Discussion:
Diabetes Mellitus (DM) is a chronic ailing metabolic disorder, affect millions of population throughout the world, gives little scope to be cured, cause profound suffering, factor of economic burden of the individual and the country, produce poor quality of life, offer the subject a painful miserable life which makes them ultimately to wait for painful death. Relentless effort is required to generate data towards the management of this disease for a contribution of help for this suffered people.

Burdwan Medical College Hospital is an important tertiary care hospital in the west Bengal. It serves millions of population involving several districts of West Bengal even part of Jharkhand and Bihar state. Biochemistry and medicine department of this college is upgraded. Place of study had been chosen for this reason.

Etiologically type2 DM (t2dm) is the most common type (90%) of diabetes throughout the world. This is true for India also, near about 57 million of people suffer from t2dm in India. t2dm develops as a result of insulin resistance and abnormal insulin secretion. The treatment modalities available for diabetes mellitus are few. Commonly used drugs for the treatment of t2dm are secretagouses (like sulfonylurea, meglitinides,
incretin analogs , incretin protectors ie DPP4 inhibitors), insulin sensitizers (like biguanides, thiazolidinediones), carbohydrate digestion inhibitors (like acarbose, miglitol, voglibose) and finally insulin. Some other drugs are also present but are not used due to cost and non-availability.

Abnormal insulin secretion is due to β-cell dysfunction. Secretagogues stimulate for the secretion of insulin from β-cell. Among the secretagogues second generation agents have fewer adverse effects and drug-drug interaction. Gliburide (glibenclamide), a second generation agent, is one of the most commonly prescribed insulin secretagogues. Gliburide alias glibenclamide is used in this study as secretagogue. There has been concern that sulfonylurea might cause increased arrhythmic cardiovascular event in patients with diabetes as a result of their activity on vascular and cardiac SUR2 receptors, with an effect of blunting ischemic preconditioning, a protective auto regulatory mechanism in the heart. So it is a good reason to avoid high dose sulfonylurea. Sulfonylureas is the most cost effective glucose lowering agent. Limiting the dose provides significant benefit in glycemic control, minimizes the cost and adverse effect. Therefore glibenclamide had been used in this study and the dose kept low at maximum 10mg/day where maximum recommended dose is 20mg/day.

Insulin resistance is a consistent finding in patients with t2dm, and resistance is present years before the onset of DM. Prospective studies...
show that insulin resistance predicts the onset diabetes\textsuperscript{15}. Insulin sensitizers improve both endogenous and exogenous insulin action and reduce insulin resistance. Lower doses of sulfonylureas are remarkably effective in patients on concomitant insulin sensitizing therapy, and are almost uniformly well tolerated. Insulin sensitizers are of two types—a) primary action on liver (metformin) and b) primary action on peripheral tissue (pioglitazone).

The precise mechanism of action of metformin is not known. It has a well-glycemic control effect, reduce hepatic insulin resistance, prevent hepatic gluconeogenesis, reduce body weight and lipid friendly. Pioglitazone is thought to act through binding and modulation of the activity of peroxisome proliferator-activated receptor \( \alpha \). Thereby improve peripheral insulin sensitivity, cause slow glycemic control, reduce FFA level and modestly elevate body weight. Glycemic control effect of both these agents is undeniable.

But which one is better in mono-therapy and combination therapy is still remains in a state of illusion. For that reason, the study question had been set to find out the effects of metformin and pioglitazone over biochemical (glycemic control and lipid management) and physical (waist/hip ratio) parameters in this study among the t2dm pts. Therefore this study has been designed to compare the relative efficacy of these two agents on the following parameters—glycemic control and lipid
lowering effect (to assess efficacy), SGPT and serum lactic acid (to measure adverse effect), and insulin lowering effect (cost-effectivity). The design fixed with Open label self controlled prospective sequential study to rule out the ethnic, genetic, age, diet, body weight and physical activity related bias. This study has been designed such that, MET and PIO had been administered in all possible groups of hyperglycemic subjects such as—mono therapy with impaired glucose tolerance (IGT) pts, combination therapy with glibenclamide in moderately hyperglycemic (HbA1c ≤10%) t2dm pts, in severe hyperglycemic pts (HbA1c ≥10%) along with insulin.

Study was initiated by selecting more than 200 pts. Their distribution were 100 pts with t2dm (HbA1c <10mg/dl) for combined oral antidiabetic (GBCM+MET or GBCM+PIO), 50 pts with IGT for monotherapy (MET/PIO), and 50 pts with severe hyperglycemia (HbA1c ≥10mg/dl) for insulin and sensitizer (MET/PIO). Unfortunately few pts did not come for follow up. The study was done in outdoor basis. So hospital attendance solely depends upon the pts desire. Few pts did not follow the dietary instruction and life style modification (which had been counseled at the time of selection of study subjects). Some were noncompliant to the study drugs. All of them repeatedly educated, counseled but it was far from success. Ultimately 89 pts of t2dm, 35 pts of IGT, and 40 pts of insulin naïve subject’s total 164 pts had completed the study. Pts were selected on intension-to-treat basis. The study was done as per protocol of the study.
Change of MET/PIO had been done keeping the GBCM/insulin dose fixed gradually following four half life of the individual drug (MET/PIO) to washout completely the previous drug to prevent the additive effect of the previous drug.

