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Original Research Article

Real-world experience of metformin 1000 mg/day in patients with type 2 diabetes mellitus and comorbidities from Myanmar

Soe Yarzar[1], Myo Lin Aung[2], Thet Kyaw Soe[3], Aung Ko Ko Win[4], Thuzar Lwan Thar[2], Santosh Revankar[5]*, Tripti Sharmaa[5]

[1]M.B.B.S (Ygn), M. Med. Sc (Internal Medicine), M.R.C.P (UK), Yangon, Yangon Division, Myanmar
[2]Medical Department, M.B.B.S (Ygn), M.R.C.P (UK), M. Med. Sc (Int Med), Hin-Tha-Da, Ayeyarwaddy Division, Myanmar
[3]General Practitioner, M.B.B.S (Mgy) Mawlamyine, Mon State, Myanmar
[4]General Practitioner, M.B.B.S (Mdy), Diploma in Dermatology and Dermatosurgery (BKK), Mawlamyin, Mon State, Myanmar
[5]Scientific Services, USV Private Limited, Mumbai, Maharashtra, India

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***Correspondence:**
Dr. Santosh Revankar,
E-mail: usvpublications@gmail.com

ABSTRACT

Background: The study was conducted to assess the efficacy and safety of 1000 (mg/day) metformin in patients with type 2 diabetes (T2DM) with comorbidities and special reference to elderly people in Myanmar.
Methods: This was a retrospective, post surveillance study conducted in patients diagnosed with T2DM receiving treatment of metformin (1000 mg/day). Baseline characteristics, comorbidities, random blood sugar level (RBS) and RBS changes pre- and post-therapy were retrieved from patient's medical records. A paired sample t-test was used for comparing the pre- and post-treatment RBS levels.
Results: A total of 303 patients with T2DM were included. A total of 88, 115 and 100 patients belonged to age groups ≤50, >50-≤60 and >61 years, respectively. Duration of T2DM was significantly higher in elderly patients (>61 years) compared to ≤50 and >50-≤60 age group. Hypertension was the most common comorbid condition observed in all age groups followed by cardiovascular disease. However, both hypertension and cardiovascular disease were significantly higher among elderly patients (>61 years) compared to ≤50 and >50-≤60 age group ($p<0.001$). The mean RBS was significantly reduced at 3 months with metformin treatment in all age groups. However, mean change from baseline was comparatively higher in elderly patients with diabetes (≤50 years, 94.6 mg/dL; >50-≤60 years, 86.2 mg/dL and >61 years, 97.2 mg/dL). Metformin was well tolerated with minimal gastrointestinal adverse events (n=27).
Conclusions: In this post marketing surveillance study, metformin (1000 mg/day) was found to be effective in reducing RBS in T2DM patients with comorbidities especially older adults and well tolerated with no risk of hypoglycemia.

Keywords: Metformin, Large dose, Random blood sugar, Hypertension, Gastrointestinal

INTRODUCTION

Diabetes is a non-communicable disease and leading cause of morbidity and mortality globally. The pandemic of diabetes is estimated to be 463 million adults in 2019 which projected to increases to 643 million by 2030 and 784 million by 2045.[1] Prevalence of diabetes in older people increases with increasing age. Approximately,

111.2 million people (19.9%) in the age group of 65-79 years were living with diabetes worldwide.[2] Myanmar is a Southeast Asian country with an estimated population of 53.9 million and changing pattern in the epidemiology of diseases. Despite its out-of-the-pocket expenditure, proportion of patients with chronic diseases including diabetes, hypertension, stroke, and cancer are increasing, however, it continues to face the huge burden of infectious diseases.[3,4] The primary goal of type 2 diabetes mellitus (T2DM) treatment is to achieve optimal glycemic control while avoiding the drug interactions, limiting unnecessary medications, and choosing the most appropriate drugs for better efficacy. American Diabetes Association [ADA] and European Association for the Study of Diabetes [EASD]) guidelines have recommended the use of metformin as the first-line therapy for the management of T2DM.[5,6] Metformin monotherapy should be continued as long as it is tolerated and not contraindicated.[5] Furthermore, metformin has several additional benefits that include improvements in endothelial dysfunction, hemostasis and oxidative stress, insulin resistance, lipid profiles, and fat redistribution. These pleiotropic effects of metformin may aid in reducing adverse cardiovascular outcomes in patients with T2DM.[7] There is overall evidence emerging from both clinical trials and real-world registry in favor of a cardioprotective effect of metformin with respect to both coronary events and progression to heart failure.[8] Given this potential, its efficacy and safety, metformin has remained the central pillar of the therapy of diabetes. Rationally, the use of metformin achieved glycemic goal in elderly patients with T2DM and remains a manageable and economic drug with a good risk-benefit profile.[9] In addition, previous literature highlighted that metformin is associated with a reduced risk of age-related comorbidities and frailty in older adults with T2DM.[10,11] There is a limited literature on the management of diabetes in elderly patients in Myanmar. The present post marketing surveillance study was conducted to assess the efficacy and safety of dose (1000 mg/day) of metformin in patients with type 2 diabetes (T2DM) with special reference to elderly people in Myanmar.

