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Single-centre case–control study investigating the association between acanthosis nigricans, insulin resistance and type 2 diabetes in a young, overweight, UK population

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ABSTRACT

Objective To determine the extent to which the presence of acanthosis nigricans confers additional risk for insulin resistance, in addition to obesity alone (body mass index, BMI) within a young, overweight, UK population.

Research design and methods Retrospective data were collected to compare the degree of insulin resistance within a sample of 94 young people with acanthosis nigricans, and a matched cohort of 94 participants with obesity alone. Insulin resistance was assessed by fasting glucose, fasting insulin and Homeostatic Model Assessment of insulin resistance (HOMA-IR) score (a mathematical model derived to measure insulin resistance).

Results The acanthotic and control group were well matched for age, BMI, BMI SDS and sex, although the groups were not matched for ethnicity. The acanthotic group showed a significantly greater median fasting insulin (215 pmol/L), mean fasting glucose (4.7 mmol/L) and median HOMA-IR score (6.4), compared with the control group (126 pmol/L, 4.5 mmol/L and 3.7, respectively). The presence of acanthosis nigricans as an indicator of insulin resistance was found to have a positive predictive value of 81% (within this study population).

Conclusion Individuals with both acanthosis nigricans and obesity had significantly greater degrees of insulin resistance than individuals with obesity alone. The findings support the potential for acanthosis nigricans as a visible marker of type 2 diabetes in young people.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies maintain that the presence of acanthosis nigricans suggests an additional risk factor for insulin resistance.

⇒ Most previous research has generally involved American populations with a predominance of Hispanic and African-American populations.

WHAT THIS STUDY ADDS

⇒ The potential for acanthosis nigricans to be used as a visible marker of type 2 diabetes risk.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides a basis for the use of acanthosis nigricans to identify obese individuals at risk of type 2 diabetes.

BACKGROUND

Acanthosis nigricans is a dark brown velvety discolouration of the skin typically presenting on the back of the neck and the axillae. Acanthosis is associated with hyperinsulinism and insulin resistance, and is most commonly linked to obesity. While not all individuals with obesity and insulin resistance exhibit acanthosis, those individuals with acanthosis have almost double the risk of type 2 diabetes compared with those who do not.[1]

However, the extent to which acanthosis is an independent marker of insulin resistance, or is simply a reflection of the extent to which individuals are overweight, is debated. Some authors have suggested that obesity is the key determinant of insulin resistance and that the presence or absence of acanthosis offers no additional information compared with evaluating body mass index (BMI).[2] Others have suggested that acanthosis is an important factor in addition to measures of obesity alone in predicting insulin resistance and the risk of type 2 diabetes.[3]

A Texan study of 34 obese adults reported the mean fasting insulin of obese subjects with acanthosis to be twice that of non-acanthotic obese patients.[3] Similarly, Burke *et al* reported that within a sample of 406 Mexican-American adults, those with acanthosis had significantly higher fasting insulin and 2-hour glucose levels than those without acanthosis, and the severity of acanthosis was found to correlate with and be predictive of, the degree of insulin resistance.[4 5]

In children, a US study of 145 obese individuals found acanthosis nigricans to be indicative of impaired glucose metabolism, even when adjustments for BMI were made.[6] A further study of 675 children in New Mexico found acanthosis to be the most effective predictor of hyperinsulinaemia with a positive predictive value (PPV) of 39%, which increased to 47% when combined with obesity. Obesity alone had a PPV of 34% for hyperinsulinaemia.[7]

In contrast, a study of 139 American children found that a BMI SDS of ≥3.0 captured 88% of children with insulin resistance compared with 65% identified by the presence of acanthosis nigricans. The authors expressed doubt as to the extent to which the presence of acanthosis can be used as a reliable independent marker for hyperinsulinaemia in overweight children.[2]

Previous studies have generally involved American populations with a predominance of Hispanic and African-American subjects.[1–10] Ethnicity is important in the evolution of acanthosis nigricans.[11 12] This research study aims to be the first UK-based study to determine whether acanthosis nigricans remains an additional independent risk factor for insulin resistance among a young, UK population.

Research design and methods

Study design

This was a retrospective case–control study. Data were obtained from the medical records of 188 individuals who were reviewed for advice regarding managing their weight between 2010 and 2020 at Sheffield Children's Hospital. Ninety-four participants with acanthosis were individually matched for age, sex, BMI and BMI Z-score (BMI SDS) to a sample of 94 controls with similar levels of obesity but without acanthosis. Set thresholds for a match to be acceptable were agreed on and were as follows: age±12 months; same sex; BMI±0.5; BMI SDS±0.5.

