# "COMPARISION AND EVALUATION OF ORAL HYPOGLYCEMIC DRUGS COMBINATION THERAPY FOR CONTROL OF T2DM"

*A Thesis Submitted In Partial Fulfillment of*

*The Requirements for the Award*

**OF**

**THE DEGREE OF**

**BACHELOR OF TECHNOLOGY**

SUBMITTED BY

**RANJAN KUMAR PRAJAPATI**

Department of Biotechnology & Medical Engineering, IV$^{th}$ Year, 111BT0024

NATIONAL INSTITUTE OF TECHNOLOGY,Rourkela-769008.

UNDER THE SUPERVISION OF

**Prof. (DR.) BIBHUKALYAN PRASAD NAYAK**

Department of Biotechnology & Medical Engineering

National Institute of Technology, Rourkela

# CERTIFICATE

This is to certify that the project report entitled "**Comparision and Evaluation Of Oral Hypoglycemic Drugs Combination Therapy For Control of T2DM**" submitted by Ranjan Kumar Prajapati (111BT0024) in the partial fulfillment of the requirement for the degree of the Bachelor in Technology in Biotechnology Engineering, National Institute of Technology, Rourkela is an authentic work carried out by him under my supervision. To the best of my knowledge the matter embodied in the report has not been submitted to any other Institute/University for any degree.

**Date:** 11th May 2013

**Prof. (Dr.)Bibhukalyan Prasad Nayak**
**(**Supervisor**)**
Department of Biotechnology and Medical Engineering
National Institute of Technology,
Rourkela-769008

**ACKNOWLEDGEMENT**

I would like to take this opportunity to extent my hearty gratitude to my guide and advisor **Prof.(Dr.) Bibhukalyan Prasad Nayak**, Department of Biotechnology and Medical Engineering, National Institute of Technology, Rourkela, for his constant guidance, support, motivation and encouragement throughout the length of the period. His readiness for consultation at all times, His educative comments, and assistance have been invaluable for completion of my B.Tech thesis possible.

I also thank National Institute of Technology Rourkela, for permitting me to utilize the facilities.

I would also like to thank all the lab members**,** for guiding me throughout the length of this project.

I would like to express my gratitude towards all the people who have contributed their precious time and effort to help me in completing this project, without whom it would not have been possible for me to understand and analyze the project.

Submitted by:

Ranjan Kumar Prajapati

Roll No: 111BT0024

Department of Biotechnology and Medical Engineering

National Institute of Technology,

Rourkela-769008.

# Table of Contents


| List | Page No: |
|---|---|
| **List of Figures** | 4 |
| **Abbreviations** | 5 |
| **1. Abstract** | 6 |
| **2. Introduction** | |
| 2.1.Diabetes Mellitus | 7 |
| 2.2.T2Diabetes mellitus | 9 |
| 2.3.Therapautic for T2DM. | 10 |
| **3. Objective** | 14 |
| **4. Literature** | |
| 4.1.Drug effectiveness. | 15 |
| 4.2.Current study description | 16 |
| **5. Methodology** | |
| 5.1.Work Flow Diagram | 18 |
| 5.2.Subject selection | 20 |
| 5.3.Estimation of FBS,PPBS and HbA1c. | 20 |
| 5.4.Statistical analysis. | 22 |
| **6. Result and Discussion** | |
| 6.1.One Factor ANOVA | 25 |
| 6.2.Paired t test | 30 |
| **7. Conclusion** | 35 |
| **8. Reference** | 36 |
| **9. Appendix-I** | 38 |

# List of Figures


1. Figure 1: Oral Hypoglycemic Drugs site of action.
2. Figure 2: Values for HbA1c.
3. Figure 3: Values for HbA1c and FBS & PPBS .
4. Figure 4: Group 1,2 and 3. Divided on the basis of FBS level.
5. Figure 5: Group 1,2 and 3. Divided on the basis of PPBS level.
6. Figure 6: Group 1,2 and 3. Divided on the basis of HbA1c level.
7. Figure:7 Result of ANOVA : single factor for FBS Group 1.
8. Figure:8 Result of ANOVA : single factor for FBS Group 2.
9. Figure:9 Result of ANOVA : single factor for FBS Group 3.
10. Figure:10 Result of ANOVA : single factor for PPBS GROUP 1.
11. Figure:11 Result of ANOVA : single factor for PPBS GROUP 2.
12. Figure:12 Result of ANOVA : single factor for PPBS GROUP 3.
13. Figure:13 Result of ANOVA : single factor for HbA1C GROUP 1.
14. Figure:14 Result of ANOVA : single factor for HbA1C GROUP 2.
15. Figure:15 Result of ANOVA : single factor for HbA1C GROUP 3.
16. Figure: 16 Result of Paired t test for FBS(Group 1).
17. Figure: 17 Result of Paired t test for PPBS(Group 1).
18. Figure: 18 Result of Paired t test for HbA1c(Group 1).
19. Figure: 19 Result of Paired t test for FBS(Group 2).
20. Figure: 20 Result of Paired t test for PPBS(Group 2).
21. Figure: 21 Result of Paired t test for HbA1c(Group 2).
22. Figure: 22 Result of Paired t test for FBS(Group 3).
23. Figure: 23 Result of Paired t test for PPBS(Group 3).
24. Figure: 24 Result of Paired t test for HbA1c(Group 3).

# Abbreviations

1. **T2DM-** Type 2 Diabetes Mellitus
2. **FBS-** Fasting Blood Sugar.
3. **PPBS-**Post Prandial Blood Sugar.
4. **HbA1c-**Hemoglobin A1c.
5. **DPP-4-** Dipeptidyl peptidas IV inhibitors
6. **OHG-** Oral hypoglycemic drug

