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Research Article

Berberine mitigates insulin resistance in newly diagnosed type 2 diabetics

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ABSTRACT:

Objective: To estimate the mitigating effect of Berberine on insulin resistance, glycemic control, and blood lipids in newly diagnosed type 2 DM (T2DM) subjects.

Study design: Case control study

Place and Duration: Department of Medicine, Liaquat University of Medical and Health Sciences Jamshoro/Hyderabad from February 2016 to August 2016.

Subjects and Methods: A sample of 68 newly diagnosed T2DM subjects divided into 2 groups; Group 1- metformin 500 mg x 3 daily and Group 2- berberine 500 mg x 3 daily were studied. Baseline blood samples were checked. After 3 months of metformin and berberine therapy; blood samples were collected again and analyzed on Roche Biochemical analyzer. HOMA was calculated as HOMA-IR = fasting insulin × fasting glucose/22.5. *Statistix 10.0* (USA) software was used for data analysis at 95% confidence interval ($P \leq 0.05$).

Results: After 3 months of BBR and metformin therapy; the fasting glucose and fasting insulin were decreased by 23.6% and 31%, & 9.5% and 9.01% respectively.

The BBR and metformin treated diabetics showed a 29.5% and 8.12% decrease in insulin resistance (HOMA-IR) respectively. HOMA-IR in metformin and berberine treated diabetics was decreased to 3.90±1.13 and 2.75 ± 0.73 respectively (p=0.0001).

Conclusion: The present study reports the Berberine is effective in mitigating the insulin resistance in newly diagnosed type 2 diabetics. Berberine decreased insulin resistance by 29.5% and metformin by 8.12%.

Key words: Berberine Metformin Insulin resistance Diabetes mellitus

INTRODUCTION

Diabetes mellitus (DM) is a multifaceted metabolic disorder of glucose which has now become a challenging health problem. DM is fast growing the World over. Asian countries such as Pakistan are now considered as the "diabetes capital".[1] Type 2 DM (T2DM) accounts for >90% of disease burden. The etiology of insulin resistance is complicated by multiple factors such as genetic, environmental and epigenetic factors, oxidative stress and inflammation.[2] The insulin resistance needs further comprehensive research on the pathophysiology of insulin resistance.[2,3] Newer drug discovery is also essential for handling the insulin resistance effectively.[2] Response to drug therapy is unsatisfactory despite effective medications. Most of hypoglycemic drugs eventually fail after long use in ameliorating the hyperglycemia.[4]

Berberine (BBR) is a natural herbal agent. It is the active ingredient of an ancient Chinese herb *Coptis chinensis* Franch. BBR is an isoquinoline alkaloid which differs from existing drugs such as biguanides, sulfonylureas, sitagliptin, rosiglitazone, thiazolidinediones, etc. The BBR has been used in China since centuries for the DM as traditional medicine. In China, it has been used as remedy for the

gastrointestinal problems also.[4,5] If BBR proves its efficacy and safety in type 2 DM then it may be used as a new class of anti hyperglycemic agent. A few clinical studies have reported the BBR is effective in controlling hyperglycemia. A previous study reported BBR decreased fasting blood glucose from 11.6 - 6.6 mmol/l after three months therapy.[6]

Another study reported BBR in doses of 0.3–0.5 g, three times daily improved the fasting and postprandial blood glucose by 21% and 27% respectively.[7] Wei et al reported BBR (0.5 gram thrice a day) decreased total cholesterol by 23%, triglyceride by 40% and fasting blood glucose by 31%.[8] In continuity to above studies, the present study was conducted to evaluate the effects of Berberine in type 2 diabetics at our tertiary care hospital. The primary objective was to evaluate the effect of BBR on insulin resistance.

SUBJECTS AND METHODS

The present case control open labelled interventional single centre study was conducted at the Department of Medicine, Liaquat University of Medical and Health Sciences Jamshoro/Hyderabad, Sindh from February 2016 to August 2016.

