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Распространенность, предикторы и морфологические особенности черного акантоза у пациентов с ожирением, не страдающих диабетом и принимающих нейролептики второго поколения, по сравнению с пациентами с инсулинозависимым сахарным диабетом без ожирения: исследование «случай-контроль»

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АННОТАЦИЯ

Актуальность. В литературе отсутствуют исследования черного акантоза (ЧА) при ожирении или гиперхолестеринемии, индуцированных психотропными веществами.

Цель. Изучить распространенность, предикторы и морфологические закономерности ЧА у пациентов с гиперхолестеринемией, индуцированной нейролептиками, по сравнению с пациентами с сахарным диабетом.

Материалы и методы. Был проведен скрининг 491 пациента с шизофренией, принимающих нейролептики второго поколения. 26 пациентов из 491 имели ЧА, уровень холестерина > 200 мг/дл и не страдали диабетом. Были использованы U-критерий Манна–Уитни, $\chi 2$ Пирсона, точный критерий Фишера и коэффициент корреляции Спирмена.

Результаты. В группе гиперхолестеринемии, вызванной нейролептиками (5,29%, 26 человек из 491), наблюдалась значимо большая частота вовлечения суставов пальцев ($p < 0,001$), а также коленнных ($p = 0,002$) и локтевых ($p = 0,042$) суставов по сравнению с пациентами без гиперхолестеринемии. Индекс тяжести поражения шеи по Burke ($p < 0,001$), тканей шеи ($p = 0,001$) и подмышечной впадины ($p = 0,007$) также показал значимые различия по U-тесту Манна–Уитни и W-тесту Уилкоксона. Наиболее значимый коэффициент корреляции Спирмена при гиперхолестеринемии, вызванной нейролептиками, был зарегистрирован для специфического при СА поражения шеи ($\rho = 0,413$, $p = 0,003$) по сравнению с другими областями тела.

Заключение. Зарегистрирована распространенность ЧА в группе с ожирением, вторичным по отношению к психотропным препаратам, на уровне 5,29%, что оказалось существенно ниже, чем у пациентов с инсулинозависимым диабетом, не страдающих ожирением (распространенность ЧА 13,55%, почти в три раза выше). Это связано с тем, что диабет патогенетически тесно связан с возникновением ЧА и является конечной стадией развития в парадигме метаболического синдрома, тогда как ожирение является начальной стадией в этом процессе.

Ключевые слова: *черный акантоз; гиперхолестеринемия, индуцированная антипсихотиками; клинический биомаркер*

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Prevalence, Predictors and Morphological Patterns of Acanthosis Nigricans Between Obese Non-diabetic Patients on Second Generation Antipsychotics Versus Non-obese Insulin Dependent Diabetes mellitus: A Nested Case-Control Study

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ABSTRACT

INTRODUCTION: There is no study in literature for analyzing acanthosis nigricans (AN) in psychotropic induced obesity or hypercholesterolemia.

AIM: To assess the prevalence and explore the predictors and morphological patterns in AN in patients on antipsychotics induced hypercholesterolemia versus those with diabetes mellitus.

MATERIALS AND METHODS: 491 schizophrenia patients on second generation antipsychotics were screened. 26 out of 491 patients have AN and cholesterol > 200 mg/dl but non-diabetic. We used Mann–Whitney U-test, Pearson's $\chi 2$ test, Fischer Exact and Spearman's correlation coefficient.

RESULTS: In the group of antipsychotics induced hypercholesterolemia having developed AN in 5.29% (26 out of 491) of individuals, we observed significance of Burke's knuckle ($p < 0.001$), knee ($p = 0.002$), elbow ($p = 0.042$) compared to patients without hypercholesterolemia. Interestingly Burke's neck severity ($p < 0.001$), neck texture ($p = 0.001$) and axilla ($p = 0.007$) index also showed marked differences on Mann–Whitney U-test and Wilcoxson W-test. On Spearman's correlation coefficient antipsychotics induced hypercholesterolemia was found to affect most positively and significantly as the emergence of AN specifically for neck texture ($\rho = 0.413$, $p = 0.003$) compared to other bodily regions.

CONCLUSION: About 5.29% prevalence of AN in the group having obesity secondary to psychotropic drugs which was significantly less than what even non-obese, insulin dependent diabetic patients who almost had 13.55% prevalence, close to three times. This suggests that diabetes is strongly linked with occurrence of AN lesions and might reflect the continuity in the paradigm of metabolic syndrome as its definitive predictor of severity while obesity is the initiation of phase shift in the process.

