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A Comparative Study on Effect of Oral Hypoglycemic Agents on Serum Electrolytes in Type-2 Diabetic Patients

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ABSTRACT
AIM:
To compare the effect of oral hypoglycemic agents on serum electrolytes in Diabetic patients. Objectives; to compare the effect of monotherapy and combination therapy of oral hypoglycemic agents on serum electrolytes in Diabetic patients and to prevent further complications related to electrolyte disturbances.
MATERIALS AND METHODS:
A prospective observational study was conducted in a tertiary care hospital for about 6months in department of general medicine. Study population: 99 patients of either sex were taken into consideration. Inclusion criteria: Known diabetic patients (more than 1 year), Subjects In and out patient departments. Exclusion criteria: Patients with de Novo diabetes, known electrolyte abnormalities renal impairment hepatic impairment, CHF.
RESULTS:
In this study, 33% (11 patients) of the patients who were taking Metformin HCl observed with hyponatremia, 27% (9 patients) of the patients taking Glimepiride observed with hyponatremia,
9% (3 patients) of the patients taking Metformin HCl and Glimepiride were observed with hyponatremia. This study indicates that the patients taking monotherapy Metformin HCl and monotherapy Glimepiride exhibits decreased Na+ levels (Hyponatremia) when compared to combination therapy Metformin HCl and Glimepiride. When all groups were compared, Na+ levels showed statistical significance. In this study, 6% (2 patients) of the patients taking Metformin HCl were observed with hypokalemia and 3% (1) of the patients with hyperkalaemia, none of the patients Glimepiride alone were observed with hypokalemia, 9% (3 patients) of the patients who were taking Metformin HCl and Glimepiride were observed with hypokalemia. When all groups were compared, K+ levels showed non-statistical significance. For Na+, the mean and SD of Metformin HCl was 133.09±5.258. the mean and SD of Glimepiride was 134.76±3.725, mean and SD of Metformin HCl and Glimepiride was 137.52 ±6.094. For K+, the mean and SD of Metformin
HCl was 4.082±0.5992. the mean and SD of Glimepiride was 4.264±0.5010, mean and SD of
Metformin HCl and Glimepiride was 3.928±0.6512.
CONCLUSION: In T2DM patients, combination therapy Metformin HCl and Glimepiride exhibited reduced electrolyte abnormalities when compared to monotherapy Metformin HCl and Glimepiride. This study showed the importance of serum electrolytes determination in Diabetic patient care.
KEY WORDS: Hypoglycemic agents, Electrolyte abnormalities, Monotherapy.

I. INTRODUCTION

The use of antidiabetic drugs is expected to substantially increase since diabetes mellitus incidence rises. Currently used antidiabetic drugs like Metformin and Glimepiride have a positive safety profile, but they are associated with certain electrolyte abnormalities[1]. The electrolytes disturbances should be taken in account in the surveillance of diabetes. Electrolyte disorders are mainly observed in hospitalized patients but also community subjects are frequently affected[6]. In this study , it is an attempt to find out the effect of Metformin HCl- Glimepiride based combined therapy over the treatment with single oral hypoglycaemic agent on serum electrolytes in patients with T2DM[5] .The normal range of serum sodium level is 135-145 mEq/L and potassium level is 3.5-5.5mEq/L. Below the normal levels of sodium and potassium can result in hyponatremia and Hypokalemia respectively. Hypernatremia can lead to Confusion, muscle twitching, bleeding in or around the brain. Hyponatremia can lead to confusion, altered sensorium, cerebral edema. Hyperkalemia can lead to cardiac arrest. Hypokalemia can lead to abnormal heart rhythm.

AIM AND OBJECTIVES

To compare the effect of monotherapy (i.e. Metformin HCl or Glimepiride) and combination therapy (Metformin + Glimepiride) on serum electrolytes in Type 2 DM patients.

II. MATERIALS AND METHODS:

It is a prospective observational study conducted at a tertiary care hospital for a period of 6 months after obtaining approval from Institutional Human Ethics Committee. It includes collection of patient's demographic details, provisional diagnosis of patient, past medical history, past medication history, social history, laboratory data (blood glucose levels and serum
electrolytes), comorbidities and present medications which are the main sources to find out the electrolyte disturbances.

