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Medicine

Therapeutic Role of Metformin in Non-Diabetic Osteoporosis

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Abstract | **Original Research Article**

Introduction*:** The bone mass decreases with age, especially in postmenopausal women. Many drugs are used to preserve bone health. Metformin has also been shown to impact bone mass by activating AMP-activated protein kinase. This study is to evaluate bone preserving modality of metformin. ***Material & Method*:** 106 patients of either sex were studied for 1 year. They were distributed into two groups. Group -1 was recommended Metformin 250 mg twice a day, calcium (1000 mg), vitamin D_3 (1000 units) and vitamin C (500 mg) and Group-2, all medicines except metformin. ***Results: 106 Participants (19 male and 87 female) completed the study. Age (Mean ± SD) of female patients was 48.9 ± 13.05 and of male 48.91 ± 13.1. Presenting complaints were generalized aches and pain, symptoms of osteoarthritis and spondylosis, hypertension, coronary artery disease, obesity and generalized weakness. Nine months after therapy female patients of age below 60 years, in both study groups, improved significantly, whereas in elderly male, patients with osteopenia improved better than with osteoporosis. Symptoms of generalized aches and pain improved in either sex of both groups. BMD improved appreciably in obese patients especially of Group-1 even without losing weight. Osteoarthritis and spondylosis patients also found to have significant BMD improvement in either sex of both groups. ***Conclusion*:** Though vitamin D has its own physiological action in maintaining bone health yet metformin also seems to be complementary, through different mechanism, in maintaining bone health. More studies for longer period are required, before metformin form part of prescription in maintaining bone health.

Keywords: Osteoporosis, AMP – activated protein kinase, Metformin.

INTRODUCTION

Various physiological mechanisms acting through pathways preserve bone mass. One of them is AMPK signalling pathway, which plays an important role in bone physiology. Osteoporosis, considered a metabolic disorder, is under AMP-activated protein kinase (AMPK) regulation. Its activation promotes bone formation and the deletion of α or β subunit of AMPK decreases bone mass. AMPK activation is also under control of hormones or drugs that regulate appetite and energy expenditure. Metformin by activating AMPK seems likely to impact skeletal cellular metabolism and bone mass. Because of this unique mechanism, we studied the bone preserving modality of metformin in compromised bone health population.

MATERIALS & METHODS

This study was carried out in MM Medical College & Hospital Kumarhatti – Solan (Himachal Pardesh). The study was single centred, prospective, non-randomized study. It included participants with high risk of osteoporosis / osteopenia.

Duration of study: about one year, from April 2017 to July 2018

Inclusion criteria

- Patients of either sex of age irrespective of weight and ethnicity.
- Both indoor and OPD patients.

Exclusion criteria

- Patients of endocrinopathies
- Patients on hormonal replacement therapy (HRT).
- Patients taking drugs which influence bone metabolism.
- Haematological or lymphoreticular malignancies.
- Infiltrative disorders.
- Bony metastasis.
- Chronic Kidney Diseases.

Ethical Issue

The research was approved by the Ethical Committee of the institution and conducted as per its laid down norms.

Participants

When enrolment in the study, each patient was informed about the nature of the study and, if agreed, consent taken and a Participation Number allotted. During clinical assessment important aspects were recorded i.e. symptoms, history of diabetes mellitus (DM), other endocrinopathies, if any, hormonal therapy / drugs, weight (Kg), height (mtrs), Body Mass Index (BMI), and relevant systemic examination performed.

Laboratory tests panel

Relevant laboratory tests done: routine haematological profile, Erythrocytic Sedimentation Rate, Blood Sugar, Lipid profile, Blood urea & Serum Creatinine, Serum Calcium, Phosphate, Serum alkaline phosphatase, vitamin D (by *DIAsource 25OH Vitamin D Total ELISA 90 kit standard*). Vitamin D deficiency is considered if blood level less than 30 ng/ml. Bone mineral density (BMD) measured by *Multi-site Ultrasound – based Bone Mineral Densitometer*, as DXA Scan facility is not available in this institution. BMD gm/cm² is estimated as average of two separate readings taken for one minute each, and participants are classified into (***1***):

- Normal : BMD T-score > - 1
- Osteopenia : BMD T-score < -1 and up to -2.5
- Osteoporosis : BMD T-score < -2.5

Study group: Initially 163 patients were recruited for the study. They were grouped into:

- Study Group – 1 (Gp – 1), were recommended Metformin 250 mg twice a day and supplements of calcium (1000 mg), vitamin D_3 (1000 units) and vitamin C (500 mg).
- Control Group – 2 (Gp – 2), were recommended only supplements of calcium (1000 mg), vitamin D_3 (1000 units) and vitamin C (500 mg) and not metformin.