Inclusion criteria

Newly diagnosed type 2 DM patients of 20 - 60 years age taking metformin therapy were included.

Exclusion criteria

Newly diagnosed cases of type 2 DM, taking sulfonylurea drugs, herbal therapy, cholesterol lowering agents, anti hypertensive drugs, and multivitamin pills were excluded. Newly diagnosed T2DM subjects presenting with complications were also exclusion criteria. Those suffering from a concomitant major disease such as chronic viral hepatitis and chronic kidney disease, ischemic heart disease, psychiatric problems and pregnancy were also exclusion criteria. Other drugs were not allowed which might affect the study variables; such cases were also excluded.

Study Groups

- Group 1 (n=33). Newly diagnosed type 2 DM taking metformin therapy
- Group 2 (n=35). Newly diagnosed type 2 DM given berberine therapy

Drug therapy – berberine or metformin

Subjects were prescribed metformin – 500 mg x 3 daily (Merck Pharmaceuticals) and Berberine – 500 mg x 3 daily for 3 months.

Patients counseling and consent form

Subjects were interviewed and informed about the purpose of study. Merits and demerits of study were negotiated. Patients were informed that the new drug is reported very effective for the DM and the present study is intends to evaluate the efficacy of the drug Berberine. Volunteer subjects were asked to sign the consent form. They were informed that they can withdraw at any time because of any reason without telling, and this will not affect their future medical treatment.

Ethical approval and Performa

The study was approved by the ethical review committee. A performa was designed for the data collection

Patient examination

Diabetic subjects were examined by a medical officer, subjects who fulfilled the inclusion and exclusion criteria were referred to consultant physician. Demographic characters were entered in the Performa.

Blood sampling

Blood samples were taken at baseline and after third month of intervention. Blood sampling area was cleaned with alcohol swab after tourniquet was applied. 10 ml blood was taken into a disposable syringe (BD, USA) by venesection. Centrifugation of blood was performed at 4000 rpm for 10 minutes. Clear sera were stored at -20^{0}C for analysis. Sera contaminated with blood were excluded.

Biochemical testing

Blood glucose, HbA1c, fasting insulin, blood lipids, and serum creatinine were estimated by standard methods on Roche Biochemical analyzer (Cobas e 411 analyzer, Roche Diagnostics GmbH, Mannheim, Germany). HOMA was calculated as HOMA-IR = fasting insulin × fasting glucose/22.5.[9]

Statistical analysis

Statistix 10.0 (USA) software was used for data analysis using Student's t test and Chi square test (for continuous and categorical variables respectively). Data was analyzed at 95% confidence interval ($P \leq 0.05$).

RESULTS

Demographic characteristics of diabetics study subjects are shown in table 1. Diabetics were age, gender, height, weight and BMI matched (p>0.05). Difference was noted for the rural and urban diabetic subjects, the later predominated in the present study (p=0.034).

- **Baseline findings:**

Baseline body weight, BMI, systemic blood pressure, fasting and random blood glucose, HbA1c, serum creatinine, serum cholesterol, serum triglycerides, serum LDLc, serum HDLc, fasting blood glucose, fasting insulin and HOMA-IR are shown in table 1. Two groups were matched for above parameters except for diastolic BP (p = 0.038).

- **Third month findings**

Compared to metformin, the Berberine treated diabetics showed statistical significant decrease in the systemic blood pressure, body weight, BMI, fasting and random blood glucose, glycated HbA1, serum creatinine, serum cholesterol, serum triglycerides, serum LDLc, serum HDLc and fasting insulin after three months of BBR therapy ($p< 0.05$) as shown in table 3. Fasting blood glucose, fasting insulin and HOMA-IR showed statistically significant differences (p=0.0001) (Graphs 2 and 3).