# 1. Abstract

Oral hypoglycemic drug therapy has successfully been used for controlling type-2 Diabetes Mellitus. Several new OHGs are flooding into the market and are prescribed to the patients depending upon effect and patient compliance, but no accurate combination of drugs has either been established or being customized that can exactly adapt to the biological system of patents. Since physical parameter differs from person-to-person, a comprehensive analysis is required to determine the right combination of OHGs. The current study aims towards a survey based analysis of OHG therapy in T2DM patients to observe the glycemic control through measurement of FBS, PPBS and HbA1c at specific time intervals. Briefly, 15 T2DM patients were observed longitudinally over 6 months for their glycemic control in response to different combination/mono OHG therapy. It was hypothesized that combination therapy of Biguanides (i.e Metformin) with other OHDs should give the best therapeutic benefits. For this subjects were selected within the Institutional community and the nearby locality. They were divided into three groups as per the OHG therapy (Group 1: Biguanide only; Group 2 Thiazolidinedion+Biguanide +Sulfonolyrea; and Group 3: Dipeptidyl Peptidas -4 inhibitor+Sulfonolyrea). With informed consent, they were instructed to respond to a prepared Questionnaire involving diabetic history along with medical concerns like any complication of vital organs and limbs. The glycemic control was evaluated from FBS, PPBS and HbA1c measurements. Survey was conducted in 2 phases with a gap duration of 6 months. Data was obtained and statistical analysis was done. Subject variation was calculated by ANOVA. Paired –t test was carried out to derive the response difference at two time points ($p \leq 0.05$) among three groups. Single factor ANOVA test was done. The results showed that Gr-I with Biguanides got significant therapeuric benefit over 6 months as obtained from FBS ($p = 0.009$) and HbA1c ($p = 0.01$). It also conclude that in starting phase of OHGs, Biguanide monotherapy has the best therapeutic benefit over the combination therapies.

Keywords:,T2DM, OHGs, Biguanide, Thiazolidinedion , ANOVA, Paired –t- test.

# 2. Introduction

Diabetes (also called diabetes mellitus) is group of metabolic disease in which person experiences rise in blood Glucose. Reasons can be Insulin production is inadequate or because Body's cell fails to respond properly to insulin or both.

- Person experience following change.
- Polyuria (Frequent urination),Polydipsia (thirsty) and Polyphagia (hungry).
- DM generally cannot be cured but it can be administered by controlling blood glucose. Poor management can lead to serious long-term body complications, and can increase the risk of cardiovascular disease. Usually good quality DM support and management increase the cost, complex, intensive-labor and time taking task.

- Medicinal services benefit in 21st century have taken another measurement concentrating on out of Hospital Care, and a solid participatory segment from patients i.e particularly in long-term and way of life related conditions, for example, DM. Individuals living with diabetes are confronted day by day with various difficulties in dealing with their condition. Treatment for T2DM administration includes meds as well as developing proof, which has recognized way of life alterations as the key element.

## 2.1 There are three types of diabetes:

### Type 1 Diabetes

T1DM also called Insulin-dependent where people take Insulin from outside the body other than insulin-dependent diabetes it is also called as early onset diabetes or juvenile diabetes. People usually develop Type 1 diabetes before reaching the age of 40, it has no age limit it can develop in early teenage or adulthood years.

- Type 1 is very different from type 2 diabetes.

- Patients with type 1 diabetes take insulin injections for the rest of their life. They regularly check proper glucose levels by doing regularly blood tests and maintaining a proper Diet and Exercise.

## Type 2 Diabetes

T2DM is a case where body does not produce enough insulin for proper functioning of metabolic activity or the body cells does not react to insulin i.e insulin resistance.

- Some people may be able to control their T2DM symptoms by losing weight, doing regular exercise, maintaining a healthy diet and monitoring their blood glucose levels. However, T2DM is typically a progressive disease and it gradually gets worse.
- Overweight and obese individuals have a much higher danger of creating T2DM contrasted with those with a solid body weight. Individuals with a considerable measure of instinctive fat, otherwise called focal weight, tummy fat, or stomach corpulence, are particularly at danger. Being overweight/fat causes the body to discharge chemicals that can destabilize the body's cardiovascular and metabolic frameworks.
- Being overweight, physically inactive and eating the wrong foods all contribute to our risk of developing T2DM. According to a report published by researchers from Imperial College London in the journal *Diabetologia* "Drinking just one can of (non-diet) soda per day can raise our risk of developing type 2 diabetes by 22% ".
- The risk of developing T2DM is also greater as we get older. Experts are not completely sure why, but say that as age increase we put on weight and become less physically active.
- Researchers from the University of Edinburgh, Scotland, gave a report that low testosterone levels are linked to insulin resistance "Men whose testosterone levels are low have been found to have a higher risk of developing type 2 diabetes".

## Gestational Diabetes

Gestational Diabetes affects females during pregnancy. Ladies having large amounts of glucose in their blood, and their body fails to create enough insulin to transport the greater part of the glucose into their cells, bringing about logically rising in level of blood glucose. In Gestational diabetes the diagnosis is done during pregnancy.

- The most of gestational diabetes patients controls their diabetes with regular exercise and healthy diet. Undiagnosed or uncontrolled gestational diabetes can raise the risk of complications during childbirth.
- Scientists from the National Institutes of Health and Harvard University found that women whose diets before becoming pregnant were high in animal fat and cholesterol had a higher risk for gestational diabetes as compared to women had less amount of animal fat and cholesterol.

### Prediabetes

Vast number of patients with T2DM at first had prediabetes. Their blood glucose levels are higher than ordinary, yet not sufficiently high to number a diabetes diagnosis. The cells in the body are getting to be impervious to insulin.

## 2.2 Diabetes Is A Metabolism Disorder

- Diabetes (diabetes mellitus) is under the category as a metabolism disorder.
- The metabolism of diabetes is our body use digested food for getting energy and to obtain essential nutrients. Carbohydrate that we take is broken down into glucose, which is the main source of fuel for our body. Glucose is transported to various part of our body through bloodstream and glucose enters into the cytoplasm by the help of hormone called Insulin.
- Under normal condition through the help of Insulin (produced by pancreas) glucose is broken down to produce energy. But A person with diabetes proper mechanism is halted either cell signaling molecules are mutated or passage of glucose molecule inside the cell is blocked or there is a large deposition of fat molecules over somatic cell that blocks

insulin-glucose molecules, resulting in deposition of glucose in extracellular matrix. This excess blood glucose eventually passes out of the body by urinal passage. So, even though the blood has plenty of glucose, the cells are getting less glucose producing less energy.

