The prevalence and clinical significance of acanthosis nigricans in diabetic and non-diabetic women of mixed ancestry

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Objectives: The purpose of this study was to improve our understanding of the prevalence of acanthosis nigricans (AN) and its clinical relevance in our mixed-ancestry population and to investigate its association with abnormal glucose metabolism, obesity and hypertension.
Design: This was a cross-sectional study.
Settings and subjects: A total of 390 healthy mixed-ancestry females were recruited from the dermatology outpatient clinic at Tygerberg Hospital.
Outcomes measured: A short questionnaire was administered, whereafter participants were inspected for the presence and degree of AN. Height, weight, blood pressure and random fingerpick blood glucose were measured.
Results: AN was observed in 30% ($n = 116$) of participants, and most commonly found in the nape of the neck (94%, $n = 109$). Participants with AN were younger ($p = 0.005$), and of higher body mass ($p < 0.001$) with a higher random blood glucose ($p = 0.04$). AN was more commonly seen in diabetics ($p = 0.004$). The presence and severity of AN in the neck correlated far better with BMI and blood glucose than other sites, including the axilla.
Conclusion: AN was found to be extremely common, with a prevalence of 30% in this group. An association with blood glucose levels, diabetes and obesity was demonstrated, proving that it is not just a normal ethnic phenomenon. No association with blood pressure or hypertension was found.

Keywords: Acanthosis Nigricans, diabetes, insulin resistance, mixed ancestry, obesity

Introduction

Acanthosis nigricans (AN) is characterised by a symmetrical, hyper-pigmented velvety thickening of the skin that is usually confined to the flexural areas of the body, particularly the nape of the neck (> 90%) and the axillae.[1,2]

A number of studies have associated AN with malignancy,[3] but mostly with insulin resistance, obesity, hyperinsulinaemia and an increased risk of developing type 2 diabetes mellitus (T2DM) in both paediatric and adult populations.[4,5] Insulin signalling affects both metabolic as well as mitogenic pathways. Numerous defects in insulin signalling have been described, which may result in insulin resistance.[6] It is conceptually attractive to propose that defects in the 'metabolic' limb of the signalling pathway, which lead to hyperglycaemia, hyperinsulinaemia and increased circulating IGF-1, result in activation of the intact 'mitogenic' pathway, with consequent overstimulation of mitogenesis in various organs including the ovaries (polycystic ovary syndrome, PCOS), endothelial and vascular smooth muscle cells (atherosclerosis), as well as the skin (acanthosis nigricans).[7] If this is the case, the presence of AN can potentially be put to clinical use as an easily identifiable marker of underlying insulin resistance and mitogenesis.

AN has been described as rare, but in selected patient groups the prevalence of this skin condition has reportedly ranged from 5% to 50%.[4,5] This may be due to an increased prevalence of obesity and T2DM in these populations, but may also simply represent a normal phenotype. It is well established that AN has a significant ethnic predisposition, being rare among whites, but more common among Blacks and especially prevalent among Asians and individuals of mixed ancestry.[2,4,5,8,9]

Our clinical impression at the Tygerberg Academic Hospital is that AN is relatively common, especially in our patients of mixed ancestry, and that both diabetic and non-diabetic populations appear to be affected. We are not aware of any previous studies in South Africa looking at the prevalence and clinical significance of AN in diabetic and non-diabetic populations. If a clear association between T2DM and AN exists, the latter could be used as a marker of diabetes. However, if AN merely represents an ethnic phenomenon, over- investigation of patients with AN may lead to wasted resources and should be discouraged.

The proposed study was therefore undertaken to improve our understanding of the prevalence of AN and its clinical relevance in our mixed ancestry population and to investigate the extent to which the prevalence and severity of AN is related to abnormal glucose metabolism, obesity and hypertension.

