Abstract

Background: Acanthosis nigricans has been associated with conditions of insulin resistance such as obesity, polycystic ovary syndrome, and type 2 diabetes. Metformin and alpha-lipoic acid, two types of insulin-sensitizing agents, have been demonstrated to reduce insulin levels and improve insulin sensitivity. Alpha-lipoic acid is available as a fixed-dose combination with biotin, calcium pantothenate, and zinc sulfate as Canthex™. Aims: This study aimed to compare the effectiveness, safety, and improvement of the insulin resistance profile of Canthex™ and metformin in acanthosis nigricans. Materials and Methods: In this double-blind, randomized (1:1), active-controlled trial (CTR1/2017/02/007880), participants received either metformin 500 mg BD or Canthex™ BD for 12 weeks. Effectiveness parameters were improvement of severity of neck lesions and neck texture. Serum fasting insulin level, glucose, lipids, body weight, waist circumference, body mass index (BMI), and homeostatic model assessment-insulin resistance (HOMA-IR) were also assessed at baseline and at the end of the study. Adverse effects and changes in routine laboratory parameters were taken as safety parameters. Results: Thirty-three patients were analyzed by modified-intention-to-treat criteria. Severity of neck lesions and texture were comparable at baseline and it showed significant reduction (P<0.001) in both the treatment arms from the first follow-up onward. No intergroup variation was observed in any of the follow-ups. There was reduction in the values of fasting insulin, blood sugar, total cholesterol, and thyroid-stimulating hormone in both the groups. Weight, BMI, and waist circumference and BMI reduced significantly in both the groups. HOMA-IR decreased significantly in metformin group (P=0.001). Conclusion: Canthex™ is as effective and safe as metformin in the management of acanthosis nigricans and associated features of insulin resistance.

Key Words: Acanthosis nigricans, alpha-lipoic acid, Canthex™, insulin resistance, metformin

Introduction

Acanthosis nigricans is an asymptomatic dermatosis distributed symmetrically over the intertriginous areas as dark and thickened skin of velvety texture.[1] Histopathology reveals hyperkeratosis and papillomatosis with dermal papillae projecting upward in a finger-like fashion.[2] Obesity is a common association with acanthosis nigricans in children,[1] adolescents,[4] as well as in adults. Verma et al.[1] proposed using facial acanthosis nigricans as a marker for insulin resistance. Insulin resistance is characterized biochemically by hyperinsulinemia. At increased levels, insulin having crossed the dermoepidermal junction binds to the insulin-like growth factor-1 receptors, thereby exerting its growth promoting effects through proliferation of fibroblasts and keratinocytes, giving rise to the characteristic features of acanthosis nigricans.[6]

In patients with type 2 diabetes mellitus, polycystic ovary syndrome (PCOS), and in conditions characterized by insulin resistance, metformin and alpha-lipoic acid, two types of insulin-sensitizing agents have been demonstrated to reduce insulin level and improve insulin sensitivity.[7,8] Canthex™ consists of a fixed-dose combination of alpha-lipoic acid 200 mg, biotin 5 mg, calcium pantothenate 200 mcg, and zinc sulfate 25 mg. Alpha-lipoic acid, a potent biological antioxidant and a naturally occurring cofactor of mitochondrial

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dehydrogenase complexes, has been found to improve glucose metabolism in patients with type 2 diabetes in clinical trials.\(^9\) It appears to act by direct engagement of signaling pathways, thereby increasing insulin sensitivity in patients.\(^10\) Biotin is thought to improve abnormal glucose metabolism by stimulating glucose-induced insulin secretion in pancreatic beta-cells and by accelerating glycolysis in the liver and pancreas.\(^11\) Biotin also enhances muscle insulin sensitivity by increasing guanylate cyclase activity.\(^12\) Zinc has a clear role in the synthesis, storage, and secretion of insulin as well as conformational integrity of insulin in the hexameric form, which affects the ability of the islet cell to produce and secrete insulin.\(^13\)

Since both metformin and Canthex™ have an effect on improving insulin sensitivity, we considered comparing the effectiveness, safety, and improvement of the insulin resistance profile of these two agents on patients of acanthosis nigricans.

Materials and Methods

The study was designed as a double-blind, randomized, active-controlled trial. Institution Ethics Committee clearance was obtained before commencement of the study. Written informed consent was obtained from all trial participants. Adult patients (≥18 years) with acanthosis nigricans attending the outpatient department of dermatology in a tertiary care hospital in eastern India were included. Pregnant and lactating mothers, those with renal or hepatic compromise, and not willing to participate in the trial were excluded from the study. The trial was registered with Clinical Trial Registry India (CTRI) and bears the registration number CTRI/2017/02/007880.

