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THE IMPACT OF METFORMIN ON THE BONE MINERAL DENSITY AND QUALITY OF LIFE IN NON DIABETIC POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS

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ABSTRACT
To determine the effects of metformin on bone mineral density changes and quality of life in non-diabetic post menopausal women with osteoporosis. Fourty patients of age 40-65 years meeting inclusion criteria were equally divided into 2 groups. Patients of group-A received medications of osteoporosis for a period of 12 months while patients of group – B received tablet metformin 500 mg as add on to medications of osteoporosis a period of 12 months. Bone mineral density, biochemical parameters and quality of life were assessed at 0, 3, 6 and 12 months of the study. Addition of metformin to medications of osteoporosis could not produced significant changes in bone mineral density and was found to be comparable in patients not received metformin after completion of 12 months of the study.It was found that the quality of life had improved significantly in metformin group ($p<0.001$). Metformin was well tolerated without any significant adverse effects and bone fractures. However, further studies with larger number of patients and of longer duration are required to reach concrete conclusion regarding impact of metformin on bone mineral density in postmenopausal women with osteoporosis.

KEYWORDS: Osteoporosis, post menopause, metformin, quality of life.

INTRODUCTION
Osteoporosis is a major health problem in our aging society. Osteoporotic fractures are important causes of morbidity and mortality.[1, 2] As the population ages, the prevalence of osteoporosis increases sharply and there is consequently a pressing need for the discovery of new molecular targets with potential drug development for prevention and treatment of this bone disorder.The osteoporosis is a spongy bone disease most commonly affecting post menopausal diabetic females. It is reasonable to expect that close metabolic control of diabetes may improve bone status, although its effect on reduction of fracture risk has not yet been demonstrated.[3] Metformin is widely prescribed as a first-line therapy for typeII diabetes mellitus either alone or in combinations with other anti-diabetic drugs. Several studies have indicated that metformin may have osteogenic property.[4] Metformin increases osteoblast proliferation, alkaline phosphatase activity and the number of mineralized nodules formed in rat primary osteoblasts. In contrast, some studies have shown no effect of metformin on the osteogenic differentiation of bone marrow derived mesenchymal stem cells.[5] A high concentration of metformin even clearly inhibited osteoblast differentiation.[6]There are inconclusive insufficient and controversial data are available regarding the effects of metformin on osteoporosis and quality of life in postmenopausal women associated with diabetes. It was lucrative to find out the clinical outcomes of metformin added to medications of osteoporosis in non diabetic post menopausal women. We planned the study to see influence of metformin as add on to medications of osteoporosis in non-diabetic postmenopausal women.

MATERIAL AND METHODS
Study design: The present study was a prospective, randomized; open-label clinical study conducted in non-diabetic, post-menopausal women with osteoporosis. After getting approval from Institutional Review Board Pt. BD Sharma University of Health sciences, Rohtak the study was started. Written informed consent was taken from all patients prior to inclusion in the study. The osteoporotic patients were screened according to

inclusion and exclusion criteria in accordance with the principles of good clinical practice (ICH-GCP) and declaration of Helsinki. The effect of metformin on bone mineral density changes and quality of life was evaluated in collaboration with Departments of Pharmacology, Orthopedics and Medicine at Pt. B.D. Sharma PGIMS, Rohtak.

Inclusion criteria: Non diabetic postmenopausal women with H/O osteoporosis and not on HRT of age group 40-65 years attending Orthopedics/ Medicine OPD and for the treatment of osteoporosis.

Exclusion criteria

- Diabetic post menopausal female on anti-diabetic agent including TZD / metformin.
- Postmenopausal women on hormone replacement estrogen therapy (HRT).
- Elderly female patients above 65yrs of age with history of uncontrolled diabetes.
- Severe osteoporosis and multiple fractures of bones.
- Severe osteoporosis leading to multiple bone fractures requiring immediate surgery.
- Patients of Parkinson's disease.
- Patients showing metastasis in bone.
- Patient of renal failure, Patients of hypothyroidism.

Methods: Adequate number of patients attending Orthopedics and Medicine OPD were screened and forty patients were enrolled for the study. Patients were randomly divided into two groups. Each group had twenty patients. The patients were already managed with standard medications of osteoporosis and continued to period of study.