METHODS

This was a retrospective, post surveillance study conducted in 13 cities of Myanmar between September 2020 and November 2020. Patients of either sex, aged >18 years, diagnosed with T2DM and receiving metformin (sustained release [SR]) (1000 mg/day) therapy were included in this study. Patients having incomplete data profiles or with any condition that according to the discretion of the investigator indicated that the patient was not suitable for inclusion in the study were excluded. Information on baseline characteristics, comorbidities, random blood sugar level (RBS) and RBS changes pre- and post-therapy were retrieved from patient's medical records available at hospital/clinics. A data of 303 patients were retrieved during 3-months of study period. Data were analyzed using Statistical Package for The Social Sciences (SPSS) software, version 23.0. Demographic characteristics were summarized with descriptive statistics, including median and interquartile range (IQR) for continuous variables, and frequency and percentages for categorical variables. A comparison of qualitative and quantitative variables between the groups was done using the chi-square test and Mann-Whitney U test, respectively. A paired sample t-test was used for comparing the pre- and post-treatment RBS levels. A $p<0.05$ was considered statistically significant.

RESULTS

A total of 303 patients with T2DM were included. A total of 88, 115 and 100 patients belonged to age groups ≤50, >50-≤60 and >61 years, respectively (Table 1).

Table 1: Demographic characteristics.

Characteristics	≤50 years N=88	>50-≤60 years N=115	>61 years N=100	P value
Age (years)	44.5 (4.5)	56.6 (2.6)	67.4 (5.3)	<0.001[a, b, c]
Sex, n (%)				
Male	34 (38.6)	49 (42.6)	44 (44.0)	0.075
Female	54 (61.4)	66 (57.4)	56 (56.0)	
RBS (mg/dL)	26=-83.7 (90.1)	277.2 (79.6)	272.6 (78.4)	0.673[a], 0.505[b], 0.804[c]
Duration of T2DM (years), median (IQR)	1.0 (0.1-3.0)	2.0 (0.5-5.0)	3.0 (0.5-8.0)	0.002[a], <0.001[b], 0044[c]
Comorbidities, n (%)				
Hypertension	35 (39.8)	74 (64.3)	69 (69.0)	<0.001
CVD	13 (10.0)	17 (14.8)	21 (21.0)	<0.001
Stroke	0	3 (2.6)	2 (2.0)	0.332
Neuropathy	2 (2.3)	3 (2.6)	2 (2.0)	0.957
Dyslipidemia	1 (1.1)	0	1 (1.0)	0.537
LVH	0	1 (0.9)	1 (1.0)	0.658

Continued.

Characteristics	≤50 years N=88	>50-≤60 years N=115	>61 years N=100	P value
Any other	2 (2.3)	5 (4.3)	1 (1.0)	-

Data shown as mean (SD), unless otherwise specified. CVD, cardiovascular disease; IHD, ischemic heart disease; LVH, left ventricular hypertrophy; MI, myocardial infarction; RBS, random blood sugar; T2DM, type 2 diabetes mellitus.

Table 2: Mean change in RBS at 3 months from baseline.

Age group	Baseline	3 month	Mean change from baseline	95% CI	P value
≤50 years (N=88)	283.7 (90.1)	189.1 (54.6)	94.6 (75.1)	78.7-110.5	<0.001
>50-≤60 years (N=115)	277.2 (79.6)	190.9 (56.6)	86.2 (69.0)	73.5-99.0	<0.001
>61 years (N=100)	272.5 (78.3)	175.4 (50.2)	97.2 (69.4)	83.3-110.9	<0.001

Table 3: Number of GI adverse effects during 3 months.

