomatosis, mild acanthosis, basal cell pigmentation, and mild superficial perivascular inflammatory cell infiltrate
Granular parakeratosis (1,4)	Axilla	Lesions heal with desquamation, resembling peeling of pellagra	Pruritus	Hyperkeratotic brown to red papules that coalesce into plaques	May resolve spontaneously	Hyperkeratosis with eosinophilic staining, compact parakeratosis with retention of basophilic keratohyalin granules
Linear epidermal nevi (1,7,8)	Curvilinear lesions distributed along lines of Blaschko, trunks and limbs	Present at birth or within first year of life	May be associated with epidermal nevus syndromes	Curvilinear hyperpigmented well-defined papillomatous plaques	Hyperkeratotic texture *vs.* velvety texture of AN	Variable with prominent corrugated epithelial hyperplasia, hyperkeratosis and papillomatosis
Dowling-Degos disease, "dark dot disease" (1,7,8)	Intertriginous sites, flexural surfaces	Adult onset	Comedones and pitted facial scars; autosomal dominant	Hyperpigmented macules, flat topped papules progress into reticulate configuration	Less confluent pigmentation, lack of velvety textural changes	Hyperkeratosis with small horn cysts and thinning of suprapapillary epidermis—epithelial strands extend into superficial dermis
NAN, RAVEN (1,7,8)	Localized midline, chest, back, rare involvement of periumbilical, inframammary, face and scalp	Present in early childhood, initial period of growth for 4–5 years, followed by stability without resolution		Unilateral or localized hyperpigmented plaques	Lack predilection for intertriginous areas; no association with endocrinopathy or malignancy	Papillomatosis with minimal acanthosis, thickened stratum corneum
Acquired atopic hyperpigmentation, "atopic dirty neck" (1,7,8)	Neck, intertriginous sites	Presents in adolescence	Occurs in 2% of patients with atopic dermatitis	Frictional melanosis and post-inflammatory hyperpigmentation resulting in rippled appearance and accentuation of skin markings	Affects anterior neck *vs.* posterior neck of AN	Eczematous changes and pigmentary incontinence

Table 3 (*continued*)

Table 3 (*continued*)

Condition	Location	Course	Associated symptoms/ syndromes	Clinical characteristics	Key distinction from AN	Histology/diagnostic tests
Terra firma-forme dermatosis, retention hyperkeratosis (1,7-9)	Neck, posterior malleolus	Children and adolescents	Reported association with atopic dermatitis and xeroderma	Hyperpigmented/ brown to black patches resembling dirt	Lesions can be removed with 70% isopropyl alcohol	Dermoscopy: polygonal brown scales in mosaic pattern; histology: nonspecific; papillomatosis, acanthosis, ortho-hyperkeratosis, keratin whorls
Erythrasma (1,7-9)	Intertriginous sites	Slowly enlarging lesions		Well-defined pink to brown patches with fine scale and superficial fissures	Bacterial infection caused by Corynebacterium minutissimum, will respond to antibiotics; No velvety thickening or accentuation of skin markings	Wood's lamp evaluation: coral red color fluorescence due to porphyrins released by bacteria
Superficial fungal infections/Candidal intertrigo (1,7-9)	Intertriginous sites, trunk, extremities		Pruritus	Erythematous patches or plaques, satellite pustules, rarely red-brown hyperpigmentation	More erythematous lesions	KOH prep or fungal culture evaluation

AN, acanthosis nigricans; CARP, confluent and reticulated papillomatosis; NAN, nevoid acanthosis nigricans; RAVEN, rounded and velvety epidermal nevus; KOH, potassium hydroxide.

mass index (BMI) and pubertal development (19). The researchers found that the positive predictive value for hyperinsulinemia using AN alone was 39.4%, compared to 34.1% for obesity alone (19). Similarly, in a sample of US children aged 8 to 14 years, those with AN had more severe insulin resistance than age, sex, puberty, and BMI score matched controls without AN (20).