Obese participants were suggested appropriate physical activities and dietary restriction to reduce to acceptable weight. Treatment for other associated diseases was continued. Drug that expected to affect bone was stopped or substituted with another drug. Participants instructed to disclose on next visit if they were prescribed new medicine for unrelated disease, or participant preferred medication from other sources. Patients were followed fortnightly. On each visit, patient was clinically evaluated and recommended relevant investigations and after every three months- BMD.

Statistical analysis

The data is analysed based on mean ± SD. Statistical analyses were performed by one way analysis of variance (ANOVA) followed by T. Test for comparison between control and subject groups. *P* value of ≤ 0.05 was taken as significant or vice a versa.

RESULTS

Out of 163, following patients (M=9 & F=48) were excluded from the study, because:

- 5 male and 37 female patients were either irregular on follow up or not available after initial evaluation.
- 3 male and 10 female patients adopted "alternative system of medicine" for therapy.
- 1 male and 1 female patient died during study period.

Participants (N=106: M=19 & F=87) completed the study. Age-wise distribution of female patients (*N*=87, mean age 48.9 ± 13.05) and of male (*N*=19, mean age = 48.91 ± 13.1) are shown in Table – 1, and presenting symptoms / disabilities in Table – 2.

Table-1: (Age and Sex – wise distribution of patients)

Age (yrs)	Male (N= 19)		Female (N= 87)		Total
	S	C	S	C	
< 50	1	4	23	25	53
50 – 60	4	1	16	11	32
>60	6	3	6	6	21
	11	8	45	42	106

(Table - 1: S = Subject; C = Control)

Table-2: Presenting symptoms / disabilities on recruitment in study

Major symptoms / Disabilities	Total patients	Male	Female
Gen aches and pains, and bony pain (Clinical Ostalgia)	64	10	54
OA, LBA, Cx spondylosis	33	8	25
Hypertension	21	5	16
CAD	5	1	4
Obesity	29	5	34
Multiple disabilities	17	2	15
Gen weakness & Easy Fatigability	10	1	9
Post -Menopausal symptoms	4	-	4
Asymptomatic	3	1	2

(Table - 2: S = Subjects; C = Control; Gen=Generalized; OA= Osteoarthritis; LBA= Low back ache; Cx = cervical; CAD = Coronary artery disease. Multiple disabilities= combination of various morbid conditions i.e. hypertension, CAD, dyslipidemia, obesity, metabolic syndrome etc.)

BMD Response to Therapy

BMD was measured at 9 months therapy, depicted in Table – 3, in male significant improvement was noticed in Gp-1 (P=0.000302) and not in Gp-2 (P=0.87444). In female, at all ages, BMD improvement was statistically significant in both groups (Gp-1: P=0.006687 and Gp-2: P < 0.00001). BMD improvement was quite evident in less than 60 years (P=< 0.00001 vs P=0.012854 in above 60).

Above results were analysed based on BMD criteria (Normal: up to ≥ -1, Osteopenia: <-1 & up to -2.5, and Osteoporosis: ≤ -2.5). We further sub-fractionized the BMD score. After sub-fractioning, we found that, either sex had appreciable improvement in BMD in Gp-1 than in Gp-2 as depicted in Fig-1 to Fig - 4

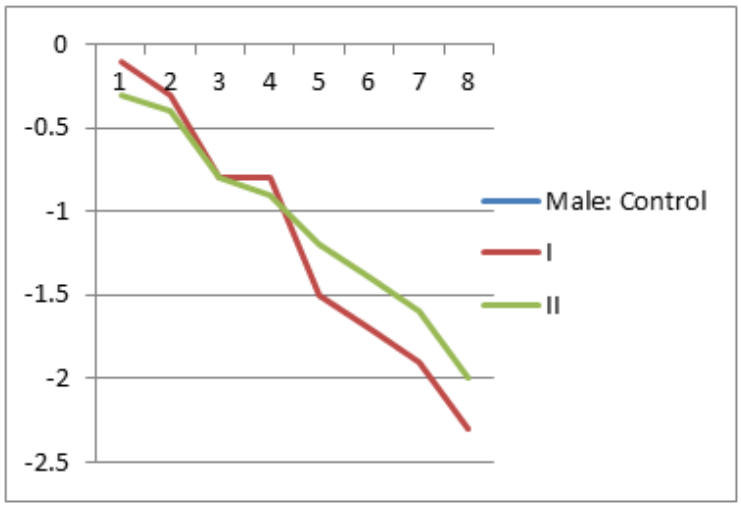

Fig -1: BMD response in male Control: Red line depicts (BMD –I) before and Green line (BMD - II) after therapy

