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COMPARISON OF PIOGLITAZONE + METRORMIN VS SITAGLIPTIN + METFORMIN IN THE MANAGEMENT OF TYPE 2 DIABETES MELLITUS

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Abstract:

Objectives: *To assess the efficacy of both groups in term of Glycemic control versus comparative side effects.*

Material and Methods: This Quasi-experimental study is conducted at MTI/Hayatabad Medical Complex Peshawar, from November 2017 to October 2018. Ninety patients of type 2 diabetes mellitus came to OPD, were chosen. In OPD, every patient was analyzed altogether. The restorative alternative was assigned to the patients primarily by utilizing a table of arbitrary numbers and separating them into two equivalent groups. Every patient was pursued on follow up visits (six altogether) and his HbA1c, fasting, and random blood glucose were recorded. Every bit of information along these parameters was handled and examined utilizing SPSS. Mean, and SD was determined for age, BMI, fasting blood glucose, random blood glucose, and HbA1c levels.

Results: *Mean drop of each of the three parameters were looked at among two groups. Toward the finish of a half year, it was revealed that fasting and arbitrary (2 hours postprandial) blood glucose dropped more in Pioglitazone + Metformin group; P=0.000 and 0.02 separately while the practically equivalent impact was seen in HbA1c (P=0.2).*

Conclusion: *Pioglitazone + Metformin + Sitagliptin + Metformin has a significantly better hypoglycemic effect than Sitagliptin + Sitagliptin + Metformin in type 2 diabetes mellitus at the end of six months of therapy.*

Keywords: *Hypoglycemic, Pioglitazone + Metformin, Sitagliptin + Metformin, Sitagliptin, Diabetes Mellitus, Quasi-Experimental, OPD, BMI, and Blood Glucose.*

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INTRODUCTION:

Uncontrolled diabetes is an alarming situation that can result in a physical, emotional, and unaffordable burden on the person just as on society [1]. The first practical approach to keep away from complications of diabetes is an adequate glycemic control, which can be accomplished by medications along with exercise and dietary measures. In recent years, new medicines have risen to focus on better pharmacokinetic and low symptom profile. Among them have been different insulin sensitizers (Metformin), secretagogues and glucagon-like peptides are one of them. In the United Kingdom Prospective Diabetes Study, type 2 diabetes is described by an inflexible movement of glucose control deterioration [2]. Both ß-cell dysfunction and insulin resistance are center in the progression of type 2 diabetes and the related metabolic syndrome [3]. Sitagliptin + Metformin brings down plasma glucose elevations while at the same time mimicking plasma insulin and may act by reducing hepatic glucose generation, expanding splanchnic and hepatic glucose usage, by reducing insulin resistance3. The metabolic impacts of Sitagliptin + Metformin might be because of its capacity to phosphorylate and actuate AMP-enacted protein kinase [4]. In fat patients with creatinine 1.2mg/dl, Sitagliptin + Metformin ought to be considered as beginning therapy [5].

Pioglitazone + Metformin, a thiazolidinedione, is a peroxisome proliferator-initiated receptor agonist that affects controllers of starch and lipid metabolism [6]. Pioglitazone + Metformin diminishes insulin opposition by upgrading the activity of insulin, along these lines advancing glucose usage in fringe tissues, affecting gluconeogenesis, and reducing lipolysis [7]. Pioglitazone + Metformin is a generally new medication. It can securely be utilized as immunotherapy for glycemic control in patients of type 2 diabetes mellitus. Pioglitazone + Metformin has been shown to give clinically equal control of HbA1c in examination with Sitagliptin + Metformin, generally the specialist of decision for treatment of hefty patients with type 2 diabetes [8]. Essentially more noteworthy decreases in fasting blood glucose have been seen with Pioglitazone + Metformin + Sitagliptin + Metformin contrasted to Sitagliptin + Sitagliptin + Metformin [9]. Utilization of this medication is very constrained in spite of its great decency and adequacy. While, Sitagliptin + Metformin is utilized more in type 2 diabetics conventionally [10]. No relative preliminary could be seen among the other two drugs (Pioglitazone + Metformin vs. Sitagliptin) in our nation. Wherever Pioglitazone + Metformin is utilized, it is being recommended without having knowledge about the safety profile of the given medication in the light of the fact that no such study has been done on its efficacy especially in our Pakistani setup. In the current study, both groups of medications were compared in term of efficacy and safety profile for type 2 diabetes mellitus i.e., Pioglitazone + Metformin vs. Sitagliptin, which has genuinely shifted our management paradigm.

