ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

A Comparative Assessment of Antidiabetic Medications on Postprandial Blood Sugar (PPBS), Fasting Blood Sugar (FBS), and Vitamin B12 in a Tertiary Care Setting: A Randomised Prospective Open-Labeled Study in Eastern Uttar Pradesh Population

Dr. Varun Vikas, Junior Resident,
Department of Pharmacology, B. R. D. Medical College, Gorakhpur
Contact Number: 7017493618,
Email-Id: varunsingla252841@gmail.com
Second Author: Dr. Vikas Seth, Professor & Head,
Department of Pharmacology,
B.R.D. Medical College, Gorakhpur
Email-Id: oshochamp@gmail.com
Third Author: Dr. Jamal Haider, Associate Professor,
Department of Pharmacology,
B. R. D. Medical College, Gorakhpur
Email-Id: jamalatbrd@gmail.com
Fourth Author: Dr. Azahar Ali Khan, Professor,
Department of Medicine,
B.R.D. Medical College, Gorakhpur

Abstract

Introduction: Type 2 diabetes is a chronic metabolic disorder characterized by elevated blood sugar levels and impaired insulin function. Achieving optimal glycemic control is crucial in preventing complications associated with diabetes. Antidiabetic medications play a pivotal role in managing diabetes and improving patients' overall health outcomes.Eastern Uttar Pradesh, India, is a region with a high prevalence of diabetes, posing significant challenges for healthcare providers.The study aimed to provide valuable insights into the efficacy and safety profiles of commonly prescribed antidiabetic medications, including metformin, sulfonylureas, DPP-4 inhibitors, and SGLT2 inhibitors, in this population

Objective: This prospective open-labeled study aimed to compare the effects of various antidiabetic medications on HbA1c levels, postprandial blood sugar (PPBS), fasting blood sugar (FBS), and vitamin B12 status in patients with diabetes receiving care at a tertiary healthcare setting in Eastern Uttar Pradesh, India.

Material and Methods:The present entitled study of antidiabetic medication is an institution based, prospective, randomized, open-label, single center and parallel group study conducted inDepartment of Pharmacology and Department of Medicine OPD at BRD Medical College, Gorakhpur from march 2022 to September 2022 .The cases were selected basing on following inclusion and exclusion criteria after informed consent followed by meticulous history taking and clinical examination .Patients diagnosed with type 2 diabetes were enrolled in the study. The patients were divided into four groups based on the prescribed antidiabetic medication: metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors), and sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors). Baseline demographic information, clinical characteristics, and medication details were recorded. HbA1c levels, PPBS, FBS, and serum vitamin B12 levels were measured at baseline and at regular intervals over six month follow-up period. Changes in HbA1c, PPBS, FBS, and vitamin B12 levels were analyzed

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

using paired t-tests, and comparisons between medication groups were made using analysis of variance (ANOVA).

Results: A total of 259 patients (mean age59.08±12.17 years; 61% male).The study included four treatment groups: Group A (Metformin monotherapy), Group B (Metformin plus Pioglitazone), Group C (Metformin plus Tenagliptin), and Group D (Metformin plus Glimepiride). After one year of follow-up, all groups showed significant improvements in postprandial blood sugar (PPBS) and fasting blood sugar (FBS) levels ($p < 0.001$). However, Group A had a higher incidence of vitamin B12 deficiency compared to the other groups. The combination therapies (Groups B, C, and D) did not significantly affect vitamin B12 levels.

Conclusion: The combination therapies demonstrated comparable efficacy to metformin monotherapy in improving blood sugar control. However, metformin monotherapy was associated with a higher risk of vitamin B12 deficiency. These findings highlight the importance of monitoring vitamin B12 levels in patients receiving metformin therapy and suggest the need for further research to optimize vitamin B12 status in individuals with type 2 diabetes**.**

INTRODUCTION: Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. DM is associated with abnormalities in carbohydrates, fats and protein metabolism.[1]Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. The chronic hyperglycemia of diabetes is accompanied with long-term damage, dysfunction, and failure of various organs, especiallythe kidneys, eyes, nerves, heart, and blood vessels. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome.[2]

Worldwide, 3.2 million deaths are attributable to diabetes every year. One in 20 deaths is attributable to diabetes; 8700 deaths every day; six deaths every minute. At least one in ten deaths among adults between 35 and 64 years is attributable to diabetes.[3]Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease.[4] Estimates of global diabetes prevalence predicts, 6.4% in 2010 affecting 285 million adults and will increase to 7.7% and 439 million adults by 2030.[5]

According to the latest American Diabetes Association (ADA) guidelines, [6] lowering HbA1c to <53 mmol/mol (7%) has been shown to reduce microvascular and neuropathic complications of diabetes and, if implemented soon after the diagnosis of diabetes, is associated with long-term reduction in both micro- and macrovascular disease. Lifestyle modification can improve glycaemic control as well as bodyweight, blood pressure, insulin-resistance and lipid profile; however, the progressive decline of b-cell function, together with progressively increasing insulin resistance and poor patient compliance in maintaining behavioural modifications, often force physicians to use multiple drugs.[7]Usually, metformin, which acts by suppressing hepatic gluconeogenesis, is generally accepted as a first-line pharmacologic therapy for treatment of Type 2 diabetes mellitus.[8]

Metformin, a biguanide class of oral hypoglycemic agents, is the first line drug for the treatment of type 2 diabetes mellitus.[9] Metformin is used clinically for the treatment of obesity and diabetes, and its mechanism of actions include the following: (1) lowers plasma glucose levels by inhibiting gluconeogenesis in liver (2) decreasing the intestinal absorption of glucose, and (3) improving insulin