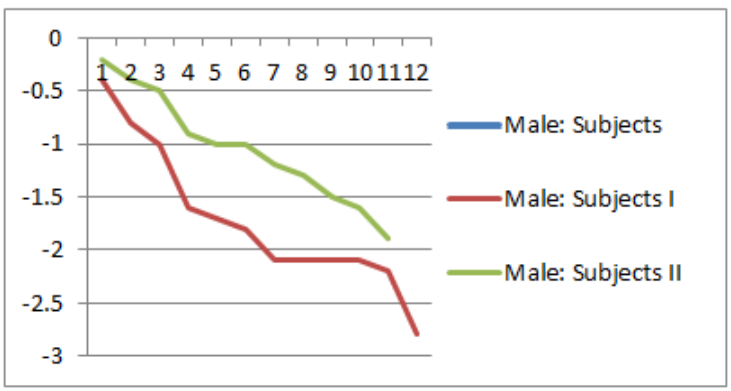

Fig-2: BMD response in male Subject: Red line depicts (BMD–I) before, Green line (BMD– II) after therapy

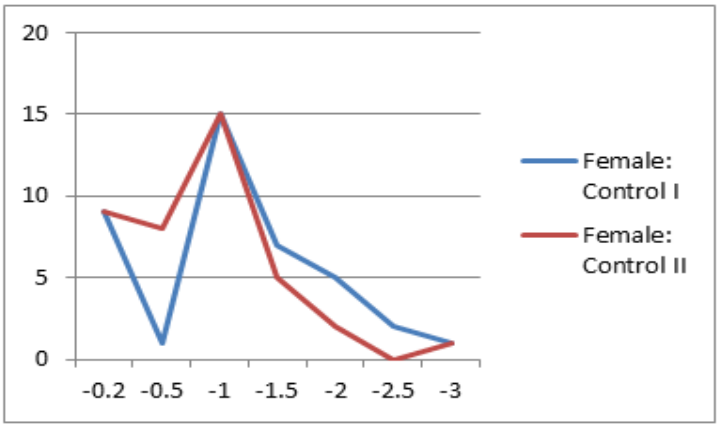

Fig-3: BMD response in Female Control: Blue line depicts (BMD –I) before therapy, Red line (BMD - II) after therapy

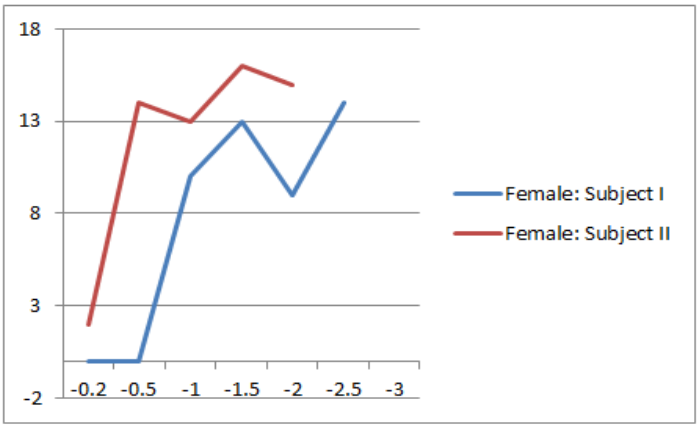

Fig-4: BMD response in Female Subjects: Blue line depicts (BMD –I) before therapy, Red line (BMD - II) after therapy