Keywords: *acanthosis nigricans; antipsychotic-induced hypercholesterolemia; clinical biomarker*

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ECO•VECTOR

LIST OF ABBREVIATIONS

AN — acanthosis nigricans
BMI — body mass index
Wisp1 — Wnt1-inducible signaling pathway protein-1

INTRODUCTION

Acanthosis nigricans (AN) is characterized by dark, coarse, and thickened skin with at times velvety texture, being mostly symmetrically distributed predominantly on the neck, axillae, ante-cubital and popliteal fossae as well as groin folds. It is histopathologically characterized by *papillomatosis* and *hyperkeratosis* of the skin. The term '*acanthosis nigricans*' was although originally proposed by Dr. Paul Unna from Hamburg, Germany but the first case of AN was described and published by Pollitzer and Janvosky from Prague in 1981 and thus it was included in the International Atlas for rare skin diseases [1].

It mostly occurs in individuals younger than 40 years, may be genetically inherited and is typically associated with obesity, endocrinopathies, such as hypothyroidism or hyperthyroidism, acromegaly, polycystic ovarian syndrome, insulin–resistant diabetes, or Cushing's disease [2–4]. The most common cause of AN is observed to be an insulin resistance, which leads to increased circulating insulin levels. Insulin and insulin-like growth factor-1 with their receptors on keratinocytes and fibroblast are obviously implicated in the complex regulation leading to the peculiar epidermal hyperplasia. In fact, excess insulin levels cause the normal skin to reproduce rapidly and in obese patients it's not insulin but insulin-like growth factor-1 levels that may contribute to keratinocyte and fibroblast proliferation [5, 6]. Thus, patients with diabetes mellitus and obese individuals are at least two times more prone to have AN compared to others [7, 8]. However, literature does not have so far found specific and distinctive predictors or categorical differences on morphologies of AN lesions, but it would be interesting to look out from psychiatric aspect if AN can help differentiating psychotropic drug induced weight gain versus drug induced diabetic patients.

Metabolic syndrome is on rise in chronic psychotic patients particularly on second generation antipsychotics like olanzapine and clozapine [9, 10] which basically is a clustering of factors including central obesity, glucose intolerance, hyperinsulinemia, low high-density lipoprotein cholesterol, high low-density lipoprotein cholesterol, high triglycerides and arterial hypertension. Some studies attributes occurrence of metabolic syndrome in psychotic patients to their sedentary lifestyle, lack of exercise and physical work, poor nutrition, chronic stress and abnormal hypothalamic-pituitary-adrenal axis [11]. However, accumulating evidence suggests that varying degrees of insulin resistance may be the common etiological factor for the individual components of metabolic syndrome [12]. In a randomized, 10-week, parallel-group, double-blind trial, the effect of second generation clozapine and conventional haloperidol on weight gain were tested. Among 19 patients on clozapine group all gained a mean weight of 5.3 kg over their baseline compared to 0.68 kg in 20 patients of haloperidol [13]. The patients of metabolic syndrome also have about five-fold greater risk of developing type 2 diabetes (if not already present) based on meta-analysis of 42,419 participants from 16 cohorts [4, 14, 15]. Indeed, predictability of metabolic syndrome for incident diabetes was found to be superior to the predictability associated with either Framingham risk score or classical clinical risk factors [16–17]. Apart from AN, acne valgaris, hidradenitis suppurativa, lipoatrophy, atopic dermatitis, skin tags and psoriasis are common skin markers associated with this metabolic syndrome reflecting the causal existence of increased numbers of oxidative stress and inflammatory markers [18–20]. AN may further also be seen with certain medications that lead to elevated insulin levels (e. g., glucocorticoids, niacin, insulin, oral contraceptives and protease inhibitors). Very few drugs in the armamentarium of neuropsychiatry have AN presentation on prima facie without co-occurrence of metabolic syndrome where common pathophysiological pathway exists. Further it is not known if the qualitative morphological patterns of AN is any different when they occur in these subgroups of individuals who apparently have drug induced obesity and underlying plethora inflammatory, immunomodulatory and stress-diathesis overload due to ongoing schizophrenic process. Although obesity-associated AN used to be once labelled as pseudoacanthosis and lesions may completely regress with weight reduction, there is no study in literature for analyzing AN in psychotropic induced obesity or hypercholesterolemia.