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

sensitivity by increasing peripheral glucose uptake and utilization. Additionally, metformin has a variety of pleiotropic effects including improved lipid and cholesterol metabolism, decreased inflammation and inhibition of cell growth. (4) Increases plasma levels of glucagon-like peptide 1 (GLP-1) is a member of the in cretin family of peptide hormones release incretin from the gut in response to ingested glucose. It induces insulin release from pancreatic β-cells, retards gastric emptying, inhibits glucagon release from α cell, and produces a feeling of satiety.[10]

Although recent guidelines encourage the use of metformin in combination with life style modification as the first choice for T2DM,[11] unfortunately metformin use in patients with type 2 diabetes is associated with decreased vitamin B_{12} and folate levels and increased level of homocysteine (Hcy).[12]

Pioglitazone, a thiazolidinedione derivative, is an insulin-sensitizing agent developed for the treatment of T2DM. Pioglitazone is a peroxisome proliferator activated receptor-gamma (PPAR-γ) agonist which can reduce insulin resistance in liver, muscle and adipose tissue and improve glucose and lipid metabolism. Pioglitazone treatment in T2DM results in improving lipid profile including decrease in triglycerides and low-density lipoprotein (LDL), increase in high- density lipoprotein (HDL) and decrease in serum fatty acids as well as improved liver function tests. Unlike these findings, other studies were not able to demonstrate any significant improvement in liver function tests or lipid profile.[13]

Glimepiride (Amaryl) is a second generation sulfonylurea, acts as an insulin secretagogue. It is indicated for the management of type 2 diabetes mellitus (T2DM) in adults along with diet and exercise. It binds to & inhibits ATP sensitive K+ channel on beta cells of pancrease and thus increasing the insulin production from pancrease & also stimulates peripheral GLUT 4 receptors thus increases peripheral uptake of glucose. It leads to hypoglycemia & weight gain.[14]

Dipeptidyl peptidase-4 (DPP-4) inhibitors, such as sitagliptin, saxagliptin, linagliptin, alogliptin, and vildagliptin, nominally enhance endogenous incretin levels, which results in a moderate reduction (0.6–0.9 %) in A1C. DPP-4 inhibitors are considered weight neutral with modest effects on lipid parameters, including reduction in total cholesterol and TG levels. Sitagliptin has been found to have modest effects on serum lipid levels in general populations of patients with T2DM and to reduce total cholesterol and LDL-C levels in patients with elevated baseline TG levels. Vildagliptin has been shown to decrease total cholesterol and TG.[15, 16]

In the context of Eastern Uttar Pradesh, India, where the prevalence of diabetes is high, it is crucial to assess the effectiveness and safety profiles of commonly prescribed antidiabetic medications. This understanding will help healthcare providers make informed decisions regarding treatment strategies and optimize patient care.

OBJECTIVE: This prospective open-labeled study aimed to compare the effects of various antidiabetic medications on HbA1c levels, postprandial blood sugar (PPBS), fasting blood sugar (FBS), and vitamin B12 status in patients with diabetes receiving care at a tertiary healthcare setting in Eastern Uttar Pradesh, India.

MATERIAL AND METHOD

Prospective, Randomized, Open-Label, Single Center and Parallel study was conducted after getting permission from the Institutional Ethics Committee (IEC: 1275/2020). The study was

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

done at Department of Pharmacology and Department of Medicine OPD at BRD Medical College, Gorakhpur of a tertiary care teaching hospital in Eastern India.

SCREENING

Study Subjects: Patients with Type 2 DM diagnose according to American Diabetes association (ADA) criteria (FBG ≥ 126 mg/dl and 2hrs PPBG 200 mg/dl) in the age group of 30-65 years of either sex

The study was conducted after institutional ethical committee approval, informed consent regulations, as per Declaration of Helsinki, ICH good Clinical Practice (GCP) guidelines and the ICMR guidelines for Biomedical Research on Human Subjects, 2006.

Inclusion Criteria

1. Patients with Type 2 DM diagnose according to American Diabetes association (ADA) criteria (FBG ≥ 126 mg/dl and 2hrs PPBG 200 mg/dl) in the age group of 30-65 years of either sex,
2. All patients provided written, vernacular, witnessed, informed consent to participate in the trial and Patients willing to take medications as directed & willing to come for the follow-ups.

Exclusion Criteria

1. Patients with history of Type 1 DM, with acute medical emergencies like diabetic ketoacidosis, polycystic ovarian disease, liver disease, and kidneys disease.
2. Any microvascular complication, with chronic GIT disease, concomitant with steroid therapy and
3. History of hypersensitivity to test drug
4. Pregnant and lactating women.

Sample Size:

n = n = Z2p%q%/ d%2.

where p is the observed incidence

q = 100- p

d is the margin of error

Za/2 is the ordinate of standard normal distribution at α% level of significance

Calculations:

p (Prevalence of Diabetes: Anjana RM, Deepa M, Pradeepa R, Mahanta J, Narain K, Das HK, Adhikari P, Rao PV, Saboo B, Kumar A, Bhansali A. Prevalence of diabetes and prediabetes in 15 states of India: results from the ICMR–INDIAB population-based cross-sectional study. The lancet Diabetes & endocrinology. 2017; 5(8 p (Prevalence of Diabetes) 129: = 7.3%

q = 92.7%

d = 0.05% = 1.96

Z2.5% at α = 5% level of significance

n= 103.94

Hence the minimum sample size required in the present study is 103.94. Considering the error and attrition, the same size was increased to 259 for the present study.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

Intervention drugs

After meeting the inclusion criteria, patients were randomized by a computer-generated randomization sequence into four groups, each consists of 50 patients.

1. In group A: Tab. Metformin 500 mg, orally, BD after meals
2. Group B: Tab. metformin plus Pioglitazone 7.5 mg single dose orally for 6 months was given,
3. Group C: Metformin plus Tenagliptin, orally, single dose after meals
4. Group D: Metformin plus Glimepiride, orally, dose, and the patients were directly started at this dose.

To check compliance and ensure regular medication by the patient, a log book was checked regularly which will be given to each patient.

