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The Interplay of Acanthosis Nigricans, Obesity, and Cardiovascular Health in Pediatric Patients

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Abstract

Background: One skin condition that often goes hand in hand with obesity and insulin resistance is acanthosis nigricans (AN), which manifests as velvety, darker skin in intertriginous regions. This study delves into the correlation between anorexia nervosa (AN), obesity, and cardiovascular health, specifically looking at NT-proBNP levels in children.**Aim:** With a focus on NT-proBNP as a possible biomarker for heart health in juvenile patients, this study seeks to investigate the relationship between acanthosis nigricans, obesity, and cardiovascular function.

Pathophysiology, categorization, diagnostic methods, and the relationship between AN, obesity, and insulin resistance are all included in this review. It delves further into the intricate web of connections between AN, obesity, and CVD, drawing attention to the part played by adipokines and metabolic syndrome. Additionally, the study explores the use of NT-proBNP in evaluating heart function, with a focus on metabolic diseases and obesity.

Conclusion: One of the risk factors for cardiovascular disease, acanthosis nigricans is a visual indicator of metabolic abnormalities, especially obesity and insulin resistance. Obesity may affect the levels of NT-proBNP, yet this biomarker shows promise as a tool for evaluating heart function in children with AN. We still don't know enough about the complex interplay between AN, obesity, and children's cardiovascular health for NT-proBNP to have any practical use in clinical practice with this group of patients.

Keywords: N-Terminal Pro-B-Type Natriuretic Peptide, cardiac functions, pediatric acanthosis nigricans, insulin resistance, cardiovascular health.

1. Introduction:

An inflammatory skin condition with numerous causes, acanthosis nigricans is defined by a velvety darkening of the skin often seen in intertrigonous regions. A thickening of the skin may accompany this hyperpigmentation, which often manifests in places with folds of skin like the groin, axilla, and back of the neck and has ill-defined boundaries. Although internal cancer is an extremely uncommon symptom of acanthosis nigricans, it is most often linked to diabetes and insulin resistance. In addition to hormonal imbalances, it is a side effect of several drugs, such as oral contraceptives and systemic glucocorticoids (1).

Activation of insulin-like growth factor (IGF) on keratinocytes and elevated levels of growth factors are likely involved in the pathophysiology of acanthosis nigricans. The pathophysiology of acanthosis nigricans seems to be associated with increased stimulation of epidermal keratinocytes and fibroblast proliferation (2).

Acanthosis nigricans develops due to a combination of circumstances. One of the most prevalent disorders linked to Acanthosis nigricans is obesity. Although lesions are more frequent in adults, they may happen to anybody at any time. Insulin resistance might be a symptom. Acanthosis nigricans may recur if obesity is treated with diet, weight loss, or medicine (3).

When cardiomyocytes enlarge owing to pressure or volume overload, they secrete the 32-residue peptide known as B-type natriuretic peptide (BNP). Vasodilation, natriuresis and diuresis that are independent of blood pressure, reduced preload, and sympathetic tone are all promoted by BNP, which is a clinical indicator of ventricular dysfunction in heart failure. Therefore, BNP promotes a drop in blood pressure in response to myocardial strain, which is a protective mechanism against volume overload (4).

The 108-amino acid pro-BNP is proteolytically hydrolyzed to provide the N-terminal BNP fragment. Its potential function in tracking heart failure and differentiating acute coronary syndromes has lately piqued a lot of interest in this 76-amino acid protein. Its influence on natriuresis and diuresis in CHF patients is a defense mechanism against myocyte stress, which causes ventricular dysfunction. Not only are natriuretic peptide levels in the blood a sign of several cardiovascular problems, but they also indicate the severity of these problems (5).

The link between obesity and heart failure was established with great clarity. An intriguing phenomenon known as "the obesity paradox" (6)

occurs when obese patients with heart failure have a better prognosis than normal weight patients, despite the fact that obesity increases the risk of cardiovascular disease and heart failure. The reasons for this seem to remain a mystery.