The BBR group decreased the fasting glucose and fasting insulin by 23.6% and 31% respectively (p= 0.0001) and metformin group showed a reduction by 9.5% and 9.01% respectively at third month compared to baseline (p= 0.0001).

Insulin resistance (HOMA-IR) in metformin and berberine treated diabetics was reduced to 3.90± 1.13 vs. 2.75 ± 0.73 respectively at 3rd month compared to baseline 4.20± 0.33 vs. 3.95 ± 0.56 respectively (p=0.0001) (table 2 and 3). Approximate decrease in insulin resistance (HOMA-IR) was 29.5% in BBR group and 8.12% in metformin group compared to baseline. Graph 3 shows the insulin resistance (HOMA-IR) distribution, curve shows significant difference ($p<0.05$).

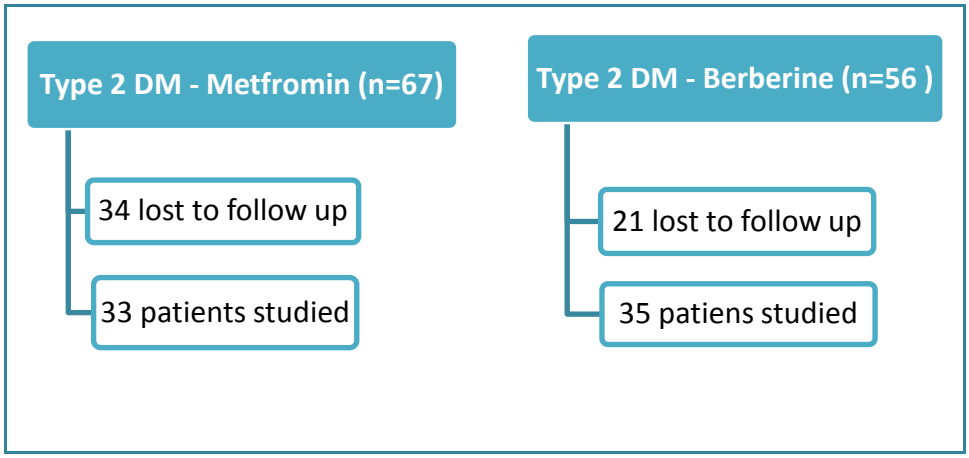


Chart 1. Showing diabetics studied and lost to follow ups

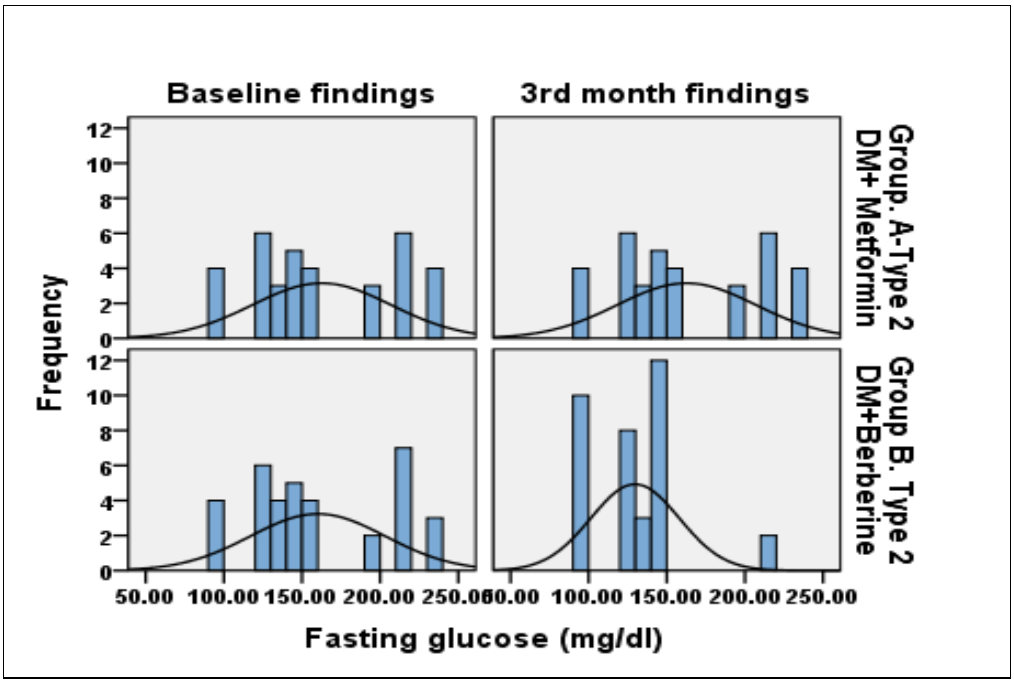
Table 1. Demographic characteristics of study subjects (n=68)			
	Group A. Metformin (n=33)	**Group. Berberine (n=35)**	**P-value**
Age (years)	51.88± 4.81	52.77±6.03	0.52
Body weight (kg)	56.9±19.7	55.7±16.73	0.07
Height (cm)	163.3±4.5	161.2±5.6	0.81
BMI	28.5±7.1	28.3±4.3	0.08
Male	19 (%)	20 (57.17%)	0.09
Female	14 (%)	15 (42.85%)	
Rural	09 (%)	14 (40%)	0.034
Urban	26 (%)	21 (60%)	