	Number of patients (N=303)
Anorexia	2
Constipation	7
Dyspepsia	2
Flatulence	6
GI upset	2
Heart burn	3
Indigestion	4
Loss of appetite	1
Data shown as n.	

The mean age of patients was 44.5, 56.6, and 67.4 years in groups ≤50, >50-≤60 and >61 years, respectively (P<0.001). The proportion of female patients was higher than male patients across the age groups. Duration of T2DM was significantly higher in elderly patients (>61 years) compared to ≤50 and >50-≤60 age group.

However, hypertension was significantly higher among elderly patients (>61 years) compared to ≤50 and >50-≤60 age group (p<0.001). Similarly, the prevalence of CVD is significantly higher in elderly patients (>61 years) followed by >50-≤60 age group and ≤50 age group (p<0.001) while all other comorbidities were comparable between the groups (Table 1).

In ≤50 years age group, mean RBS at baseline was 283.7 mg/dL and significantly reduced to 189.1 mg/dL (p<0.001). In >50-≤60 years age group, mean RBS at baseline was 277.2 mg/dL and significantly reduced to 190.9 mg/dL. In elderly patients (above 60 years) the mean RBS was 272.5 mg/dL at baseline which significantly reduced to 175.4 mg/dL at 3 months of metformin treatment (p<0.001). The mean change from baseline was comparatively higher in elderly patients with diabetes (≤50 years, 94.6 mg/dL; >50-≤60 years, 86.2 mg/dL and >61 years, 97.2 mg/dL) (Table 2).

A total of 27 (8.9%) patients reported mild to moderate GI adverse effects during 3 months follow-up. (Table 3).

Regression analysis showed large variability between increased age and % change in RBS (Figure 1). A total of 100 patients with >60 years of age reported change in RBS in the range of -6% to -82%. The mean % change in RBS was highest (-40.5%) in patients with having diabetes duration 0.5 years (Figure 2).

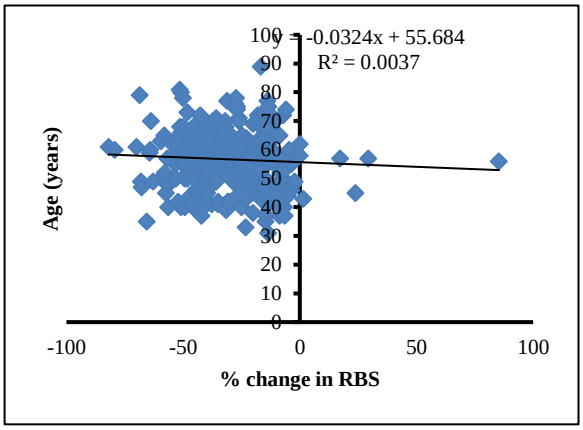

Figure 1: Age versus % change in RBS.

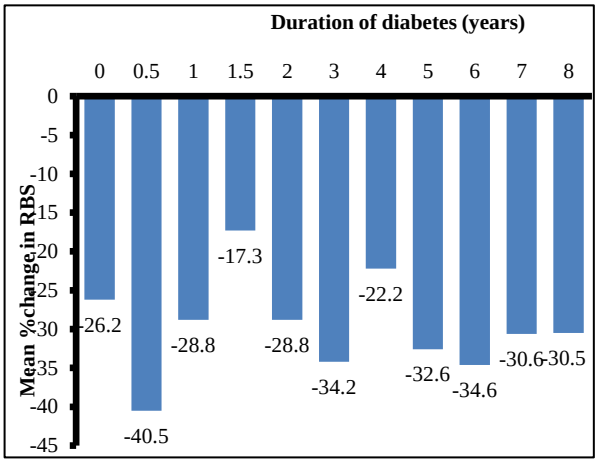

Figure 2: Mean % change in RBS according to duration of diabetes.

Hypertension was the most common comorbid condition observed in all age groups (≤50, 39.8%; >50-≤60, 64.3%;

>61, 69%) followed by CVD (≤50, 10.0%; >50-≤60, 14.8%; >61, 21%).

