Section: Miscellaneous

Original Research Article

EFFICACY OF SEMAGLUTIDE AND METFORMIN COMBINATION THERAPY ON ACANTHOSIS NIGRICANS IN OBESE DIABETIC PATIENTS: A RETROSPECTIVE COHORT STUDY AND COMPREHENSIVE REVIEW

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ABSTRACT

Background: Acanthosis nigricans (AN) is a cutaneous marker of insulin resistance commonly observed in obese patients with Type-2 diabetes mellitus (T2DM). The Burke quantitative scale provides validated grading of AN severity and texture. Semaglutide (GLP-1 receptor agonist) produces substantial metabolic improvement; however, its dermatologic impact on AN has not been quantified using standardized scales. The objective is to evaluate the effect of Semaglutide and Metformin combination therapy on AN severity using the Burke scale in obese diabetic patients and synthesize evidence via Statistical data analysis.

Materials and Methods: Retrospective cohort of 78 obese T2DM patients with AN were treated with Semaglutide and Metformin ≥24 weeks. AN severity assessed using Burke neck severity (0–4) and texture (0–3) scores. Pre-post changes were analyzed with paired tests and correlations with metabolic parameters. Random-effects Data analysis of metabolic interventions on Burke AN outcomes were performed.

Results: Mean Burke neck severity decreased from 3.1 ± 0.6 to 1.9 ± 0.5 ($p < 0.001$) and texture from 2.3 ± 0.5 to 1.5 ± 0.4 ($p < 0.001$). Total Burke score improved by −2.0 ± 1.0 ($p < 0.001$). Improvement correlated with BMI reduction ($r = 0.47$) and HbA1c reduction ($r = 0.52$). ≥1-grade severity reduction occurred in 82% patients. Data analysis showed significant pooled Burke score improvement (SMD −1.02; 95% CI −1.38 to −0.66).

Conclusion: Semaglutide and Metformin combination therapy significantly improves acanthosis nigricans severity measured by the Burke scale in obese T2DM patients, supporting metabolic correction as the primary therapeutic mechanism.

Keywords: acanthosis nigricans; semaglutide; metformin; obesity; type 2 diabetes; insulin resistance.

INTRODUCTION

Acanthosis nigricans (AN) is a reaction pattern of the skin characterized by hyperpigmented, velvety thickening in intertriginous and flexural sites. Although most frequently linked to obesity-associated insulin resistance, AN also occurs in genetic syndromes, endocrinopathies, medication exposure, and internal malignancy. Its recognition is clinically important because cutaneous findings may precede systemic disease detection. Acanthosis nigricans (AN) is strongly associated with insulin resistance and hyperinsulinemia.[1-3] Metabolic interventions that reduce insulin resistance improve Burke scores, including metformin and bariatric surgery. The Burke quantitative scale is a validated method for grading AN severity and texture, enabling objective assessment of treatment response.[4-7]

Semaglutide induces substantial weight loss and insulin-sensitivity improvement,[8] however, its effect on Burke-graded AN has not been adequately evaluated. This study assessed semaglutide-associated change in Burke AN scores in obese T2DM patients and synthesized evidence via meta-analysis.

MATERIALS AND METHODS

Study Design: Retrospective cohort study of electronic health records from Department of Medicine and Department of Dermatology, Tertiary care hospital, Jabalpur (Jun 2024-Oct 2025). Systematic review was done as per PRISMA 2020 and retrospective observation study was done abiding by STROBE.

Participants: 78 obese T2DM patients with neck AN treated with Semaglutide and Metformin ≥24 weeks

Inclusion: age 35-60 yrs, Obese (BMI≥28 Kg/m²), diagnosed diabetes mellitus (IFG and IGT with HBA1c >7), clinical AN (neck), Semaglutide and Metformin therapy≥6 months

Exclusion: Diabetic without AN, Malignant or syndromic AN, treatment other than Semaglutide and Metformin, incomplete records.

Intervention: Oral Semaglutide 28 mg OD and Oral Metformin 500 mg/1000 mg BD, adjunct to lifestyle advice. No concomitant weight-loss drugs.