Table-3: Comparative BMD values before and after Metformin therapy

Age Groups (Years) T – Score	BMD – 1 (On Enrolment)				BMD – 2 (~ after 3 months)				BMD – 3 (~ after 6 months of BMD - 2)			
	Male		Female		Male		Female		Male		Female	
	S	C	S	C	S	C	S	C	S	C	S	C
BMD ≥ & up to -1 (Normal)												
≤ 50	1	4	1	12	1	4	9	16	1	4	13	24
50 – 60	-	1	20	16	2	-	-	1	2	-	1	4
≥ 60	-	-	6	-	-	-	1	-	3	-	2	-
BMD: ≤ -1 to -2.5 (Osteopenia)												
≤ 50	2	-	-	-	-	-	17	12	-	1	14	4
50 – 60	2	-	8	7	2	-	11	6	2	-	10	5
≥ 60	-	-	3	2	6	3	7	2	3	3	7	2
BMD: ≤ -2.5 (Osteoporosis)												
≤ 50	-	-	-	-	-	1	1	-	-	-	-	-
50 – 60	5	3	5	2	-	-	-	2	-	-	-	-
≥ 60	1	-	4	1	-	-	1	1	-	-	-	1

(Table – 3: Depicts response to therapy in Group – 1 (Subject) and Group –2 (Control)

Nutritional status and BMD

Based on the WHO and Asian comparative criteria for BMI (***2***), we evaluated the nutritional status based on Asian criteria (Table – 4). Obesity, (BMI 30 & above), was present in 37 (34.91%): [M=5 (26.32%) mean age 52.1±11.8)] and [F=32 (36.78%) (Gp-1: N=20 & Gp-2: N= 12 with mean age 49±13 & 48±13 respectively), 13 overweight [M=1 &F= 12 (Gp-1= 4: mean age 27.66±6.36, Gp-2= 8: mean age 27.56±6.33)], Pre – obese 34 (32.08%) [F= 26 (26.41%) [Gp-1=15: mean age 27.4±6.86; Gp-2=11: mean age 27.6±6.44 years] and (M= 8 (7.55%)] [Gp-1= 3: mean age 27.5±6.37 and Gp-2 = 5: mean age 27.6±6.38), underweight 4 (F= 3 & M= 1) and normal weight in 18 (16.98%): (M=4 & F=14).

Table-4: (Nutritional status of participants based on Asian criteria for BMI: on Enrolment)

BMI	Nutritional Status	M	F	Total
≤ 18.5	Under-weight	1	3	4
18.5 – 22.9	Normal	4	14	18
23 – 24.9	Over-weight	1	12	13
25 – 29.9	Pre – Obese	8	26	34
≥ 30	Obese	5	32	37
Total		19	87	106

In obese patients associated co-morbidities [i.e. diabetes mellitus (DM), hypertension (HTN), dyslipidemia, coronary artery disease (CAD), and degenerative joints disease (DJD)] were present in [(F=20 (62.5%) & M= 4 (80%)]. 80% female and 75% male *obese patients with these co-morbidities were vitamin D deficient* (mean vitamin D levels: for female and male 22.97 ±16.66 and 23.46± 16.74 ng/ml respectively). All these patients had either osteopenia (84.21%) or osteoporosis (15.78%). Overweight Vitamin D deficient with above disabilities were 5 female (Gp-1 = 3 & Gp-2 = 2) and 2 male (Gp-1 = 1 & Gp-2 = 1).

Based on nutritional state, BMD measurement before and after 9 months of therapy in all patients (F=87 & M=19) is depicted in (Table - 5). It was found, after 9 months of therapy, that obese female patients in Gp–1 (*P=0.274315*) and pre-obese in Gp-2 did not show statically significant BMD improvement (*P=0.23483*). The patients in either sex of both groups with normal BMI also did not show significant BMD change to therapy.

Table-5: BMD response to nutritional state of patients

BMI (Kg/m²)	Female		Male	
	S	C	S	C
>30	N=20 *P*=0.273655	N=12 *P*= 0.001293	N=4 *P*= ≤ 0.0001	N=2 *Not done*
25 – 29.9	N=15 *P*=0.015	N=11 *P*=0.23483	N=2 *Not done*	N=5 *P*=0.000546
23 – 24.9	N=4 *P*=0.0012373	N=8 *P*=0.00059	N=0	N=0
18.5 – 22.9	N=6 *P*=0.11751	N=8 *P*=0.190163	N=4 *P*=0.190163	N=1 *Not done*
< 18.5	N=2 *Not done*	N=1 *Not done*	N=1 *Not done*	N=0
Total	47	40	11	8

(N.B. BMI: Body Mass Index, S= Subjects and C= Control)

Vitamin D and BMD: 85 of 106 (80.19%) patients [M=14 (S=9 & C=5) & F=71 (S=35 & C=36)] were vitamin D deficient (Table – 6). In these patients, initial BMD, (Table - 7), was in Male: [S=9 (Normal BMD=2, Osteopenia=6 & Osteoporosis= 1), and C=5 (Normal BMD=3, Osteopenia=2)]; Female: [S=35 (Normal =1, Osteopenia= 24 and Osteoporosis=10), and C= 36 (Normal= 10, Osteopenia=23 and Osteoporosis=3)].