Laboratory investigation

Vitamin B12 levels, folic acid levels were measured in serum. Levels of plasma fasting glucose were determined by the calorimetric method using a Cobas Mira Plus autoanalyzer (Roche Diagnostics, Mannheim, Germany). Low-density lipoprotein cholesterol levels were calculated by the Fried Wald formula.

Vitamin B12 concentrations were measured with the chemiluminescent method using an Immulite 2000 immunoassay analyser (DPC, Los Angeles, USA). Insulin sensitivity was calculated using the homeostasis model assessment (HOMA) [formula: fasting glucose (mmol/l) fasting insulin (mum/ml)/22.5.[114]

Procedure

On the start of the study, (Day 0), after taking the medical history, demographic details, physical measures (waist circumference, body mass index (BMI)), general and systemic examination of the patients, routine laboratory investigations were sent.

The baseline fasting Blood glucose (FBG), postprandial blood glucose (PPBG), factors related and serum B_{12} was measured.

Patients were given a 15 days' supply of either drug with proper directions and asked to report back after 15 days. Initially patients were followed after 15 days and subsequently every month up to 6 months. FBG and PPBG was recorded monthly while serum vitamin B12 was recorded at 3- and 6-months' intervals.

Compliance with treatment and from the pre-specified in terms of the study visits (baseline, three and six months) the patients were followed up as before they entered the study, as part of the normal clinical practice (most commonly every two or three months).

Data was collected and subjected to statistical analysis.

Statistical analysis: The collected data was compiled in MS Excel sheet for analysis in Statistical Package for the Social Sciences (SPSS) version 24 was applied. The qualitative data was represented in the form of frequencies and percentage also represented in visual impression like bar diagram etc. Quantitative data was represented in the form of mean and standard deviation. To check significance difference between baseline and after three months' effect of Metformin and Pioglitazone, paired't' test was applied and also quantitative data was represented

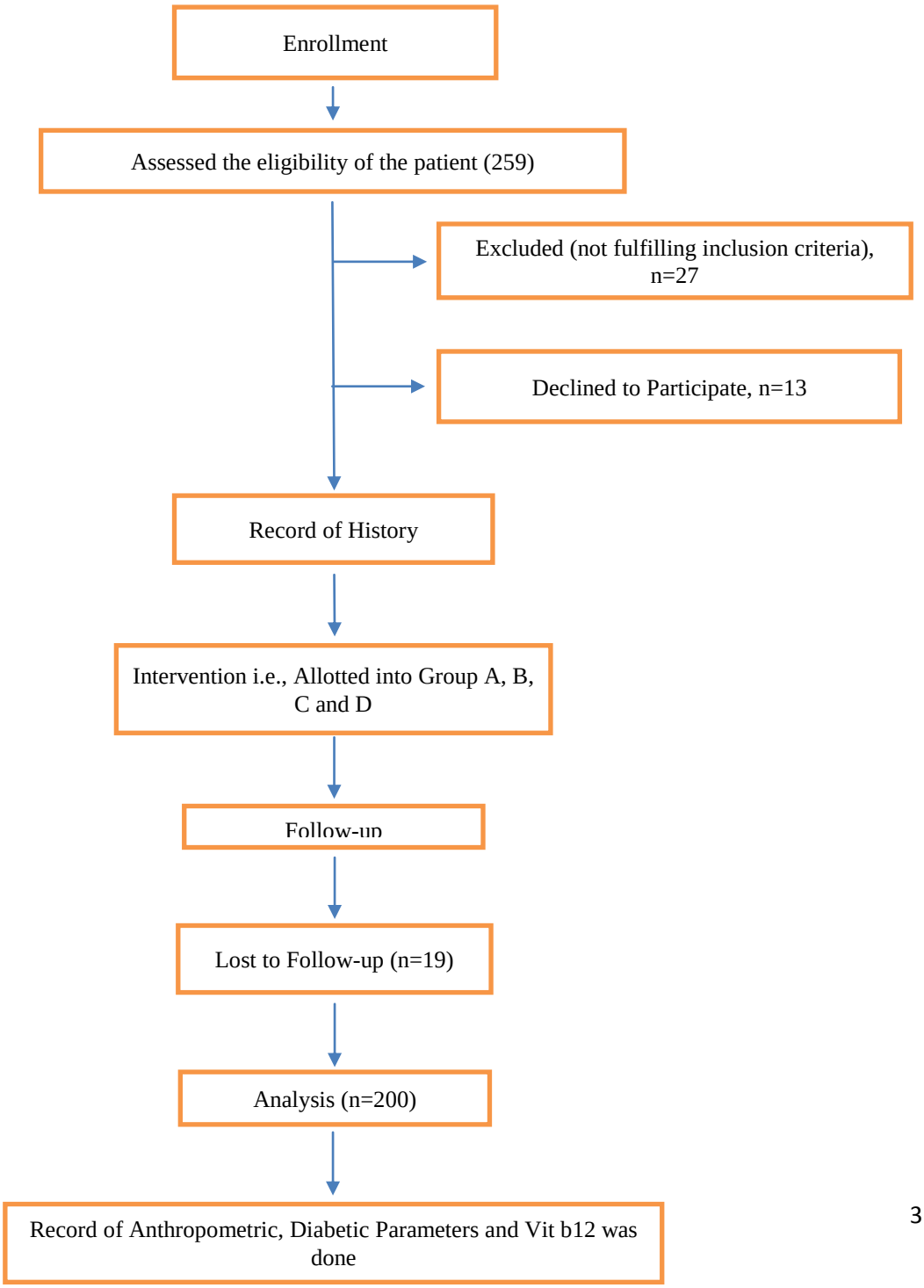
ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

in the form of bar diagram. The level of significance was determined as its 'p' value with p <0.05 was taken as significant at 5% significance level.