MATERIALS AND METHODS:

This Quasi-experimental study was conducted at MTI/Hayatabad Medical Complex Peshawar, from November 2017 to October 2018. Ninety patients of Type 2 Diabetes Mellitus coming to the OPD of the hospital were chosen and isolated into two categories with 45patients in each group by utilizing a table of random numbers. Analyzed patients of type 2 Diabetes Mellitus between 35-65 years old of the two sexual orientations were included in the study. Lactating mothers, pregnant females, or the individuals who have required particular use (>6 months) of insulin for glycemic control, had a history of ketoacidosis or requiring insulin administration were excluded. Patients on sulphonylureas and having unstable angina, CAD, congestive heart failure or hypertensive emergencies, hepatic or renal impairment, history of medication or alcohol addiction were likewise excluded.

Data Collection Procedure: Patients were selected from the Medical outpatient department with poor glycemic control those on routine diet were analyzed for type 2 Diabetes Mellitus with readings of fasting blood glucose(>126mg/dl). Random and fasting blood glucose was estimated at withstanding HbA1c levels. Confounding factors were removed by excluding pregnant or lactating patients (based on history), patients taking other drugs for diabetes mellitus (on history and record), patients on treatment of IHD/CCF, hepatic or renal diseases. Informed consent was taken before prescribing the given medications to the patient and was given awareness regarding the safety profile and relative side effects (especially gastrointestinal reactions from Sitagliptin + Metformin and hepatotoxicity in the event of Pioglitazone + Metformin, similarly acute pancreatitis related to Sitagliptin). Patients were clarified that all the treatment modalities are universally prescribed for the treatment of diabetes mellitus as per evidence-based. Patient's number was divided into two groups, with 45 patients in each group. Group 1 was prescribed Pioglitazone + Metformin + Sitagliptin + Metformin. Similarly, group 2 was prescribed Sitagliptin + Sitagliptin + Metformin in equivalent dose. Care was taken that any patient having a contraindication to one

treatment methodology (for example, hepatotoxicity in Pioglitazone + Metformin) was exposed to the next method of treatment. These subjects were encouraged to pursue an eating regimen containing about half starch, less fatty food, and high fiber diet, with an overall of less caloric value. Fasting blood glucose was estimated before breakfast. History plus clinical examination, along with dietary counseling and consistency chart, were completed.

Blood tests for HbA1c, fasting, and random (2 hours postprandial) blood glucose were recorded and kept up in the patient proforma. On each monthly visit, patients were again evaluated for the given parameters except for HbA1c% (recorded at every 3rd month). The mean HbA1c, fasting, and arbitrary blood glucose was additionally determined for each group at each visit and compared with for the extreme values. All the parameters were recorded on a proforma, compared, and analyzed in both the study groups. The efficacy and safety profile of both medications (Sitagliptin + Sitagliptin + Metformin vs. Pioglitazone + Metformin + Sitagliptin + Metformin).