Table-6: (Vitamin D status of patients)

Accepted Vitamin D level (ng/ml)	Male		Female		Total	
	S	C	S	C	S	C
≤ 10 Deficient	3	1	5	7	16	-
10-29 Insufficiency	10	-	59	-	69	-
30-100 Sufficiency	5	-	16	-	21	-
≥ 100 Toxicity	-	-	-	-	-	-
Total	19	1	87	7	106	-

Table-7: BMD in Vitamin D Deficient patients at the time of inclusion in the study

BMD	Male		Female	
	S	C	S	C
Normal (> -1)	2	3	1	10
Osteopenia (< -1& up to -2.5	6	2	24	23
Osteoporosis (< -2.5)	1	-	10	3
Total	9	5	35	36

(N.B. S= Study subject; C= Control)

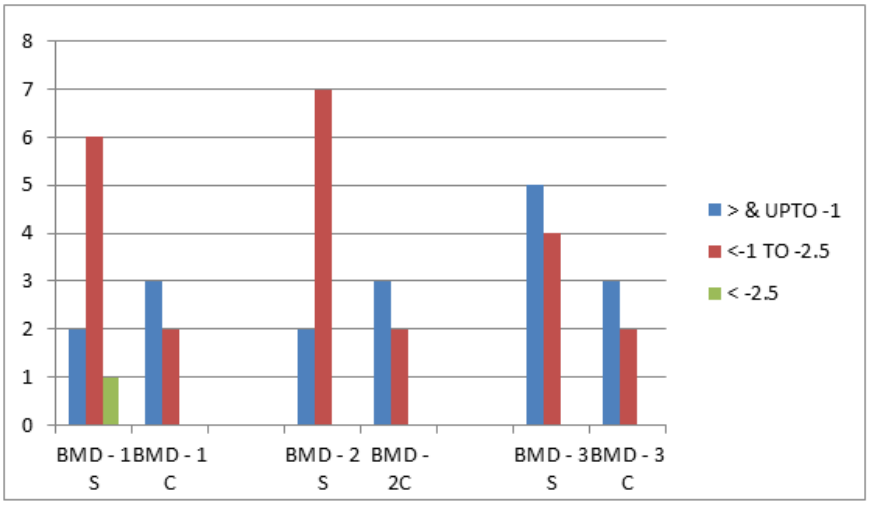

Fig-5: Depicts response to therapy in vitamin D deficient Male (S= Subjects and C= Control)

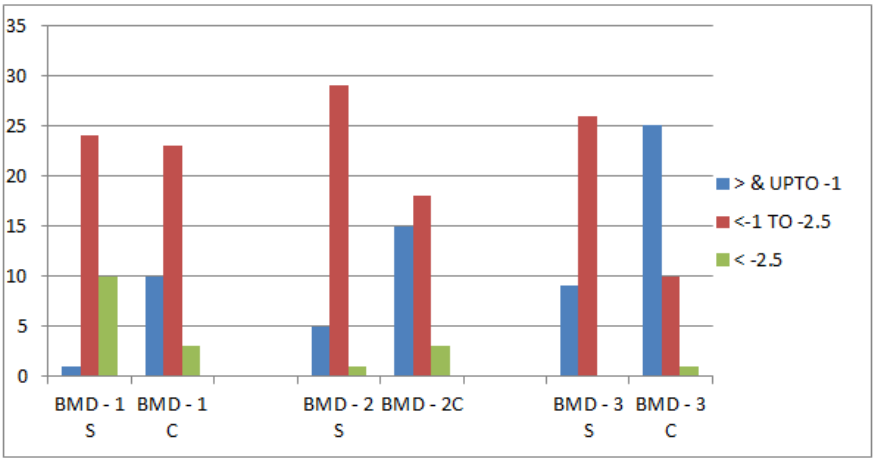

Fig-6: Depicts response to therapy in vitamin D deficient Female (S= Subjects and C= Control)

In 85 vitamin D deficient patients, there was statistically significant overall improvement in BMD in either sex of both groups [Female: Gp-1 vs Gp-2 (*P=0.006588 vs P=≤0.00001*) and Male: Gp-1 vs Gp-2 (*P=0.000045 vs P=≤0.000546*). All patients with osteoporosis improved to osteopenia, and 6 female from Group -1 and 11 from Group-2 had normal BMD score after 9 months therapy. Females in Group -2 had also significant BMD improvement.