INCLUSION CRITERIA: Known diabetic patients (more than 1 year), Subjects in In and out patient departments.

EXCLUSION CRITERIA: Patients with de Novo diabetes, known electrolyte abnormalities, renal impairment (creatinine levels >1.5mg/dl), hepatic impairment, CHF (Congestive Heart Failure), SIADH (Syndrome of inappropriate Anti-Diuretic Hormone), Hypothyroidism, chronic severe vomiting or diarrhea, Addison's disease and patients taking medications like diuretics (thiazides, furosemide), antidepressants (SSRI's, TCA's-amitriptyline), pain medications (NSAIDS, Acetaminophen, opioids), amphetamine, ACE inhibitors, ARB's.

Blood samples of 99 diabetic patients receiving oral hypoglycaemic agents for more than one year; were collected from a tertiary care hospital. Patients were divided into 3 groups, according to three specific treatments. These groups are further divided into subgroups based on maximum daily dosage.

Group I: This was comprised of 33 diabetic patients each taking Metformin HCl.

1. Subgroup M1 – ≤ 500mg
2. Subgroup M2 – ≤ 1000mg
3. Subgroup M3 – ≥ 1700mg

Group II: This was also comprised of 33 diabetic patients taking Glimepiride

1. Subgroup G1 – ≤ 2mg
2. Subgroup G2 – ≥ 4mg

Group III: This group was again comprised of 33 diabetic patients taking Metformin HCl and

Glimepiride

1. Subgroup MG1 – ≤ 4/1000mg
2. Subgroup MG2 – ≤ 2/1000mg
3. Subgroup MG3 – ≥ 4/1700mg

STATISTICAL ANALYSIS:

Data was analyzed with SPSS version 25.0 and MS-Excel (2019). The results were expressed as proportion of subjects with abnormal values in the diabetic population were evaluated using multivariate analysis of variance (MANOVA) test. Following the stratification of diabetic patients in regard of plasma glucose levels and electrolytes Na+, K+ levels in three groups, mean values and standard deviations of electrolytes were calculated. The p values < 0.05
were considered statistically significant.

III. RESULTS AND DISCUSSION:

Age wise distribution:

Age (in years)	Number of patients(n)	Percentage of patients
31-40	7	7.07
41-50	9	9.09
51-60	23	23.23
61-70	33	33.33
71-80	26	26.26
81-90	1	1.01
TOTAL	**n= 99**	**100%**

Table 1: Age wise distribution of diabetic patients

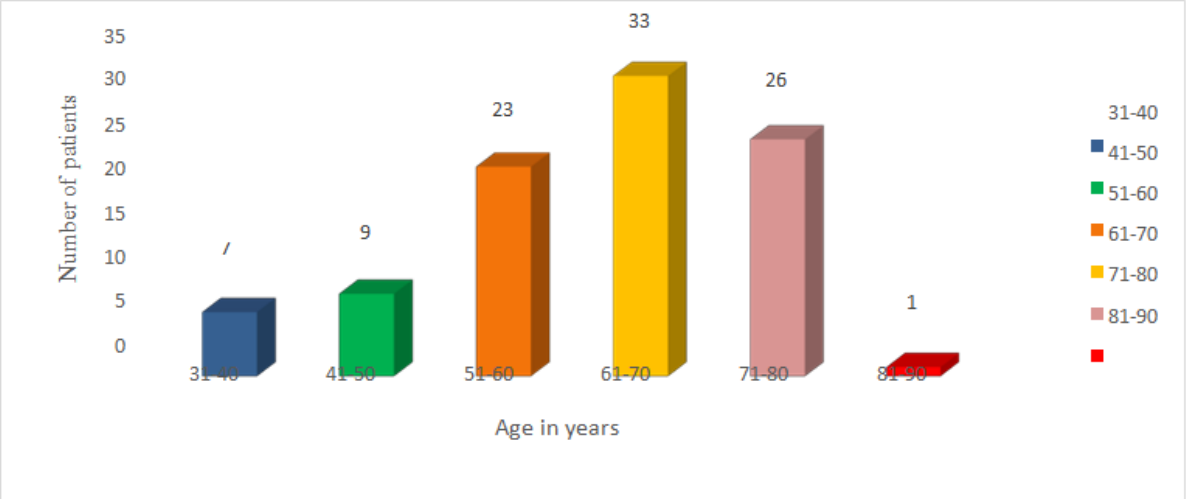

Fig 1: Age wise distribution of diabetic patients

Out of 99 patients, maximum T2DM patients fall under the category of 61-70 years (33%) followed by 71-80 years (26%), 51-60 years (23%) and then followed by 41-50 years (9%) and 31-40 years (4%). The smaller number of T2DM patients were under the category 81-90 years (1%).