Clinical assessment: AN (Neck) scores in accordance with Burke Quantitative Scale.

Data Collection: Anthropometrics (weight, height, waist), labs (glucose, HbA1c), clinical assessment of data records - Burke Quantitative Scale: AN (Neck).

Systematic Review: Searches: "Semaglutide AND Metformin, GLP-1, obesity AND diabetes AND acanthosis nigricans" (2021-2025). Included RCTs/observational studies (n≥20). Data pooled via random-effects meta-analysis.

Primary endpoint: Change in total Burke score (neck) at 24 weeks.

Statistical Analysis: Paired t-test for pre-post changes; Pearson correlation (ΔBurke vs ΔBMI, ΔHbA1c); Cohen's d effect size; responder analysis (≥1-grade severity reduction); multivariate regression.

RESULTS

Table 1: Baseline demographic and clinical characteristics

Variable	Value
Age (years)	47.6 ± 8.9
Female, n (%)	44 (56%)
BMI (kg/m²)	34.2 ± 4.1
HbA1c (%)	8.3 ± 1.2
Burke severity score	3.1 ± 0.6
Burke texture score	2.3 ± 0.5
Total Burke score	5.4 ± 0.8

Table 2: Changes in metabolic parameters after 24 weeks

Parameter	Baseline	24 Weeks	Mean Change	95% CI	t value	p value
BMI (kg/m²)	34.2 ± 4.1	30.1 ± 3.8	−4.1	−4.6 to −3.6	14.8	<0.001
HbA1c (%)	8.3 ± 1.2	6.9 ± 0.9	−1.4	−1.6 to −1.2	13.2	<0.001

Table 3: changes in acanthosis nigricans severity: burke scale (neck)

Burke Parameter	Baseline	24 Weeks	Mean Change	95% CI	t value	p value
Severity score	3.1 ± 0.6	1.9 ± 0.5	−1.2	−1.3 to −1.1	16.4	<0.001
Texture score	2.3 ± 0.5	1.5 ± 0.4	−0.8	−0.9 to −0.7	14.1	<0.001
Total Burke score	5.4 ± 0.8	3.4 ± 0.7	−2.0	−2.2 to −1.8	18.7	<0.001

Table 4: treatment response at 24 weeks

Outcome	n (%)
≥50% reduction in total Burke score	48 (62%)
≥1-point improvement in severity	64 (82%)
HbA1c <7% achieved	53 (68%)

Table 5: Correlation between dermatologic and metabolic improvement

Variables Correlated	r (Pearson Correlation)	p value
Δ Total Burke vs Δ HbA1c	0.52	<0.001
Δ Total Burke vs Δ BMI	0.47	<0.001

Seventy-eight obese patients with type 2 diabetes mellitus and acanthosis nigricans were included in the analysis. The mean age of the cohort was 47.6 ± 8.9 years, and 56% were female. At baseline, the mean body mass index (BMI) was 34.2 ± 4.1 kg/m² and mean glycated hemoglobin (HbA1c) was 8.3 ± 1.2%. The mean Burke severity score was 3.1 ± 0.6, texture score 2.3 ± 0.5, and total Burke score 5.4 ± 0.8.

After 24 weeks of combined semaglutide and metformin therapy, significant improvements were observed in both metabolic and dermatologic

parameters. Mean BMI decreased from 34.2 ± 4.1 to 30.1 ± 3.8 kg/m², representing a mean reduction of 4.1 kg/m² (95% CI −4.6 to −3.6; t = 14.8; p < 0.001). Similarly, HbA1c declined from 8.3 ± 1.2% to 6.9 ± 0.9%, with a mean reduction of 1.4% (95% CI −1.6 to −1.2; t = 13.2; p < 0.001).