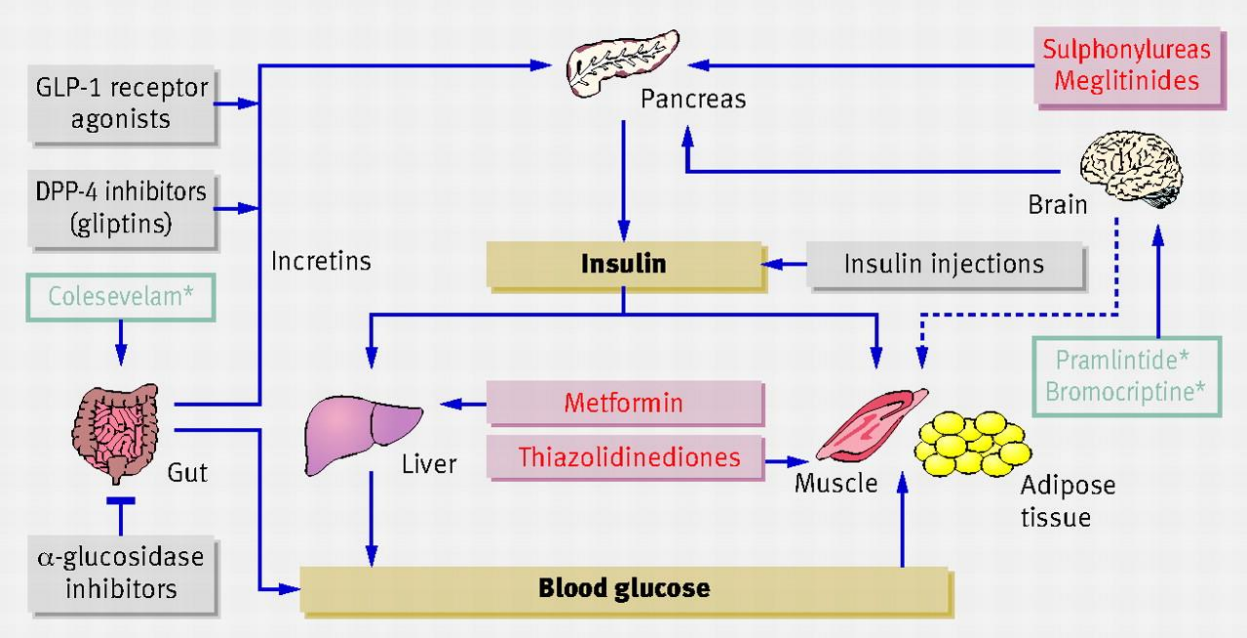



Figure 1: Oral Hypoglycemic Drugs site of action.

## 2.3 Therapautic in T2DM

At present Six Class of Oral Hypoglycemic Drugs are available

1. Biguanides(e.g Metformin).
2. Sulfonylureas(e.g Glimepiride)
3. Meglitinides(e.g Rapaglinide)
4. Thiazolidinediones (e.g Pioglitazone)
5. Dipeptidyl peptidas IV inhibitors (e.g Sitagliptin)
6. α glucosidase inhibitors (e.g Acarbos)

# 1. Biguanides

Biguanide an insulin sensitizer drug act against insulin resistance is considered to be effective in T2DM. Metformin is most preferred drug of biguanide because of its safety and effiency, it is also suggested for monotherapy or joint with other drugs. Joint guidelines from the AACE and ACE states that metformin can be initiated as initial line of monotherapy unless a contradiction such as renal disease, gastrointestinal intolerance ,hepatic disease or risk of lactic acidosis exists.

Metformin is most widely used OHD in the world, but it can reach its peak value of effectiveness due to progressive β – cell failure. Metformin is only effective when sufficient insulin is present inside the cell as well as outside, because of this generally patients cannot maintain high tight glycemic control as disease progress.Due to safety and efficiency of Sulfonylureas and Metformin a commonly prescribed combination.

## 2. Sulfonylureas

SU are the most established and most broadly utilized drugs for the treatment of T2DM. In spite of the fact that SU treatment viably brings down blood glucose focuses by animating insulin emission from β-cells, treatment with Sulfonylureas is connected with a dynamic straight decrease in β-cell capacity. Possible powerlessness to keep up glycemic control mirrors a propelled phase of β-cell disappointment.

Hypoglycemia is the most widely recognized and most genuine unfriendly occasion connected with SU treatment, primarily in view of insulin discharge being launched notwithstanding when glucose focuses are beneath the typical limit for ordinary physiologic glucose-fortified insulin discharge. Attributable to diminished viability of Sulfonylureas over the long haul and a related decrease in the insulin secretory store, blend treatment has concentrated basically on including insulin-sharpening meds, including metformin and thiazolidinedione.

## 3. Meglitinides

Meglitinides, for example, repaglinide and nateglinide are prandial insulin releasers that stimulate fast insulin emission. Repaglinide (NovoNorm®, Prandin®, GlucoNorm®) is the first clinically accessible insulin secretagogues that particularly improves early-stage prandial insulin

reaction by expanding the affectability of β-cells to raised glucose levels, delivering a more noteworthy insulin discharge under hyperglycemic conditions. Repaglinide is taken orally instantly before a feast and has been demonstrated to especially lessen postprandial hyperglycemia.Lower danger of hypoglycemia makes these operators an appealing choice for some elderly patients. This could be identified with an in vitro finding that repaglinide expands insulin discharge from β-cells just in the vicinity of glucose.

## 4. Thiazolidinediones

The thiazolidinediones are insulin-sensitizing drugs that enhance entire body insulin affectability through gene regulation. These operators expand glucose uptake and diminish rates of gluconeogenesis in the liver. Diminishments in plasma insulin concentration and bringing down of circling triglycerides are extra backhanded components that may help enhance entire body insulin affectability. Thiazolidinediones have additionally been known to enhance β-cell work and decrease insulin resistance.

## 5. Dipeptidyl peptidas IV inhibitors

The dipeptidyl peptidase-4 (DPP-4) inhibitors are another class of oral medications for the treatment of T2DM. As the name proposes DPP-4 inhibitors repress the activity of DPP-4, the enzyme in charge of the peripheral degradation of GLP-1. There are as of now three medications accessible for clinical use in this class – sitagliptin, vildagliptin and saxagliptin. DPP-4 will be utilized either as monotherapy or as a part of blend with metformin, sulphonylureas or a mix of both. The rates of hypoglycaemia connected with these medications are 6–10 times lower than with sulphonylureas. They have likewise been indicated to be weight neutral.DPP-4 inhibitors are all around endured, with hypoglycaemia just happening when utilized as a part of mix with sulphonylurea treatment. The present medications are cleared by hepatic metabolism and renal discharge. Sitagliptin and vildagliptin are not authorized for utilization in renal debilitation, though saxagliptin can be utilized at a diminished measurements. There is a proposal from pooled information of expanded rates of contaminations, particularly nasopharyngitis and urinary

tract diseases, which recommends a part for DPP-4 action in typical safe reconnaissance, however whether this is clinically huge is still to be established.