Gender wise distribution:

Gender	Metformin HCl + Glimepiride [n (%)]	Glimepiride [n (%)]	Metformin HCl [n (%)]	TOTAL	Percentage {%}
Male	16	16	13	45	45.45
Female	17	17	20	54	54.54
TOTAL	33 (33.33%)	33(33.33%)	33(33.33%)	**99**	**100%**

Tab 2: Gender wise distribution of three groups of diabetic patients

n = Number of patients

% = Percentage

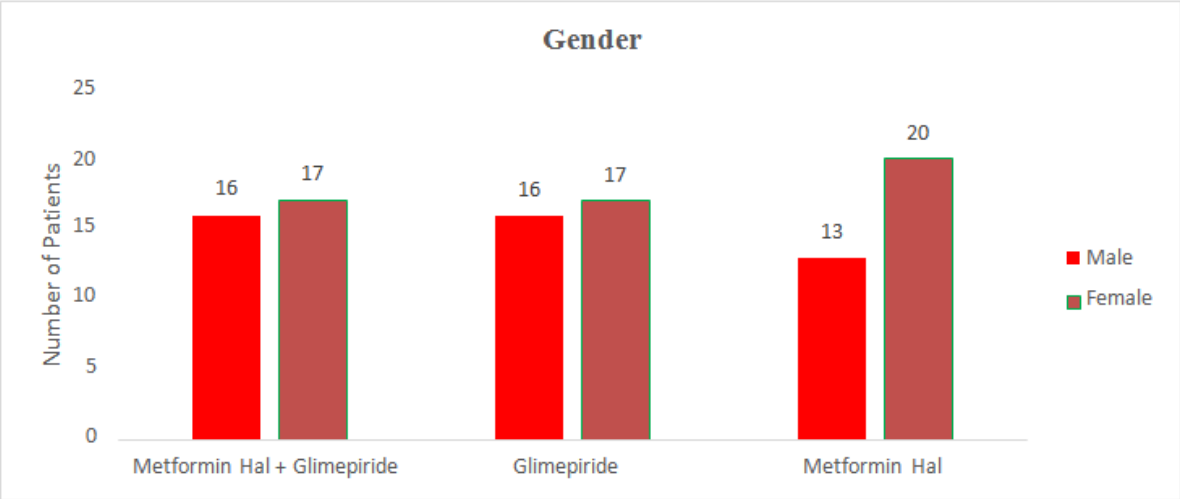

Fig 2: Gender wise distribution of three groups of diabetic patients

A total of 99 type 2 diabetic patients were enrolled into the study. Out of them, 45.45% were male patients and 54.5% were female patients. Among them, patients who were taking combination therapy Metformin HCl + Glimepiride, 48% were male patients and 52% were female patients; patients who were taking monotherapy Glimepiride, 48% were male patients and 5% were female patients; patients who were taking monotherapy Metformin HCl, 39% were male patients and 61% were female patients.

Glucose:

In group I, 33 patients treated with Metformin HCl showed a different variation. 26 patients showed glucose level 120-180 mg/dl of blood. Only 1 patient showed below 120 mg/dl. Whereas 6 patients showed above180 mg/dl blood glucose (fig 3); however, when all the groups were compared; they showed statistically a non-significant difference in the blood glucose level.

In group II, 33 patients treated with Glimepiride also showed a variable effect. Only 18 patients showed random blood glucose of 120-180 mg/100 ml. 14 patients of this group showed glucose level of above 180 mg/100 ml and only 1 patient showed a blood glucose level over 300 mg/100 ml (fig 3).