Group A. Patients received medications of osteoporosis only for a period of 12 months.
Group B. Patients received metformin 500 mg OD orally in addition to medications of osteoporosis for a period of 12 months.

Efficacy assessment
Primary endpoint
1. Mean percentage change in bone mineral density after 12 month treatment with metformin from baseline by DEXA scan.

Secondary endpoint
1. Improvement in quality of life after 12 months of treatment with metformin.
2. Mean percentage change in biochemical markers after 12 month treatment with and without metformin from baseline.

Bone mineral density Measurement
Bone mineral density (BMD) was assessed at 0 month, 3 months, 6 months and 12 months of treatment. Bone mineral density (BMD), bone mineral content (BMC) and body composition (Lean body mass and Fat mass) were measured using DEXA scan (Dual energy X-ray absorptiometry). HOLOGIC QDR-2000 scanner (explorer) was used to estimate bone mineral density and body composition. The subjects were asked to lie on a table, and whole body scanning was carried out with a congruent beam of stable dual energy radiation.

Laboratory Investigations
Serum calcium, serum phosphate, vitamin D, urine examination, complete hemogram, blood glucose level, lipid profile, liver function test, kidney function test at 0 month,3 months,6 months and12 months of treatment were assessed by adopting standard methods of estimation.[7-14]

Quality of Life assessment
Health status was assessed using Qualeffo-41 questionnaire.[15] The questionnaire has seven domains from A to G. It is valid and reliable instrument, with lower score representing better health status. It is multipurpose survey form with 41 questions.

Safety profile
The adverse effect of metformin on addition of standard medications of osteoporosis assessed pertaining to blood glucose, GIT, CVS, CNS and skin allergy by clinical examination and by blood tests.

STATISTICAL ANALYSIS
Both descriptive and analytical statistics was used in the study. Collected data were entered in the MS Excel spread sheet, coded appropriately and later cleaned for any possible typing errors. Analysis was carried out using SPSS for windows version 20.0. The data were collected and presented as mean ± SEM. Categorical data are presented as percentage. All the parameters were subjected to analysis using repeated measures ANOVA. Unpaired student's t-test had been applied wherever required. P-value less than 0.05 were considered significant.

OBSERVATIONS
Demographic pattern: Demographic pattern of osteoporotic non-diabetic post-menopausal female patients, who received metformin or no metformin as add on to standard medications of osteoporosis. 14 (70 %) patients in metformin group and 13 (65 %) patients in non-metformin group were in age group of 51-60 years (Table no.1). The difference of age group distribution in the groups was not statistically significant.10 (50 %) patients in metformin group and 12 (60 %) in non-metformin group were illiterate. 8(40 %) patients in metformin group and 6 (30 %) patients in non-metformin group were below matriculation. The distribution of education status of patient in both the groups was not statistically significant.

As shown in table no.1 all the patients in metformin group and 19 (95 %) patients in non-metformin group were married (Statistically non significant). All the participants had normal blood pressure and normal pulse

rate at all the four visit. None of the participants reported any co-morbidity. None of the participant reported any history of allergy in the past. The baseline characteristics of the study population are shown in Table 1, 2 and 3.

Bone Mineral Density: Bone mineral density (BMD) at the base line in terms of T score and Z score were comparable (Table No. 2) in both the groups Mean T score in metformin group was 3.41 and in Non-metformin group were 3.4. Mean Z score in metformin group was 2.1 and in non-metformin group was 2.0. The difference of T-score (p-0.98) and Z-score (p-0.21) in both the groups was not statistically significant.

Biochemical parameters: The table no.3 shows base line values of biochemical parameters i.e. serum calcium, serum phosphate, serum parathormone, serum alkaline phosphatase, serum 1, 25–dihydroxy vitamin-D in both the group. The biochemical parameters were comparable in both the groups (statistically non significant). The mean serum calcium was 9.6 mg/dl in metformin group and 9.6 mg/dl in non-metformin group. The difference in both the groups was not statistically significant (p-value-0.52).The mean Serum phosphate was 3.7 mg/dl in both the groups and the difference in both the groups was not statistically significant (p-value- 0.96). The mean Serum parathormone level was 22 pg/ml in metformin group and 24.5 pg/ml in non-metformin group. The difference in both the groups was not statistically significant (p-value-0.38).