Results:

1. A total of among 259 patients with Type 2 DM diagnosed according to American Diabetes Association (ADA) criteria (FBG ≥ 126 mg/dl and 2hrs PPBG 200 mg/dl) in the age group of 30-65 years of either sex. Out of these 259 patients, 27 patients did not fulfill the inclusion criteria, 13 patients declined to participate, and 19 of those were lost to follow-up.

Figure: 1

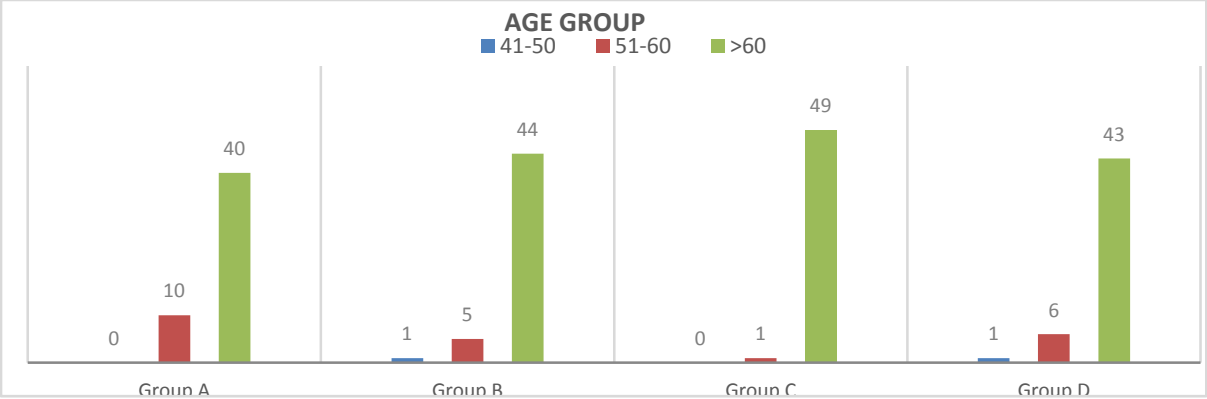


ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

2. Mean age among the study subjects was 59.08±12.17 years. Maximum subjects were from age group of 50-59 years (42%) while minimum subjects were from <40 years (10.5%) as shown in table 1, graph 1.

Age Group (in years)	Group A		Group B		Group C		Group D		Total	
	N	%	N	%	N	%	N	%	N	%
41-50	0	0	1	2	0	0	1	2	2	1
51-60	10	20	5	10	1	2	6	12	22	11
>60	40	80	44	88	49	98	43	86	176	88
Total	50	100	50	100	50	100	50	100	200	100

Table: 1



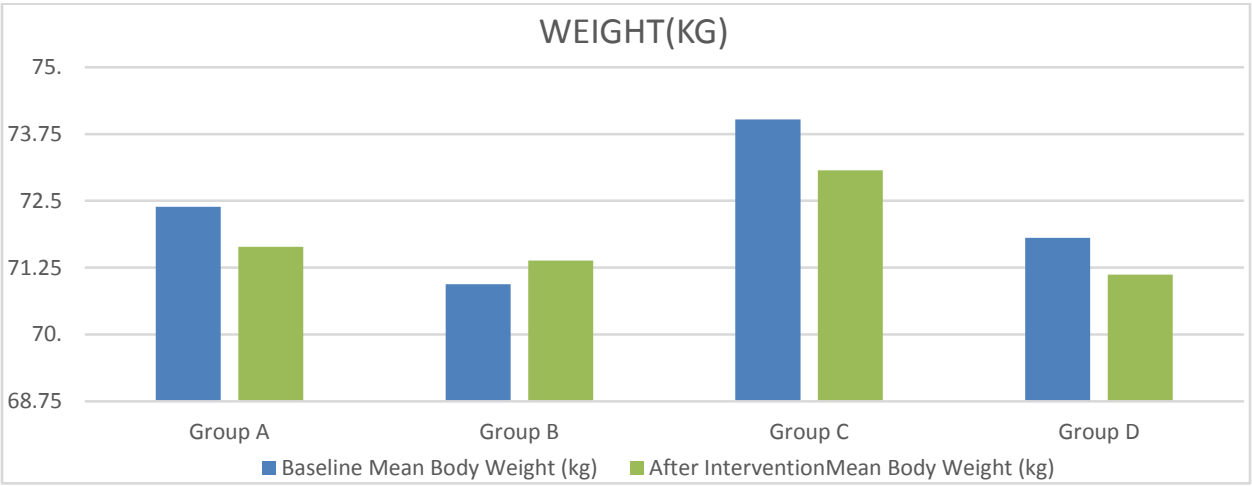
Graph: 1

3. After intervention; except in group B, mean body weight was reduced in all the groups with statistically significant difference (table 2, graph 2).

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

Group	Baseline		After Intervention		p value
	Mean Body Weight (kg)	SD	Mean Body Weight (kg)	SD	
Group A	72.39	9.28	71.64	10.04	0.010
Group B	70.94	8.71	71.38	8.56	0.008
Group C	74.02	7.47	73.07	7.51	0.046
Group D	71.81	8.58	71.12	8.73	0.001