In group III, the estimated range of blood glucose in patients given Metformin HCl + Glimepiride was 96-300 mg/dl. The effect of metformin HCl + Glimepiride combination was not similar in all the individuals. 17 patients out of 33 showed 120-180mg/dl of blood glucose; the other 12 showed above 180 mg/dl and below 300 mg/dl blood glucose, and the remaining 1 showed 300 mg/100 ml
of glucose (fig 3).

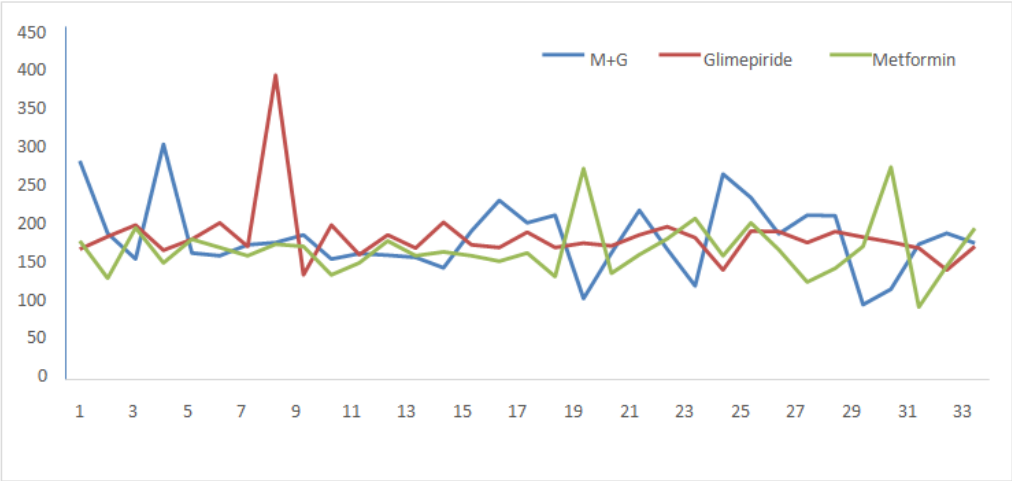

Fig 3: The separate and combined effect of Metformin HCl and glimepiride on random blood glucose

Therapy	No of cases	Total no of cases	Mean and SD of Na^+	No of Cases of $\downarrow Na^+$	No of Cases of $\uparrow Na^+$	Mean and SD of K^+	No of Cases of $\downarrow K^+$	No of Cases of $\uparrow K^+$
Metformin • M1 – ≤500mg • M2–≤1000mg • M3–≥1700mg	11 20 2	33	133.09±5.258	11	0	4.082±0.5992	2	1
Glimepiride • G1 – ≤2mg • G2 – ≥4mg	19 14	33	134.76±3.725	9	0	4.264±0.5010	0	0
Metformin + Glimepiride • MG1– ≤4/1000mg • MG2– ≤2/1000mg • MG3– ≥4/1700mg	12 19 2	33	137.52±6.094	3	0	3.928±0.6512	3	0

Tab 3: Comparison of statistical parameters among three drug groups

Electrolytes	Metformin + Glimepiride	Glimepiride	Metformin HCl
Na^+ (135-145mmol/L)	137.52 ± 6.094	134.76 ±3.725	133.09 ± 5.258
K^+ (3.5-5.5mmol/L)	3.928 ± 0.6512	4.264 ± 0.5010	4.082 ± 0.5992

Tab 4: Comparison of Mean and SD of Na+ and K+ among three groups

For Na+, the mean and SD of Metformin HCl was 133.09 ± 5.258. The mean and SD of Glimepiride was 134.76 ± 3.725, mean and SD of Metformin HCl and Glimepiride was 137.52 ± 6.094.

For K+, the mean and SD of Metformin HCl was 4.082 ± 0.5992. The mean and SD of Glimepiride was 4.264 ± 0.5010, mean and SD of Metformin HCl and Glimepiride was 3.928 ± 0.6512.