In Group -1, only 1 male patient with osteoporosis and 3 with osteopenia had shown significant BMD improvement. Group -2 had only 1 male patient with normal BMD Score.

BMD in Generalized bony pain (clinical ostalgia)

64 patients had clinical ostalgia. 52 of these patients [F=44 (S=21, C=23) & M=8 (S=7, C=1)] were vitamin D deficient. Age of female patients was from 23 to 76 years and of male 52 to 67 years. Mean and SD

age of female and male patients was 48.85 years ± 13.14 & 50.32 ± 12.94 respectively. Majority of female were below 50 years (S= 13 and C= 15), whereas, male elderly. Initial BMD score in female [Normal in S=1 & C=6; Osteopenia in S=16 & C=16; and Osteoporosis in S=4 & C=1] and in male [Normal in S=1 & C=1; Osteopenia in S=5; and Osteoporosis in S= 1). In female, after therapy, showed significant BMD improvement in Gp – I, especially in osteopenia patients (*P=0.004201*) than in Gp – II (*P=0.10843*). There was statistically insignificant improvement in Gp – II with normal BMD and Gp – I with osteoporosis (*P= 0.23185 and 0.118593 respectively*), also depicted in (Fig: 3-4, 6). Male patients with osteopenia had significant BMD improvement (*P=0.001033*) than osteoporotics as depicted in (Fig: 1-2, 5). (*They were not subjected to statistical analysis as number were too less*). BMD improvement was also appreciated in both in vitamin D deficiency and vitamin D sufficient (*P*=≤ 0.00001), especially with osteopenia, female patients than male.

BMD in Degenerative joint diseases (DJD)

Under this category, presenting disabilities were osteoarthritis (OA) of knees and other joints, lumbar and / or cervical spondylosis. 33 (31.13%) patients [F=25 (S=14, C=11) & M= 8 (S=4, C=4)] had DJD. Mostly they were vitamin D deficient [F=16 (S=9, C=7) & M= 5 (S=2, C=3)]. In vitamin D deficient female, osteopenia (S=4, C=4) and osteoporosis (S=5, C=1) were common. Even with normal vitamin D levels, 7 female and 2 male had osteopenia. Only 2 patients each in Gp-2 with deficient and normal vitamin D had normal BMD. Male patients were mostly above 60 years.

After therapy, there was statistically significant improvement in vitamin D deficient female in both study groups (Gp-1: *P= 0.000157 and* Gp-2: *P=0.000085*). Male showed improvement in both groups (Gp-1: *P=0.038861*), analysis for male Gp-2 not done because of only 2 patients.

Female with normal vitamin D levels did not show statistically significant improvement in Gp-1 (*P=0.097629*) after therapy, whereas statistical analysis was not done for Gp-2 female and both groups in male because of less number of patients. Two female patients with osteoporotic in Gp–1 and 1 in Gp - 2 were found to have improved BMD score (Fig: 7).