## 6. α glucose inhibitors

A Drug may be characterized by the chemical type of the active ingredient or by the way it is utilized to treat a specific condition. Every drug can be characterized into one or more medication classes.

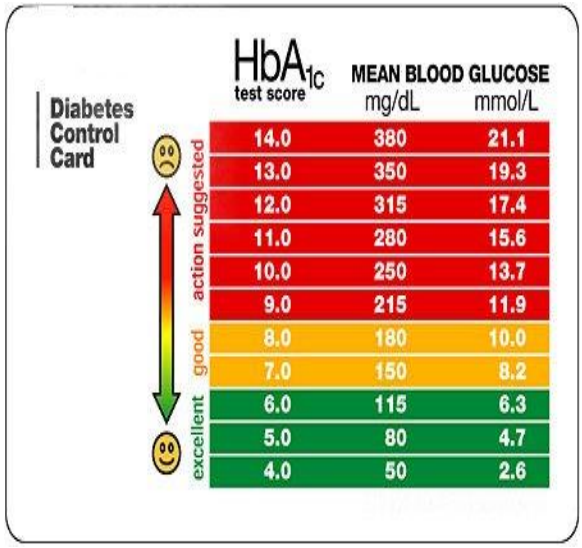
Alpha-Glucosidase is one of the enzymes in charge of breaking down carbohydrates to smaller sugar particles like glucose, sothat carbohydrates can be re absorbed.

Alpha-Glucosidase inhibitors work by focused and reversible inhibitors of these intestinal enzymes. They decrease the processing of sugars and postponement glucose retention. This outcomes in a smaller and slower ascent in blood glucose levels taking after suppers, and viably for the duration of the day.

# 3. Objective:

- Comprehensive analysis will help to study the working of Oral Hypoglycemic drugs better.
- With proper combination of different groups effect of drugs could be maximized.
- Pinpointing which drug or combination of drugs gives the best result.

# 4. Literature Review




**Blood Sugar Chart**

| Category | Fasting Value (mg/dl) | | Post Prandial (mg/dl) |
|---|---|---|---|
| | Minimum Value | Maximum Value | Value 2 hours after consuming glucose |
| Normal | 70 | 100 | Less than 140 |
| Early Diabetes | 101 | 126 | 140 to 200 |
| Established Diabetes | More than 126 | - | More than 200 |

Figure 2 & 3: Values for HbA1c and FBS & PPBS respectively.

## 4.1 Drug effectiveness

In a recent analysis ,Rao *et al.* have shown combination therapy with Metformin and Sulfonylureas significantly increased the relative risk of cardiovascular hospitalization or mortality.

1. Blood glucose level reduced when T2DM were diagnosed with **Pioglitazone** , on the other hand triglyceride levels were decreased with increase in high-density lipoprotein cholesterol levels were observed which lead to reduction in cardiovascular risk benefit could be boomeranged with elevation in weight gain. Combination therapy of Pioglitazone with metformin or a sulfonylurea were given to those patients whose condition were worst, and the blood glucose level were not controlled with mono-therapy. the results obtained were very much favorable to combination therapy. There is a need for large-scale, long-term studies comparing the effectiveness of combination therapy that includes pioglitazone with that of other combinations of anti-diabetic drugs. A large-scale and long-term studies comparing

the effectiveness of combination therapy including pioglitazone with that to other combinations of OHDs.

2. **Metformin** and **Troglitazone** have different mechanisms of action, despite of variation in mechanism are equally effective in lowering blood glucose concentrations in patients with T2DM. Combination therapy of metformin and troglitazone therapy had improvement in blood glucose control, without interfering of insulin secretion and with reversal of the two principal pathophysiologic abnormalities.

   Combination therapy of troglitazone and metformin resulted in no further decrease of endogenous glucose production. mono-therapy of troglitazone had no significant effect on endogenous glucose. However, reason for lowering of endogenous glucose production when metformin was added to troglitazone became a difficult task to explain, particularly because these patients had a significant improvement in glycemic control during combined treatment.

3. **Sitagliptin** indicated more prominent adequacy and preferable decency over a α-glucosidase inhibitor when added to stable measurements of metformin or pioglitazone. These discoveries bolster the utilization of sitagliptin in Japanese patients with sort 2 diabetes deficiently controlled by insulin-sharpening specialists.

- Both HbA1c and FPG diminished from standard with every treatment, with no measurably huge contrasts between medicines. An essentially lower frequency of reported hypoglycaemia was seen with sitagliptin contrasted and sulfonylurea (6.2% versus 27.8%; $p < 0.001$). Body weight diminished altogether with sitagliptin yet not with sulfonylurea. Fundamentally a larger number of patients on sitagliptin than on sulfonylureas attained to a composite end-purpose of >0.5% HbA1c decrease with no reported hypoglycaemia or increment in body weight (44.1% versus 16.0%; $p < 0.001$).

- In this investigation of elderly patients with T2DM, contrasted and sulfonylurea, sitagliptin gave comparable glycaemic adequacy less hypoglycaemia and with body weight reduction.

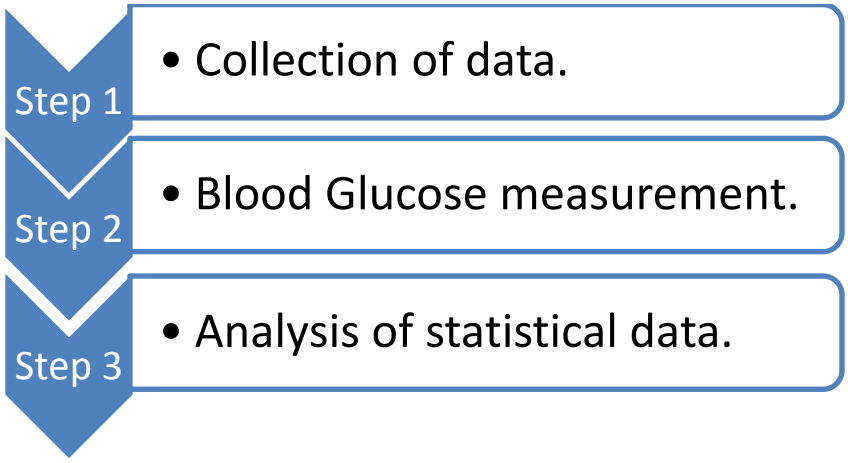
4. The blend of metformin and a sulfonylurea is generally utilized as a part of sort 2 diabetes mellitus. Numerous patients on this mix treatment don't accomplish or keep up glycemic targets and require the expansion of a third antihyperglycemic specialists.