Visits

Baseline visit

After screening and including patients based on the inclusion criteria, at baseline, written informed consent was obtained. Eligible study participants were randomized equally (1:1 allocation ratio) into either treatment arm according to a computer-generated random number table. The randomized allocation was concealed by SNOSE technique. Group A received Canthex™ capsules twice daily (manufactured by Curatio, batch no. S15837081, date of manufacture: September 2015, date of expiry: February, 2017). Group B received metformin 500 mg tablets twice daily (Glycomet, manufactured by USV Ltd., batch number. 28012215, date of manufacture: July 2016, date of expiry: June 2019).

Acanthosis lesions were graded and texture was defined according to gradation by Burke et al.\(^14\) A run-in period of 2 days were given for each patient. Waist circumference, height, and weight were measured as well as blood collected for routine investigations and fasting insulin level, fasting lipids, thyroid-stimulating hormone (TSH), and fasting blood sugar. Each study patient was provided with coded boxes containing medications for 4 weeks as per randomization and explained regarding dosage – twice daily for 3 months. The study participants were asked to come back for monthly follow-ups for 3 months.

Follow-up visits

Follow-ups were carried out at 4 weekly intervals for 12 weeks. At each subsequent follow-up, the study parameters were noted, adverse events (if any) were recorded and study medications were dispensed. At the final visit at 12 weeks, end-of-treatment blood investigations were again performed.

Blinding

Since one study medication was a tablet and the other a capsule, each of the medication was encapsulated in a slightly bigger sized opaque empty capsule (supplied by La Chemico Pvt. Ltd.) which made both the trial drugs similar looking. A third person (nurse) who was not a part of the trial did the above-mentioned packaging. Study participants were thus blinded by supplying each patient with similar looking capsules in coded airtight boxes (according to group), asked to be taken twice daily. The assessing physician was different from the dispensing physician who randomized and dispensed the study medications. Thus, double blinding was achieved.

Effectiveness parameters

The primary outcome measures for effectiveness were improvement of severity of neck lesions and neck texture. The severity of neck lesions was graded in a scale from 0 to 4, where 0 meant absent or lesions not detectable on close inspection, 1 meant lesions clearly present on close observations, 2 meant mild lesions limited to the base of the skull but did not extend to the lateral margins of the neck (usually, <3 inches in breadth), 3 meant moderate lesions extending to the lateral margins of the neck (posterior border of the sternocleidomastoid) (usually, 3–6 inches), and 4 meant severe lesions extending anteriorly (>6 inches), visible when the participant is viewed from the front.\(^14\) Improvement of neck texture was also assessed by a 4-point grading scale (0–3): 0 for neck texture meant smooth to touch with no differentiation from normal skin on palpation, 1 meant rough to touch and clearly differentiated from normal skin, 2 meant coarseness could be observed visually with portions of the skin clearly raised above surrounding area and 3 meant extremely coarse with “hills and valleys” observed on visual examination.\(^14\) The outcome measures for insulin resistance were serum fasting insulin level (measured by enzyme-linked immunosorbent assay), serum fasting glucose, and serum fasting lipids. Obesity parameters such as changes in body weight,
waist circumference, and quantification of body mass index (BMI) were also taken. Homeostatic model assessment-insulin resistance (HOMA-IR) was derived from fasting glucose level and fasting insulin level and was taken as a secondary parameter. HOMA-IR quantifies insulin resistance and beta cell function.[15]

**Safety parameters**
Solicited and unsolicited adverse events reported by patients and elicited by clinicians were recorded at each follow-up. Changes in laboratory measures of routine hemogram, serum urea, creatinine, and liver function tests were noted at baseline and at the end of 12 weeks.

**Statistical analysis**
The target sample size was 40, with 20 evaluable patients in each treatment arm, considering an effect size of 2 units reduction in severity of neck lesions, with 80% power and 5% probability of type 1 error and assuming a standard deviation of 2.25 for this parameter. Considering a 10% possible dropout rate, this translated to a recruitment target of approximately 22 patients per group or 44 patients overall. Continuous variables were compared within group by paired t-test, repeated-measures analysis of variance (ANOVA), and between groups by independent samples t-test. For comparison of unpaired nonparametric data, Mann–Whitney U-test was employed. Friedman’s ANOVA was carried out with nonparametric data for within group repeated-measures comparisons, followed by post hoc Dunn’s test. Categorical data were compared between groups by Chi-square test or Fisher’s exact test, as applicable. MedCalc version 12.5.0.0 (MedCalc Software, 2011, Mariakerke, Belgium) was used for statistical analysis. Insulin resistance was calculated using HOMA Calculator version 2.2.3.