The mean serum alkaline phosphatase level was 62.2 IU in metformin group and 74.5 IU in non-metformin group. The difference in both the groups was not statistically significant (p-value-0.10). The mean serum 1,25 –dihydroxy vitamin –D level was 24.3 IU in metformin group and 24 IU in non-metformin group. The difference in both the groups was not statistically significant (p-value-0.71). The mean serum SGOT level was 36.45 IU in metformin group and 37.25 IU in non-metformin group. The difference in both the groups was not statistically significant (p-value-0.81). The mean serum SGPT level was 36.25 IU in metformin group and 32.05 IU in non-metformin group. The difference in both the groups was not statistically significant (p-value-0.19). The mean serum B. urea level was 26.8 mg/dl in metformin group and 25.3 mg/dl in non-metformin group. The difference in both the groups was not statistically significant (p-value-0.54). The mean serum creatinine level was 0.95 in metformin group and 0.96 in non-metformin group. The difference in both the groups was not statistically significant (p-value-0.58).

T-score values: Intra group analysis of table 4 show gradual decrease in T- score, a marker of bone mineral density, with initiation of treatment from 3.41 of baseline to 3.16 at the end of 12 months of treatment. The decrease in T-score was statistically non significant (p-Value-0.082) in metformin group. There was also decrease in T- score with initiation of treatment from 3.40 of baseline to 3.04 at the end of 12 months of treatment. In non-metformin group decrease in T-score was also statistically non significant (p-value-0.51).

Inter group analysis of table 4 show decrease in T- score at the end of 12 months of treatment in both the groups however the difference was statistically non significant at any point of time in between the groups. The response of metformin was comparable with the patients in non-metformin group.

Decrease in T-score means that there was improvement in bone mineral density.

Z-score values: Intra group analysis of table 5 show decrease in Z- score a marker of bone mineral density with initiation of treatment from 2.17 to 1.98 at the end of 12 months of treatment. The decrease in Z-score was statistically significant (p-value<0.001) in metformin group. There was also decrease in Z- score with initiation of treatment from 2.0 to 1.88 at 12 months of treatment. The decrease in Z-score was also statistically significant (p-Value0.003) in non-metformin group.

Inter group analysis of table 5 show decrease in Z- score at the end of 12 months of treatment in both the groups however the difference was statistically non significant at any point of time in between the groups. The response of metformin was comparable with the patients in non-metformin group.

Decrease in Z-score means that there was improvement in bone mineral density.

Quality of life scores: Intra group analysis of table 7 show gradual decrease in Quality of life score with initiation of treatment from 59.30 to 46.15 at the end of 12 months of treatment in metformin group. The decrease in Quality of life score was statistically significant (p-Value-0.001) in metformin group. There was gradual decrease in Quality of life score with initiation of treatment from 60.90 to 47.45 at the end of 12 months of treatment in non-metformin group. The decrease in Quality of life score was statistically significant (p-Value-0.001) at 12 months of treatment.

Inter group analysis of table 7 show gradual decrease in Quality of life score at the end of 12 months of treatment in both the groups the difference between the groups was also statistically significant all point of time.

Table 1: Distribution of non diabetic postmenopausal women in Metformin and Non-metformin group according to basic profile

Variable (s)	Group A Non-Metformin group (N=20)	Group B Metformin (N=20)
Age-groups Less than 50 years 51 to 60 Years More than 60 years Mean ± SD	 3 13 4 56.1 ± 5.3	 5 14 01 54.2 ± 6.1
Marital Status Married Un-married	 19 1	 20 0
Education Illiterate Below Matriculation Matriculation Graduation	 12 6 0 2	 10 8 2 0
Blood Pressure and Pulse rate	All the participants were normotensive and having normal pulse rate at all the four visits.	
Co- morbidity	None of the participant reported any co-morbidity.	
Any history of allergy	None of the participant reported any history of allergy in the past.	