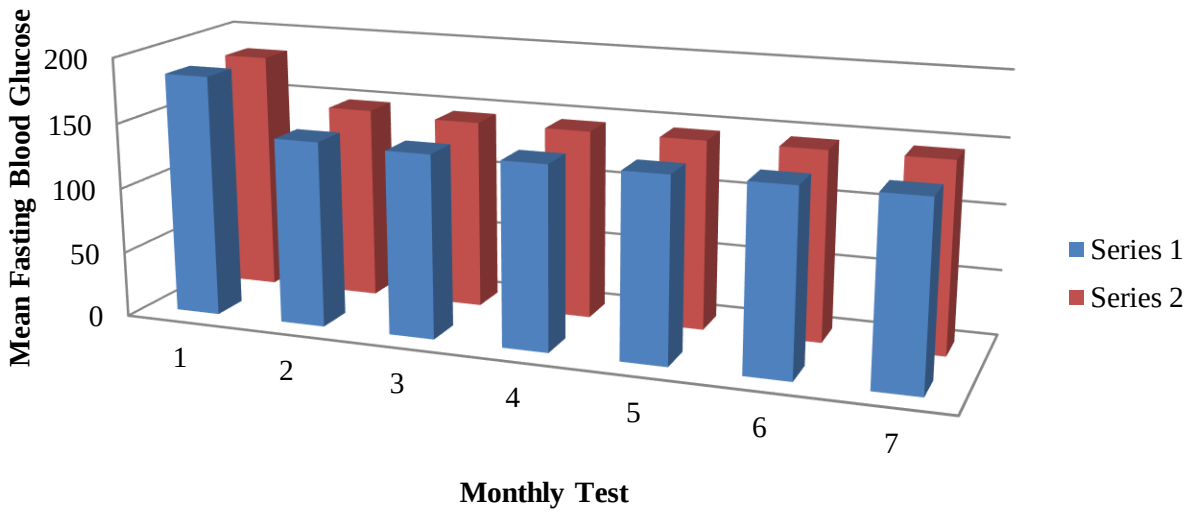
Data Analysis Procedure: Information was broken down, utilizing measurable programming SPSS. Straight out information for male and female was given in rates. Distinct insights were used to compute mean and SD for age, BMI (weight in kilograms/stature in meters squared), fasting blood glucose, random blood glucose, and HbA1c levels. Mean, and SD for fasting blood glucose, arbitrary blood glucose, and HbA1c was determined for each visit. T-test was applied to research methods for fasting blood glucose, arbitrary blood glucose, and HbA1c estimations of the two groups at standards and at each visit. Drop-in fasting blood glucose, arbitrary blood glucose, and HbA1c was determined among criteria and last follow up visit, for example, following a half year of treatment. Their mean was determined and was additionally figured out by utilizing the equivalent standardized test to evaluate whether there was any difference in hypoglycemic effect among the two groups. A p-value of < 0.05 was found significant.

RESULTS:

Ninety patients with type 2 Diabetes Mellitus were chosen satisfying given criteria. They were categorized into two groups for treatment, 45 patients in each. Group 1 was given Pioglitazone + Metformin + Sitagliptin + Metformin and group 2 received Sitagliptin + Sitagliptin + Metformin. Every one of the patients was followed up for six months. Graphic insights (for age) of the two groups appear in table 1 (P=0.6). In group 1 there were 60 % males and 40% females. In group 2 there were 73.3 % males and 26.7 % female (p=0.2). Weight Index (BMI) was additionally determined in 2 groups utilizing the standard equation of weight (in kilograms) per height2 (in meters). It indicated the mean BMI (kilograms per meter squared) of 22.6 in group 1 and 23.2 in group 2 (P=0.11). There was no distinction as far as age, sex, and BMI among the two groups. In groups 1 and 2, the mean fasting blood glucose was observed to be (186.7±5.83) and (185.7±7.76) (p=0.575), respectively. Most extreme values are being 204 mg/dl in group 1 and 204 mg/dl in group 2 while the lowest values are being 175 mg/dl in group 1 and 174 mg/dl in group 2. Mean fasting blood glucose on initial and follow up visits in both the groups is given in table 2.

Correlation of mean fasting blood glucose among the two groups (more than a half year) appears in figure 1.