Table: 2



Graph: 2

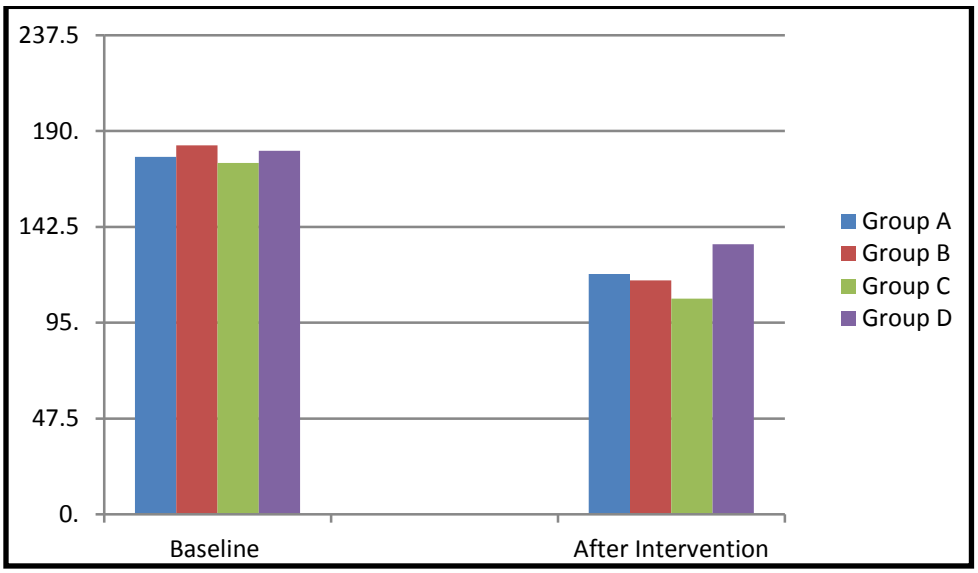
4. Significant reduction in FBS was found after the intervention among all the study groups as $p<0.05$ (table 3, graph 3).

Group	Baseline		After Intervention		p value
	Mean FBS	SD	Mean FBS	SD	
Group A	177.17	19.12	119.12	11.89	0.001**

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

Group B	182.96	15.20	115.94	10.59	0.001**
Group C	174.18	17.93	106.96	3.83	0.001**
Group D	180.23	16.83	133.94	13.72	0.001**

Table: 3



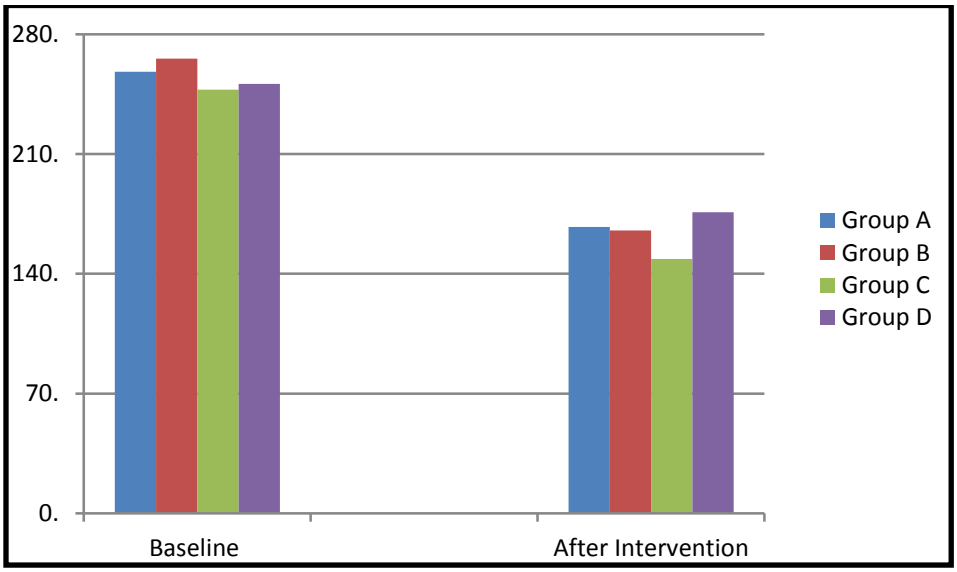
Graph: 3

5. Significant reduction in PPBS was found after the intervention among all the study groups as p<0.05 (table 4, graph 4).

Group	**Baseline**		**After Intervention**		**p value**
	Mean PPBS	**SD**	**Mean PPBS**	**SD**	
Group A	258.05	12.57	167.42	12.64	0.001**
Group B	265.86	13.01	165.40	14.27	0.001**
Group C	247.62	15.86	148.64	12.34	0.001**
Group D	250.99	17.95	175.98	16.77	0.001**

Table: 4

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023



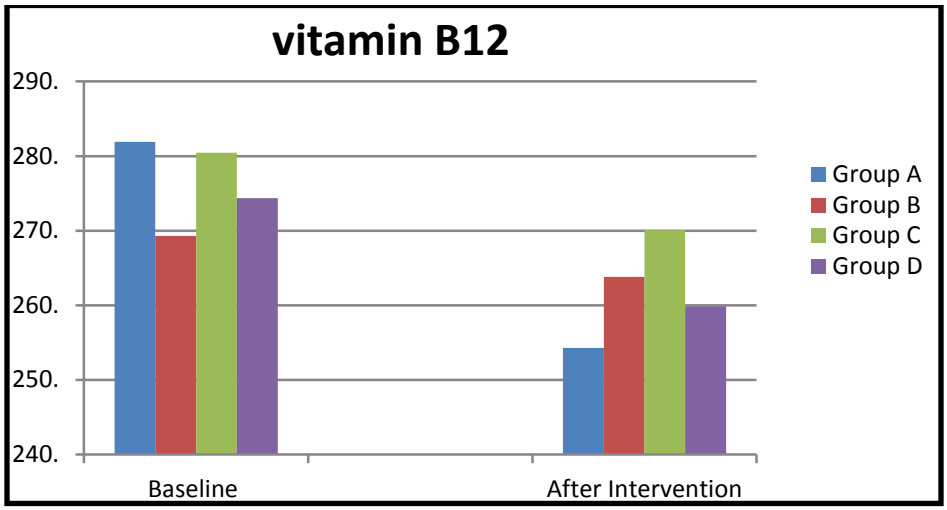
Graph: 4

6. Mean vitamin b12 was 281.08±78.77, 269.72±74.68, 280.39±81.59 and 274.18±90.02 in group A, B, C and D respectively. After intervention, vitamin b12 was decreased in all the groups with statistically significant difference only in case of group A (table 5).