Table 2. Biochemical tests and HOMA-IR of study subjects (n=68)			
	FININDGS AT BASELINE		
	Group A. Metformin (n=33)	**Group. Berberine (n=35)**	**P-value**
	Mean ± SD	**Mean ± SD**	
Body weight (kg)	87.8±9.7	91.14±7.58	0.56
BMI (kg/m^2)	30.5±5.3	29.9±9.3	0.67
Systolic BP (mmHg)	159.3±25.0	161.0±23.7	0.91
Diastolic BP (mmHg)	91.57±14.4	83.85±15.9	0.038
Blood glucose (R) (mg/dl)	268.5±56.4	254.0±66.1	0.32
Glycated HbA1 (%)	12.91±4.7	11.80±4.1	0.72
Serum creatinine (mg/dl)	1.02±0.23	1.12±0.24	0.072
Serum cholesterol (mg/dl)	167.9±63.1	159.6±61.1	0.58

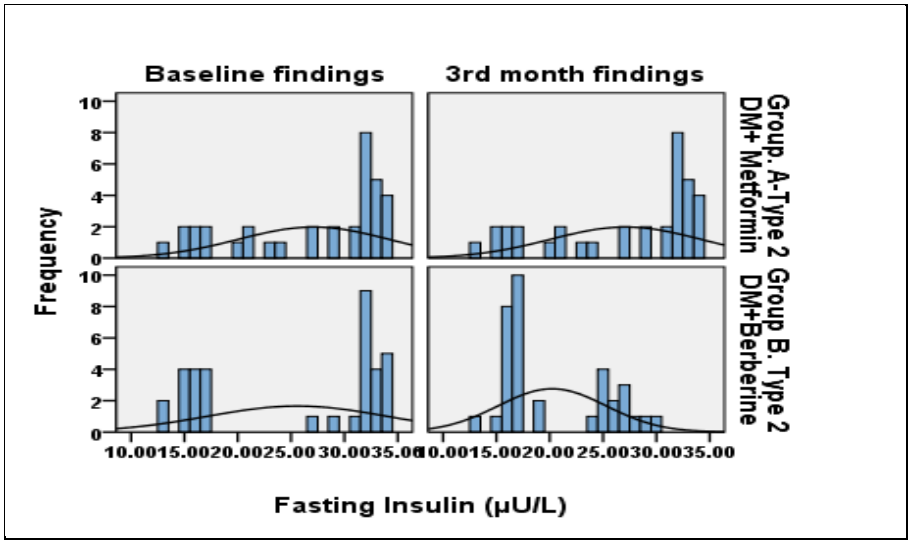
Serum triglycerides (mg/dl)	143.9±60.9	140.87±50.1	0.90
Serum LDLc (mg/dl)	157.9±	147.9±9.87	0.31
Serum HDLc (mg/dl)	39.9±9.7	39.87±5.35	0.35
Blood glucose (F) (mg/dl)	170.6 ±35.36	169.6± 31.3	0.81
Fasting Insulin (µU/L)	30.21±6.04	29.8± 7.06	0.40
HOMA-IR (%)	4.20±0.33	3.95±0.56	0.61