Suspicion that these proteins may be implicated in pathophysiological pathways linked with obesity was bolstered by the finding that brain natriuretic peptides (BNPs), notably amino terminal proBNP, were considerably lower in obese individuals compared to lean ones (7).

The importance of the relationship between the neurohormonal systems—including gonadal function—and cardiac endocrine function in explaining the increased risk of cardiovascular disease in disorders like metabolic syndrome and obesity has only just been highlighted (8).

With a focus on NT-proBNP as a possible biomarker for heart health in juvenile patients, this study seeks to investigate the relationship between acanthosis nigricans, obesity, and cardiovascular function.

- **Prevalence**

Obesity and diabetes are on the rise, which is leading to an increase in the prevalence of AN. Depending on factors such as age, race, type of AN, degree of obesity, and concomitant endocrine disorders, the prevalence of the disease may range from 7% to 74% in the general population. Among Native Americans, Black Americans, Hispanics, and Caucasians, AN is most often found (9)**.**

Pathophysiology

Multiple factors contribute to the pathogenesis of AN, which is characterized by the activation of dermal fibroblast and epidermal keratinocyte growth. Some have hypothesized that insulin and insulin-like growth factor (IGF) enable this proliferation to occur. Tyrosine kinase receptors, such as epidermal growth factor receptor (EGFR), and fibroblast growth factor receptor (FGFR) are among the other potential mediators. Keratinocytes and fibroblasts both have growth-inducing receptors (10). By lowering circulating levels of IGF binding proteins 1 and 2, free IGF-1 levels in tissues may be increased, and IGF-1 receptors on skin cells can be directly activated, as is seen in obesity and type 2 diabetes, leading to hyperinsulinemia (11). Genetic disorders linked to anaphylaxis include Crouzon syndrome, hypochondroplasia, and severe achondroplasia with developmental delay and anaphylaxis (SADDAN) (10). In paraneoplastic AN, transforming growth factor-a (TGF-a) and other cytokines secreted by tumor and metastatic cancer cells bind to epidermal growth factor receptors (EGFR) in skin cells, resulting in hyperkeratosis and papillomatosis (12). The transcription factors FGFR, HRAS, and PTEN control cell growth and death.

Classification

AN was categorized by Curth as either syndromic, pseudo-associated with obesity, benign hereditary, or malignant (13). Hernandez-Perez defined AN as either paraneoplastic or simple, with the former category containing nevoid, obesity-related, drug-related, and syndromic cases (14). The eight varieties of AN outlined by Schwartz are: (8) mixed type, where two types are present; (1) benign; (2) obesity-associated; (3) syndromic; (4) malignant; (5) acral; (6) unilateral; (7) medication-induced; and (8) monomorphic.

Diagnosis and diagnostic tools

The traditional look makes clinical diagnosis easy. Confirmation of the diagnosis may sometimes need a biopsy and histological evaluation. Common histopathologic signs include moderate acanthosis and epidermal hyperkeratosis, as well as papillomatosis, which is caused by the protrusion of dermal papillae into a thinned epidermis. Dermis often does not have any inflammatory infiltration. Occasionally, there may be an increase in melanosomes. Misdiagnosis is possible in rare cases of cutaneous illnesses with identical appearances. Psoriasis, atopic dermatitis, atopic papillomatosis, terra firma-forme dermatosis, confluent and reticulated papillomatosis, and epidermal naevi are all examples of such conditions (16).

A correct diagnosis may be made with the use of a thorough physical examination, medical history, and histopathology report. There are few options for treating obesity and insulin resistance:

Homeostasis model assessment-insulin resistance (HOMA-IR)—a

competent method for determining IR using fasting glucose and insulin levels simultaneously.

To diagnose IR, the fasting glucose (mmol) divided by the fasting insulin (μU/mL) multiplied by 22.5 is used.

Quick and easy, but not standardized, fasting insulin level

a sensitivity and specificity of the glucose/insulin ratio

Research has used this ratio as a measure of IR. As a measure of insulin sensitivity, it is both precise and very sensitive. A ratio below 4.5 is considered abnormal in adults, whereas a ratio below 7 is considered pathological in children who are not yet fully grown (17).