Group	**Baseline**		**After Intervention**		**p value**
	Mean Vitamin b12	**SD**	**Mean Vitamin b12**	**SD**	
Group A	281.92	52.54	254.28	52.51	0.001**
Group B	269.32	47.35	263.80	47.11	0.001**
Group C	280.46	51.88	270.06	51.64	0.001**
Group D	274.36	47.81	259.86	43.91	0.001**

Table: 5

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023



Graph: 5

DISCUSSION:

The present Prospective, Randomized, Open-Label, Single Center and Parallel Group study was conducted in the OPD of the Department of Medicine along with the Department of Pharmacology at BRD Medical College, Gorakhpur, among 259 patients with Type 2 DM diagnosed according to American Diabetes Association (ADA) criteria (FBG ≥ 126 mg/dl and 2hrs PPBG 200 mg/dl) in the age group of 30-65 years of either sex. Out of these 259 patients, 27 patients did not fulfil the inclusion criteria, 13 patients declined to participate, and 19 of those were lost to follow-up. The reasons for the loss were as follows: financial burden; lack of interest in follow-up due to occupational compulsions. After meeting the inclusion criteria, patients were randomly divided by a computer-generated randomization sequence into four groups, i.e., A, B, C, and D, each consisting of 50 patients. Group A received metformin 500 mg orally twice daily after meals, while Group B received metformin plus pioglitazone 7.5 mg orally once daily after meals. Simultaneously, Group C was prescribed Tab Metformin plus Tenagliptin 20 mg, single dose orally, after meals. Likewise, Group D was prescribed Tab. Metformin plus Glimepiride, single dose, orally, after meals, and patients were directly started at this dose.

Age

Mean age among the study subjects was 59.08±12.17 years. Maximum subjects were from age group of 50-59 years (42%) while minimum subjects were from <40 years (10.5%) in this study. The observations regarding age distribution in type 2 diabetes patients are due to the combined effects of increasing insulin resistance and impaired pancreatic islet function with aging, and the findings are almost similar to what has already been reported by Leena Varghese et al[18], in which the mean age of the patients was 52 years. 53% of patients were above the age of 55, and 47% were below the age of years. Piyush Agarwal et al[17] in their study reported a mean age of 49.6 years.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

Body Weight (kg)

The mean body weight (kg) was found to be comparable among all the groups. After intervention, mean body weight (kg) in group A, B, C and D was 71.64±10.04, 71.38±8.56, 73.07±7.51 and 71.12±8.73 respectively. Except in group B, mean body weight was reduced in all the groups with a statistically significant difference due to metformin, which improves insulin sensitivity and reduces glucose in the systemic circulation while also decreasing stored fat in the body. While in group B, pioglitazone causes water retention in the body due to increased fluid reabsorption and vascular permeability in adipose tissues, leading to weight gain. The observations regarding mean body weight are similar to what has already been reported by Mustafa Sahin et al[19] in their study, in which it was revealed that Metformin significantly decreased body weight.

N Aghamohammadzadeh et al[20] in their study similarly reported that weight was significantly increased ($p < 0.001$) after the intervention of pioglitazone.

Similar to previous findings by Chawla et al[21].2013; Nafrialdi, 2012[22]; Sanyal et al. 2010[23], we observed a significant increase in patients' weight following pioglitazone use. However, this increase was only 1.07%. Some previous studies have reported an increase of 5% in body weight after pioglitazone use. Chawla et al. 2013[21]; Nafrialdi,2012[22]; Sanyal et al. 2010[23]; however, similar to our findings, Pavo and colleagues found a lower weight increase (0.9%) following pioglitazone use Pavo et al. 2003.[24] Unlike all of these findings, You and colleagues did not find weight gain following pioglitazone use You et al. 2010[25].

Piyush Agarwal et al[17] in their study reported that the difference in body weight between screening and week 16 was not significant.

According to Leena Varghese et al[18], no change in BMI was observed, which shows that it is weight neutral like other DPP4 inhibitors due to increased satiety and delayed gastric emptying.

However, a review by Bohannon reported that the use of gliptins is associated with no increase in weight among patients with T2DM[26].

FBS and PPBS

The mean FBS at baseline in groups A, B, C and D was 177.17±12.56, 182.96±10.43, 174.18±8.12 and 180.23±11.54 respectively. Mean PPBS at baseline in groups A, B, C and D was 258.05±10.71, 265.86±9.63, 247.62±10.54 and 250.99±12.13 respectively. Mean FBS after intervention in groups A, B, C and D was 158.30±10.45, 139.91±10.09, 128.82±9.33 and 151.24±11.57 respectively. Mean PPBS at baseline in groups A, B, C and D was 201.46±10.44, 193.60±9.51, 172.59±10.01 and 198.22±11.25 respectively. A significant reduction in FBS and PPBS was found after the intervention among all the study groups, as $p<0.05$. The observations

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

regarding FBS and PPBS are almost similar to what has already been reported by T. Yamanouchi et al[27] in whose study revealed that patients were randomly assigned to pioglitazone, metformin, or glimepiride. Although there were no significant differences among the three groups at the end of the study, patients taking pioglitazone had a relatively lower FPG than patients taking metformin and glimepiride. These results suggest that pioglitazone acts predominantly on nocturnal metabolism rather than at mealtimes.

Pioglitazone may have the strongest action on changes in body composition, such as transferring fat tissue from visceral to subcutaneous tissue, which takes some time to accomplish. This implies that 3 or 4 months after starting pioglitazone is too short a period to judge whether the patient is responding to the drug[27].

According to N Aghamohammadzadeh et al[20], the levels of FBS ($p < 0.001$) were significantly decreased ($p < 0.001$) after the intervention of pioglitazone, and Mustafa Sahin et al[19] reported in their study that there is significant reduction in diabetic parameters.