Fig 1:Comparison of Mean Fasting Blood Glucose Over Six Months



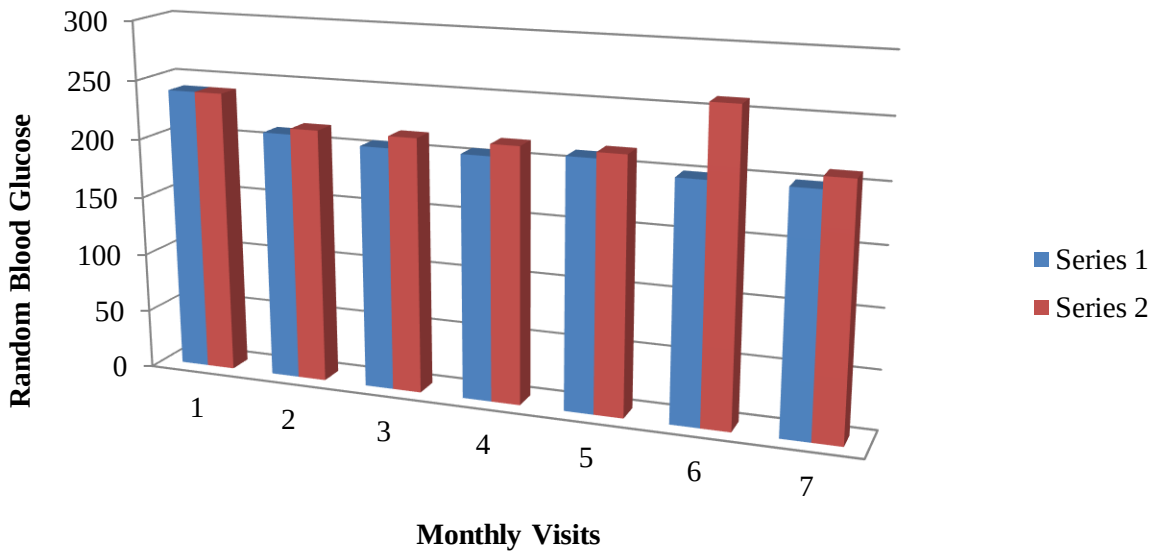
In groups 1 and 2, the mean random blood glucose measurement was observed to be (241.8±5.73) and (241.7±6.82) individually (p=0.96). Highest measure being 250 mg/dl in group 1 and 252 mg/dl in group 2 while lowest measure being 245mg/dl in group 1 and 234 mg/dl in group 2. Mean random blood glucose on initial and follow up visits in both the groups is given in Table – I.

Table – I: Mean Random Blood Glucose of Both Groups (Over 6 Months) (90)

Mean random blood glucose	Treatment group	Number	Mean	Std deviation	p-value
Baseline	Pioglitazone + Metformin	45	241.80	5.71	0.966
	Sitagliptin + Metformin	45	241.73	6.25	
At 1 month	Pioglitazone + Metformin	45	210.40	8.04	0.174
	Sitagliptin + Metformin	45	213.40	8.3	
At 2 months	Pioglitazone + Metformin	45	208.46	9.13	0.092
	Sitagliptin + Metformin	45	212.36	8.48	
At 3 months	Pioglitazone + Metformin	45	207.06	11.02	0.086
	Sitagliptin + Metformin	45	211.60	8.94	
At 4 months	Pioglitazone + Metformin	45	209.13	8.50	0.116
	Sitagliptin + Metformin	45	212.70	8.80	
At 5 months	Pioglitazone + Metformin	45	205.90	7.93	0.005
	Sitagliptin + Metformin	45	278.96	8.83	
At 6 months	Pioglitazone + Metformin	45	205.80	9.36	0.066
	Sitagliptin + Metformin	45	210.40	9.61	

And their comparison over six months is shown in figure 2.

