Original Article

Clinical outcome of metformin treatment in patients of acanthosis nigricans with insulin resistance

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Abstract

Background: Acanthosis nigricans (AN) is known to be associated with obesity, insulin resistance (IR) and other systemic morbid conditions. Proper treatment modalities of AN has not been established yet. Metformin may have some therapeutic effects on AN by reducing IR. Objective of the study was to examine the effect of metformin on AN in insulin resistant cases.

Methodology and Results: This prospective, controlled trial was conducted in Dermatology OPD of BIRDEM General Hospital, Dhaka from September 2012 to August 2013. All the participants of the study had clinical presentation of AN on different anatomic locations such as neck, axilla, elbow, knuckle and knee and biochemical evidence of IR. Participants were of either sex with age ranging from 18 to 80 years. Any case who had contraindications to metformin therapy were excluded. Severity of AN was examined and assessed by a quantitative scale for measuring acanthosis nigricans. After detecting IR by Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), cases and controls were selected by random sampling method. Randomization was done for metformin in ratio of 2:1. Every third patient was a control. Forty study participants were assigned to receive tablet metformin 500mg thrice daily after meal for three months and twenty control participants were continued on their existing therapy. To maintain a static metabolic status, patients were allowed to remain with their previous diet and lifestyle habit. After 3 months of metformin therapy, improvement was assessed and was compared with control group.

Mean age of the participants in case of male: 19.75±2.36 and in case of female: 26.58±9.38, M:F= 1:14, BMI of male: 32.15±4.15 and female: 33.18± 8.05. Mean baseline neck severity score of AN: 3.57 ± 0.78 and after metformin therapy: 2.65 ± 1.02, t-test value: 4.53. Baseline neck texture score of AN: 1.87±0.80, after metformin therapy: 1.25 ± 0.86, t-test value: 3.30. Baseline AN on axilla: 3.05 ± 0.94, after metformin therapy: 2.10 ± 0.98, t-test value: 4.56. Significant improvement of AN was observed clinically on neck and axilla ($P < 0.005$) when compared with control. However, in case of AN on knuckle, elbow and knee, improvement rates were not statistically significant. No side-effect except nausea in 4 patients was reported during study period.

Conclusion: Metformin therapy for AN with IR had a significant beneficial effect clinically and was safe and well-tolerated. The effect was more pronounced in neck and axilla.

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Introduction

Acanthosis nigricans (AN) is a common skin manifestation of obesity, insulin resistance (IR), dyslipidemia, hypertension (HTN), diabetes mellitus (DM) and malignancy [1-4]. It provides cosmetic unimpressiveness that secondarily may cause depressive state [5]. AN clinically presents with hyperpigmented, hyperkeratotic, verrucous plaques with velvety texture on intertriginous skin such as neck, axilla, elbow, groin and even on other non-intertriginous areas as well[6-9]. Mucocutaneous involvement has also been reported [10]. IR associated AN has strong association with obesity, cardiovascular diseases and it is very much common in non-whites [5, 11]. Early detection, diagnosis and treatment of AN can help to reduce morbidity, improve appearance and have a positive impact on the quality of life of these patients [12].

Metformin is abundantly used in insulin resistant cases [13,14]. It may have some effects on AN by reducing IR and thus ultimately may reduce clinical manifestations of AN [15-17].

In view of the above, the objective of the present study was to examine the clinical effect of metformin treatment on AN in insulin resistant patients.

Materials and Methods

Selection of study population

This randomized prospective controlled trial was conducted in the Department of Dermatology of Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), Shahbag, Dhaka from September, 2012 to August, 2013. One hundred adult cases with clinical presentation of AN on neck and axilla with or without involvement of knuckles, elbows and knees and with the biochemical evidence of IR were primarily selected. Out of which, sixty patients consented to participate in the study. Patients with AN due to causes other than IR namely impaired renal or liver function and pregnant and nursing mothers were excluded. Interview was conducted at a suitable time and place that was convenient to the responder.