Piyush Agarwal et al[17] in their study similarly found that the reduction in HbA1c was statistically significant in the teneligliptin group at week 16 compared with baseline. Ghosh S et al[28] conducted a study to find out the glycemic efficacy of teneligliptin when given as monotherapy as well as add-on treatment, which significantly improved glycemic control in type 2 diabetes.

The results obtained with teneligliptin are in agreement with previous studies[29].

Vitamin B_{12}

The mechanisms causing the deficiency of vitamin B_{12} are controversial and have been subjected to various studies. The postulated mechanisms are competitive inactivation and inhibition of cobalamin, individual variation in intrinsic factor level, gastrointestinal motility disorders, alteration in bowel bacterial flora, and inhibition at or alteration of the cubilin receptors. A more appropriate explanation could be antagonism of the calcium mediated transport in the terminal ileum of the B_{12} complex. This is substantiated by calcium supplementation improving the vitamin B level in these patients[30].

Mean vitamin b_{12} was 281.08±78.77, 269.72±74.68, 280.39±81.59 and 274.18±90.02 in group A, B, C and D respectively. After the intervention, vitamin b_{12} levels decreased in all the groups, with a statistically significant difference only in the case of group A.

Previous studies have reported that metformin treatment is associated with decreases in serum vitamin B12 [31-32]. Metformin is thought to induce malabsorption of vitamin B12 $_2$.

In a study by Kim J et al[33]., documented serum vitamin B_{12} deficiency occurred in 22.2% of patients (n=247). After adjusting for confounders, a 1mg increase in daily metformin dose was

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

associated with a 0.142pg/mL decrease in vitamin B12 (P<.001). Serum homocysteine levels were negatively correlated with vitamin B12 levels, implying that metformin use may cause B_{12} deficiency at the tissue level.

The American Diabetes Association guidelines now recommend routine evaluation for Vitamin B12 deficiency in patients taking metformin, as studies conducted in recent years have linked metformin use to diabetic neuropathy. Previously, the American College of Endocrinology had also recommended monitoring vitamin B12 levels in patients taking metformin.

Jager D et al[34]., reported Long-term metformin use raises the risk of vitamin B-12 insufficiency, which leads to elevated homocysteine levels. Because vitamin B-12 insufficiency is avoidable, our findings imply that regular monitoring of vitamin B-12 concentrations during long-term metformin use should be highly considered.

In a study by Mustafa Sahin et al[35], after treatment metformin use was associated with decreases in vitamin B12. During Pioglitazone treatment, vitamin B12 levels remained unchanged. These findings are similar to those of the present study.

In my study, Group B has significant effect in reducing fasting blood sugar and had better lipid lowering activity. As per the biochemical parameters and evaluation performed in the present study and the presented results and the previous studies we analysed, it has been observed that group B has maximum benefit therapeutic potential. So, it would be the preferential treatment protocol that could be followed.

In my research, I observed that vitamin B12 supplementation should always be recommended in conjunction with Metformin to prevent diabetic neuropathy.If glycemic control is not maintained by Metformin, the patient will have deranged lipid levels, for which we have to add Pioglitazone for better glycemic control and a reduction in the risk of cardiovascular events.

LIMITATIONS

This study had some limitations. We did not have a control group, because my study has been done in tertiary center where most of the cases were preliminary diagnosed with DM or mostly are follow up cases, so could not exactly compare the changes observed in glycaemia control, liver function and weight gain. Patients 'physical activity was not evaluated which limits the findings on weight gain. Patients were also not on a similar diet. This may be another limitation, as the diet used has significant effects on the evaluated variables.

CONCLUSION

All the drugs in this study are equally effective in reducing blood glucose in patients with newly diagnosed Type 2 diabetes. However, their specific characteristics, such as the rapid action

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

onblood glucose levels of Pioglitazone and the favourable action on FBG, should be considered when choosing an appropriate agent. Pioglitazone carries a trivial risk of weight gain, which would be overcome by other oral hypoglycemic agents like Tenagliptin, an alternative option and diet control. The present study found a higher incidence of vitamin B12 deficiency among the patients on metformin medication. The study also discovered that chronic metformin therapy, as well as higher doses, were linked to an increased incidence of vitamin B12 deficiency. There is also a strong positive correlation between Metformin dose and duration of use and vitamin B12 levels in people with type 2 diabetes mellitus.

CONFLICT OF INTREST-None

SOURCE OF FUNDING- None

CONSENT- As per international or university standards, authors are collected and preserved written participants consent.

ETHICAL APPROVAL- Authors have collected and preserved written permission from college research committee.

References

1. Reaven GM. Role of insulin resistance in human disease. Diabetes. 1988 Dec 1;37(12):1595-607.
2. Hovind P, Hansen TK, Tarnow L, Thiel S, Steffensen R, Flyvbjerg A, Parving HH. Mannose binding lectin as a predictor of micro albuminuria in type 1 diabetes: an inception cohort study. Diabetes. 2005;54(5):1523-7.
3. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care.2004; 27: 5-10.
4. World Health Organization, Global Health Observatory (GHO) data.http://www.who.int/gho/ncd/risk_factors/bmi_text/en/. Last accessed on 21 June 2021.
5. Kumar A, Goel MK, Jain RB, Khanna P, Chaudhary V. India towards diabetes control: Keyissues. Australas Med J. 2013;6(10):524–31.
6. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).Diabetes Care 2012; 35: 1364–1379.
7. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. J AmMed Assoc 1999; 281: 2005–2012.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

8. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R et al. American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009; 32: 193–203.
9. Abhishek Raj. Formulation and In-vitro evaluation of Voglibose Dispersible tablets. EJBPS, 2016;3(2): 226-30.
10. Pernicova I, Korbonits M. Metformin mode of action and clinical implications for diabetes and cancer. Nat Rev Endocrinol. 2014; 10: 143-56.
11. Raz I. Guideline approach to therapy in patients with newly diagnosed type 2 diabetes. Diabetes Care 2013;36: S139-144.
12. Aghamohammadi V, Gargari BP, Aliasgharzadeh A. Effect of folic acid supplementation on homocysteine, serum total antioxidant capacity, and malondialdehyde in patients with type 2 diabetes mellitus. J. Am. Coll. Nutr. 2011; 30(3): 210-215.
13. Aghamohammadzadeh N, Niafar M, Dalir Abdolahinia E, Najafipour F, Mohamadzadeh Gharebaghi S, Adabi K, et al. The effect of pioglitazone on weight, lipid profile and liver enzymes in type 2 diabetic patients. Ther Adv Endocrinol Metab 2015;6(2): 56–60.
14. McCall AL. Clinical review of glimepiride. Expert Opinion on Pharmacotherapy. 2001;2(4):699-713.
15. Choe EY, Cho Y, Choi Y, Yun Y, Wang HJ, Kwon O, et al. The effect of DPP-4 inhibitors on metabolic parameters in patients with type 2diabetes. Diabetes Metab J. 2014; 38:211–9.
16. Shigematsu E, Yamakawa T, Kadonosono K, Terauchi Y. Effect of sitagliptin on lipid profile in patients with type 2 diabetes mellitus. J Clin MedRes. 2014; 6:327–35.
17. Agarwal P, Jindal C, Sapakal V. Efficacy and safety of teneligliptin in Indian patients with inadequately controlled type 2 diabetes mellitus: A randomized, double-blind study. Indian Journal of Endocrinology and Metabolism. 2018; 22(1): 41.
18. Varghese L, Murthi K, Pandey K. Teneligliptin as an add on Therapy to Oral Anti diabetic agents in type 2 Diabetes Mellitus. Research Journal of Pharmacy and Technology. 2020; 13(5): 2310-4.
19. Hovind P, Hansen TK, Tarnow L, et al. Mannose binding lectin as a predictor of microalbuminuria in type 1 diabetes: an inception cohort study. Diabetes. 2005; 54(5): 1523-7.
20. Aghamohammadzadeh N, Niafar M, DalirAbdolahinia E, et al. The effect of pioglitazone on weight, lipid profile and liver enzymes in type 2 diabetic patients. Ther Adv Endocrinol Metab 2015; 6(2): 56–60.
21. Chawla S, Kaushik N, Singh N, Ghosh R, Saxena A. Effect of addition of either sitagliptin or pioglitazone in patients with uncontrolled type 2 diabetes mellitus on metformin: A randomized controlled trial. J PharmacolPharmacother 2013; 4: 27–32.
22. Nafrialdi. Efficacy and safety of pioglitazone in type 2 diabetes mellitus: a postmarketing observational study. Acta Med Indones 2012; 44: 28–34.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

23. Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. New England Journal of Medicine. 2010; 362(18): 1675-85.
24. Pavo I, Jermendy G, Varkonyi TT, et al. Effect of pioglitazone compared with metformin on glycemic control and indicators of insulin sensitivity in recently diagnosed patients with type 2 diabetes. The Journal of Clinical Endocrinology & Metabolism. 2003; 88(4): 1637-45.
25. You SH, Kim BS, Hong SJ, Ahn CM, Lim DS. The effects of pioglitazone in reducing atherosclerosis progression and neointima volume in type 2 diabetic patients: prospective randomized study with volumetric intravascular ultrasonography analysis. Korean circulation journal. 2010; 40(12): 625-31.
26. Ito D, Shimizu S, Inoue K, et al. Comparison of ipragliflozin and pioglitazone effects on nonalcoholic fatty liver disease in patients with type 2 diabetes: a randomized, 24-week, open-label, active-controlled trial. Diabetes care. 2017; 40(10): 1364-72.
27. Yamanouchi T, Sakai T, Igarashi K, Ichiyanagi K, Watanabe H, Kawasaki T. Comparison of metabolic effects of pioglitazone, metformin, and glimepiride over 1 year in Japanese patients with newly diagnosed Type 2 diabetes. Diabet Med. 2005; 22(8): 980-5.
28. Ghosh S, Trivedi S, Sanyal D, Modi KD, Kharb S. Teneligliptin real-world efficacy assessment of type 2 diabetes mellitus patients in India (TREAT-INDIA study). Diabetes, metabolic syndrome and obesity: targets and therapy. 2016; 9: 347.
29. Monami M, Vitale V, Ambrosio ML, et al. Effects on lipid profile of dipeptidyl peptidase 4 inhibitors, pioglitazone, acarbose, and sulfonylureas: meta-analysis of placebocontrolled trials. Adv Ther. 2012; 29: 736–46.
30. Infante M, Leoni M, Caprio M, Fabbri A. Long-term metformin therapy and vitamin B12 deficiency: An association to bear in mind. World J Diabetes. 2021; 12(7): 916-931.
31. Callaghan TS, Hadden DR, Tomkin GH. Megaloblastic anaemia due to vitamin B12 malabsorption associated with long-term metformin treatment. British medical journal. 1980; 280(6225): 1214.
32. Caspary WF, Zavada I, Reimold W, Deuticke U, Emrich D, Willms B. Alteration of bile acid metabolism and vitamin-B12-absorption in diabetics on biguanides. Diabetologia. 1977; 13(3): 187-93.
33. Kim J, Ahn CW, Fang S, Lee HS, Park JS. Association between metformin dose and vitamin B12 deficiency in patients with type 2 diabetes. Medicine. 2019; 98(46).
34. De Jager J, Kooy A, Lehert P, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. Bmj. 2010; 340.
35. Sahin M, Tutuncu NB, Ertugrul D, Tanaci N, Guvener ND. Effects of metformin or rosiglitazone on serum concentrations of homocysteine, folate, and vitamin B12 in patients with type 2 diabetes mellitus. Journal of diabetes and its complications 2007; 21(2): 118-23.