Quantitative insulin sensitivity check index (QUICKI) — Consistent, precise, high positive predictive value

When compared to clamp-IR, the quantitative insulin sensitivity check index (QUICKI) is the superior IR index. It offers a more accurate and reliable measure of insulin sensitivity and is more predictive of future outcomes. The formula for QUICKI is half of the logarithm of both insulin μU/mL and glucose mg/dL.

A increased risk of IR or metabolic syndrome symptoms is often seen in patients with a QUICKI score lower than 0.357.

Plasma glucose levels (fasting, random, and oral glucose tolerance tests), glycohemoglobin levels, lipid profiles, urinalysis for microalbuminuria, homocysteine, and Plasminogen activator inhibitor (PAI)-1 levels are routine laboratory investigations in the evaluation of patients with insulin resistance.

A new pro-inflammatory adipokine, serum WISP-1/CCN4 level, has been suggested as an indicator of obesity (18).

Burke et al. ranked AN from 0 to 4 for severity, with 0 being the least afflicted region and 4 being the most severely impacted. An easy-to-use tool with strong correlations to fasting insulin and body mass index (BMI) and great inter-observer reliability (19).

Association between obesity and cardiovascular disease and Acanthosis nigricans

- **Obesity and cardiovascular disease**

High metabolic and cardiovascular risks, as well as an increased likelihood of dying at a young age, make obesity a serious issue in public health. As the prevalence of type 2 diabetes among young people continues to rise at an alarming rate, metabolic comorbidities such as hyperinsulinemia and insulin resistance are receiving more attention (20).

Obesity in children is a chronic condition with complex causes that is on the rise. Between 2009 and 2011, the World Obesity Federation reported that 26.7% of boys and 34.6% of girls were overweight or obese. Metabolic alterations linked to the epidemic of juvenile obesity are major contributors to the development of cardiovascular disease and type 2 diabetes (21).

Obesity is strongly linked to heart failure (HF). "The obesity paradox" refers to the fact that, despite the fact that obesity increases the risk of CVD and HF, people who are obese and diagnosed with HF actually have a better prognosis than those who are normal weight. As a result, the vascular system is complexly affected by obesity (6).

Obesity is only one of the metabolic illnesses that make up metabolic syndrome, which also includes dyslipidemia, arterial hypertension, insulin resistance (which is a key component in its development), and other metabolic disorders linked to cardiovascular disease. Metabolic syndrome is only the accumulation of the cardiovascular hazards posed by its individual components. Although there is still debate about how metabolic syndrome should be defined, the presence of cardiometabolic risk factors has been recognized from childhood (22).

Due to the absence of a standardized way to estimate insulin sensitivity, the frequency of insulin resistance in children is unknown, and diagnosing the condition is challenging (23). The hyperinsulinemic-euglycemic clamp has been the go-to for measuring insulin resistance, but it's not an easy test to administer, particularly to children. Additional markers have been used, including the oral glucose tolerance test and the HOMA-IR. It is generally agreed upon to evaluate insulin levels in order to identify insulin resistance, as hyperglycemia is uncommon in children. However, recent findings have highlighted the need to build reference curves in order to make an accurate assessment (23) about this matter.

Acanthosis nigricans (AN), a prevalent feature typically linked with hyperinsulinemia and juvenile obesity, and an enlarged waist circumference are further clinical symptoms of insulin resistance that individuals may exhibit. Obesity is another possible symptom. It would seem that neither age nor pubertal stage are predictive indicators, but rather hyperinsulinism and extreme obesity. Among children, AN most often affects the neck (93–99%), with the axilla following at 73% (24).

Acanthosis nigricans and obesity

Being a reliable indicator of insulin resistance, AN puts patients at risk for obesity, hypertension, hyperinsulinemia, type 2 diabetes, and hypertension, particularly in children with benign AN. However, AN should not be relied upon as the only indicator for determining whether overweight children have elevated insulin levels (25), as obesity is a more significant predictor of IR.