Methods

This was a cross-sectional study of 390 healthy female patients of mixed ancestry attending the Dermatology Outpatient Clinic at Tygerberg Academic Hospital, Western Cape, South Africa, to determine the prevalence of AN. Sample size was calculated based on an estimated AN prevalence of up to 50%. The study was approved by the Health Research Ethics committee of Stellenbosch University, Cape Town, South Africa.

Table 1: Grading of severity of acanthosis nigricans in the neck and axillae

Grade	AN in the neck	AN in the axillae
0	Absent	Absent
1	Clearly present on close visual inspection but extent not measurable	Clearly present on close inspection, extent not measurable
2	Limited to the base of the skull and not extending to the lateral margins of the neck	Mild, located to central portion of the axilla
3	Extending to the lateral margins of the neck, but not visible from the front	Moderate, involving entire axillary fossa, but not visible when the arm is against the participant's side
4	Extending anteriorly and visible from the front	Severe; visible from the front or the back in the unclothed participant when the arm is against the participant's side

The inclusion criteria included all females of mixed ancestry, aged 30–70 years, seen consecutively at the clinic between 2012 and 2013, by a single observer (MH). Patients known to have malignancies, heavy alcohol use, known secondary diabetes or current systemic corticosteroid use were excluded. The single investigator (MH) was responsible for participant recruitment, obtaining informed consent, administration of a standardised questionnaire and clinical examination.

Mixed ancestry/Coloured describes a heterogeneous South African population group, with diverse ancestral links, which is the largest population group in the Western Cape. In this study, individuals were identified as being of mixed ancestry based on clinical perception, data capturing from identity documents, as well as self-classification by female patients attending the dermatology clinic.

Anthropometric measurements included weight, height and the calculation of body mass index (BMI). Weight was determined with a digital scale (Healthometer®, Sunbeam/Pelsar LLC, USA) and reported to the nearest 200 g. Height was recorded with a stadiometer and reported to the nearest centimetre, BMI was calculated as weight/ (height in metres)^2 and expressed in kg/m^2. An individual was categorised as either underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25–29.9 kg/m^2) or obese (class I BMI 30–34.9 kg/m^2, class II 35–39.9 kg/m^2 and class III 40 kg/m^2 and above). A resting blood pressure was recorded in the sitting position with the Boso-medicus Uno automated blood pressure apparatus (Bosch and Sohn, Jungingen, Germany) and reported in mmHg. An obese cuff was used where indicated. An individual was classified as hypertensive if previously diagnosed, or with a systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg on the day of participation.

The presence and degree of AN was assessed using the Burke scale for AN.[2] Five locations were examined (neck, axilla, elbows, knuckles and knees), with the severity in the neck and axilla graded on a scale of 0 to 4 (Table 1). This AN scale enables the reliable identification of AN with little inter-observer variability, with AN in the neck showing the least variability. In cases where the classification was difficult, a single specialist dermatologist (WIF) was consulted.

A random finger-prick blood glucose was performed with the Accu-Check® Active (Roche, Mannheim, Germany) point of care testing device and reported in mmol/l. Glucose measurements were done on all participants after the skin inspection to prevent observer bias. In subjects without known diabetes, for the purposes of this particular study, a random blood glucose > 11.1 mmol/l was regarded as being compatible with diabetes and the participant was referred for appropriate further management. Those with a random glucose < 7.8 mmol/l were regarded as having normoglycaemia. A venous blood sample for haemoglobin A1C (HbA1C) was collected when the random blood glucose was between 7.8 and 11.1 mmol/l. Those individuals with HbA1C values of ≥ 6.5% were regarded as probably having diabetes.