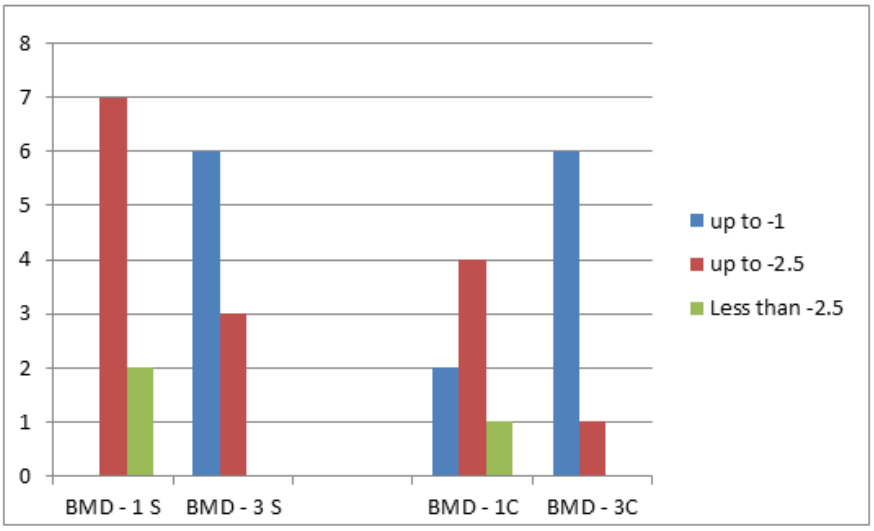

Fig-7: Degenerative joint diseases: Results after 9 months of therapy. *Blue* column depicts normal BMD, *Magenta* = Osteopenia and *Green* = Osteoporosis. BMD – 1S & BMD - 1C columns and BMD – 3S and BMD – 3C show BMD measurement before and therapy

BMD in Associated Morbidities

In our participants, various comorbidities associated with patients were HTN, DM and CAD either alone or in combinations. 16 female (S=12, C=4) and 5 male (S=4, C=1) had vitamin D deficient levels. Improvement in BMD score in both study groups was significant, but Gp – I improved more (*P=≤0.00001*) than Gp-2 (*P=0.002914*). Improvement in BMD in male in Gp-I (*P=0.*027726) was lesser than female. Gp – I female with normal vitamin D levels also had significant improvement in BMD (*P=0.0047487*) but lesser than same group with vitamin D deficiency.

DISCUSSION

In India population of people above 65 years is expected to increase from present 6%, to expected 8.8% by 2030 [3]. It was possible because of improved health care facilities and economic conditions with reduction in cardio vascular disease (CVD) and DM associated mortalities. Therefore, survival is prolonged, but at the cost of increased sedentary habits and hence obesity and related disorders. Apart from these morbidities peculiar to old age, bone health is reduced in elderly patients and post-menopause women [1, 4-5]. In developed countries, osteoporosis ranges from 2 – 8% in male and

9 – 38% in female, and incidence in developing countries not clear [6].

Osteoporosis considered as metabolic disorder and regulated by AMPK. Therefore, AMPK seems to be important for bone mass in vivo [7]. *In vitro* bone formation is promoted by activated AMPK, whereas deletion of α or β subunit of AKMP decreases bone mass. Role of Metformin has been recognized in the maintenance of bone health, through various mechanisms i.e. by activation of AMPK, and induction of endothelial nitric oxide synthase (eNOS) and bone morphogenetic protein-2 (BMP-2) expression, by differentiation of non-transformed osteoblastic cells of mouse (MC3T3-E1) and bone matrix synthesis [8-10], by regulating Small Heterodimer Partner (SHP) in MC3T3-E1 cells, thereby stimulating osteoblastic bone formation by interacting with the transcription factor Rounx2 [11], by increasing osteoblast proliferation in rat primary osteoblasts by stimulation of Rounx2 and IGF – 1 production [7, 12], by acting on bone marrow mesenchymal cells progenitors (BMPCs) results in osteogenic effect by osteoblastic differentiation [10], and probably acting indirectly, particularly in DM, by reducing inflammation, accumulation of advanced glycation end-products and reactive oxygen species (ROS) [13].

Many studies have evaluated the role of metformin on bone health primarily in diabetic patients than in non-diabetics. Our study has evaluated the role of metformin in improving and preserving bone mass in non-diabetics. Female were the main participants in this study. Initial BMD has shown osteopenia (38.37% vs 29.07%) and osteoporosis (15.12% vs 3.49%) in Gp-1 and Gp-2 respectively. No female had normal BMD after 45 years of age. Recapitulating again, during study period, both groups were given bone maintaining supplements (Vitamin D, Vitamin C and calcium), and Gp-1 also got metformin 250 mg twice a day.

BMD and Metformin

We evaluated the results after nine months of therapy in contrast to study which evaluated after 2 months treatment in rats [10]. As both groups were recommended bone maintaining supplements and appropriate physical activities, there was statistically significant improvement in BMD in both groups. Improvement was quite evident in female patient's age below 60 years. But on further fractionation of BMD score (Fig: 3-4), it was found that female patients taking metformin had significant improvement in BMD than control. Studies, *in vitro*, have also shown osteogenic effect of metformin [7-12, 18], but our results are in contradiction with some studies e.g. most studies were on rat and murine, where metformin had adverse bone health outcome [8, 15-18] or study reporting metformin has no osteogenic or anti-osteoporotic effect in post-menopausal diabetic women [19]. Male patients have shown improvement in Gp-1 and not in Gp-2, and those above 60 years of age (Fig: 1-2).