Table 3. Biochemical tests and HOMA-IR of study subjects (n=68)

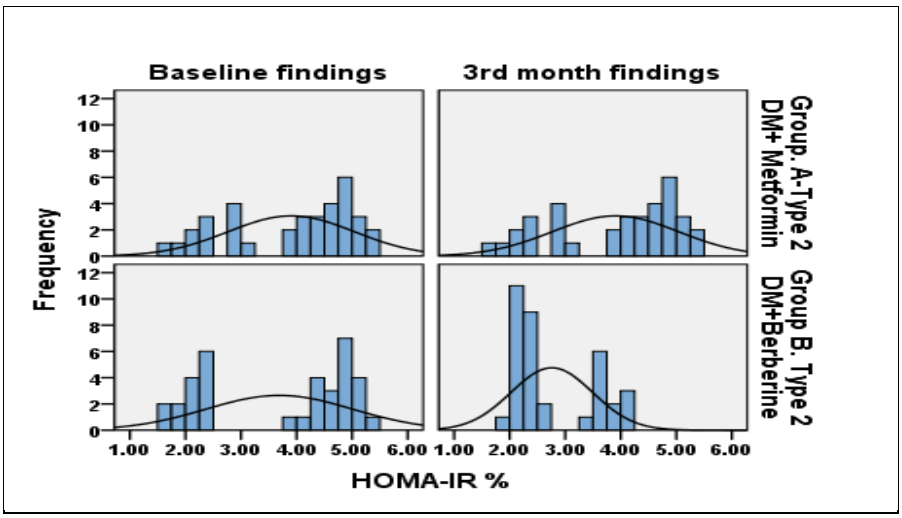
	FINDINGS AFTER 3rd MONTH		
	Group A. Metformin (n=33)	**Group. Berberine (n=35)**	**P-value**
	Mean ± SD	**Mean ± SD**	
Body weight (kg)	56.9±19.7	55.7±16.73	0.07
BMI (kg/m^2)	28.5±7.1	28.3±4.3	0.08
Systolic BP (mmHg)	159.43±25.01	147.91±22.03	0.046
Diastolic BP (mmHg)	91.57±14.48	84.17±14.8	0.047
Blood glucose (R) (mg/dl)	268.54±56.46	184.17±71.82	0.039
Glycated HbA1 (%)	11.71±1.24	10.47±3.33	0.047
Serum creatinine (mg/dl)	1.01±0.24	0.94±0.18	0.043
Serum cholesterol (mg/dl)	158.97±63.18	131.57±45.56	0.015
Serum triglycerides (mg/dl)	130.85±60.9	127.8±98.11	0.90
Serum LDLc (mg/dl)	141.0±32.88	117.40±26.55	0.001
Serum HDLc (mg/dl)	39.08±7.9	44.67±5.35	0.001
Blood glucose (F) (mg/dl)	162.6 ±44.36	149.6± 28.34	0.0001
Fasting Insulin (µU/L)	27.11±7.04	21.2±5.06	0.001
HOMA-IR (%)	3.90±1.13	2.75±0.73	0.001