Effectiveness analysis was done on modified intention-to-treat basis with patients reporting for at least one postbaseline follow-up visit. The last observation was carried forward to deal with the missing values. Modified intention to treat analysis was done and patients reporting for at least one postbaseline follow-up were taken.

**Results**
Among the 50 study participants screened, 44 were randomized equally into two groups receiving either metformin or Canthex™. Eleven participants were lost to first follow-up leaving 33 evaluable participants as per our modified intention-to-treat analysis. The flowchart of study participants is given in Figure 1.

There was predominance of female patients in both treatment arms and were of the younger age group in their early twenties. They were comparable with respect to age, sex, rural–urban status, and economic status. There was no significant difference in the mean duration of acanthosis nigricans. Only 2 patients (11.7%) had diabetes mellitus as comorbidity [Table 1].

Severity of neck lesions was comparable at baseline, and it showed significant reduction in both the treatment arms from the first follow-up onward (P<0.001). However, no intergroup variation was observed in any of the follow-ups [Table 2]. Significant improvement in neck texture was evident from first follow-up onward.

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**Figure 1:** Algorithm depicting the flow of the study participants
in both treatment groups (P<0.001), without any intergroup differences observed at any of the follow-ups [Table 3, Figures 2 and 3].

The mean fasting insulin level at baseline was higher than normal (<25 mIU/L) in both the treatment groups. There was a reduction in the values of fasting insulin, fasting blood sugar, total cholesterol, and serum TSH from baseline in both the groups, though this reduction was not significant. The reduction of fasting blood sugar in the Canthex™ group showed near significant reduction (P=0.054). There was a slight increase in serum triglycerides in the metformin group, though this change was within normal limits and not significant. There were no significant changes in the above-mentioned biochemical parameters between the two treatments at the study end [Table 4].

Body weight and BMI reduced significantly from baseline from 8th week onward with metformin and at 12th week with Canthex™. Waist circumference also decreased significantly from baseline in both metformin (P<0.001) and Canthex™ (P<0.001) from 8th week onward. Between-groups comparison showed no significant difference in body weight, BMI, and waist circumference at all follow-up visits [Table 5]. Insulin resistance as estimated by HOMA-IR decreased in both the study arms, however, significant difference was found in the metformin group (P<0.001). There was no significant intergroup variability of insulin resistance at baseline or at the study end [Table 6].

Adverse events were mild, including nausea (6%), vertigo (15.1%), and indigestion (12.1%). However, they were comparable in both the study groups.

**Discussion**

Acanthosis nigricans poses a therapeutic challenge. Established modalities of treatment of acanthosis nigricans

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**Table 1: Clinicodemographic profile of acanthosis nigricans patients in the study**

| Parameters                      | Canthex™ (n=17) | Metformin (n=16) | P (between groups) |
|---------------------------------|-----------------|------------------|--------------------|
| Age (years), mean±SD            | 23.38±12.74     | 21.83±10.96      | 0.697              |
| Gender, n (%)                   |                 |                  |                    |
| Male                            | 6 (35.29)       | 6 (37.5)         | 1.000              |
| Female                          | 11 (64.71)      | 10 (62.5)        |                    |
| Income, n (%)                   |                 |                  |                    |
| APL                             | 15 (88.23)      | 14 (87.5)        | 1.000              |
| BPL                             | 2 (11.76)       | 2 (12.5)         |                    |
| Residence, n (%)                |                 |                  |                    |
| Urban                           | 7 (41.17)       | 7 (43.75)        | 1.000              |
| Rural                           | 10 (58.82)      | 9 (56.25)        |                    |
| Duration of disease (months), mean±SD | 46.27±54.56   | 40.66±38.36      | 0.810              |
| Comorbidities                   |                 |                  |                    |
| Present                         | 2               | 0                | 1.000              |
| Absent                          | 15              | 16               |                    |

*P value obtained by unpaired Student’s t-test for age, Fisher’s exact test for gender, income, residence, comorbidities, and Mann–Whitney U-test for duration. SD: Standard deviation, APL: Above poverty line, BPL: Below poverty line.