BMD and obesity

Obese female patients with or without vitamin D deficiency, in Gp-2 there was significant BMD improvement, but not in Gp-1, whereas pre-obese has improved BMD in Gp-1 and not in Gp-2. We failed to explain this discrepancy (reversal in BMD response from pre-obese to obese in both groups), despite vitamin D deficiency in both groups [female (S=8 & C=8)], associated co-morbidities, and same therapy. It seems pathogenesis of declining bone health in both, with age and obesity is multifactorial guided by unrelated mechanisms of genetic and environmental factors, and in female hormonal imbalance also. It could be that these pre-obese female were below 50 years (S=10, C=10) with insignificant bone loss (BMD maintained) and hence not responded to metformin and other bone maintaining supplement therapy. It is documented that obesity correlates with increased bone mass [20] and weight loss is associated with reduction in bone mass [21, 22]. Metformin role in this subset seems to be reproductive (maintain bone health) and counter-productive (causing weight loss with hence decrease in bone health) and hence has resulted in unchanged BMD, and that pre-obesity has preserved bone mass, so no change in BMD after therapy.

BMD and Generalized Bony Pain (Clinical Ostalgia)

54 Female and 10 male patients had these symptoms. They were mostly osteopenic and vitamin D deficient. There was appreciable symptomatic and statistically significant BMD improvement in Gp-1 but not in Gp-2. Similar improvement in male (both groups) was also recorded. Our results are in accordance with others, reporting beneficial effect of metformin in osteoporosis and improved quality of life in non-diabetic female [23]. Others have also reported osteogenic effect of metformin on osteoblasts in DM, irrespective of blood glucose levels [24], enhances osteoblastic differentiation and inhibits osteoclastic differentiation *in vitro* [25].

BMD in Degenerative Joint Diseases

In our participants, various DJD were common in female (N=25) than male (N=8). They were associated with vitamin D deficiency, osteopenia and osteoporosis. These symptoms were common in female below 50 years and elderly male. In vitamin D deficient category, after therapy, either sex in both groups had appreciable symptomatic and BMD improvement.

Female patients with normal vitamin D levels, after therapy, had appreciably improvement in symptoms, but no improvement in BMD in Gp-1 (*P=0.097629*). Patients in other groups also felt subjective improvement, but statistical analysis could not be done because of less number of patients. But it is

apparent from Table-3, BMD has improved in 9 female patients in Gp-1 with osteoporotic and 2 in Gp – 2.

As seen above, patients of either sex of both groups with DJD and vitamin D deficiency had symptomatic and BMD improvement, whereas female patients with normal vitamin D had only symptomatic improvement but not the BMD. It shows metformin has no significant role in improvement in BMD, but quality of bone, in DJD patients. It has been shown *in vitro* and in animal studies, that metformin could save nucleus pulposus cells against apoptosis and senescence via AMPK based autophagy stimulation and intervertebral disc degeneration [26], by stimulating osteoblasts differentiation and protecting them from hyperglycemia, especially in DM and improving the quality of bone rather than BMD [27]. Therefore, metformin improves both BMD and the quality of bone formation, may be through unrelated mechanism.

CONCLUSION

Declining bone health with age is of great concern today. Metformin preserves bone mass and quality through various mechanisms, AMPK regulation in particular. We have concluded that metformin is effective below 60 years i.e. at an early age when bone mass starts declining. There is appreciable improvement in BMD and symptoms especially in generalized bony pain, degenerative joint diseases associated with vitamin D deficiency. We failed to explain conflicting results in obese and pre-obese patients. We can deduct from patients data about changes in symptoms and BMD that metformin apart from improving BMD also contributes to the quality of bone formation.

Limitations of the Study

(i) Short duration of the study, follow up for more than 1 year could not be done. (ii) Participants were less in number. (iii) Study is based on BMD Scan, as facility for DEXA Scan not available in this institution. (iv) We are unable to explain the conflicting results in obese and pre-obese female patients.

Acknowledgment

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Authors' contribution: All authors participated in study design, collection and collating relevant medical literature, preparation of manuscript and editing and final revision.

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