Hence, the **aim** of this study to investigate morphological pattern differences and predictors of acanthosis nigricans in patients of hyperlipidemia with the psychotropic medications versus those of conventionally seen lesions of acanthosis nigricans in insulin dependent diabetes mellitus without hypercholesterolemia.

MATERIALS AND METHODS

The current study was conducted in collaboration with out-patient department of Psychiatry, Dermatology, Internal Medicine and Biochemistry of our tertiary care hospital after receiving institutional ethical approval and

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consent from the patients. We used a nested case-control study design since the estimates of diagnostic accuracy in such sampling method were observed to be very similar to those in full study population [21] and recruited patients from January 2019 to June 2021 for a period of 30 months.

A pool of 491 patients of chronic schizophrenia and other psychosis (≥ 2 years of disorders) who were either on Olanzapine, Clozapine, Risperidone or Quetiapine were screened to find out for the presence of obesity induced by psychotropics and further investigated for hypercholesterolemia / hypertriglyceridemia and/or weight gain (at least > 10% of body mass index (BMI)) over last 6 months or more after the use of medications and who also eventually developed AN skin lesions in their due course.

The other group was pooled from Department of Internal Medicine and Dermatology after screening out 177 patients of insulin dependent diabetes mellitus for identifying AN patients from insulin resistant diabetes mellitus subgroup receiving treatment from our tertiary care hospital. We used the data from this particular group of AN who were already diagnosed with diabetes mellitus and had insulin resistance but screened particularly those individuals who does not have obesity (BMI > 29.9 kg/m^2) and/or hypercholesterolemia (cut off level of serum cholesterol > 200 mg/dl).

Thus, in the duration of last 30 months, we could get 26 out of 491 patients in ***group A*** (AN with hypercholesterolemia secondary to antipsychotics without comorbid diabetes mellitus) and 24 patients in ***group B*** (AN with diabetes mellitus without obesity or hypercholesterolemia). The insulin resistance was calculated using commonly used formula: *(Blood Glucose Level × Blood Insulin Level) /22.5*.

The confirmation of the clinical diagnosis of AN was essentially done by senior consultants from department of dermatology whichever patients were having skin lesions characterized by velvety papillomatous brownish or black, thickened, hyperpigmented plaques typically of inter-trigonous surfaces on neck and in case of diagnostic doubt, the biopsy of plaqueswas taken to identify histopathological patterns as and when required. We used Burke's Indices [22] for grading the texture and severity of AN as well as clinical acumen for comparing the differences of morphological patterns between these two groups. Specific warning sign evaluations for any presence of malignancy in AN were ruled out by applying the following exclusive points, for example we excluded the patients who have rapid onset of extensive AN, specifically with atypical sites, florid cutaneous papillomatosis and unintentional weight loss. We also excluded the cases of comorbid presence of other simultaneous metabolic disorders like Addison's disease, acromegaly, hypothyroidism, primary biliary cirrhosis and few auto-immune conditions like systemic lupus erythematosus, systemic sclerosis and dermatomyositis. To identify the presence of hypercholesterolemia we ensure that the patient had been on their psychotropics for more than 6 months with regular compliance and screened the serum cholesterol levels for at least two times over a period of 12 weeks with standard laboratory assessments, whereas for the patients of insulin resistant diabetes mellitus we evaluated the serum levels of glycosylated hemoglobin levels and fasting glucose and Insulin levels.

All the data of the patients was analyzed using statistical software IBM SPSS Statistics 21 (IBM Corp., USA). Since most of our data is quantitative and ordinal in nature wherein these clinical and laboratory variables exist in naturally occurring ordered categories, we used a Mann–Whitney U test for identifying the degree of differences between these two independent groups for identifying the significance. Because Mann–Whitney U test is a non-parametric test, it clearly does not assume any assumptions related to the distribution of scores which makes it more pertinent. We further used Pearson's correlation coefficient for comparing the predictors and quantitative nature of associations with increased insulin, cholesterol and triglyceride levels to severity of AN using Burke's Index. A p-value of < 0.05 was considered significant and < 0.005 was considered very significant.