Fig 2: Comparison of Mean Random Blood Glucose Over Six Months



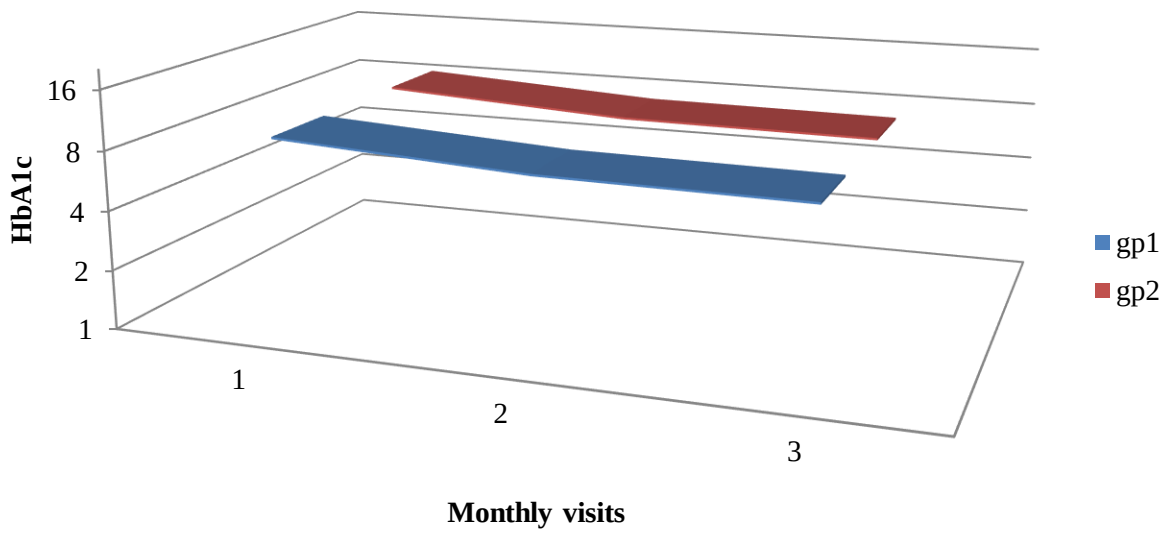
HbA1c was checked multiple times, first on initial visit, and then at 3 months interval. In group 1 and 2, the mean HbA1c measure was observed to be (8.6±0.39) and (8.51±0.41) individually. Highest value being 9.4% in group 1 and 9.6% in group 2 while lowest measurement being 7.7% in group 1 and 7.9% in group 2. Mean HbA1c on follow up visits in both the groups is given in Table – II.

Table – II: Mean HbAlc of both groups (Over Six Months) (60)

Glycosylated Hb	Treatment group	Number	Mean	Standard deviation	p-value
Baseline	Pioglitazone + Metformin	45	8.670	0.394	0.140
	Sitagliptin + Metformin	45	8.513	0.415	
At 3 Months	Pioglitazone + Metformin	45	7.357	0.496	0.272
	Sitagliptin + Metformin	45	7.223	0.434	
At 6 Months	Pioglitazone + Metformin	45	7.173	0.426	0.207
	Sitagliptin + Metformin	45	7.033	0.425	

And comparison among both groups over six months is shown in figure 3.

Fig 3:Comparison of mean Hba1c over six months visits



However, this decrease in group 1 was considered significant than group 2 (p=0.02). Moreover, the mean drop in HbA1c from the standards was observed to be (1.49±8.8) in group 1 and (1.48±8.0) in group 2. There was no significant difference in HbA1c drop among the two treatment groups (p=0.4).