These findings are replicated in multiple studies across the age spectrum, all of which lend support to the theory that AN is an independent variable associated with hyperinsulinemia. In a sample of children 3–19 years of age from the Winnebago/Omaha tribe in Nebraska, subjects who exhibited AN had two-fold higher fasting insulin concentration compared to weight-matched subjects without AN. The authors concluded that AN prevalence among American Indians increases risk of insulin resistance and type 2 diabetes (21). In a comparable study of adolescents of Cherokee Indian background, after adjusting for weight, sex, and pubertal development, the mean insulin level was greater in those with AN than subjects without (22). Similar findings were reported by several other studies (18,23).

Although most studies report that AN is a clinical indicator of underlying insulin resistance, some researchers believe that AN is not an independent marker and as such all children with a BMI standard deviation score above or equal to 3 should be screened for hyperinsulinemia (24,25). Numerous studies have suggested that in children with both AN and obesity, the incidence and positive predictive value of insulin resistance increases compared to either factor alone (19,26,27).

In clinical practice, no single laboratory test is used to diagnose insulin resistance or measure insulin sensitivity. The Endocrine Society appointed Pediatric Task Force

Table 4 Classification of Acanthosis nigricans

Type	Description
Mixed-type AN	Combination of two or more types. Usually paraneoplastic and additional etiology from below types (1,7)
Obesity associated AN	Most frequent type. Severity of AN correlates with degree of weight excess (1,7)
Syndromic AN	Type A: HAIR-AN syndrome, presents with hyperandrogenism, insulin resistance, and acanthosis nigricans (1,7) Type B: uncontrolled diabetes mellitus, ovarian HA, or autoimmune disease
Paraneoplastic AN	Extensive involvement, sudden onset, unexplained weight loss, associated with abdominal adenocarcinomas[†]
Medication associated AN	Systemic steroids, nicotinic acid, estrogen, injected insulin, niacin, OCPs, protease inhibitors, palifermin, testosterone, and aripiprazole (1,3,7)
Genetic disorders related AN	Familial benign AN (FGFR3 mutation); Benign genetic, non-endocrinopathy related (1,3,7)
Autoimmune AN	AN associated with known autoimmune condition[‡] (due to development of insulin receptor antibodies in autoimmune diseases, e.g., systemic lupus erythematosus (1,3,7-9) AN associated with only autoantibodies (ANA, antimicrosomal, increased immunoglobulins without recognizable syndrome)

[†], very rare in children with 10 cases reported, of which gastric carcinoma is the most common association (7,9), screening indicated if warning signs are present (10,11); [‡], screening for autoimmune conditions indicated when autoimmune symptoms are present (12,13). AN, acanthosis nigricans; HAIR-AN, hyperandrogenism, insulin resistance, acanthosis nigricans syndrome; HA, hyperandrogenism; OCP, oral contraceptive pill; ANA, anti-nuclear antibody.

Table 5 Genetic disorders related to acanthosis nigricans

Disorder	Mechanism	Phenotypic features
Crouzon syndrome with AN (14)	Activating mutation of FGFR3	Premature craniosynostosis
	Autosomal dominant	Midface hypoplasia
		Hearing loss
		Acanthosis nigricans
		Choanal stenosis/atresia
		Hydrocephalus
Thanatophoric dysplasia (14)	Activating mutation of FGFR3	Severe skeletal dysplasia
	Autosomal dominant	Redundant skin
		Short limbs
		Platyspondyly
		Acanthosis nigricans
Severe achondroplasia with developmental delay and AN (14)	Activating mutation of FGFR3	Severe skeletal dysplasia
	Autosomal dominant	Dwarfism
		Acanthosis nigricans in infancy
		Apnea
		Redundant skin
		Bowed legs

AN, acanthosis nigricans; FGFR3, fibroblast growth factor receptor-3.

recommends against these routine measurements due to lack of standardized assays and poor reproducibility (28,29). However, in early stages of insulin resistance, the body releases more insulin in a compensatory manner, to maintain glucose homeostasis (8,20). At this stage, diabetes remains undiagnosed due to euglycemia while hyperinsulinemia may predominate. We suggest that testing for both impaired glucose tolerance and abnormal insulin levels together should therefore be included in the recommended screening for individuals at risk so that early diagnoses are not missed. The ADA has organized a task force to standardize assays in order to establish measures of insulin sensitivity and draft guidelines for their use in the clinical setting (30).