Multiple Comparisons: MANOVA

Dependent Variable	(I) Drug Group	(J) Drug Group	Sig. *(p)*
Na^+	Metformin+Glimepiride	Glimepiride	0.031
		Metformin	0.001
	Glimepiride	Metformin+Glimepiride	0.031
		Metformin	0.189
	Metformin	Metformin+Glimepiride	0.001
		Glimepiride	0.189
K^+	Metformin+Glimepiride	Glimepiride	0.054
		Metformin	0.491
	Glimepiride	Metformin+Glimepiride	0.054
		Metformin	0.212
	Metformin	Metformin+Glimepiride	0.491
		Glimepiride	0.212

Tab 5: Comparison of p value of Na+ and K+ among three groups

- Based on observed means: The error term is Mean Square (Error) = 0.345*.
- The mean difference is significant at the 0.05 level.

Sodium (Na+) (135-145mmol/L):

In group I, the blood Na+ ranged from 111–141 mmol/L Altogether 33 patients were Metformin HCl daily; 3 out of them showed blood Na+ values lower than that of the normal level i.e. 133mmol/L (fig 4).

In group II, 33 patients were treated with Glimepiride. 24 of them showed blood Na+ ranging from 129-147 mmol/L. However, 9 of them showed Na+ value less than 133mmol/L (fig 4).
In group III, 10 patients kept on a combination of Glimepiride and metformin HCl, showed Na+ value ranging from 111-145 mmol/L (fig 4). When statistically analyzed the data showed a significant difference in the mean Na+ concentration of all the groups.

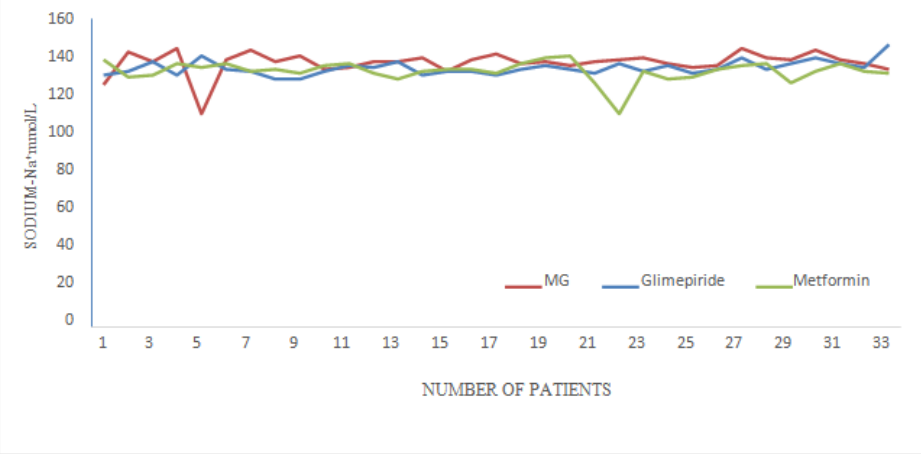

Fig 4: The separate and combined effect of Metformin HCl and glimepiride on blood sodium Na^+