**Table 2: Changes in the severity of neck lesions in the treatment arms**

| Severity of neck lesion | Canthex™ (n=17) | Metformin (n=16) | P (between groups) |
|-------------------------|-----------------|------------------|--------------------|
| Baseline, mean±SD       | 3.41±0.61       | 3.25±0.77        | 0.600              |
| 1st follow-up, mean±SD  | 2.82±0.72*      | 3.00±0.81*       | 0.531              |
| 2nd follow-up, mean±SD  | 2.47±0.79*      | 2.43±0.62*       | 0.907              |
| 3rd follow-up, mean±SD  | 1.88±0.69*      | 1.87±0.61*       | 1.000              |

*P value within group by Friedman’s ANOVA followed by posthoc Dunn’s test, P value between groups by Mann–Whitney U-test.
*Denotes significant difference from baseline for that particular follow-up. ANOVA: Analysis of variance, SD: Standard deviation.

*Figure 2: Pretreatment photograph showing acanthosis nigricans lesions of the neck at baseline*
have been topical use of retinoids, α-hydroxy acids, or salicylic acid in adjunct with treatment of underlying condition.[13] Among the orally used drugs, insulin sensitizers such as metformin, rosiglitazone,[14] sitagliptin,[15] and oral retinoids such as isotretinoin and acitretin[16] have been assessed to have some effect in reduction of cutaneous lesions in acanthosis nigricans. However, to the best of our knowledge, effectiveness of alpha-lipoic acid in acanthosis nigricans has not yet been studied.

Metformin is an oral biguanide antidiabetic agent. Hyperinsulinemia and insulin receptor dysfunction lead to endocytosis of GLUT-4 receptors. Metformin facilitates utilization of peripheral glucose, reduction of hyperinsulinemia, and improvement of insulin sensitivity by preventing endocytosis of GLUT-4 receptor and by expression on the cell surface.[19] Alpha-lipoic acid has been demonstrated to enhance insulin sensitivity by interfering with oligomycin-induced mitochondrial dysfunction.[20]

An open-label trial from Mexico on obese acanthosis nigricans patients showed modest improvement in skin texture with 12 weeks of metformin, administered 500 mg thrice daily and rosiglitazone 4 mg once daily, with significant reduction in insulin levels evidenced only with

| Table 3: Changes in the neck texture in the treatment arms |
|---------------------------------------------------------|
| Changes in neck texture | Canthex™ (n=17) | Metformin (n=16) | P (between groups) |
|-------------------------|-----------------|-----------------|-------------------|
| Baseline, mean±SD      | 2.00±0.93       | 1.62±0.88       | 0.244             |
| 1st follow-up, mean±SD | 1.64±0.86*      | 1.18±0.91*      | 0.171             |
| 2nd follow-up, mean±SD | 1.29±0.77*      | 0.87±0.61*      | 0.113             |
| 3rd follow-up, mean±SD | 0.88±0.60*      | 0.50±0.73*      | 1.000             |
| P (within group)       | <0.001          | <0.001          |                   |

P value within group by Friedman’s ANOVA followed by posthoc Dunn’s test, P value between groups by Mann–Whitney U test.

*Denotes significant difference from baseline for that particular follow-up. ANOVA: Analysis of variance, SD: Standard deviation

| Table 4: Changes in biochemical parameters in the study groups |
|---------------------------------------------------------------|
| Biochemical parameters | Canthex™ (n=17) | Metformin (n=16) | P (between groups) |
|------------------------|-----------------|-----------------|-------------------|
| Fasting insulin       |                 |                 |                   |
| Baseline               | 29.51±28.895    | 27.10±19.463    | 0.782             |
| EoT                    | 26.89±27.94     | 19.99±20.918    | 0.427             |
| P (within group)       | 0.538           | 0.123           |                   |
| Fasting blood sugar    |                 |                 |                   |
| Baseline               | 92.51±32.78     | 101.18±21.37    | 0.377             |
| EoT                    | 86.33±30.52     | 96.81±21.35     | 0.264             |
| P (within group)       | 0.054           | 0.231           |                   |
| Total cholesterol      |                 |                 |                   |
| Baseline               | 173.76±39.41    | 161.31±31.80    | 0.327             |
| EoT                    | 174.05±36.15    | 158.37±32.67    | 0.201             |
| P (within group)       | 0.977           | 0.642           |                   |
| Serum triglycerides    |                 |                 |                   |
| Baseline               | 152.33±73.87    | 140.31±69.42    | 0.633             |
| EoT                    | 143.81±51.35    | 155.68±86.88    | 0.633             |
| P (within group)       | 0.316           | 0.340           |                   |
| Serum TSH              |                 |                 |                   |
| Baseline               | 4.90±5.85       | 3.29±2.52       | 0.316             |
| EoT                    | 2.85±2.77       | 2.13±1.03       | 0.340             |
| P (within group)       | 0.062           | 0.137           |                   |