Fasting glucose levels, oral glucose tolerance test (OGTT), hemoglobin A1C (HbA1C)

The ADA recommends that a child who is overweight and has any 2 of the following risk factors be screened for diabetes every two years beginning at the age of 10 or at pubertal onset: (I) 1st or 2nd degree relative with type 2 diabetes, (II) belonging to certain race/ethnic group at higher risk (Native American, African-America, Asian/South Pacific, Hispanic) and (III) signs of insulin resistance including AN, hypertension, dyslipidemia, and polycystic ovarian syndrome (2).

AN has been found in 56% to 92% of children and adolescents with type 2 diabetes mellitus. Not all children with AN develop type 2 diabetes, but are likely to have multiple risk factors for the disease (31). It is therefore important to identify these at-risk individuals as a part of healthcare maintenance.

A retrospective comparative study of obese Japanese children found that subjects with AN showed significantly more glucose intolerance, as measured by OGTT, or preexisting diagnosis of type 2 diabetes, compared to children without the dermatosis (23). This finding is supported by several other studies conducted in the United States (19,22,32), India (33) and Australia (34).

In a sample of US eighth grade students with a high proportion of overweight/obese adolescents (BMI >95th percentile), AN was found to double the likelihood of dysglycemia after adjustment for BMI and pubertal development, suggesting AN imposes an additional risk for dysglycemia over that from obesity alone (35). Authors concluded AN is an easily identifiable marker for impaired glucose tolerance and elevations in hemoglobin A1C (35).

In a sample of Italian obese children, researchers found that presence of AN was significantly associated with a higher risk of metabolic syndrome and abnormal glucose control (36). Fasting blood glucose was not different between children with and without metabolic syndrome, however insulin and glucose levels after OGTT were significantly higher (36). The observation seen by several studies (20,36) reflects the increased insulin resistance of these children prior to development of fasting glucose derangements, highlighting the false negatives for type 2 diabetes and insulin sensitivity that can occur when relying on fasting glucose levels alone.

BMI and waist-to-hip ratio (WHR)

As a part of health maintenance, BMI is checked indirectly with weight and height measurements. Increased BMI and in particular increased WHR is correlated with increased likelihood of metabolic alterations in both children and adults (18). The increase in adipose tissue in childhood is the most probable initial event that leads to changes in glucose metabolism and later insulin resistance, contributing to metabolic syndrome and development of AN (37). For example, in a prospective study of kindergarten through 12th grade students, the prevalence of AN in the context of other risk factors for diabetes was evaluated, showing that children with a higher BMI at baseline were at increased risk for having AN in the follow-up year (38). Children with AN were six times more likely to be obese, and four times more likely to be overweight, compared to normal weight children (38).

Several studies suggest that despite normal BMI, increased waist to hip circumference and abnormal distribution of body fat is associated with increased risk of metabolic abnormalities (18,37,39). In a study of US children in the Pacific Islands, the prevalence of AN among all healthy weight children was 2.2%, compared to 7.8% among all obese children (40). Similar data has been reported among adolescents in New Mexico, where the prevalence of AN was 49.2% in obese adolescents compared to 7.7% among normal weight subjects (19), and in regions of the Southwest US, where among 500 children sampled, only 3% of normal weight individuals had AN (32).

The first screenings that can help with initial management and prevention of metabolic abnormalities are the calculation of BMI and WHR. When presenting with AN, calculation of these factors enables the clinician to target at-risk individuals and initiate early interventions.

Total cholesterol panel [high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), triglycerides]

Metabolic syndrome is believed to play a central role in the development of cardiovascular disease and type 2 diabetes. The third National Cholesterol Education Program Adult Treatment Panel defines metabolic syndrome as the presence of three of the following risk factors: central/abdominal obesity, hypertension, high fasting glucose levels, hypertriglyceridemia, and low HDL cholesterol (41). In addition, high triglyceride levels and IR are considered factors for vasculature thickness, providing a noninvasive measurement of subclinical atherosclerosis in children (2). The presence of dyslipidemia in children and adolescents tends to track into adult life, thus identifying the at-risk individuals at an early age may help prevent potential cardiometabolic complications.