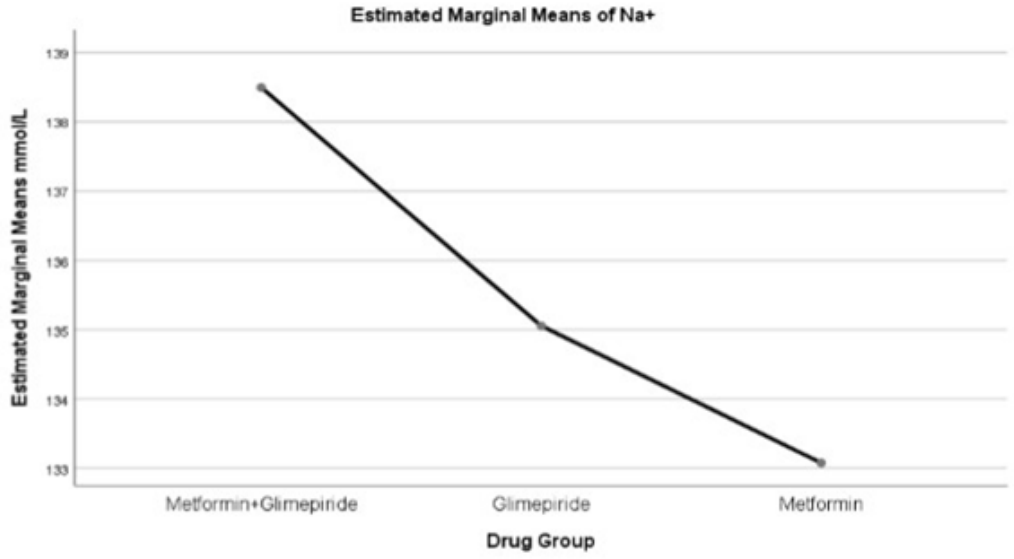

Fig 5: Estimation of marginal means of Na^+ in three drug groups

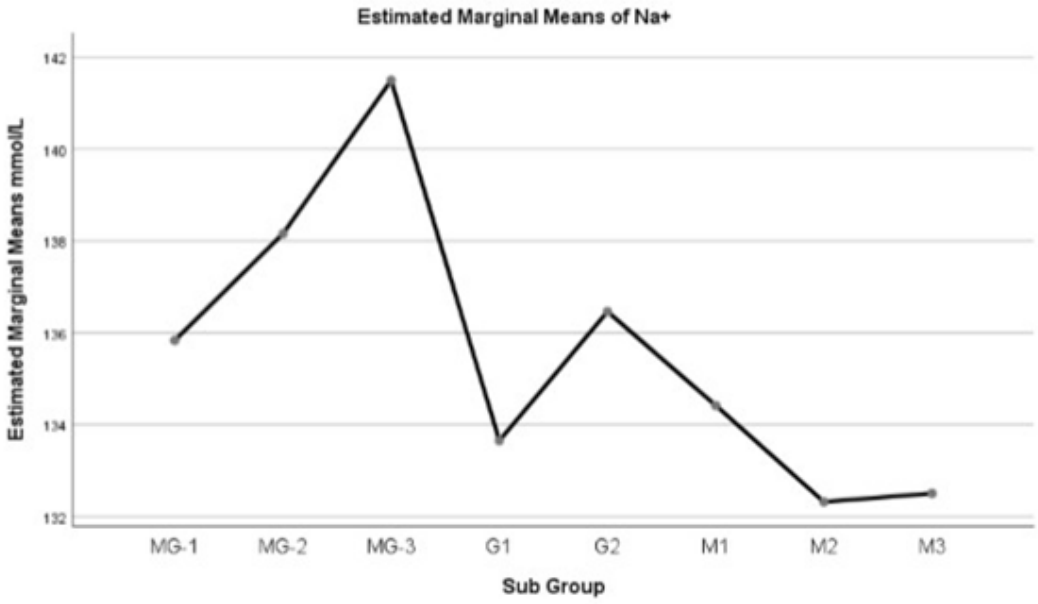

Fig 6: Estimation of marginal means of Na^+ in sub groups of three drug groups

In group I, 18% (2/11 patients) of the patients taking Metformin HCl (M1 ≤ 500mg) were observed with hyponatremia, 40% (8/20 patients) of the patients taking Metformin HCl (M2 ≤ 1000mg) were observed with hyponatremia, 50% (1/2patients) of the patients taking Metformin HCl (M3 ≥ 1700mg) were observed with hyponatremia.

In group II, 31.5% (6/ 19patients) of the patients taking glimepiride (G1 ≤ 2mg) were observed with hyponatremia, 21.4% (3/14 patients) of the patients taking glimepiride (G2 ≥ 4mg) were observed with hyponatremia.

In group III, 25% (3/12 patients) of the patients taking Metformin HCl and Glimepiride (MG1 ≤4/1000mg) were observed with hyponatremia, none of the patients who were taking Metformin HCl and Glimepiride MG2 ≤ 2/1000mg), Metformin HCl and Glimepiride (MG3 ≥ 4/1700mg).

Potassium (K+) (3.5-5.5mmol/L):

In group I, 33 patients administered Metformin HCl showed blood K+ levels of 2.8–6.2 mmol/L (Fig. 7). However, 1 of them showed K+ value >5.7 mmol/L and 2 patients below 3.3mmol/L. All the three groups compared statistically, showed a non-significant difference in the mean K+ concentration.