DISCUSSION

Metformin has been used successfully from last seven decades as a first line therapy in all patients with T2DM along with lifestyle modification to achieve glycemic target. Metformin has potential to improve insulin resistance and decrease hepatic gluconeogenesis.[12] Guidelines of American Diabetes Association (ADA), International Diabetes Federation (IDF), and American College of Physicians have recommended the use of metformin as monotherapy or in combination with other antidiabetic agent in elderly population due to its efficacy, low risk of hypoglycemia, few side effects, ease of use, low cost, and beneficial effects on weight loss.[5,13,14] Also, it was well-tolerated in patients with stable renal function.[15]

This retrospective study was conducted to assess the efficacy and safety of large dose (1000 mg/day) of metformin in 303 patients with T2DM in the South East Asian country Myanmar. In this study, the mean duration of T2DM was significantly higher in elderly patients (>61 years) compared to ≤50 and >50-≤60 age group. Hypertension was the most common comorbid condition observed in all age groups followed by CVD. However, hypertension and CVD were significantly higher among elderly patients (>61 years) compared to ≤50 and >50-≤60 age group ($p<0.001$). Patients with diabetes are known to be more likely to have hypertension and CVD as the most common comorbid conditions due to common risk factors.[16] Several observational studies have demonstrated consistent beneficial effects of metformin in patients with comorbid conditions including coronary heart disease, heart failure and chronic kidney disease.[17,18] The United Kingdom Prospective Diabetes Study (UKPDS) was the first large trial changed the position of metformin in T2DM management.[19] Patients with T2DM randomized with metformin experienced 42% reduced diabetes related mortality and 36% reduced all-cause mortality compared to the diet alone arm.[19] In addition, significant association was observed between metformin use and reduced mortality and hospitalization rate in patients with T2DM and heart failure.[20,21] Therefore, metformin can be used safely in patients with T2DM along with comorbidities due to its pleiotropic effects.

In recent years, Myanmar is facing rising burden of non-communicable diseases and the age-standardized prevalence of diabetes is increasing due to rapid urbanization, socioeconomic status, lifestyle modification and changes in dietary patterns.[22] In the present study, 303 patients with T2DM received metformin (1000 mg/day) treatment to achieve glycemic goal. All patients showed decreased mean RBS level at 3 months post treatment and according to age group analysis, elderly group showed higher reduction in RBS. These finding were similar with the previous prospective study of 24 patients (aged 70-88 years) who received metformin over two months as the sole therapy at a dosage of either 850 mg or 1,700 mg/day dependent on creatinine clearance values.[23] Safety and efficacy profile of metformin in patients with 65 years old or older appears to be better than other anti-diabetic agents for the management of T2DM.[24]

Further this study highlighted the use of metformin in older people due to its lower mortality risk and reduced risk of adverse events including hypoglycemia and nonfatal cardiovascular events. A recent meta-analysis of randomized controlled trials also showed a reduced body weight with slight improvement in lipid profile in older patients who treated with metformin.[25] A systematic review on the use of metformin in the elderly indicates that the safety and efficacy profiles of metformin appear to be better, than other treatments for the management of T2DM in older adults.[24] While there is limited data on the tolerability of metformin in the elderly, the results of the present study suggest good tolerability in the study population across all age groups. In this study, one fourth of patients reported with mild to moderate GI adverse effects during 3 months follow-up. This is in accordance with the previous study, where up to 25% patients encountered with metformin associated GI side effects.[26] This frequently reported GI side-effects are usually linked with rapid dose titration and initiation of higher metformin dosage. These effects have been observed with early course of time and can be subsided over time.[27] The GI side-effects may be minimized by slowly reducing the rate of dose escalation, taking the agent with meals, or transferring to a prolonged-release formulation.[28]

The present study has some limitations. This is a post surveillance study and results were based on relatively small sample size. Therefore, prospective studies with a larger sample size, more data related to glycemic parameters and longer follow-up are necessary to confirm these findings.

CONCLUSION

In this post marketing surveillance study, a metformin (1000 mg/day) was found to be effective in reducing RBS in T2DM patients with comorbidities. The drug was well tolerated with no risk of hypoglycemia and very few GI adverse events in 3 months follow-up.

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