Scoring of AN and determination of IR

Clinical presentation of AN was verified and diagnosed by dermatologist. The classification and scoring of AN was done by a qualified dermatologist on the basis of a quantitative scale for measuring acanthosis nigricans [18]. IR was measured by Homeostatic Model Assessment-Insulin Resistance (HOMA-IR) equation from fasting insulin and glucose levels.

The approximating equation for IR, in the early model, used a fasting plasma sample and was derived by use of the insulin-glucose product, divided by a constant:

$$\text{HOMA-IR} = \frac{\text{Glucose} \times \text{Insulin}}{22.5} \text{ (Glucose in mmol/L)}$$

Our cut-off value of having IR in HOMA-IR was 1.82 [19].

Randomization of cases

Randomization was done for drugs (metformin) in ratio of 2:1. Every third patient was a control. Therefore, forty patients were in the drug group (metformin) and twenty were in control group. Patients in drug group were given tablet metformin 500mg thrice daily after meal for three months and controls were maintained in their usual therapeutic regime for same duration. Other factor such as amount of food was not restricted and physical exercise was not added. After 3 months, status of AN of each participant was measured by the previous quantitative scale.

Data were expressed as mean and standard deviation. Paired Student's t test was done for analysis of variables and Fisher's Exact test was used to test for differences in proportions for categorical variables. A p value of <0.05 was considered as significant. The International Business Machines Corporation- Statistical Package for the Social Sciences (IBM-SPSS) version 20.0 software was used to analyze the data.

Informed written consent was obtained from all participants. The study was approved by the Ethical Review Committee of Diabetic Association of Bangladesh.

Results

Among the sixty participants, forty were in study group and twenty were in control group. Mean age of male: 19.75±2.36 and female: 26.58± 9.38, M:F= 1:14 (M 6.66%, F 93.33%), Body Mass Index (BMI) of male: 32.15 ± 4.15 and female:33.18 ± 8.05. History of gestational diabetes mellitus: 11.76%, family history of diabetes mellitus and/ or hypertension: 88.33%, hirsuitism: 46.55 % and menstrual irregularity: 46.55%. There was no significant difference between study and control groups in case of age, BMI and HOMA-IR levels. Baseline characteristics of the all participants are shown in Table-1.

Table-1: *Baseline characteristics of the participants*

Variables	Mean score ± SD		t-test	Sig.
	Study group	Control group		
Age	26.15±10.10	26.1±7.42	-0.02	0.98
BMI	34.45±8.55	30.43±5.41	-1.91	0.06
HOMA-IR*	9.41±8.63	6.34±2.38	-1.55	0.12
Sex (M/F)	3 / 37	1 / 19		

**Cut-off value of having insulin-resistance in HOMA-IR was 1.82 [18].*

All participants in both groups had AN on neck and axilla. In addition to AN in neck and axilla, 31, 30 and 27 cases had AN on elbows, knees and knuckles respectively.Their distribution in drug and control group are shown in Table-2.

After 3 months treatment with metformin, significant improvement (P< 0.005) of AN was observed clinically on neck and axilla compared to controls. Improvement rates with metformin in case of neck severity, neck texture and axilla were estimated as 67.5%, 62.2% and 70% consequently. However, regarding AN on knuckles, elbows and knees, the improvement rates with metformin were respectively 25%, 29.16% and 37.5% which were not significant. On the other hand, improvement rates of neck severity, neck texture and axilla among cases of control group was11.11%. Improvement rates in cases of control group of elbow, knee and knuckle were 14.28%, 16.66% and 0% respectively. No side-effect except nausea in four subjects was reported during study period.

Table-2: *Improvement rates of AN on different anatomic locations*

Severity / Presence of AN		Improved (%)	Not Improved (%)	P value
Neck Severity	Control (n=20)	11.11	88.89	
(n= 60)	Drug (n=40)	67.5	32.5	<0.005
Neck Texture	Control (n=20)	11.11	88.89	
(n=60)	Drug (n=40)	62.2	37.8	<0.005
Axilla	Control (n=20)	11.11	88.89	
(n=60)	Drug (n= 40)	70.0	30.0	<0.005
Elbow	Control (n=7)	14.28	85.72	
(n=31)	Drug (n=24)	29.16	70.84	>0.05
Knee	Control (n=6)	16.66	83.34	
(n=30)	Drug (n=24)	37.50	62.50	>0.05
Knuckle	Control (n=7)	00.00	100.00	
(n=27)	Drug (n=20)	25.00	75.00	>0.05