Insulin resistance was assessed using fasting insulin, fasting glucose and Homeostatic Model Assessment of insulin resistance (HOMA-IR) score. HOMA-IR score is a mathematical model derived to measure insulin resistance and beta cell function from a single fasting sample of glucose and insulin. The HOMA-IR score is reported to have high sensitivity and specificity for insulin resistance.[13]

Participants

The inclusion and exclusion criteria for participants is outlined below.

Inclusion criteria

- Children aged ≤18 years.
- Children recorded to have a negative or positive finding of acanthosis nigricans.
- Children whereby height (cm), weight (kg), BMI (kg/m^2), fasting glucose (mmol/l) and fasting insulin (pmol/l) recordings were available.

Exclusion criteria

- Children previously diagnosed with, and being treated for type 2 diabetes.
- Children with any other endocrine disorder (with the exception of polycystic ovarian syndrome).

Statistical analysis

IBM SPSS V.27 was used for statistical analysis. P values of ≤0.05 have been used to indicate statistical significance and 95% CIs have been used throughout.

Statistical analysis involved an independent samples t-test (or Mann-Whitney U test when the principal assumptions for the parametric test were not met) to determine the difference in the measured descriptive statistics (age, BMI and BMI SDS) across the acanthotic and control group. Similarly, the aforementioned tests also determined the difference in the measures of insulin resistance across the acanthotic and control group. An analysis of covariance (ANCOVA) was used to examine differences in the measures of insulin resistance while adjusting for covariates. Additional covariates incorporated into the ANCOVA analysis were BMI, BMI SDS, decimal age, ethnicity and sex.

Ethical considerations

Formal ethical approval was not required for this study as the following criteria were fulfilled.

- Data were recorded as a result of the individual's existing healthcare relationship with Sheffield Children's Hospital.
- Data were being analysed under the team responsible for the individual's care.
- All data were pseudonymised in conducting the research, including during the data analysis process.

Table 1 Descriptive statistics and p values to indicate the appropriateness of matching decimal age, BMI, BMI SDS and sex for the acanthotic and control group for any potentially confounding variables

Variable	Acanthotic group (n=94)	Control group (n=94)	P value
Median decimal age (years)	13.5 (95% CI 12.9 to 13.9)	14.1 (95% CI 12.2 to 13.6)	0.64
Median BMI (kg/m^2)	33.3 (95% CI 33.6 to 37.0)	33.3 (95% CI 33.1 to 36.3)	0.66
Mean BMI SDS	3.25 (95% CI 3.1 to 3.4)	3.35 (95% CI 3.2 to 3.5)	0.35
Sex (%)	Male=50%; Female=50%	Male=50%; Female=50%	-

BMI, body mass index.

Table 2 Ethnicity of the study population

Ethnicity	Acanthotic group, %	Control group, %	Total, %
British	36.2	80.1	58.5
Pakistani	23.4	5.3	14.4
Any other ethnic group	6.4	2.1	4.3
Black Afro-Caribbean	5.3	0.0	2.7
Any other white background	6.3	8.5	7.4
Bangladeshi	3.2	0.0	1.6
White and Black Caribbean	6.3	0.0	3.4
Any other black background	4.3	1.0	2.7
Any other mixed background	3.2	1.0	2.1
Any other Asian background	5.3	1.0	3.2

Patient and public partnership involvement

This study involved secondary data collection during the COVID-19 pandemic, and thus, PPI was not deemed appropriate.

RESULTS

Table 1 illustrates the descriptive statistics and confirms that following individually matching participants, the groups were well matched.

Table 2 demonstrates the ethnic origin of the study population. Significantly greater levels of fasting glucose, fasting insulin and HOMA-IR score were found in those with acanthosis and obesity compared with individuals in the matched control group with obesity alone (see table 3). This effect persisted even when additional diabetic risk factors were accounted for.

The presence of acanthosis was the only diabetic risk factor investigated that produced a significantly greater degree of insulin resistance (fasting insulin: p=0.003; fasting glucose: p≤0.001; HOMA-IR score p=<0.001).

Within the literature, a variety of HOMA-IR score cut-off points have been proposed to define paediatric prediabetic insulin resistance.[14] A HOMA-IR score of ≥3.4 was selected for this study to define insulin resistance.[15 16] Within our study population (n=188), the overall prevalence of insulin resistance was 64.5% (HOMA-IR score ≥3.4). The prevalence of insulin resistance was greater within the acanthotic group (76%) compared with the control group (53%). The presence of acanthosis as a screening tool for insulin resistance showed a sensitivity, specificity, PPV and NPV of 59%, 70%, 81% and 44%, respectively.