AN has been identified as a marker for increased risk of hypertriglyceridemia and decreased HDL cholesterol (2). When AN and high WHR are seen simultaneously, the odds of dyslipidemia are raised further (41). In a sample of 543 overweight/obese children, significantly higher mean values for fasting triglycerides and lower HDL levels were found in children with AN than in those without (42). Authors concluded that the presence of AN, high triglycerides, and low HDL levels were independent variables that predicted the presence of IR and metabolic syndrome in children and adolescents (42). This finding is supported by several other studies conducted in the US (20), India (33), and Iran (43) where subjects with AN had higher levels of triglycerides and decreased HDL cholesterol, known factors for metabolic syndrome (20).

These findings delineate the importance of early metabolic screenings to evaluate triglycerides (both fasting and non-fasting) and HDL levels in particular in the initial workup of a patient with AN. Early identification of abnormal cholesterol levels may then allow for interventions to protect future cardiovascular health.

Blood pressure (BP)

Elevated BP is a criterion included in the definition of metabolic syndrome in both adults and children. Although the BP cut-off for diagnosis of hypertension in adults (130/85 mmHg) is high for the pediatric population, several studies have reported increased systolic BP (SBP) and diastolic BP (DBP) readings in individuals with AN compared to the general population (37). BP levels greater than or equal to 95th percentile for age, gender, and height were considered high. These findings are supported by several studies in Japan (23) and the US (20,22,39). Furthermore, it was demonstrated that for each 14 mmHg increase in SBP, the likelihood of having hyperinsulinemia increased approximately 1.3 times (22).

After controlling for obesity, a significant positive association was found between presence of AN and elevated SBP in young male subjects from India (33). In addition, increased severity of AN, as measured by thickness and distribution, were associated with higher SBP levels (44).

In a longitudinal study of kindergarten through 12th grade students who were part of the Northern Plains American Indian population, students with AN were more than two times as likely to have elevated BP (39). The study team followed subjects for 1 year and showed a 2.34 relative risk of incident AN for children who had abnormal BP measures at baseline compared to those with normal BP (39).

Liver function tests (LFT)

Although thought of as predominately a disease in adulthood, with the increased prevalence of obesity and insulin resistance in children, non-alcoholic fatty liver disease (NAFLD) may arise in childhood and adolescence (42).

In a retrospective study of 543 overweight/obese children and adolescents, researchers evaluated the degree of liver dysfunction, finding significantly higher levels of alanine aminotransferase (ALT) among subjects with AN (42). Of those subjects, ultrasound scans revealed a high proportion of fatty liver (42). These findings are supported by several other studies (43,45,46), where higher ALT levels were found among patients with AN. Sayarifard *et al.* found elevations in both aspartate aminotransferase (AST) and ALT in subjects with AN (43).

In a similar sample of obese adolescents, approximately 30% diagnosed with NAFLD had AN (47). Authors determined that AN was an independent risk factor for NAFLD in children with obesity (47).

Recent studies suggest fatty liver is likely present in most pediatric obesity regardless of LFT elevation, and high ALT levels suggest a more advanced stage of NAFLD, hepatitis, or fibrotic changes (28,48,49). Sonography has been found to be an adequate screening method in fatty liver evaluation (28,49). In patients with AN, prevalence of ALT elevation and fatty liver is increased. With increase in adiposity, the level of liver function disturbance and severity of AN is

Table 6 Adapted from Burke's quantitative scale for acanthosis nigricans (50)

Location	Score description
Neck severity	
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 margin of the neck (usually <3 inches in breadth)
3	Moderate: extending to the lateral margins of the neck (posterior border of the sternocleidomastoid) (usually 3–6 inches), should not be visible when the participant is viewed from the front
4	Severe: extending anteriorly (>6 inches), visible when the participant is viewed from the front
Axilla	
0	Absent: not detectable on close inspection
1	Present: clearly present on close visual inspection, not visible to the casual observer, extent not measurable
2	Mild: localized to the central portion of the axilla, may have gone unnoticed by the participant
3	Moderate: involving entire axillary fossa, but not visible when the arm is against the participant's side
4	Severe: visible from front or back in the unclothed participant when the arm is against the participant's side
Neck texture	
0	Smooth to touch: no differentiation from normal skin to palpation
1	Rough to touch: clearly differentiated from normal skin
2	Coarseness can be observed visually, portions of the skin clearly raised above other areas
3	Extremely coarse: "hills and valleys" observable on visual examination

increased further (47,49). The Endocrine Society Pediatric Task Force recommends obtaining screening ALT levels when assessing patients with AN or overweight children. A subsequent liver scan or ultrasound may be performed as a reflex test after abnormal laboratory results (28).