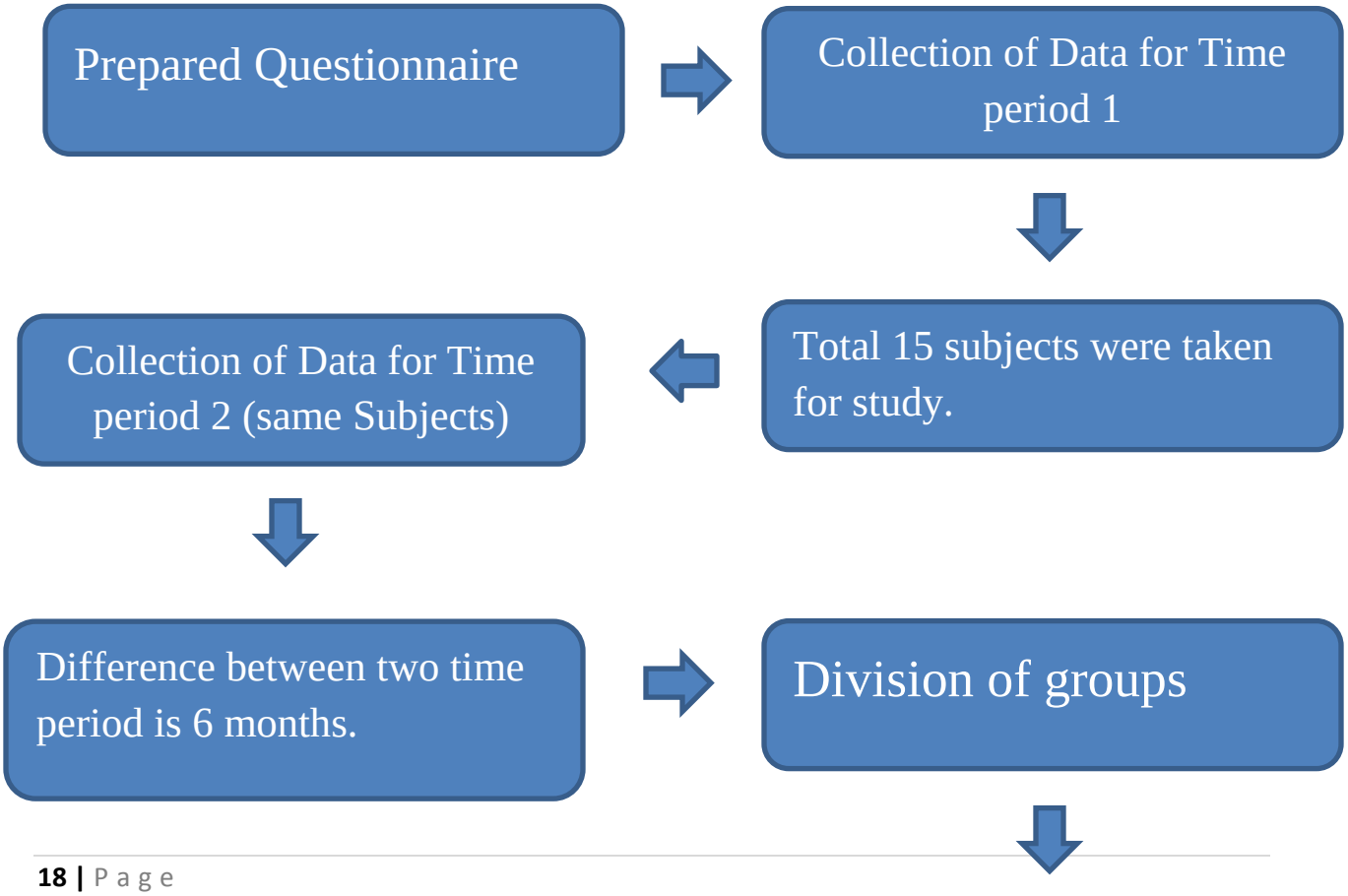
5. The unfavorable impacts of metformin primarily comprise of measurements ward gastrointestinal issue and uncommon cases or life-debilitating lactic aciaosis. Kidney disappointment decreases metformin end. Metformin once in a while causes hypoglycaemia and has no impact on body weight. It doesn't build tumor related mortality. It at times reasons vitamin B12 lack prompting macrocytic weakness or fringe neuropathy. Metformin chiefly conveys a danger of cooperations with medications that disable renal capacity, for example, non-steroidal calming medications and iodinated differentiation media. Renal disappointment can prompt metformin gathering and an expanded danger of lactic acidosis.