In group II, blood K+ levels were estimated in the other 33 diabetic patients; taking Glimepiride, showed the blood K+ levels from 3.4–5.5mmol/L (fig 7).
In group III, blood K+ levels were estimated in 33 diabetic patients which were using Glimepiride and metformin HCl. However, 3 of them showed K+ value less than 3.3mmol /L blood K+ levels ranged from 2.7-5.2mmol/L (fig 7).

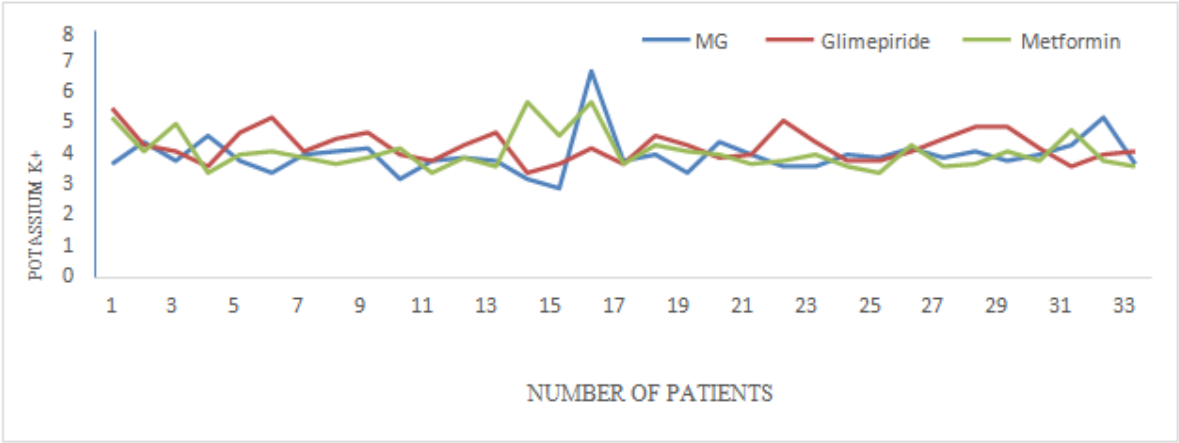

Fig. 7: The separate and combined effect of Metformin HCl and glimepiride on blood K^+