High risk acanthosis nigricans (AN)

AN can be graded on a standardized scale of 0–4, from not visible to severe, including grading of texture, and extending beyond the neck or beyond the axilla, originally classified by Burke *et al.* (*Table 6*) (50). A higher score may predict higher likelihood of insulin resistance (sensitivity 56.8%, specificity 83.9%) (51,52). Although the neck is the most common area affected by AN, appearance on the knuckles, dorsal hands, and dorsal feet, is commonly found in patients of normal or slightly overweight BMI (51). The presence in these non-classical and often ignored locations may occur earlier in the clinical course, with AN progressing to the neck in parallel with the rise in both BMI and insulin resistance (8,51). Therefore, AN on these areas in a patient, regardless of BMI, may indicate early clinical manifestations of insulin resistance (51,53), a finding that further establishes the import of a thorough dermatologic assessment in the primary care setting.

The dermatosis is more common and clinically more severe in adolescents as compared to younger children, correlating with increased IR in older children (7). While examining various characteristics of AN in adolescents, rougher texture, higher degree of pigmentation, and increased width of pigmented area were shown to be significantly correlated with hyperinsulinemia, paralleling serum insulin levels (19). In African-American subjects with AN, a significant positive correlation was seen between epidermal thickness, fasting plasma insulin levels, and increasing WHR (54). High severity of AN, according to the degree of skin affected and epidermal thickness, correlates with higher triglyceride, VLDL, fasting glucose levels, and lower HDL levels (20,44).

As reported by various studies, not only does the presence or absence of AN correlate with metabolic changes, but the degree of AN may predict more severe laboratory

abnormalities. Therefore, primary care physicians should be trained in identification of AN to be able to implement interventions at an early stage.

Dermatologic management for AN

Therapy for AN involves a multidisciplinary approach, targeting the underlying associated conditions, as well as topical/oral agents and cosmetic surgery (*Table* 7). Diminishing hyperkeratosis has been described in some patients following insulin, glucose, and obesity control, however, hyperpigmentation and thickness may remain (7,9,58). Improvement of the lesions is often the patient's primary concern, and consulting with a dermatologist may be beneficial. While the goal of therapy may be to treat the underlying cause, cosmetic resolution of AN lesions is often important for patients' quality of life.

Topical treatments

Topical treatments with keratolytics are considered first-line options and are generally well tolerated by children and adolescents (7,55). Topical tretinoin 0.25–0.1% is effective in reducing hyperkeratosis after consistent application, with mild improvement in skin pigmentation (10). However, maintenance with intermittent application may be necessary as relapse has been noted after discontinuation (58). Topical adapalene gel is found to be effective in reducing skin pigmentation in children with AN (56). It is available over-the-counter and causes less irritation than other retinoid derivatives (56). In a randomized comparative study between topical 0.01% adapalene gel and 0.025% tretinoin cream for childhood AN, no significant difference was seen between the two groups, and both achieved improvement in hyperpigmentation (55). Over-the-counter ammonium lactate cream with lactic acid can be applied to affected areas of the body. Combination therapy with topical tretinoin and 12% ammonium lactate has shown efficacy in treating AN (57). Further combinations, including triple therapy with tretinoin, depigmenting agent 4% hydroquinone, and 0.01% fluocinolone acetonide, may reduce the appearance of AN (62).

Vitamin D analogs are another option for the topical treatment of AN. Calcipotriol cream has been reported as safe, effective, and well-tolerated for AN, and hyperkeratosis of the nipple has shown good response to this agent (59).

Oral treatments

For treatment of more extensive AN, comorbid conditions, or in areas less conducive to topical application, oral therapy with various medications may be an option.