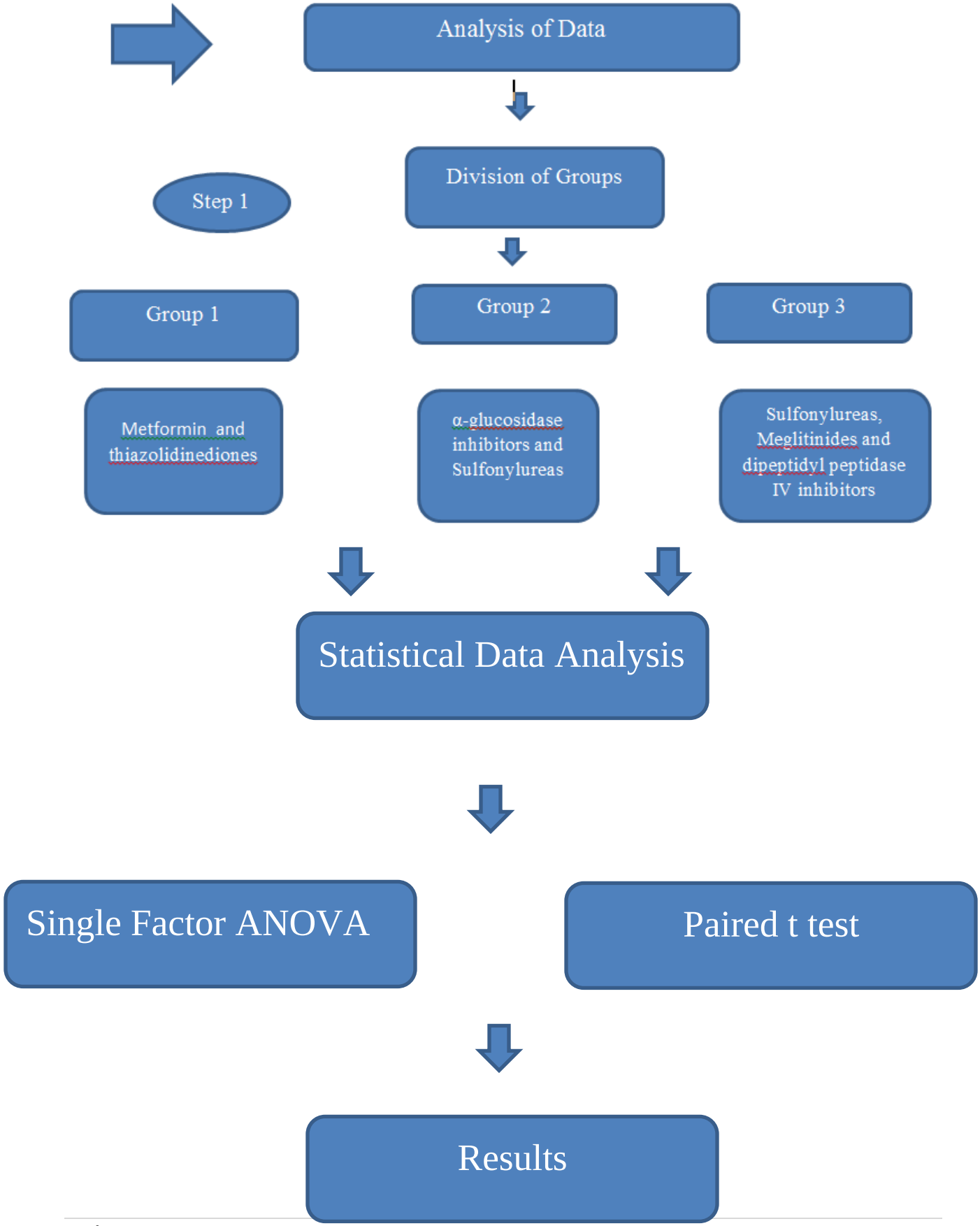
6. Vildagliptin was the most utilized medication among DPP-4 inhibitors. Conclusions.Sulfonylureas were the most utilized medication for diabetes treatment. Patients treated with DPP-4 inhibitors had higher adherence and control of diabetes, with lower rates of hypoglycemia and CVE, bringing about lower social insurance costs.

# 5. Methodology

## 5.1 WORK FLOW DIAGRAM




Analysis of Data
Division of Groups
Step 1
Group 1
Group 2
Group 3
Metformin and thiazolidinediones
α-glucosidase inhibitors and Sulfonylureas
Sulfonylureas, Meglitinides and dipeptidyl peptidase IV inhibitors
Statistical Data Analysis
Single Factor ANOVA
Paired t test
Results

## 5.2 Subject selection

Professors, currently employed in an institute, community or public health setting, Government employers ,private businessman, workers working in any site, security Guards, were recruited to participate. All of them were recruited through convenience sampling in cooperation with several proper agreement in relation to consent form that was prepared.

# Procedures

Study was done by visiting each professors office and data was collected. Apart from that to maximize the number of participation ; information form friend circle was also taken. Study advertisements provided a brief overview of the purpose of the survey and directed participants to an online survey created using Survey Monkey and Google Forms. Instructions for completing the surveys and relevant information regarding of the purpose of the research and confidentiality procedures were included within the online survey itself.

Data collection was done between November 2014 to May 2015. Exactly six months gap was maintained between 2 successive survey to the same person so as to do comparison.

## 5.3 Estimation of FBS, PPBS and HbA1c.

FBS should be taken before intake of food. And PPBS should be taken after 2 hours of uptake of food . these 2 measurement were taken by the help of instrument called “Glucometer”.

With correctly calibrated. To measure HbA1c level subject were asked to provide the data of recently obtained HbA1c level.

Data collected was divided among groups as follows:-

FBS data collected was divided into 3 groups according to intake of medicine.

1. G1 Biguanide
2. G2 (Thiazolidinedion + Biguanide + Sulfonolyrea)
3. G3 (DPP-4+ Biguanide + Sulfonolyrea)

There are 2 test date

Difference between 2 test date  i.e Test Date 1 and Test date 2 is 6 months. Deviation from 126 was also measured, greater than 126 mg/dl seperate subjects form normal.some values comes out to be positive some are negative.

F20

| | A | B | C | D | E | F | G | H | I | J |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | | | | | | Gap of 6 months | | | | |
| 2 | Groups | | | FBS | test day 1 | Deviation from 126 | test date 2 | Deviation from 126 | | |
| 3 | G1 | | | | 195 | 69 | 160 | 34 | | |
| 4 | | | | | 145 | 19 | 150 | 24 | | |
| 5 | Biguanide | | | | 163 | 37 | 160 | 34 | | |
| 6 | | | | | 140 | 14 | 150 | 24 | | |
| 7 | | | | | 170 | 44 | 160 | 34 | | |
| 8 | G2 | | | | 160 | 34 | 130 | 4 | | |
| 9 | Thiazolidinedion | | | | 175 | 49 | 160 | 34 | | |
| 10 | Biguanide | | | | 120 | -6 | 125 | -1 | | |
| 11 | Sulfonolyrea | | | | 190 | 66 | 145 | 19 | | |
| 12 | | | | | 133 | 7 | 147 | 21 | | |
| 13 | G3 | | | | 270 | 144 | 140 | 14 | | |
| 14 | | | | | 110 | -16 | 140 | 14 | | |
| 15 | DPP-4 | | | | 180 | 54 | 200 | 64 | | |
| 16 | Sulfonolyrea | | | | 135 | 9 | 133 | 7 | | |
| 17 | Biguanide | | | | 159 | 33 | 155 | 29 | | |

Figure 4: Group 1,2 and 3. Divided on the basis of FBS level.