89 Study t2dm subjects who received GBCM, GBCM+MET, GBCM+PIO therapy sequentially show male predominantly male (65.17%) and mean age 47.9±10.58yrs. This disorder is common in women and increasing prevalence with age. This is probably due to more male coming to the hospital for treatment. They were nonobese mean BMI of these pts were 20.97±4.86 kg/m² and majority were within the normal range (18.5 to 24.9kg/m²). Family history of diabetes was found in only 24 cases (27%). Study Population was mixed dweller- rural and urban 48 an41 cases respectively and having mixed occupation like house wife29, service20, others40 pts. GBCM reduced blood glucose adequately (from base line mean 187.21±38.01to132.02±21.96 for fbg and 275.71±48.41to197.39±32.71 for ppbg) and mean reduction was 55.19mg/dl for fbg and 78.32mg/dl for ppbg. It was statistically significant. Addition of MET /PIO cause further reduction of blood glucose. Such reduction were 83.06mg/dl for fbg and 119.71mg/dl for ppbg with MET, and 68.13mg/dl for fbg 98.48mg/dl for ppbg with PIO. So the analysis of observed data with paired sample t-test showed that GBCM+MET combination reduces blood glucose significantly (p= 0.000) more than
GBCM+PIO combination both fbg and ppbg. Lactic acid was raised from baseline (mean 6.84mg/dl) when MET (mean 7.01mg/dl) is added and this was not significant. SGPT was raised from baseline (mean 23.35iu/l) when PIO was added (mean 29.51iu/l) and this was within normal limit. But alteration of lactic acid and SGPT label was not observed from baseline with PIO and MET respectively. Waist/hip circumference ratio (from mean baseline 0.944), LDL-c (from mean baseline 115.19mg/dl) and TGL (from mean baseline 178.48mg/dl) were significantly reduced (to mean w/h-0.933, LDL-c-102.78mg/dl, TGL-158.06) with the addition of MET. Such reduction is reasonably low than PIO combination. MET combination therapy increased HDL-c from 47.67mg % (baseline) to 52.76mg % (after therapy). These all are beneficial in the treatment of t2dm. Small doses of sulfonylurea are remarkably effective in diabetes particularly in patients on concomitant insulin sensitizing therapy, and are almost uniformly well tolerated. The same was observed in the GBCM+MET combination in this study. Sulfonylureas are arguably the most cost effective glucose lowering agents and glibenclamide is one of the most commonly prescribed insulin secretagogue.

There was 40 pts who received insulin, insulin+MET, insulin+PIO sequentially and HbA1c was ≥10%. These pts were 25 male (62.5%), mean age 48.65±12.13 yrs, per capita monthly income Rs. 1034/-, mean duration of diabetes 4.51yrs, positive family history of diabetes found in 18 (45%).
cases, mixed urban/rural group (19/21), BMI 21.25±4.04 mg/m². These pts are mostly nonobese and low income group.

In these pts insulin was administered to keep the subjects euglycemic. All of them maintained at euglycemic state (HbA1c<6.5%). After that MET was given reducing dose of insulin gradually. MET was administered with increasing dose gradually up to maximum dose 2550 mg (850 mg thrice daily) and dose of insulin was reduced accordingly and recorded. After a washout period of one week PIO administered in the same way. It was observed that MET administration reduce the dose of insulin from 29±7.0463 (baseline mean) to 22.87±6.03 (after MET). Whereas PIO administration cause insulin dose reduction from 29±7.0463 (mean baseline) to 25.725±6.47 (after PIO). This reduction was 21.12% with MET and 11.3% with PIO. The difference was statically significant (p≤ 0.05).

Insulin is weight gaining antidiabetic agent has tendency to increase the body weight as well as increase waist/hip ratio. But co-administration of MET with insulin significantly reduce waist/hip ratio than insulin+PIO (95%CI -0.034 to -0.011 df 38 sig.(2tailed) 0.000 and pearson's correlation was 0.896.)

35 pts with impaired glucose tolerance received MET and PIO sequentially. The pts were of mean age 48.42±14.60 yrs, male predominant (65.71%), more rural (65.71%) mostly hw 13 (37.1%), mean duration of the diabetes 3.68 yrs, family history positive only in 12
cases, mean BMI 23.00±5.71 kg/m². Per capita monthly income was Rs 740.909/-.

Analysis of observed data showed that the mean reduction of fbg and ppbg were 32.12 mg/dl and 49.32 mg/dl respectively from the baseline by MET. PIO reduce fbg and ppbg 18.95 mg/dl and 28.40 mg/dl respectively (95% CI -16.48 to -11.86, df 34, p=0.000 and 95% CI -24.92 to -16.30, df 34, p=0.000 for fbg and ppbg respectively). Pearson correlation for TGL, HDL-c, LDL-c were 0.847, 0.735, 0.948 respectively when relationship was observed MET and PIO. These were significant.

