Effect of Metformin on Mitophagy in Newly Diagnosed patients with T2DM: A Randomized, Placebo-Controlled Study

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INTRODUCTION

Besides insulin deficiency and insulin resistance, patients with T2DM exhibit abnormalities in cell reparative process like mitophagy (selective autophagy of mitochondria). Metformin is widely prescribed as a first-line drug in the management of T2DM. It is a potent insulin sensitizer and exerts its pleiotropic effects via AMPK, however, it’s effect on mitophagy remains unexplored.

AIM & OBJECTIVES

The present study aims to elucidate the effect of metformin on mitophagy in newly diagnosed patients with T2DM (NDT2DM). Following parameters were assessed at baseline and 3 months post follow-up :

- Mitochondrial stress indices including mitochondrial ROS (mtROS) content and mitochondrial membrane potential (MMP)
- Translational expression of mitophagy-related markers (PINK1, PARKIN, MFN2, NIX, LC3-II and LAMP-2)
- Quantification of damaged mitochondria in the study subjects by transmission electron microscopy (TEM)

METHODS

- Forty five drug-naïve NDT2DM patients with a duration of diabetes < 6 months and HbA_{1c} levels 7-8% (53-63.9 mmol/mol) were randomized into 3 groups (n=15 each):
 - Group-I received metformin at a dose of 2g/day in divided doses
 - Group-II received voglibose at a dose of 0.3 mg thrice/day
 - Group-III received placebo at a dose of 2g/day
 - All study subjects were advised to follow lifestyle modifications to achieve a target HbA_{1c} level ≤ 6.5% (47.5 mmol/mol)
- Voglibose was used as an active comparator to eliminate the effect of glucotoxicity on mitophagy, with respect to metformin
- Anthropometry, parameters of glucose-insulin homeostasis were assessed at baseline and after 12 weeks of treatment
- Mitochondrial oxidative stress indices, translational expression studies of mitophagy-related genes (*PINK1*, *PARKIN*, *MFN2*, *NIX*, *LC3-II*, and *LAMP-2*) and TEM studies were performed in peripheral blood mononuclear cells (PBMCs)

RESULTS

Baseline characteristics of NDT2DM Subjects				
Variables	Metformin (n=15)	Voglibose (n=15)	Placebo (n=15)	P value
Age (years)	47.8 ± 7	45.5 ± 8.7	44.1 ± 8.4	0.345
Gender (M:F)	7:8	6 :9	8:7	-
Ht. (cms)	155.0 ± 9.5	157.8 ± 9.2	156.2 ± 8.1	0.708
Wt. (Kgs)	70.1 ± 11.1	74.4 ± 9.3	72.9 ± 8.3	0.468
BMI (kg/m ²)	29.2 ± 3.3	29.9 ± 3.4	29.9 ± 3.5	0.824
WC (cms)	95.7 ± 5.3	99.3 ± 6.5	97 ± 8.6	0.361
Body Fat (%)	35.6 ± 10.6	37.5 ± 9.3	39.2 ± 8.9	0.596
Systolic BP	126.0 ± 12.9	127.3 ± 10.9	122.0 ± 10.8	0.434
Diastolic BP	82.0 ± 8.6	88.0 ± 7.4	80.4 ± 7.1	0.028*
FPG (mg/dl)	138.4 ± 17.2	140.9 ± 21.4	160.2 ± 22.1	0.010**
2hPG (mg/dl)	255.4 ± 57.5	241.4 ± 58.9	299.5 ± 58.9	0.025*
HbA _{1c} (%)	7.7 ± 0.4	7.6 ± 0.4	7.72 ± 0.4	0.664
FPI (μ IU/ml)	13.7 ± 5.3	15.9 ± 6.0	13.7 ± 5.1	0.438
HOMA-IR	4.8 ± 2.2	5.5 ± 2.1	5.6 ± 2.8	0.588
HOMA-β %	67.2 ± 27.7	75.3 ± 35.9	50.3 ± 14.0	0.084
CHOL (mg/dl)	188.5 ± 35.6	205.0 ± 40.7	204.0 ± 25.5	0.355
LDL-C (mg/dl)	125.1 ± 33.8	137.7 ± 31.0	133.7± 27.5	0.549
TG (mg/dl)	141.0 ± 41.9	159.0 ± 49.0	160.0 ± 66.6	0.559
HDL-C (mg/dl)	41.9 ± 6.4	41.2 ± 6.6	46.6 ± 13.5	0.277

Δ change in biochemical characteristics following treatment						
Variables	Metformin group	Voglibose group	Placebo group	Met vs. Vogli P value	Met vs. Plac P value	Vogli vs. Plac P value
ΔWt. (Kgs)	- 4.6 ± 3.4	- 3.9 ± 2.7	- 2.6 ± 2.9	1.000	0.277	0.863
Δ HbA _{1c} (%)	- 1.3 ± 0.5	- 1.2 ± 0.5	+ 0.2 ± 0.9	1.000	0.0001***	0.0001***
Δ HOMA-IR	- 1.8 ± 2.5	- 1.9 ± 1.6	- 1.2 ± 2.1	1.000	1.000	1.000
Δ HOMA-β %	+ 7.5 ± 32.9	+ 4.3 ± 28.4	+ 1.8 ± 24.9	1.000	1.000	1.000

Mitochondrial ROS (mtROS) Content and Mitochondrial Membrane Potential (MMP)

Protein Expression by Western Blot

Transmission Electron Microscopy (TEM)

DISCUSSION AND CONCLUSION

- Both metformin and voglibose treatment showed a similar efficacy towards the reduction in plasma glucose and HbA_{1c} levels.
- Weight loss was comparable among all the study subjects at the completion of the trial, indicating that the effect of both metformin and voglibose is neutral on weight homeostasis.
- Both the drugs reduced mitochondrial stress indices by decreasing glucotoxicity, though, mitophagy was significantly increased only with metformin treatment, resulting in reduced mitochondrial damage.

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