Similarly for PPBS and HbA1c data collected was divided into 3 groups according to intake of medicine.

1. G1 Biguanide
2. G2 (Thiazolidinedion + Biguanide + Sulfonolyrea)
3. G3 (DPP-4+ Biguanide + Sulfonolyrea)

There are 2 test date

Difference between 2 test date  i.e Test Date 1 and Test date 2 is 6 months. Deviation from 200 mg/dl for PPBS and 7.0 for HbA1c  was also measured.

| J | K | L | M | N | O | P |
|---|---|---|---|---|---|---|
| | | | | Gap of 6 months | | |
| | Groups | PPBS | test date 1 | Deviation form 200 | test date 2 | Deviation form 200 |
| | G1 | | 290 | 90 | 230 | 30 |
| | | | 160 | -40 | 175 | -25 |
| | Biguanide | | 210 | 10 | 207 | 7 |
| | | | 190 | -10 | 210 | 10 |
| | | | 240 | 40 | 220 | 20 |
| | G2 | | 180 | -20 | 160 | -40 |
| | Thiazolidinedion | | 200 | 0 | 175 | -25 |
| | Biguanide | | 180 | -20 | 180 | -20 |
| | Sulfonolyrea | | 265 | 65 | 205 | 5 |
| | | | 235 | 35 | 250 | 50 |
| | G3 | | 320 | 120 | 225 | 25 |
| | | | 180 | -20 | 180 | -20 |
| | DPP-4 | | 270 | 70 | 280 | 80 |
| | Sulfonolyrea | | 215 | 15 | 225 | 25 |
| | Biguanide | | 225 | 25 | 223 | 23 |

Figure 5: Group 1,2 and 3. Divided on the basis of PPBS level.

| Q | R | S | T | U | V | W |
|---|---|---|---|---|---|---|
| | | | Gap of 6 months | | | |
| Groups | Hba1c | test date 1 | Deviation from 7.0 | Test date 2 | Deviation from 7.0 | |
| G1 | | 9 | 2 | 8 | 1 | |
| | | 8 | 1 | 8 | 1 | |
| Biguanide | | 8 | 1 | 8 | 1 | |
| | | 8 | 1 | 9 | 2 | |
| | | 10 | 3 | 9 | 2 | |
| G2 | | 7 | 0 | 6.8 | -0.2 | |
| Thiazolidinedion | | 9.2 | 2.2 | 8 | 1 | |
| Biguanide | | 8 | 1 | 8.2 | 1.2 | |
| Sulfonolyrea | | 8.4 | 3.4 | 7.6 | 0.6 | |
| | | 10 | 3 | 10 | 3 | |
| G3 | | 14.9 | 7.9 | 7.9 | 0.9 | |
| | | 7.1 | 0.1 | 7.2 | 0.2 | |
| DPP-4 | | 8 | 1 | 9 | 2 | |
| Sulfonolyrea | | 7 | 0 | 8 | 1 | |
| Biguanide | | 11.7 | 4.9 | 11.5 | 4.5 | |

Figure 6: Group 1,2 and 3. Divided on the basis of HbA1c level.

## 5.4 Statistical Data Analysis.

1. Single factor ANOVA.
2. Paired –t- test.

ANOVA was used to compare the mean of two or more groups. Subject were taking only medication so one factor was taken into consideration.

Null Hypothesis: Single factor ANOVA was done so as to ensure the Subject Variation in the group should be insignificant.

Paired –t- test was done to compare the mean of two groups. p value determines the effectiveness of any drug therapy. p value determined through MS Excel.

# 6. Result and Discussion

## 6.1 ANOVA test result

1. ANOVA test result for Group 1 FBS p-value =0.532. ANOVA test to be considered variation between the group should be p<0.01 but here higher value states that Single factor ANOVA was very insignificant.

E2

| | A | B | C | D | E | F | G | H |
|---|---|---|---|---|---|---|---|---|
| 1 | Anova: Single Factor | | | | | | | |
| 2 | | | | | | | | |
| 3 | SUMMARY | | | | | | | |
| 4 | *Groups* | *Count* | *Sum* | *Average* | *Variance* | | | |
| 5 | Column 1 | 5 | 813 | 162.6 | 481.3 | | | |
| 6 | Column 2 | 5 | 780 | 156 | 30 | | | |
| 7 | | | | | | | | |
| 8 | | | | | | | | |
| 9 | ANOVA | | | | | | | |
| 10 | *ce of Varic* | *SS* | *df* | *MS* | *F* | *P-value* | *F crit* | |
| 11 | Between | 108.9 | 1 | 108.9 | 0.425973 | 0.532 | 5.317655 | |
| 12 | Within Gr | 2045.2 | 8 | 255.65 | | | | |
| 13 | | | | | | | | |
| 14 | Total | 2154.1 | 9 | | | | | |
| 15 | | | | | | | | |
| 16 | | | | | | | | |

Figure:7 Result of ANOVA : single factor for FBS Group 1.

2. ANOVA test result for Group 2 FBS p-value =0.353. ANOVA test to be considered variation between the group should be p<0.01 but here higher value states that Single factor ANOVA was very insignificant.

| | A | B | C | D | E | F | G | H |
|---|---|---|---|---|---|---|---|---|
| 1 | Anova: Single Factor | | | | | | | |
| 2 | | | | | | | | |
| 3 | SUMMARY | | | | | | | |
| 4 | *Groups* | *Count* | *Sum* | *Average* | *Variance* | | | |
| 5 | Column 1 | 5 | 778 | 155.6 | 839.3 | | | |
| 6 | Column 2 | 5 | 707 | 141.4 | 197.3 | | | |
| 7 | | | | | | | | |
| 8 | | | | | | | | |
| 9 | ANOVA | | | | | | | |
| 10 | *Source of Variation* | *SS* | *df* | *MS* | *F* | *P-value* | *F crit* | |
| 11 | Between Groups | 504.1 | 1 | 504.1 | 0.972603 | 0.353 | 5.317655 | |
| 12 | Within Groups | 4146.4 | 8 | 518.3 | | | | |
| 13 | | | | | | | | |
| 14 | Total | 4650.5 | 9 | | | | | |
| 15 | | | | | | | | |

Figure:8 Result of ANOVA : single factor for FBS Group 2.