RESULTS

In ***group A*** we screened 491 patients of chronic schizophrenia from our center who were either on Olanzapine, Clozapine, Quetiapine or Risperidone and developed significant weight gain over last 12 months. We identified 26 out of 491 patients who developed hypercholesterolemia, thus the prevalence of AN in obesity secondary to psychotropic drugs was 5.29%. We observed that males were slightly more preponderant (1.5:1) compared to females and their mean age was 34.25 ± 11.36 years. Their mean cholesterol levels were about 246 mg/dl and serum insulin levels were 54.6 μIU/ml which is nearly four times the normal range. None of them were found to have diabetes mellitus (mean blood glucose levels 112.74 ± 6.8 mg/dl, Table 1). The mean BMI was 26.2 kg/m^2 while mean weight gain observed in these patients who are on second generation antipsychotics was 7.2 ± 2.1 kg. 80.7% (21 out of 26) of them were on Olanzapine, 15.3% (4 out of 26) were on Risperidone, 3.8% (1 out of 26) were on Clozapine. The mean duration of darkening of AN was 9.2 months. AN lesions were predominantly noted on neck (90%), axilla (84%), periorbital (38%) and groin (22%) but uncommonly also seen in palms, soles, perioral, nipple, and antecubital fossa. Many patients have AN lesions at multiple body regions.

In ***group B*** we selected 24 patients of AN who were diagnosed case of insulin resistant diabetes mellitus without obesity after screening out 177 patients of insulin dependent diabetes mellitus. Thus, the prevalence of AN in these group of samples was found to be 13.55%. Most 62.5% (15 out of 24) of them were from 21 to 30 years, while 21.1% (7 out of 24) of them belonged to 31 to 40

Table 1. Baseline socio-demographic and clinical characteristics of acanthosis nigricans with or without obesity

Variable	Group A: AN with obesity and hypercholesterolemia	Group B: AN without obesity with insulin resistant diabetes mellitus
n	26	24
No of patients screened	491	177
Prevalence Percentage, %	5.29	13.55
Mean age, years	34.25 ± 11.36	26.8 ± 10.69
Male : Female	1.5 : 1	1 : 2
Mean blood sugar levels, mg/dl	112.74 ± 6.8	145 ± 13.5
Mean insulin levels, μIU/ml	54.6 ± 3.6	104.7 ± 17.2 μIU/ml
Mean cholesterol levels, mg/dl	246.6 ± 29.5	163.45 ± 4.01
Mean triglycerides levels, mg/dl	149.5 ± 11.4	131.1 ± 8.3
Mean BMI, kg/m^2	26.2 ± 0.7	23.2 ± 2.8
Mean weight gain in last 12 months, kg	7.21 ± 1.22	1.5 ± 0.9
History of childhood low birth weight, n	18	6
Mean duration of darkening of AN, months	9.2	14.3
Distribution of AN lesions in groups		
Periorbital, n (%)	10 (38)	9 (40)
Temples, n (%)	3 (12)	5 (22)
Perinasal, n (%)	3 (12)	5 (22)
Perioral, n (%)	2 (7)	3 (12)
Infralabial, n (%)	3 (12)	5 (20)
Skin over hyoid bone, n (%)	0	2 (10)
Neck, n (%)	23 (90)	23 (96)
Axilla, n (%)	22 (84)	21 (88)
Antecubital fossa, n (%)	4 (18)	3 (13)
Knuckles, n (%)	8 (32)	2 (10)
Sides of waist, n (%)	0	1 (6)
Inframammary, n (%)	0	2 (8)
Periumbilical, n (%)	2 (6)	0
Groin, n (%)	6 (22)	3 (13)
Popliteal fossa, n (%)	3 (12)	1 (4)
Knees, n (%)	0	5 (24)
Palms, n (%)	1 (6)	0
Nipples, n (%)	1 (2)	0
Soles, n (%)	2 (4)	0

Note: AN — acanthosis nigricans, BMI — body mass index

years age and the rest 8.3% (2 out of 24) were from 41 to 50 years age. We found that females were two times more likely to have AN in insulin dependent diabetes mellitus without having obesity compared to males as none of them were found to have hypercholesterolemia (mean cholesterol level was 163.45 ± 4.01 mg/dl). However, most of them showed increased fasting serum Insulin levels (104.7 ± 7.2 μIU/ml) and the mean fasting blood sugar level was 145.0 ± 13.5 mg/dl. Their mean BMI was found to be 24.2 ± 2.8 kg/m^2. Mean duration of AN lesions were 14.3 months which were clearly more compared to group A patients. Although neck and axilla remained the most common body regions of AN in these patients, knee, temples, perinasal area were also involved although in few cases. Thus, uncommon occurrences of AN is one of the key distinctive features in these two groups of patients. Finally, we also noted that history of low birth weight was three times more prevalent in group A patients compared

to group B reflecting obesity develops more in those who were earlier had low birth weight.