DISCUSSION:

Poor glycemic control in situation of type 2 diabetes mellitus with complications like dyslipidemias, retinopathy, neuropathy, nephropathy, coronary artery disease, cerebrovascular diseases needs the best possible treatment as per evidence based guidelines. In a multicenter randomized trial, it was demonstrated that Pioglitazone + Metformin had a relatively better decrease in fasting blood glucose than Sitagliptin + Metformin (P = 0.016) [11]. Aftermath of this enormous multicenter preliminary study are similar to the present study. Drop in fasting blood glucose was critical in the Pioglitazone + Metformin group yet drop in HbA1c was comparable. While random blood glucose was not estimated in this worldwide study trail. Another preliminary study (n=114) directed by Yamanouchi T et al [12] in the branch of the inner drug, University of Teikyo, Tokyo, Japan, thought about the metabolic impacts of Pioglitazone + Metformin , Sitagliptin + Metformin , and glimepiride (immunotherapy and consolidated) in the treatment of Japanese patients with recently analyzed Type 2 diabetes. It exhibited that patients taking Pioglitazone + Metformin had generally lower fasting plasma glucose than patients taking the other two medications yet there was no critical distinction among the three groups in HbA1c levels toward the finish of the study. Results of this study correlate with our outcomes for both HbA1c and fasting blood glucose control. However, many outcomes were found in study led by Carrillo An et al [13], held at a branch of pathology and medication, college of Udine P.le S. Maria Della Misericord, Udine, Italy. It demonstrated that there were no distinctions in the progressions in HbA1c and fasting blood glucose between the Pioglitazone + Metformin and Sitagliptin + Metformin groups yet post prandial glycaemia was decreased more in Pioglitazone + Metformin than by Sitagliptin + Metformin . In any case, Pioglitazone + Metformin had a phenomenal decrease in the measurement of fasting glucose when compared with Sitagliptin + Metformin. This study showed comparative results for post prandial glucose and HbA1c according to our observations, however, changes regarding fasting blood glucose control. Another study done by Imre Pavoet al [14], directed at Bajcsy-Zsilinszky Hospital, Budapest Hungary. In this study outcome of Pioglitazone + Metformin was different and Sitagliptin + Metformin on glycemic control. It

demonstrated that both treatment groups (Pioglitazone + Metformin and Sitagliptin + Metformin) had measurably significant decreases from standard in HbA1c ($p<0.0001$ for the two medications), and there was no real huge difference between the two groups in HbA1C change from the standards. In this way, HbA1c results correlated with our investigation. In this study, both treatment groups had an unfavorable decline from the measurement in fasting blood glucose ($P < 0.0001$ for the two medicines), and there was no really huge difference between the treatment groups in fasting glucose change from the standards. This fasting blood glucose result isn't in concordance with our examination which has demonstrated a more prominent decrease in Pioglitazone + Metformin group on follow up visits. In any case, at the endpoint of the study, a significant decrease in fasting serum glucose appeared in the Pioglitazone + Metformin treatment group ($P < 0.0001$), however, this parameter couldn't be examined in our setup. Just a single nearby study [15] was completed at King Edwards's therapeutic school Lahore, distributed in Annals of King Edwards medicinal school in March 2005. In any case, this was not quite the same as our work. Though probability of poor adherence to dietary counsel (particularly that specific breakfast), this factor was a limitation by having to guide with patients on a monthly sessions. Hence, the consequence of the mean drop in post prandial blood glucose was altogether better in the Pioglitazone + Metformin group. Results were not significant as far as HbA1c among the two groups. Along these lines, deep study is required to investigate this effect further. A large portion of the worldwide studies has comparative results in regards to the hypoglycemic impact of Pioglitazone + Metformin which were likewise found in our outcomes. Nonetheless, further research is prescribed in this field to satisfy insufficiencies.

CONCLUSION:

Type 2 diabetes is prevalent and approaching practically a plagued level. There are numerous medications available for the treatment that is comparatively insufficient, costly, poor accessibility, and outcomes. We compared Pioglitazone + Metformin and Sitagliptin + Metformin and found that Pioglitazone + Metformin has a better hypoglycemic effect over Sitagliptin + Metformin regarding efficacy. Moreover, its safety profile is comparable, too, that has been approved by comprehensive studies as well.

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