Statistical analysis
Individuals were identified with a unique study number and only the primary investigator had access to identifying patient information. A single statistician (JH) from the Centre for Statistical Consultation of the University of Stellenbosch, blinded to the study population, analysed the data using STATISTICA® version 10 of 2013 software (StatSoft Inc., Tulsa, OK, USA) and Excel® (Microsoft, Seattle, WA, USA). Descriptive statistics were used to analyse each parameter in terms of distribution, mean, median, quartiles, maximum and minimum values and standard deviation. Parametric tests were applied as data fitted a Gaussian distribution. The Mann–Whitney U test was used to compare mean BMI, blood pressure and glucose between groups with and without AN. Spearman's rank correlations were utilised in order to compare continuous variables. A p-value of $p < 0.05$ was regarded to be statistically significant in hypothesis testing.

Results
Demographics of the total study population
A total of 390 females of mixed ancestry were recruited. They had a mean age of 49.1 years (range 30 years to 70 years) with a mean BMI of 31.7 kg/m^2 (range 16.4–61.1 kg/m^2). The mean systolic and diastolic

Table 2: Clinical characteristics of individuals with and without acanthosis nigricans

	Individuals with AN	Individuals without AN	Significance
Mean age (years)	46.9	50	$p = 0.005$
Mean BMI (kg/m^2)	37.2	29.4	$p < 0.001$
Random blood glucose (mmol/l)	7.4	6.7	$p = 0.04$
Mean systolic BP (mmHg)	142.8	143.0	$p = 0.96$
Mean diastolic BP (mmHg)	94.3	92.9	$p = 0.31$

blood pressure was 143 mmHg (range 71–235 mmHg) and 93 mmHg (range 46–134 mmHg) respectively. The mean random blood glucose for the group was 6.9 mmol/l (3.3–25.6 mmol/l). Of the total study population, 18% (*n* = 70) had diabetes mellitus (55 known and 15 newly diagnosed in the study).

Prevalence and distribution of AN

AN was observed in 30% (*n* = 116) of participants. The most common site for AN was the neck (94%; *n* = 109), followed by the axillae (45%; *n* = 52), with 39% (*n* = 45) of these having AN in both the neck and axillae. AN on the elbows (*n* = 1), knuckles (*n* = 3) and knees (*n* = 0) was rarely seen. These three cases had severe AN (present in the neck and axillae, grade 3 and 4) and were obese (BMI 32, 42 and 44 kg/m^2 respectively), with poorly controlled type 2 diabetics. Two of the three had a strong family history of diabetes with two first-degree relatives affected.

Characteristics of subjects with AN

Significant differences in subjects with and without AN are summarised in Table 2.

Participants with AN were younger and of higher body mass with a higher random blood glucose. Similar blood pressures were observed and AN was not more common in hypertensive compared with normotensive participants (30.58% vs. 27.03%; *p* = 0.49).

AN was associated with a family history of AN (*p* = 0.002), with the mother reported as the most common first-degree relative. AN was not associated with a family history of diabetes (*p* = 0.11) or cancer (*p* = 0.86).

Association of AN with blood glucose and type 2 diabetes mellitus

Individuals with AN had a significantly higher mean random blood glucose (7.4 mmol/l vs. 6.7 mmol/l; *p* = 0.04) and were more commonly known to have a history of diabetes (20% vs. 11%).

AN was also more commonly seen in diabetics (old and newly diagnosed) vs. non-diabetics (47.1% vs. 25.9%; *p* = 0.004). However, neither a history of diabetes, nor treatment with insulin, was associated with more severe AN (p = 0.19 and *p* = 0.26 respectively).

When treated diabetics (*n* = 55) were excluded, HGT corrected for BMI was associated with AN overall (*p* < 0.001), AN in the neck (*p* < 0.001) and AN in the axillae (*p* < 0.001). On dividing HGT into tertiles (Figure 1), an increase in the prevalence of AN was observed with higher glucose values (tertile 1, 20%; tertile 2, 30%; tertile 3, 39%) with individuals with HGT levels in the upper tertile being twice as likely to develop AN overall compared with the lower tertile (OR 2.299).