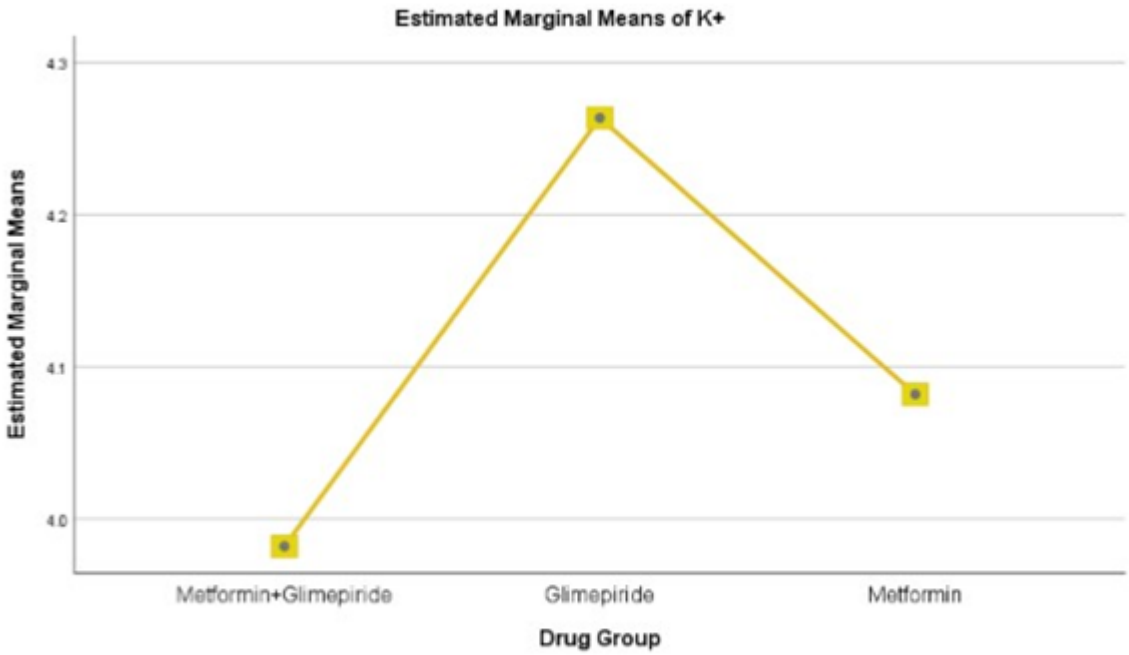

Fig 8: Estimation of marginal means of K^+ in three drug groups

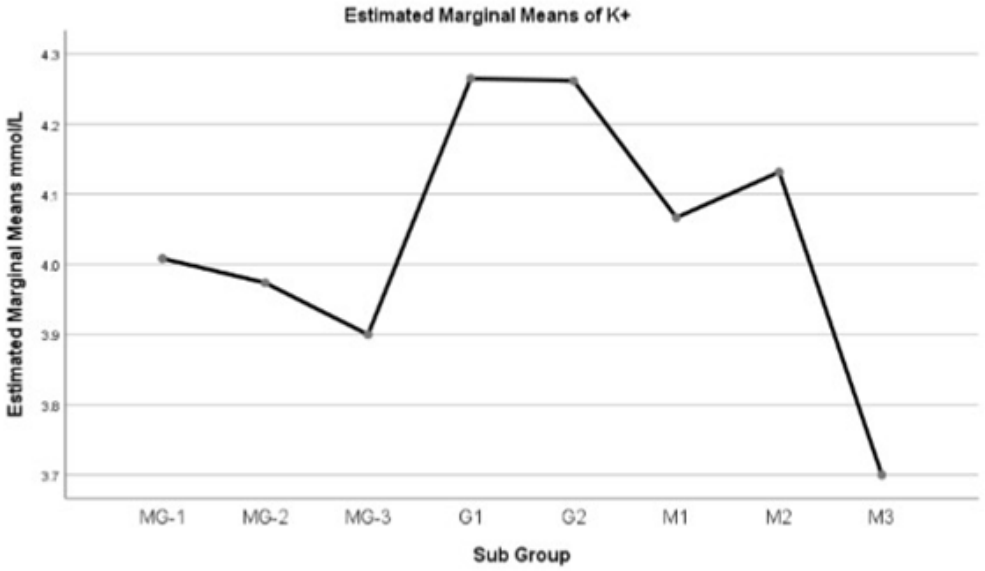

Fig 9: Estimation of marginal means of K^+ in sub groups of three drug groups

In group I, none of the patients taking Metformin HCl (M1 ≤ 500mg) were observed with hypokalemia or hyperkalemia, 10% (2/20 patients) of the patients taking Metformin HCl (M2 ≤ 1000mg) observed with hypokalemia and 5% (1/2 patients) taking Metformin HCl (M3 ≥ 1700mg) were observed with hyperkalemia.

In group II, none of the patients taking glimepiride (G1 ≤ 2mg) and glimepiride (G2 ≥ 4mg) were observed either with hypokalemia or hyperkalemia.

In group III, 8.3% (1/12 patients) of the patients taking Metformin HCl and Glimepiride (MG1 ≤ 4/1000mg) were observed with hypokalemia, 10.5% (2/19 patients) of the patients taking Metformin HCl and Glimepiride (MG2 ≤ 2/1000mg) were observed with hypokalemia, None of the patients taking Metformin HCl and Glimepiride (MG3 ≥ 4/1700mg) were observed either with hypokalemia or hyperkalemia.

IV. CONCLUSION

This study showed the importance of serum electrolytes determination in Type 2 DM patients who are receiving oral hypoglycemic agents. In Type-2 DM patients, combination therapy Metformin HCl and Glimepiride exhibited less electrolyte abnormalities when compared to monotherapy of Metformin HCl and monotherapy of Glimepiride. The proportion of hyponatremia was higher than all other determined parameters (23%). In addition to that, the p values of sodium differed significantly between all the three groups of diabetic patients. No difference was observed between the p values of potassium in all the three groups of diabetic patients.

LIMITATIONS OF THE STUDY:

- It requires more study duration.
- It requires more sample size for accurate results
- It requires regular follow up.

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