Table-3: *Improvement of AN in different sites following metformin treatment as determined by quantitative scale of measuring AN*

Presence of AN	Intervention	Mean score ± SD		t-test	Sig.
		Before	After		
¥Neck Severity	Control	2.18±1.90	2.95±1.00	-0.42	0.267
	Drug	3.57±0.78	2.65±1.02	4.53	0.000
¥Neck Texture	Control	1.35 ± 0.93	1.70±0.82	-1.27	0.069
	Drug	1.87 ± 0.80	1.25±0.86	3.30	0.000
¥Axilla	Control	2.45 ± 0.99	2.55±0.87	-0.32	0.428
	Drug	3.05 ± 0.94	2.10±0.98	4.56	0.000
*Elbow	Control Drug	P = 0.641			
*Knee	Control Drug	P = 0.632			

¥ t-test was done to compare between effect of Metformin and Placebo

** Fisher's Exact test was done in case of AN on elbows and knuckles*

Discussion

This study demonstrates that metformin therapy for AN with IR has a significant beneficial effect and is also safe and well tolerated. Improvement was assessed by reduction of score as measured by the quantitative scaling method scale [18] and vice versa. The study also reveals that metformin has different clinical effects on AN in different anatomic location. It seems that its effect is more pronounced in AN affecting axilla and neck. It could be due to the presence of more insulin-like

growth factor 1 receptors in these specific sites. But further specific study is needed to elucidate its mechanism in these sites.

Our cases had evidence of IR which was confirmed by HOMA method [20-26]. We safely used daily dose of 1.5 g metformin, whereas data from adults with type 2 diabetes suggest that a total daily dose of 3 g may be required to maximize the metabolic benefits of metformin therapy [27]. In a randomized controlled trial, the median AN neck severity score was significantly less ($p < 0.0304$) in metformin treated cases (score 3.0) compared to that of placebo group (score 4.0) [27]. In this study, healthy eating and exercise effects were also included but in our study these factors were constant. However, metformin may not be the drug of choice in AN on the other areas such as knuckle, elbow and knee. But no long term study with higher dose has yet been conducted to see the effect of metformin on AN of knuckle, elbow and knee.

Correcting hyperinsulinemia was presumably accomplished by metformin and led to improvement or resolution of AN. Oral metformin hydrochloride is a first choice drug in the treatment of AN associated to obesity and IR [1]. Metformin does not induce hypoglycemia but prevents hyperglycemia. In IR, hyperinsulinemia precedes type 2 diabetes mellitus sometimes by many years. AN develops during this non-diabetic hyperinsulinemic period. Thus, recognition of AN identifies those at increased risk of developing type 2 diabetes mellitus, dyslipidemia and hypertension. Therefore, recognition of AN offers an opportunity for both preventive measures and focused intervention.

On the other hand, few authors failed to observe any clinical or biochemical changes after metformin therapy [28,29]. These discrepancies have not been explained. In addition, controlled long-term studies assessing the clinical effects of metformin treatment are still lacking.

The present study had some limitations. The sample size was small and the long-term effects of metformin on the outcome of AN could not be assessed. The diagnostic and scoring criteria used in the study was based solely on direct visual examination. No histopathological scoring or grading technique of AN was available. Study was precisely directed to AN associated with biochemical evidence of IR and AN due to other causes was not included.

The results of the present study indicate that statistically significant anti-acanthosis efficacy in neck and axilla can be achieved by using metformin alone in the presence of IR. It is also safe and well-tolerated. Thus it may have a positive impact on the quality of life. It can provide a promising new therapeutic strategy for AN in cases with IR type 2 diabetes mellitus. However, there was no significant improvement with metformin in AN on knuckles, elbows and knees. Prospective randomized trials with larger sample sizes, assessment of outcomes by blinding of assessors are required to confirm the effects of metformin on AN in other sites. Future research should also aim to determine the histopathological changes in AN with metformin therapy in different anatomic locations of body.

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