P value between groups by unpaired Students’ t-test and within groups by paired Students’ t-test. EoT=End-of-treatment follow-up
Fasting glucose levels were reduced to a near significant level with Canthex™ in our study without any significant effect on other biochemical parameters. Cappelli investigated the association of insulin sensitizers and alpha-lipoic acid in obese PCOS patients and alpha-lipoic acid in combination with myo-inositol and metformin showed significant reduction in BMI. Our study failed to show any significant change in BMI with alpha-lipoic acid alone, though it was appreciated in the metformin group.

Metformin has been the standard oral therapy for acanthosis nigricans patients. Our study in accordance with the available published literature shows that alpha-lipoic acid is also efficacious in improving the signs of acanthosis, decreasing body weight and waist circumference, and decreasing the metabolic parameters associated with insulin resistance comparable to metformin with very few adverse effects. However, long-term studies need to be conducted with a larger sample size to establish the long-term effect of the drug.

Our study was limited by the fact that due to drop out, the sample size of our study decreased to 33 instead of the calculated 40 participants.

**Conclusion**

Canthex™ is as effective and safe as metformin in the management of acanthosis nigricans, with significant improvement in both the severity of lesion and skin texture evident after 4 weeks of therapy. Canthex™ is also instrumental in significant reduction of anthropometric parameters associated with obesity and improvement of insulin resistance comparable to metformin. Thus, Canthex™ can be recommended as a new oral medication in the armamentarium of dermatologists to combat the challenge of acanthosis nigricans and also in those patients who are not tolerating metformin.

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**Table 5: Changes in obesity parameters in the study arms**

| Obesity parameters | Canthex™ (n=17) | Metformin (n=16) | P (between groups) |
|--------------------|-----------------|------------------|-----------------|
| Weight Baseline | 66.35±9.02 | 67.93±17.93 | 0.748 |
| 4th week | 65.88±9.16 | 67.81±18.22 | 0.701 |
| 8th week | 65.58±10.25 | 66.62±17.96 | 0.838 |
| EoT | 64.88±10.68 | 65.81±18.04 | 0.857 |
| P (within group) | 0.029 | <0.001 | 0.701 |
| BMI | 26.73±3.59 | 25.77±5.10 | 0.537 |
| 4th week | 26.69±3.89 | 25.69±4.96 | 0.521 |
| 8th week | 26.43±4.13 | 25.24±4.94 | 0.457 |
| EoT | 26.13±4.19 | 24.93±4.98 | 0.459 |
| P (within group) | 0.036 | <0.001 | 0.838 |
| Waist circumference Baseline | 95.35±8.02 | 91.71±11.96 | 0.310 |
| 4th week | 94.67±9.02 | 91.18±12.01 | 0.350 |
| 8th week | 92.67±9.32 | 89.90±11.33 | 0.460 |
| EoT | 92.50±9.71 | 88.84±11.12 | 0.321 |
| P (within group) | <0.001 | <0.001 | 0.701 |

*Denotes significant reduction of that particular follow-up from baseline. P value between groups by unpaired Student’s t-test. P value within group by repeated-measures ANOVA followed by posthoc Tukey’s test. EoT: End of treatment, ANOVA: Analysis of variance

**Table 6: Changes in insulin resistance in the treatment groups**

| IR (HOMA-IR) | Canthex™ (n=17) | Metformin (n=16) | P (between groups) |
|--------------|-----------------|------------------|-----------------|
| Baseline | 2.66±1.52 | 2.94±1.03 | 0.617 |
| EoT | 2.31±1.74 | 1.64±0.93 | 0.272 |
| P (within group) | 0.537 | <0.001 | 0.701 |

P value between groups by unpaired Students’ t-test. P value within groups by paired Students’ t-test. EoT: End of treatment. IR: Insulin resistance, HOMA-IR: Homeostatic model assessment-IR
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**Conflicts of interest**

There are no conflicts of interest.

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