Association of AN with body mass index

A linear increase in the *prevalence* of AN was seen in increasing weight categories (*p* < 0.001), with 2.44% of underweight/normal weight individuals having AN, compared with 13.98% in the overweight group and 46.98% in the obese group (Figure 2). A similar increase was seen in the obese subcategories (35.11%, 47.62% and 65.52% for obese class I, II and III respectively). This association was observed for AN in both the neck (*p* < 0.001) and axillae (*p* < 0.001).

The *severity* of AN in the neck, as judged by the Burke scale, strongly correlated with BMI (*p* < 0.001), with more severe AN seen in higher weight categories (*p* = 0.010). The grade or severity of AN in the axilla was not associated with BMI (*p* = 0.85) or weight category (*p* = 0.61).
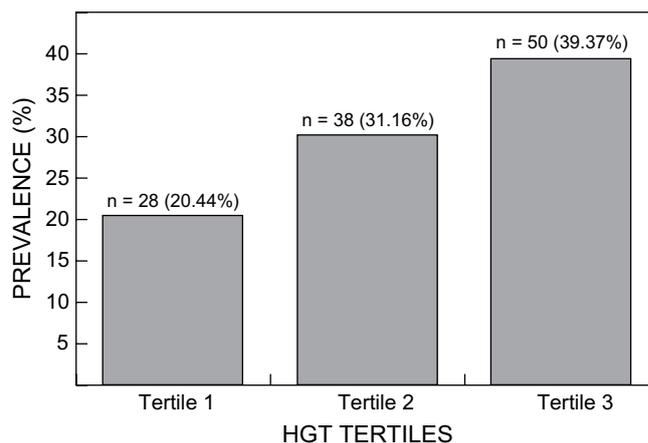

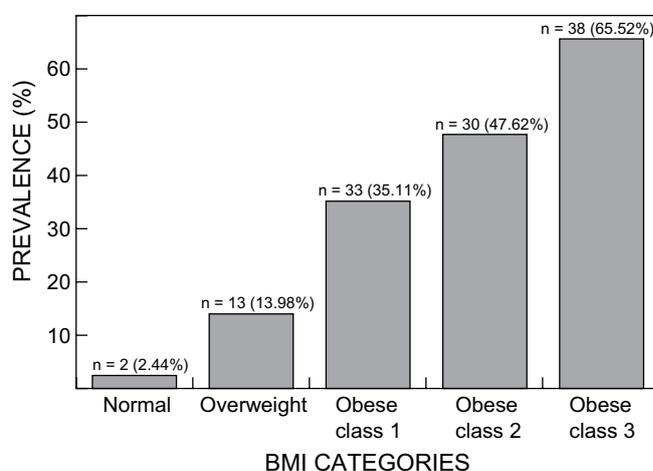**Figure 1:** The prevalence of AN in HGT tertiles.

Figure 2: The prevalence of AN in increasing weight categories.

When *adjusting for glucose*, the odds of developing AN at any site still increased with increasing weight categories when compared with normal-weight individuals. Overweight individuals were 6 times more likely to have AN, while obese individuals were 22 times, 37 times and 74 times more likely if in obese class I, II and III respectively. Similarly, increasing odds of developing AN in the neck were observed with increasing weight categories. Increasing odds of developing AN in the axillae were not seen with increasing BMI.

Discussion

The American Diabetes Association (ADA) recognises AN as a risk factor for T2DM and for this reason it has been included in risk assessment protocols since 2000. They recommend testing to detect T2DM and prediabetes in asymptomatic adults of any age who have a BMI of ≥ 25 kg/m^2 and who have one or more additional risk factor(s), with AN seen as a marker of insulin resistance.[10]

The ethnic variability of AN has been well described, with darker pigmented groups being most commonly affected. Prevalence rates vary from < 1% in whites to up to 34.2% in Cherokee patients,[11] creating the need to confirm its use as a screening tool in specific population groups.[10] Since it was our clinical impression that AN is too common in our mixed-ancestry population to point to underlying insulin resistance, this benign hyperplastic lesion became the focus of our study.