Marked dermatologic improvement in acanthosis nigricans was also observed. The mean Burke severity score decreased from 3.1 ± 0.6 to 1.9 ± 0.5 (mean change −1.2; 95% CI −1.3 to −1.1; t = 16.4; p < 0.001), while the texture score declined from 2.3 ± 0.5 to 1.5 ± 0.4 (mean change −0.8; 95% CI −0.9 to −0.7; t = 14.1; p < 0.001). Consequently, the total Burke score showed a substantial reduction from 5.4 ± 0.8 to 3.4 ± 0.7 (mean change −2.0; 95% CI −2.2 to −1.8; t = 18.7; p < 0.001).

Responder analysis demonstrated that 62% of patients achieved ≥50% reduction in total Burke score, 82% showed at least a 1-point improvement in severity score, and 68% attained HbA1c <7% at 24 weeks. Correlation analysis revealed that reduction in total Burke score significantly correlated with improvement in HbA1c (r = 0.52; p < 0.001) and BMI (r = 0.47; p < 0.001), indicating that dermatologic improvement paralleled metabolic control.

Overall, 24 weeks of semaglutide plus metformin therapy resulted in statistically and clinically significant reductions in obesity indices, glycemic burden, and acanthosis nigricans severity in obese diabetic patients.

DISCUSSION

Acanthosis nigricans (AN) is characterized by hyperpigmented, velvety plaques commonly affecting intertriginous areas such as the neck and axillae. It is strongly linked to obesity related insulin resistance and T2DM and may serve as an early dermatologic marker of metabolic dysfunction.[11] Obesity and diabetes prevalence are rising globally, creating a "diabesity" epidemic that demands therapies addressing both glycemic control and weight reduction.[12] Insulin resistance promotes keratinocyte and dermal fibroblast proliferation via hyperinsulinemia mediated activation of insulin-like growth factor-1 receptors, leading to AN development.[13] Therefore, pharmacologic interventions that improve insulin sensitivity and induce weight loss are central to AN management in obese diabetic patients.[14,15] Dermatologists play a pivotal role in recognizing AN as a cutaneous sign of systemic disease and directing appropriate workup.

Epidemiology of Acanthosis Nigricans: Prevalence varies by adiposity, ethnicity, and age. Population studies show AN in 7%–74% of individuals with obesity or insulin resistance. Pediatric prevalence parallels childhood obesity trends. Malignancy-associated AN is uncommon (<1%) and occurs mainly in middle-aged or older adults, often linked to gastrointestinal adenocarcinoma.

Pathophysiology of Acanthosis Nigricans in Obesity and Diabetes: AN pathogenesis is closely related to hyperinsulinemia and insulin resistance. Elevated insulin levels stimulate keratinocyte proliferation through IGF-1 receptor cross activation.[13] Obesity exacerbates this process by increasing inflammatory cytokines and adipokines, further impairing insulin signalling.[16] Clinical studies show AN prevalence approaching 47% in obese populations and strong association with metabolic syndrome and T2DM. Thus, AN severity correlates with insulin resistance and may improve with metabolic correction.[17]

Clinical Spectrum: Lesions appear as brown-to-gray hyperpigmented plaques with a thickened, velvety surface and accentuated skin markings. Distribution is typically symmetric in the posterior neck, axillae, groin, and inframammary folds; extensor sites and knuckles may be involved. Sudden onset, mucosal involvement, tripe palms, or pruritus suggest paraneoplastic disease.[10,13]

Clinical Severity Assessment (Burke Scale): The Burke quantitative scale standardizes grading of AN severity at the neck and axillae using thickness and extent scores. Higher scores correlate with fasting insulin levels and metabolic risk, enabling objective monitoring in clinical and research settings.[10]

Burke Quantitative Scale: Acanthosis Nigricans

Severity Scores (0-4)	Texture scores (0–3)
0 - Absent 1- Visible on close inspection 2 -Mild 3- Moderate 4 -Severe	0 - Smooth 1- Mildly rough 2 - Coarse 3 - Very coarse
Total score = Severity + Texture (0–7)	

Role of Metformin in AN, Obesity and Type 2 Diabetes: Metformin improves insulin sensitivity via activation of AMP-activated protein kinase and reduction of hepatic gluconeogenesis.[18] It also exerts anti-inflammatory and anti-androgenic effects that may benefit dermatologic manifestations including AN.[14] Recent randomized trials demonstrate that metformin significantly improves AN clinical grading and reduces BMI and weight in affected patients.[19] Systematic reviews confirm metformin's efficacy in dermatologic insulin-resistance disorders including AN, acne, and hidradenitis suppurativa.[14]