DISCUSSION

We found that within a young, overweight, UK population, insulin resistance was more common and also more severe in those with acanthosis compared with those without but with comparable levels of obesity.

As previously stated, acanthosis has a strong ethnic predisposition. The relationship between acanthosis and insulin resistance has not been previously investigated within a UK population with much of the previous research involving Mexican American and Hispanic populations.[1–10] The ethnicity of our study population, as shown in table 2, is representative of that of Yorkshire and Humber. In which, 85.8% of the population of Yorkshire and Humber is White British and the second largest single group is Pakistani (4.5%).[17]

Acanthosis is most evident in individuals with dark skin. We found that the majority of the acanthotic group were of white British (36.2%) or Pakistani (23.4%) ethnicity whereas the majority of the control group were white British (80.1%). Although these findings support the predilection of acanthosis for dark skin, they demonstrate that it was difficult to match participants for ethnicity. This study matched participants by BMI, BMI SDS, age and sex in order to control for potentially confounding variables. It was initially intended that a wider range of diabetic risk factors would be included within this analysis. However, waist circumference, smoking status and family diabetic history were unavailable due to the retrospective nature of the data collection. Similarly, other measurements of insulin resistance such as glycated haemoglobin (HbA1c) were unavailable. Our data collection relied on findings detailed in the medical records of individuals by medical professionals within the trust and thus primary data collection may have been preferred.

Excluding individuals with type 2 diabetes from our data analysis controlled for the potentially confounding variable of hyperglycaemia. Hud *et al*, in a cohort of adult patients, reported similar findings, after excluding individuals with hyperglycaemia, of a higher mean fasting insulin in an obese acanthotic cohort compared with an obese non-acanthotic cohort.[3]

The literature offers differing views with regard to the utility of acanthosis as a predictor for insulin resistance. Many

Table 3 Descriptive statistics and p values for the markers of insulin resistance for the acanthotic and control group

Variable	Acanthotic group (n=94)	Control group (n=94)	P value
Median fasting insulin (pmol/l)	215 (95% CI 213.2 to 282.8)	126 (95% CI 134.8 to 183.6)	<0.001
Mean fasting glucose (mmol/l)	4.7 (95% CI 4.6 to 4.8)	4.5 (95% CI 4.4 to 4.6)	0.025
Median HOMA-IR score	6.37 (95% CI 6.4 to 8.8)	3.71 (95% CI 3.9 to 5.5)	<0.001

HOMA-IR, Homeostatic Model Assessment of insulin resistance.

studies suggest it as a good predictor of insulin resistance in children when combined with obesity.[7 8 18] In an obese childhood population, we found acanthosis to have a PPV of 81% for insulin resistance. This is greater than previous findings whereby acanthosis, when combined with obesity, is reported as having a PPV for hyperinsulinaemia of 47.2%.[7] However, comparisons between the NPV and PPV that we report to previous research is limited as a result of the methodology of this study.

In our cohort, acanthosis had a specificity and sensitivity of 70% and 59%, respectively, for insulin resistance. Previous data by Bhagyanathan *et al* reports a higher specificity (78%) and sensitivity (75%).[18] In our study, the majority were an obese or overweight population (98.5%). Whereas Bhagyanathan *et al* studied a population that was predominantly healthy in weight (75%), with only 12% obese or overweight. The difference in sensitivity and specificity is most likely related to our selection of an obese cohort to study. Therefore, while we were unable to comment on the relationship between acanthosis and insulin resistance in a lean population of normal weight individuals, Bhagyanathan *et al*'s data suggest that acanthosis may be of greater utility in cross sections of the population rather than in higher risk individuals identified by a raised BMI.

We demonstrated greater levels of fasting glucose, fasting insulin and HOMA-IR scores for those with acanthosis. The key weakness of the study is its retrospective nature but the participant groups were well matched. Multiple regression models including other diabetes risk factors (including BMI) demonstrated that the strongest predictor for insulin resistance was the presence or absence of acanthosis. Other studies also found the presence of acanthosis to be the most effective sole predictor of hyperinsulinaemia.[7]

Acanthosis nigricans appears to be an independent marker for insulin resistance in a young, overweight, UK population. As a visible marker of type 2 diabetes risk it may offer opportunity to identify and counsel obese or overweight young people.[1]

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