We found AN to be extremely common, with a prevalence of 30% in this female group of mixed ancestry. We also demonstrated a clear association with blood glucose levels, diabetes and obesity, proving that it is not just a normal ethnic phenomenon. We found no association with blood pressure or hypertension.

The prevalence rate found in our study group ranks amongst the highest in the world. Other similar high rates were seen amongst 260 Native Americans of the Alabama-Coushatta tribe, Texas (prevalence of 38%)[9] and 2 205 Cherokee Indians (prevalence 34.2%),[8] where AN was associated with hyperinsulinaemia. A lower prevalence was seen in New Mexico (21%)[4] and Sri Lanka (17.4%),[12] while still associated with diabetes or impaired glucose tolerance.

The association of AN with higher random glucose levels and diabetes was also apparent in our study. Those with AN had higher glucose levels than those without, and diabetics were twice as likely to have AN compared with non-diabetics. In non-diabetics, AN was more commonly seen with higher glucose levels, establishing AN as a risk factor for T2DM and thus a screening tool in this group. The association with blood glucose was independent of bodyweight, a finding supported in the literature.[11]

AN was seen in nearly half (47%) of the diabetics in our study, similar to figures quoted from the Caribbean (52.7%),[10] New Mexico (47%)[4] and Texas (41.1%).[2] In the literature, a wide prevalence range is reported amongst T2DM patients, ranging from 17% in Nigeria[13] to 73.3% in Cherokee Indians.[8] Stuart et al. suggested large differences in the insulin sensitivity of the potentially affected skin areas amongst ethnic groups.[14]

In our study population, AN was extremely common in obese individuals, with a prevalence of 46.98% compared with only 2.44% in underweight/normal weight individuals. A linear increase in prevalence with increasing weight category could be demonstrated, together with more extensive AN with higher weight categories. This association was independent of blood glucose levels. The presence of AN with obesity, and the disappearance thereof with weight loss, is well documented.[2,14]

The nape of the neck was the most commonly affected site in our subjects (94%), which is in keeping with findings in studies performed on Indian (93.5%)[1] and Mexican American populations (93%).[2] We also found that the presence and severity of AN in the neck correlated best with BMI and blood glucose when compared with other sites. We therefore support the suggestion by Burke et al.[2] that only the neck needs to be inspected in epidemiological studies and in our opinion in clinical practice.

An interesting finding was that known diabetics, and those on insulin treatment (presumed to have more severe diabetes) did not have more severe AN, a possible reflection of decreased endogenous insulin in these groups. The significance of the degree of AN in diabetics therefore needs to be investigated further.

Currently more than 50% of diabetic patients remain undiagnosed,[10] a reality also in our Western Cape communities.[15] Our study clearly showed that AN has an important role in the detection of obesity-mediated insulin resistance and can therefore be used in the screening process for T2DM. The ADA recommendation that a screening process of testing obese individuals with AN should therefore be followed.

In summary, our study found that AN is common in our mixed-ancestry population, and is independently associated with higher blood glucose levels and obesity. It is not associated with higher blood pressures and hypertension. The presence and severity of AN in the neck correlates best with glucose levels and BMI and is the site of choice when evaluating our mixed-ancestry population. AN is more common in diabetics, but is not limited to this group, strengthening its role as a screening tool. The significance of the presence and degree of AN in T2DM and its association with micro- and macrovascular damage needs to be investigated further.

Our study had several strengths. A single observer evaluated participants and where the classification of AN was difficult a specialist dermatologist was consulted. AN was also observed in an unselected female mixed-ancestry group and sub-analysis in diabetics and obese individuals was only performed at the end, preventing observer bias. Our study also had several limitations, one being that fasting glucose and insulin levels were not determined and associations with insulin resistance can therefore not be confirmed. In addition AN was not evaluated in other ethnic groups.

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