The distribution of the severity of Burke's index with reference level of serum cholesterol is shown in Table 2. Mann–Whitney U test works by converting scores into ranks while ignoring the grouping variables in our nested cases (cholesterol levels < 200 mg/dl and > 200 mg/dl) and then compared the mean rank of each group. We observed a very significant difference ($p < 0.005$) between the mean ranks for Burke's neck severity, neck texture and axilla between normal versus high serum cholesterol levels.

Table 2. Comparison of Acanthosis Nigricans with or without hypercholesterolemia

Variables	Cholesterol groups, mg/dl	Mean rank	Sum of ranks	Mann–Whitney, U	p
Burke's neck severity	< 200 (n=24)	17.50	420	120	< 0.001
	> / 200 (n=26)	32.88	855		
Burke's neck texture	< 200 (n=24)	18.58	446	146	0.001
	> / 200 (n=26)	31.88	829		
Bruke's axilla	< 200 (n=24)	20.02	480.5	180.5	0.007
	> / 200 (n=26)	30.56	794.5		

Further, on Pearson's Correlation, we observed that serum cholesterol levels were positively ($ρ = 0.505$) and significantly ($p = 0.008$) associated with occurrence of AN and its neck severity, while even more significant positive association ($p < 0.005$) of serum triglycerides were noted with AN neck severity and texture but not significantly ($p = 0.165$) with axilla or other region lesions of AN (Table 3).

Table 3. Pearson Correlations among Burke's Indices and Biochemical Parameters

Variables	Serum insulin	Triglyceride levels	Burke's Neck Severity	Burke's Neck Texture	Bruke's Axilla
Cholesterol level	r = 0.187 (p = 0.361)	r = 0.697 (p < 0.001)	r = 0.505 (p = 0.008)	r = 0.352 (p = 0.077)	r = 0.330 (p = 0.100)
Serum insulin	–	r = 0.114 (p < 0.578)	r = 0.279 (p = 0.167)	r = 0.011 (p = 0.957)	r = 0.088 (p = 0.669)
Triglyceride levels	–	–	r = 0.800 (p < 0.001)	r = 0.531 (p = 0.005)	r = 0.281 (p = 0.165)
Burke's Neck Severity	–	–	–	r = 0.674 (p < 0.001)	r = 0.278 (p = 0.170)
Burke's Neck Texture	–	–	–	–	r = 0.467 (p = 0.016)

DISCUSSION

The present qualitative, nested case-control study not only evaluated the relative prevalence of AN in obese (perhaps futuristically vulnerable metabolic syndrome) chronic psychotic patients who were on second generation antipsychotics like Olanzapine or Clozapine for more than 12 months but it also compared the morphological rarities of differences in occurrence of AN lesions within the subgroup of non-obese, insulin dependent diabetes mellitus. Since the age of onset of AN in most cases irrespective of its underlying diathesis or medical comorbidities is mostly below 40 years of age, the intra-class homogeneity of both nested patient groups viz. chronic psychotics who were obese forming our predominant part of group A and also those of non-obese, insulin dependent diabetes patients from group B are in well conformity for objective phase of thematic differences evaluation in the present study. We observed about 5.29% prevalence of AN in group A having obesity secondary to psychotropic drugs which was significantly less than what even non-obese, insulin dependent diabetic patients who almost had 13.55% prevalence, close to three times. This suggests that diabetes is strongly linked with occurrence of AN lesion and might reflect the continuity in the paradigm of metabolic syndrome as its definitive predictor of severity while obesity is the initiation of phase shift in the process. Interestingly past few studies had reported the different prevalence of the AN in obesity at different

regions of the world, for example couple of studies from Texas, the United States widest range difference (T. Guran, et al. had reported 7% [23] while study by F. Sayarifard, et al. had reported 74% in obese people in Dallas [24]). The prevalence of AN in New Mexico was 49.2% in obese adolescents compared with 7.7% in those who were not obese reflecting as much as seven times more likelihood of its vicariousness [25].