Graph 1. Fasting glucose distribution at baseline and 3 month



Graph 2. Fasting insulin distribution at baseline and 3 month



Graph 3. HOMA-IR distribution at baseline and 3 month

DISCUSSION

The present study is the first case control open label interventional study being reported from Liaquat University Hospital. Baseline physical and biochemical parameters showed matched study subjects (table 2). Berberine 500 mg three times daily for 3 months was compared with metformin in newly diagnosed type 2 diabetics. The Berberine treated diabetics showed significant reduction in the systemic blood pressure, fasting and random blood glucose, glycated HbA1, serum creatinine, serum cholesterol, serum triglycerides, serum LDLc, serum HDLc and fasting insulin after three months ($p< 0.05$).

BBR treated subjects showed a decrease of 23.6% and 31% in fasting glucose and fasting insulin respectively compared to baseline ($p<0.001$), while metformin group showed a reduction of 9.5% and 9.01% respectively compared to baseline ($p<0.001$). Insulin resistance (HOMA-IR) in metformin and berberine treated diabetics was reduced to 3.90± 1.13 vs. 2.75 ± 0.73 respectively at 3rd month compared to 4.20± 0.33 vs. 3.95 ± 0.56 at baseline respectively ($p=0.0001$) (table 2 and 3). Approximate decrease in insulin resistance (HOMA-IR) was 29.5% in BBR group and 8.12% in metformin group compared to baseline. The findings are in agreement with previous studies.[10-20]

The findings of BBR of present study are in agreement with a previous study[7] which reported fasting and postprandial blood glucose reduction by 21% and 27% respectively.[7] Yet, another previous study reported BBR (0.5 gram thrice a day) therapy decreased total cholesterol by 23%, triglyceride by 40% and fasting blood glucose by 31%.[8]

A meta-analysis of 14 randomised clinical control trials (RCT) covering 1068 patients of type 2 diabetics treated with berberine, reported BBR exerts anti hyperglycemic and anti hyperlipidemia effects.[10] The present study is in agreement with above findings and reports the BBR mitigates hyperglycemia, hyperlipidemia and insulin resistance.

Shende et al[11] studied 30 newly diagnosed type 2 DM divided into metformin and berberine groups (15 in each group) and reported berberine was more effective than metformin in ameliorating the glycemic status.

Yin J et al[12] have reported similar observation on the berberine in diabetics. They concluded that the berberine reduced HbA1c by 2% more than metformin. The findings are in consistent to present study. Jin Y et al[12] used 500 mg of BBR three times daily similar to present study.

The finding of present study of BBR mitigating insulin resistance by 29.5%, and decreasing fasting blood glucose and fasting insulin are worth to report. Both metformin and berberine were well tolerated well by study subjects without any major side effects except of minor gastric upset with berberine. The findings support the previous studies. [13,14]

Underlying physiological mechanism of berberine remains to be elucidated, but some mechanisms have been suggested such as; activation of AMPK in liver, up modulation of Glucose transporter 4 in target organs, increased Glucose transporter- 1 activity in pancreas to secrete insulin and insulin receptor expression. Increased expression of LDL receptors and inhibition of intestinal α-glucosidase have been suggested underlying mechanisms.[15-20] But, these mechanisms are waiting for evidence based research.

The present study has limitations of small sample size, short duration, and open label observational study. Findings of present cannot be generalized or interpreted for uncontrolled type 2 diabetics and neither for hospitalized patients. However, the BBR mitigates insulin resistance (HOMA-IR) is a new finding being reported. Berberine is an effective anti hyperglycemia agent which may be prescribed for type 2 diabetics, however, further studies with large sample size are recommended to validate the berberine fully so that it may used as new anti diabetic drug.

CONCLUSION

Berberine is effective in mitigating the insulin resistance and improves glycemic and lipidemic status in newly diagnosed type 2 diabetics. Berberine decreased insulin resistance by 29.5% compared to 8.12% by metformin therapy. Compared to metformin, the berberine was more effective in controlling the insulin resistance.

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