SGPT increased with PIO from 25 u/l baseline to 31.77 u/l. This rise is not significant in regards to the safety and tolerability. Serum lactic not raised with MET. That was not significant.

Type 2 diabetes mellitus results from impaired insulin action on insulin sensitive tissue and abnormal insulin secretion from pancreatic islets.

Glibenclamide increase insulin secretion in dose dependent manner and control hyperglycemia adequately. It has the potentiality to produce hypoglycemia in improper dose and may increase the arrhythmic cardiovascular event by blunting ischemic preconditioning of the heart. Study showed less than maximal dose significantly reduce blood glucose label (p=0.000), but it did not make euglycemic of the study subjects. To reduce the morbidity due to t2dm it is the top priority to make the subject euglycemic.
MET individually in both monotherapy and combination therapy effectively reduce blood glucose. Such reduction was highly significant. It also had reduced the LDL-c and TGL significantly (p=0.000). It had increased the HDL-c so the effect of metformin is lipid friendly. It was concerned that MET can increased the serum lactic acid label. Study did not reveal such increment of serum lactic acid label significantly. Though the dose used in this study was maximum 2550mg/day in divided doses.

PIO was used in monotherapy and combination therapy. Effect was noted that PIO had reduced the blood glucose in both monotherapy and combination therapy. PIO had increased the LDL-c and TGL. The HDL-c was noted reduced. Study did not find any reason to say PIO as lipid friendly. Hepatic enzyme ie SGPT label had observed increased in PIO therapy. But such increment was not significant.

In this head to head PIO and MET interventional study it had been clearly seen that MET scored better in monotherapy and combination therapy both in efficacy and adverse effect concern.

Along with insulin both MET and PIO reduced insulin dose from the baseline to make the study subject euglycemic. MET reduced insulin dose more than the PIO. Such reduction was statistically significant.

Therefore metformin revealed effective in good glycemic control, proper management of dyslipidemia in type 2 diabetes mellitus patients. Lactic acidosis not also not observed. Other safety concern only a few (15 in
no.) pts complain of nasea, abdominal distension and diarrhea. But these symptoms went of in due course with proper assurance and counseling. Pioglitazone improved glycemic control but in controlling dyslipidemia did not showed such efficiency. The extent of reduction of blood by the PIO was not like that of MET.

In multiple epidemiological studies have suggested that there is an association between cardiovascular risk and HbA1c, FBG, and 2hr level in the OGTT. In UKPDS epidemiological analysis, there was a 16% reduction in cardiovascular disease rates for each percentage point reduction in HbA1c. It documented that improved rate of microvascular complication in patients with T2DM treated to lower glycemic targets. Weight loss is associated with a reduction in lipid profile.

So metformin cause good glycemic control, reduce LDL-c, increase HDL-c, decrease TGL, reduced body weight, improve weight/hip ratio, low cost, adequate safety profile, well tolerated and time tested drug. So there is enough reason to avoid the pioglitazone as better in type 2 diabetes management.
To test the hypothesis stated earlier ‘Pioglitazone (a TZD derivative) is better than Metformin (a biguanide derivative) in both efficacy profile and safety profile both in combination therapy and monotherapy’ this study had been designed and subsequently observations were obtained. That were analysed critically. Those were as following:

a) The design of study was randomized, open level, self controlled, interventional, sequential, prospective study.

b) 164 odd diabetes patients were rigorously followed up for a period of more than six months.

c) Observations were analyzed by employing paired sample students’ t’ test and association were shown by using pearson correlation test.

d) Comparison of metformin and Pioglitazone in

i) monotherapy of the impaired glucose tolerance patients: metformin reduced the blood glucose (fating and postpradial) more than Pioglitazone. Metformin reduced fasting blood glucose by 25% and postprandial blood glucose by 24% from base line where as Pioglitazone reduced by 14% in each cases. These reductions are significantly more with MET than PIO ( p=0.000 and 95%CI -16.48 to -11.86 for fbg, and p=0.000 and 95%CI -24.92 to -16.30 for ppbg). Pearson correlation for TGL, HDL-c, LDL-c were 0.847, 0.735, 0.948 respectively when association was observed with MET and PIO.

ii) In combination therapy with glibenclamide: metformin combination reduced fbg and ppbg by 44% and 43% respectively where as Pioglitazone combination reduced fbg and ppbg by 31% and 35%
respectively. Reduction is more with metformin combination than with Pioglitazone combination (p=0.000 and 95% CI 12.76 to 17.10).

iii) Reduction of insulin dose is more with metformin than Pioglitazone combination, and it is 44% vs 31% for fbg, and 43% vs 35% for ppbg.

e) This study clearly reject the hypothesis that Pioglitazone is better than metformin. This study observed the superiority of metformin over Pioglitazone in glycemic control efficacy in both monotherapy and combination therapy and also in reducing insulin dose when administered along with insulin.