Table No. 2 Baseline bone mineral density in Metformin & Non-Metformin groups

Parameter	Group A Non-Metformin group Mean ± SD (N=20)	Group B Metformin group Mean ± SD (N=20)	Mean difference (95% CI)	p-value
BMD T Score	3.4 ±0.72	3.41 ±0.83	0.005 (-0.49, 0.50)	0.98
BMD Z Score	2.00±0.66	2.17 ±0.85	0.175 (-0.31,0.66)	0.47

Table No. 3 Baseline biochemical parameters in Metformin & Non-Metformin groups

Biochemical Parameters	Group A Non-metformin Group (N=20) (Mean±SD)	Group B Metformin Group (N=20) (Mean±SD)	Mean difference (95% CI)	p-value
Serum calcium (mg/dl)	9.6±0.88	9.6±0.92	0.185 (-0.39, 0.76)	0.52
Serum phosphate (mg/dl)	3.7±0.45	3.7±0.32	0.005 (-.24, 0.25)	0.96
Serum PTH (pg/ml)	24.5±2.81	22.05±3.0	-2.00 (-0.38, -0.11	0.38
Serum alkaline phosphatase (IU)	74.8±24.4	62.2±22.8	-12.60 (-27.77, 2.57)	0.10
Serum 25-Hydroxy vitamin D (ng/ml)	24.0±2.9	24.3±3.3	0.372 (-1.65, 2.39)	0.71
SGOT (IU)	37.25±11.9	36.45±9.7	0.80 (-7.7, 6.1)	0.81
SGPT (IU)	32.05±8.81	36.25±11.2	0.19 (-2.2, 10.6)	0.19
B. urea (mg/dl)	25.30±5.5	26.80±5.85	0.54 (-2.5, 4.7)	0.54
Serum creatinine (mg/dl)	0.96±0.08	0.95±0.08	0.58 (-0.06, 0.03)	0.58
A/G Ratio	1.41±0.17	1.51±0.21	0.13 (-0.03, 0.22)	0.13

Table No. 4 Effect of metformin on T-score values

Time Point	Group A Non-Metformin Group Mean ± SD (N=20)	Group B Metformin Group Mean ± SD (N=20)	Mean Difference (95% CI)	p-value
At start of treatment	3.4±0.72	3.40±0.83	0.005 (-0.49, -0.50)	0.98
3 Months	3.38±0.70	3.4±0.74	0.02 (-0.44, 0.48)	0.93
6 Months	3.2±0.69	3.3±0.79	0.06 (-0.41, 0.53)	0.80
12 Months	3.04±0.69	3.16±0.80	0.12 (-0.36, 0.60)	0.61
p-value	0.51	0.082		

Table No. 5 Effect of metformin onZ-score values

Time Point	Group A Non-Metformin Mean ± SD (N=20)	Group B Metformin Group Mean ± SD (N=20)	Mean Difference (95% CI)	p-value
At start of treatment	2.0±0.66	2.17±0.85	0.17 (-0.31, 0.66)	0.47
3 Months	2.06±0.70	2.23±0.74	0.16 (-0.29, 0.62)	0.47
6 Months	1.98±0.65	2.07±0.68	0.09 (-0.33, 0.52)	0.65
12 Months	1.88±0.63	1.98±0.65	0.09 (-0.31, 0.50)	0.64
p-value	0.003[#]	<0.001[*]		

[#]Comparison of values of Z-score in group A the end of 1 yr treatment.(statistically significant p-value < 0.05).
[*] Comparison of values of Z-score in group A the end of 1 yr treatment.(statistically significant p-value < 0.05)