Extensive AN associated with obesity has been successfully treated with the oral retinoid isotretinoin, however may relapse upon cessation of treatment, requiring maintenance treatment with either topicals or alternative oral agents including metformin (58). The oral retinoid acitretin has been reported to induce successful clearance in several patients with AN (58). However, acitretin is not an option for adolescent females given the potential for long term teratogenicity up to 3 years after discontinuation of the medicine. Additionally, hypertriglyceridemia can be a side effect of retinoid therapy and thus should be monitored carefully.

Metformin, an antihyperglycemic agent used for the management of type II diabetes, is shown to improve both AN and insulin resistance (7). Metformin reduces glucose production by increasing insulin sensitivity, thereby reducing hyperinsulinemia, body weight, and fat mass (7,63). In a recent clinical trial, patients treated with metformin demonstrated significant improvement in AN of the neck and axilla, but not of the knuckles, fingers, or elbows (58). A case study of a patient with initial improvement of axillary AN on isotretinoin, recurred after tapering the dose; however, the lesions improved upon taking 1,000 mg of metformin twice daily (64). Combination treatment with metformin and thiazolidinediones have reported benefit in patients with AN, as thiazolidinediones work to further increase insulin sensitivity (7,12). Women with hyperandrogenemia, insulin resistance, and AN may also be treated with metformin and oral contraceptive pills (12,58).

Surgical or procedural treatments

Newer treatment modalities for AN recalcitrant to first line treatments have shown promising results (61). These procedural and surgical treatments include chemical peels with alpha-hydroxy acids, microdermabrasion, cryotherapy, laser therapy, curettage, electrodessication, and simple surgical excision (61). Procedures are recommended primarily for older adolescents due to possible pain with treatment (7,65).

Superficial chemical peels with exfoliating agents such as trichloroacetic acid (TCA) are relatively safe and effective options. Zayed *et al.* reported improvement in hyperpigmentation, thickening, and overall appearance in female patients with TCA peels (60). In a comparative study between TCA and topical tretinoin, researchers concluded

Table 7 Treatments for acanthosis nigricans

Treatments	Method of use	Mechanism of action	Appropriate ages	Side effect profile
Topical treatments				
Tretinoin 0.025–0.1% cream (7,55)	Once nightly, or BID	Corrects hyperkeratosis, normalization of epithelial growth and differentiation	Age 10	Stinging with application, erythema, scaling, dermatitis (likelihood increases with higher concentrations)
Adapalene 0.1% gel (10,56)	Once nightly, or BID	Alteration in epidermal keratinization	Age 1	Dryness, scaling, mild irritation
Ammonium lactate cream (55,57)	Once daily or BID	Reduces keratinization, decrease corneocyte cohesion	Age 2	Stinging or burning, erythema, peeling
Urea cream (7)	Once daily, BID, or TID as needed	Promote desquamation of hyperkeratosis, reduces keratinization	Age 1	Mild stinging, pruritis, rash
Salicylic acid (7,58)	Once daily or BID	Exfoliation of stratum corneum, disrupt cellular cohesion, reduces keratinization	Age 2	Dryness, peeling, erythema, dermatitis
Podophyllin (7,59)	Once daily	Reduction of keratinization, cytotoxic agent	Age 1	Swelling, burning, erythema
Calcipotriene cream (59)	BID	Inhibit keratinocyte proliferation	Age 4	Mild skin irritation, dermatitis, itching
Oral treatments				
Isotretinoin (58)	Once daily (doses vary by weight) for months	Normalization of epithelial growth and differentiation	Age 12 or after puberty	Cheilitis, epistaxis, pruritus, xerosis, dry eyes, bone or joint pain, hepatotoxicity, hypertriglyceridemia, teratogenicity (up to 1 month after discontinuation)
Acitretin (58)	Once daily (doses vary by weight) for months	Normalization of epithelial growth and differentiation	Age 12 or after puberty	Cheilitis, epistaxis, pruritus, xerosis, dry eyes, bone or joint pain, hepatotoxicity, hypertriglyceridemia, teratogenicity (up to 3 years after discontinuation)
Metformin (58)	BID to TID for several months (dose will vary)	Increases peripheral insulin responsiveness, sensitivity, reduces glucose production, body weight, fat mass	Age 8	Weakness, diarrhea, myalgias, hypoglycemia, lactic acidosis (rare)
Procedural treatments				
Trichloroacetic acid chemical peel (60)	2–3 sessions	Chemical exfoliating agent, destruction of epidermis, wound repair and re-epithelialization	Age 12 (ability to tolerate)	Burning, discomfort, skin sensitivity
Microdermabrasion (7)	Range from weekly to 8-week intervals	Exfoliating (crystal) material leads to repetitive intraepidermal injury and remodeling the dermis	Age 12 (ability to tolerate)	Swelling, erythema, bruising, photosensitivity
Alexandrite laser (755 nm wavelength) (7,61)	7–10 sessions at 4- to 8-week intervals	Targeted destruction of melanin in keratinocytes	Age 1	Pain during treatment, erythema, swelling, pruritus following procedure (lasting a few days)