Mothers whose children tested positive for AN may have fuel metabolism problems, according to research by Urrutia-Rojas et al. Fathers whose children test positive for AN are at a higher risk of having blood glucose levels of 26 mg/dL or higher. They concluded that AN screening in children is a useful tool for finding individuals who are at risk for developing prediabetes (26). Fasting lipoprotein profile, glucose, hemoglobin, insulin, and alanine aminotransferase should be investigated in all children and adults who are overweight.

Acanthosis nigricans and adipokines

Hyperinsulinemia and an increased risk of atherosclerotic cardiovascular disease are symptoms experienced by people with acanthosis nigricans. Instability in insulin signaling, decreased glucose uptake in muscle, increased triglyceride synthesis, and gluconeogenesis in the liver are all caused by an overabundance of abdominal adipose tissue, the most prevalent underlying cause of insulin resistance. Tumor necrosis factor α, adiponectin, leptin, interlukin-6, and other adipokines are additional factors that are believed to be involved in insulin resistance. As a result of insulin resistance (IR), complications such as type 2 diabetes mellitus and coronary heart disease may arise when β-cells do not release enough insulin.

Metabolic syndrome, Insulin resistance and adipokines

The metabolic syndrome is characterized by the presence of obesity in addition to type 2 diabetes, hypertension, and coronary artery disease. Intermittent fasting is crucial to metabolic syndrome. Insulin resistance is a useful clinical indicator of metabolic syndrome because it is related with elevated blood triglycerides (28).

Acanthosis nigricans and cardiovascular disease

The development of cardiac dysfunction is believed to be primarily caused by insulin resistance, which is more common in the population of people who have nonischemic heart failure. It determines a poorer prognosis on its own and occurs before cardiovascular disease develops. One possible connection between IR and a decrease in cardiovascular performance is a decrease in endothelial function. Endothelial dysfunction may be associated with IR via many pathways, including disruptions in subcellular signaling (29).

N-Terminal Pro-B-Type Natriuretic Peptide

Evidence suggests that certain proteins may play a role in the pathophysiological processes linked to obesity, as evidenced by the significantly lower levels of brain natriuretic peptides (BNPs) in obese patients compared to lean ones. These proteins include amino-terminal proBNP (NT-proBNP), the amino-terminal cleavage fragment of BNP (6).

The importance of the relationship between the neurohormonal systems—including gonadal function—and cardiac endocrine function in explaining the increased risk of cardiovascular disease in disorders like metabolic syndrome and obesity has only just been highlighted (8).

The precursor of brain natriuretic peptides (proBNP) is a prohormone. Furin and corin are proteolytic enzymes that, upon secretion, separate this propeptide into BNP and NT-proBNP, the two physiologically active components (30).

The natriuretic peptide clearance receptor (NPR-C) is responsible for the absorption and clearance of brain natriuretic peptides, while renal excretion is responsible for the clearance of NT-proBNP (31). The active peptide is BNP, although the preferred diagnostic marker for HF is NT-proBNP because to its longer half-life (31).

A major trigger for the production of NT-proBNP by cardiomyocytes, resulting to higher circulating levels, is believed to be cardiac strain produced by HF and cardiac remodelling owing to atrial and left ventricular hypertrophy. The production of BNPs is further stimulated by hormones such as catecholamines, angiotensin II, endothelin, and hypoxia (32).

So far, age, gender, body composition, and renal function have been identified as the most significant non-cardiac variables that impact circulating levels of NT-proBNP. Nevertheless, when different cut-off values are taken into account, NT-proBNP may still be a sign of left ventricular remodeling in individuals with chronic renal failure (33). It is unclear how fibroblasts contribute to circulating amounts of BNPs, but they may possibly manufacture them (34).

5. Conclusion

One of the risk factors for cardiovascular disease, acanthosis nigricans is a visual indicator of metabolic abnormalities, especially obesity and insulin resistance. Though its levels may be affected by obesity, NT-proBNP arises as a possible biomarker for evaluating heart function in children with AN. We still don't know enough about the complex interplay between AN, obesity, and children's cardiovascular health for NT-proBNP to have any practical use in clinical practice with this group of patients.

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