Table No. 6 Effects of metformin on biochemical parameters

Biochemical Parameters	Baseline	3 Months of treatment	6 Months of treatment	12 Months of treatment
Serum calcium (mg/dl)	9.6±0.92	10.08±0.70	10.05±0.58	10.3±0.47
Serum phosphate (mg/dl)	3.75 ± 0.0	3.64 ± 0.086	3.68 ± 0.27	4.01 ± 0.27
Serum PTH (pg/ml)	22.5 ± 3.06	24.0 ± 3.30	24.5 ± 2.81	27.5 ± 3.64
Serum alkaline phosphatase (IU)	62.2± (22.89)	59.45±20.73	59.65±19.60	74.55±15.41
Serum 25-Hydroxy vitamin D (ng/ml)	38.7±5.26	24.35±3.23	24.12±2.77	26.6±3.08
SGOT (IU)	36.45±9.7	35.5±10.1	35.9±8.81	38.7±5.26
SGPT (IU)	36.25±11.24	32.95±8.77	34.05±9.4	37.35±6.87
B. urea (mg/dl)	26.40±5.85	25.4±4.27	24.35±4.88	22.3±3.75
Serum creatinine (mg/dl)	0.95±0.08	0.95±0.07	0.95±0.08	0.87±0.10

Table No. 7 Effect of metformin on Quality of life score values

Time Point	Group A Non-Metformin Group Mean ± SD (N=20)	Group B Metformin Group Mean ±SD (N=20)	Mean Difference (95% CI)	p-value
Baseline	60.90 ± 0.912	59.30 ± 0.912	13.30 (12.233, 14.367)	<0.001*
3 Months	55.75± 0.968	55.05 ± 0.968	8.600 (7.508, 9.692)	<0.001*
6 Months	51.30± 0.776	50.45± 0.776	4.075 (3.619, 4.531)	<0.001*
12 Months	47.45± 0.739	46.15± 0.739	-4.075 (-4.531, -3.619)	<0.001*
p-value	0.003	0.004		

[*] Comparison of values of quality of life scores between groups the end of 1 yr treatment. (statistically significant p-value < 0.05).

DISCUSSION

We maintained the standard medications of osteoporosis throughout the study period which contained calcium 1000-1500 mg/day, vitamin D 0.5mcg/day, alendronate 10mg /day. The study was conducted in non-diabetic postmenopausal osteoporotic women. The addition of metformin to medications of osteoporosis could not yield significant effect on bone mineral density. However there was some tendency towards improvement of bone density in patients. Probably it could be due to limitation of our study including shorter duration and small number of non-diabetic postmenopausal women was included in study.

The biochemical parameters in osteoporosis including serum calcium, serum phosphate levels, serum alkaline phosphatase, serum 1.25-hydroxy vitamin-D, serum parathormone, blood urea, serum creatinine, serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) served as markers or status of prognosis of osteoporosis. They all were within normal limits. Medications for osteoporosis including calcium, vitamin D and bisphosphonates (Alendronate) with addition of metformin in non-diabetic postmenopausal women had produced more positive effects on bone mineral density, raised levels of serum calcium though not significantly compared to subject who were not given metformin. It was observed that metformin responded favourably and protected the process of osteoporosis even in estrogen deficiency and distortion of bone metabolism was decreased.

Quality of life was assessed by using Qualeffo-41 scoring method in non-diabetic postmenopausal osteoporotic patients. Patients in both the groups showed improvement in bone mineral density and serum calcium and serum phosphate (markers for bone improvement).Quality of life score was decreased in both the groups thereby showing improvement in quality of life. Since all the patients were on calcium and vitamin-

D and alendronate sodium important for the growth of bones so there was improvement in bone mineral density and thereby in quality of life.

The drugs were well tolerated by patients during the course of study. No serious adverse drug reaction (ADR) was reported during study period. Few ADR were regarding nausea and vomiting after taking tablet metformin at the start of treatment but these subsided during course of treatment. Few patients reported GI upset. Since long term treatment with metformin leads to vitamin B_{12} deficiency the same was also seen in some patients.

Our study revealed that there was tendency to improve bone mineral density and quality of life though these outcomes were not significant. This might be due to limitation of number of subjects included for the study and duration of study was short i.e. one year. Large patient population and minimum study period of 2-3 years are required to establish effectiveness of metformin in non diabetic post menopausal osteoporosis.

CONCLUSION

Oral treatment with metformin as add on to medications of osteoporosis in non-diabetic postmenopausal women improved bone mineral density and quality of life without significant adverse effects and was well tolerated. No fracture was reported in patients under study during the period of treatment. However, further studies with larger number of patients and of longer duration are required to reach any conclusion regarding impact of metformin on bone mineral density in postmenopausal women with osteoporosis.

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