To our knowledge, this is the first published study of comparative prevalence of AN in obese and diabetic population from India and there is no other study in literature that systematically explored the prevalence of AN in patients of either psychotropic induced metabolic syndrome or even hypercholesterolemia, thus head-to-head comparisons of our findings cannot be directly possible. In both the groups of our sample population, most of lesions were noted on neck (> 90%) and axilla (> 80%) but very rarely on knuckles specially in obese group who were on psychotropics. The mean level of serum insulin in insulin dependent diabetes mellitus group (B) was 104.7 ± 7.2 μIU/ml while it was 54.6 ± 3.6 μIU/ml in group A obese patients which were clearly above the mean normal serum levels. However, as we know insulin resistance is present in both disorders, G. Gonzalez–Saldivar, et al. [25] considered AN in knuckles to be a sensitive and straightforward clinical biomarker to predict insulin resistance. While this is in conformity that there lies a prolonged time lag for developing insulin resistance in drug induced obesity which may be slower and partially reversible with weight reduction strategies. Except for presence of additional acrochordons and atypical site of lesions in the body, there were hardly any morphological or biopsy differences observed in AN patients of both groups. Thus, alterations in morphological patterns and textures often do not seem to differ between hypercholesterolemic/obese and non-obese, insulin-resistant diabetic patients and subtle changes in them are dynamic and therefore they may overlap or change with time henceforth we rather need more deeper understandings and molecular evaluation either at AN evolving commencing point or end point (which is difficult to identify practically) for having enough precision in its pathophysiological pathways. For example, the Wnt1-inducible signaling pathway protein-1 (Wisp1) was recently described as a new adipokine and its expression and secretion are increased in the course of differentiation of human adipocytes. Relative changes in body weight regulate both expression of Wisp-1 in adipose tissue and plasma levels of secreted Wisp-1 [26]. Interestingly, Wisp-1 serum levels are elevated in obese patients affected with polycystic ovary syndrome and in patients with gestational diabetes mellitus and Olanzapine is known to be associated with both later conditions [27–28] and it would be more enticing to get such prototypical additional group for its variability of AN occurrence. Finally, in the backdrop of extensive work by C. E. Koro, et al. [29] who showed the strong association between olanzapine exposure and hyperlipidemia in schizophrenic patients and found nearly five-fold increase in odds of developing hyperlipidemia compared with no antipsychotic exposure [odds ratio 4.65; 95% confidence interval 2.44–8.885; $p < 0.001$] and more than a three-fold increase compared with those receiving first generation conventional agents [odds ratio 3.36; 95% confidence interval 1.77–6.39; $p < 0.001$], choosing large group of Olanzapine induced obese but non-diabetic patients from the pool of chronic schizophrenia makes this study more relevant as well as intrigued for understanding additional clinical biomarker like AN in psychiatric population. However, none of the previous studies in the literature systematically tried to evaluate if AN develops in obese patients who receives long term antipsychotics like Olanzapine and Clozapine and there is clearly much scope in future to understand trends, patterns and variabilities to be explored.

CONCLUSION

We evaluated the prevalence and predictors of acanthosis nigricans with antipsychotics induced obese patients, its various morphological differences among obese non-diabetic and diabetic non-obese patients. One of the challenges in preventing diabetes or obesity is to identify its early risk-prediction marker like insulin resistance which usually is missed or ignored clinically. Such studies were not conducted in past and these insights can perhaps potentially signify acanthosis nigricans as a clinical biomarker or component which can predict the prognosis for metabolic syndrome too in near future. More research is needed to determine the time course and magnitude of developing acanthosis nigricans to uncover the mechanisms underlying the apparent differences.

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Вклад авторов: *Vidyasagar P. — **концепция и дизайн исследования, сбор данных, статистический анализ и интерпретация, написание текста;** Kamble A.* — концепция и дизайн исследования, статистический анализ и интерпретация, написание текста; *Khairkar P.* — концепция и дизайн исследования, статистический анализ и интерпретация, написание текста; *Shravya B.* — концепция и дизайн исследования, статистический анализ, анализ и интерпретация данных, написание текста, окончательное утверждение для публикации рукописи; *Sumera Y.* — дизайн исследования, сбор данных и интерпретация, написание текста; *Mateti A. R., Reddy V.* — дизайн исследования, анализ данных, интерпретация, написание текста; *Biswas R.* — концепция исследования, написание текста; *Ransing R.* — критическая проверка интеллектуального содержания работы, окончательное утверждение рукописи для публикации. Все авторы подтверждают соответствие своего авторства международным критериям ICMJE (все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией).

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