BID, twice daily; TID, three times daily.

that TCA was less effective but better tolerated and should be considered an effective second line therapy in the management of AN (65).

The alexandrite laser with 755 mm wavelength can target melanin pigment in keratinocytes and lead to their destruction without damaging surrounding tissues. Its efficacy has been demonstrated for the treatment of axillary AN, resulting in greater than 95% clearance after 7 treatments at 4–8-week intervals (66). When compared to combination topical tretinoin and ammonium lactate, higher reduction in pigmentation was seen in the alexandrite laser treatment group (61).

Microdermabrasion is a minimally invasive procedure that is used to renew skin tone and texture, and may help reduce hyperkeratosis of AN in affected patients (7,58,67). Dermabrasion is used for smaller lesions and is limited by the cost and potential for post-inflammatory hyperpigmentation (58).

Cryotherapy is an alternative method for treatment of AN however the efficacy depends on various factors including the severity and depth of AN, the number of freezing cycles, and the vascularity of the lesions (61). In darker skin, cryotherapy may result in worsened hyperpigmentation and local recurrence is more common than other treatment modalities (61).

Multidisciplinary approach

While primary care physicians may be the first to diagnose and treat AN and associated conditions, a multidisciplinary approach is recommended. Patients may benefit from care from dieticians/nutritionists, endocrinologists, dermatologists, and behavioral health specialists. Furthermore, an important aspect of pediatric care is the involvement of the entire family, as interventions and subsequent improvement often start at home. Parents are encouraged to serve as role models, offering a healthy home environment and providing a strong support system. In a recent multicomponent randomized clinical trial, children and adolescents were included in the Children's Healthy Living Program to study the effect of early intervention on obesity and AN (40). The authors concluded that comprehensive and sustainable methods including behaviors such as sleep, physical activity, and nutrient intake are needed to improve health, and interventions at an early age may reduce the prevalence of obesity as well as AN (40).

With the aid of health care professionals, school administration, and families, strategies such as setting small achievable goals, providing education about nutrition, and incorporating physical activity both after and during school hours can be employed to educate, treat, and prevent AN, insulin resistance, and its associated comorbidities.

Conclusions

The presence and severity of AN can be used as a clinical predictor of metabolic disorders and underlying nutritional status in normal, overweight, and obese children and adolescents. The rates of obesity and AN have been shown to increase with age, with a high prevalence of AN among adolescents that suggests impending high rates of diabetes, metabolic dysfunction, and cardiovascular disease that parallel the adult population (8).

The most effective first line treatment for AN is weight loss, through both dietary modification and physical activity, to improve underlying hyperinsulinemia and dyslipidemia, and in addition to weight and metabolic control, dermatologic treatment may be implemented. Health professionals should be trained to identify AN, whether on classical areas such as the posterior neck, or atypical areas such as the hands and feet. Appropriate screening, and identifying AN among children who are at risk for developing metabolic syndrome, will allow for earlier implementation of preventive measures to better control metabolic risk factors, decreasing the risk of cardiovascular complications. If diagnosed, further testing of insulin, glucose, lipids, and transaminases is recommended. As treatment of obesity, insulin resistance, and its associated comorbidities is often complex, early identification of individuals who would benefit from such treatment is a valuable part of clinical practice.

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Footnote

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