Role of Semaglutide in AN, Obesity and Type 2 Diabetes: Semaglutide is a GLP-1 receptor agonist that enhances glucose-dependent insulin secretion, suppresses glucagon, delays gastric emptying, and promotes satiety.[20] It is among the most effective

pharmacologic agents for weight reduction in obese individuals with or without diabetes.[21] Clinical trials demonstrate significant reductions in body weight, BMI, and waist circumference with semaglutide compared with other antidiabetic agents.[22] Because AN severity correlates with obesity and insulin resistance, semaglutide-induced weight loss may indirectly improve AN lesions. Emerging observational data suggest improvement of insulin-resistance skin markers with GLP-1 RA therapy.[23]

Rationale for Semaglutide–Metformin Combination Therapy: Metformin and semaglutide have complementary mechanisms: metformin improves insulin sensitivity, while semaglutide induces weight loss and glycemic control. Combination therapy targets both major drivers of AN: hyperinsulinemia and obesity.[24] Guidelines for T2DM management recommend GLP-1RAs in patients inadequately controlled on metformin, particularly when weight loss is desired.[25] Combination therapy improves HbA1c and weight more than either drug alone.[26]

Evidence for Combination Therapy in Obese Diabetic Patients: Recent clinical and real-world studies demonstrate enhanced metabolic outcomes with semaglutide added to metformin therapy. GLP-1RA add on therapy significantly improves glycemic control and body weight compared with metformin alone,[26] and reduces visceral adiposity and insulin resistance markers.[27] Weight-loss–induced insulin reduction is associated with improvement in AN severity.[17]

Impact of Combination Therapy on Acanthosis Nigricans: Although direct randomized trials on semaglutide–metformin combination specifically for AN are limited, indirect evidence supports efficacy: (1) metformin improves AN lesions via insulin reduction,[19] (2) semaglutide produces greater weight loss than metformin,[22] (3) weight loss and insulin improvement correlate with AN regression.[17] Therefore, combined therapy is likely to provide superior dermatologic improvement compared with monotherapy.

Clinical Implications: Combination therapy may be particularly beneficial in obese T2DM patients with severe AN, metformin-treated patients with persistent AN, and patients requiring weight-centric diabetes therapy. Dermatologic improvement may serve as a visible marker of metabolic response.

Safety and Tolerability: Metformin has an established safety profile with gastrointestinal intolerance as the main adverse effect.[18] Semaglutide commonly causes nausea and vomiting but has low hypoglycemia risk.[22] Combination therapy is generally well tolerated and recommended in diabetes guidelines.[25]

Future Directions: There is a need for randomized trials evaluating AN severity scores with GLP-1RA–metformin therapy, long-term dermatologic outcomes, and correlation of AN regression with insulin resistance biomarkers.

CONCLUSION

Acanthosis nigricans (AN) is a cutaneous marker of insulin resistance frequently associated with obesity and type 2 diabetes mellitus (T2DM). Improvement of underlying metabolic dysfunction remains the cornerstone of management. Metformin has long been used to reduce insulin resistance and improve AN, while glucagon-like peptide-1 receptor agonists (GLP-1RAs) such as semaglutide provide potent weight reduction and glycemic control. Emerging data suggest that combining semaglutide with metformin may synergistically improve metabolic parameters and dermatologic manifestations in obese diabetic patients with AN

Semaglutide–metformin combination therapy produced significant improvement in Burke-graded AN severity and texture, indicating regression of epidermal hyperplasia and dermal thickening. Improvement strongly correlated with weight and glycemic reduction, supporting insulin-resistance reversal as the primary mechanism. GLP-1 receptor agonists reduce visceral adiposity, insulin resistance, and inflammatory mediators, explaining dermatologic benefit. AN may serve as a visible marker of metabolic recovery.

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