3. ANOVA test result for Group 3 FBS p-value =0.509. ANOVA test to be considered variation between the group should be $p<0.01$ but here higher value states that Single factor ANOVA was very insignificant.

| | A | B | C | D | E | F | G | H |
|---|---|---|---|---|---|---|---|---|
| 1 | Anova: Single Factor | | | | | | | |
| 2 | | | | | | | | |
| 3 | SUMMARY | | | | | | | |
| 4 | *Groups* | *Count* | *Sum* | *Average* | *Variance* | | | |
| 5 | Column 1 | 5 | 854 | 170.8 | 3760.7 | | | |
| 6 | Column 2 | 5 | 748 | 149.6 | 953.3 | | | |
| 7 | | | | | | | | |
| 8 | | | | | | | | |
| 9 | ANOVA | | | | | | | |
| 10 | *ce of Varic* | *SS* | *df* | *MS* | *F* | *P-value* | *F crit* | |
| 11 | Between | 1123.6 | 1 | 1123.6 | 0.476708 | 0.509 | 5.317655 | |
| 12 | Within Gr | 18856 | 8 | 2357 | | | | |
| 13 | | | | | | | | |
| 14 | Total | 19979.6 | 9 | | | | | |
| 15 | | | | | | | | |

Figure:9 Result of ANOVA : single factor for FBS Group 3.

4. ANOVA test result for Group 1 PPBS p-value =0.701. ANOVA test to be considered variation between the group should be p<0.01 but here higher value states that Single factor ANOVA was very insignificant.

| | A | B | C | D | E | F | G | H |
|---|---|---|---|---|---|---|---|---|
| 1 | Anova: Single Factor | | | | | | | |
| 2 | | | | | | | | |
| 3 | SUMMARY | | | | | | | |
| 4 | *Groups* | *Count* | *Sum* | *Average* | *Variance* | | | |
| 5 | Column 1 | 5 | 1090 | 218 | 2470 | | | |
| 6 | Column 2 | 5 | 1042 | 208.4 | 430.3 | | | |
| 7 | | | | | | | | |
| 8 | | | | | | | | |
| 9 | ANOVA | | | | | | | |
| 10 | *Source of Variation* | *SS* | *df* | *MS* | *F* | *P-value* | *F crit* | |
| 11 | Between Groups | 230.4 | 1 | 230.4 | 0.15888 | 0.701 | 5.317655 | |
| 12 | Within Groups | 11601.2 | 8 | 1450.15 | | | | |
| 13 | | | | | | | | |
| 14 | Total | 11831.6 | 9 | | | | | |
| 15 | | | | | | | | |

Figure:10 Result of ANOVA : single factor for PPBS GROUP 1.

5. ANOVA test result for Group 2 PPBS p-value =0.455. ANOVA test to be considered variation between the group should be p<0.01 but here higher value states that Single factor ANOVA was very insignificant.

| | A | B | C | D | E | F | G | H |
|---|---|---|---|---|---|---|---|---|
| 1 | Anova: Single Factor | | | | | | | |
| 2 | | | | | | | | |
| 3 | SUMMARY | | | | | | | |
| 4 | *Groups* | *Count* | *Sum* | *Average* | *Variance* | | | |
| 5 | Column 1 | 5 | 1060 | 212 | 1382.5 | | | |
| 6 | Column 2 | 5 | 970 | 194 | 1242.5 | | | |
| 7 | | | | | | | | |
| 8 | | | | | | | | |
| 9 | ANOVA | | | | | | | |
| 10 | *Source of Variation* | *SS* | *df* | *MS* | *F* | *P-value* | *F crit* | |
| 11 | Between Groups | 810 | 1 | 810 | 0.617143 | 0.455 | 5.317655 | |
| 12 | Within Groups | 10500 | 8 | 1312.5 | | | | |
| 13 | | | | | | | | |
| 14 | Total | 11310 | 9 | | | | | |
| 15 | | | | | | | | |

Figure:11 Result of ANOVA : single factor for PPBS GROUP 2.

6. ANOVA test result for Group 3 PPBS p-value =0.546. ANOVA test to be considered variation between the group should be $p<0.01$ but here higher value states that Single factor ANOVA was very insignificant.

| | A | B | C | D | E | F | G | H |
|---|---|---|---|---|---|---|---|---|
| 1 | Anova: Single Factor | | | | | | | |
| 2 | | | | | | | | |
| 3 | SUMMARY | | | | | | | |
| 4 | *Groups* | *Count* | *Sum* | *Average* | *Variance* | | | |
| 5 | Column 1 | 5 | 1210 | 242 | 2932.5 | | | |
| 6 | Column 2 | 5 | 1113 | 222.6 | 1806.3 | | | |
| 7 | | | | | | | | |
| 8 | | | | | | | | |
| 9 | ANOVA | | | | | | | |
| 10 | *Source of Variation* | *SS* | *df* | *MS* | *F* | *P-value* | *F crit* | |
| 11 | Between Groups | 940.9 | 1 | 940.9 | 0.397105 | 0.546 | 5.317655 | |
| 12 | Within Groups | 18955.2 | 8 | 2369.4 | | | | |
| 13 | | | | | | | | |
| 14 | Total | 19896.1 | 9 | | | | | |
| 15 | | | | | | | | |

Figure:12 Result of ANOVA : single factor for PPBS GROUP 3.

7. ANOVA test result for Group 1 HbA1c p-value =0.681. ANOVA test to be considered variation between the group should be $p<0.01$ but here higher value states that Single factor ANOVA was very insignificant.

| | A | B | C | D | E | F | G | H |
|---|---|---|---|---|---|---|---|---|
| 1 | Anova: Single Factor | | | | | | | |
| 2 | | | | | | | | |
| 3 | SUMMARY | | | | | | | |
| 4 | *Groups* | *Count* | *Sum* | *Average* | *Variance* | | | |
| 5 | Column 1 | 5 | 43 | 8.6 | 0.8 | | | |
| 6 | Column 2 | 5 | 42 | 8.4 | 0.3 | | | |
| 7 | | | | | | | | |
| 8 | | | | | | | | |
| 9 | ANOVA | | | | | | | |
| 10 | *Source of Variation* | *SS* | *df* | *MS* | *F* | *P-value* | *F crit* | |
| 11 | Between Groups | 0.1 | 1 | 0.1 | 0.181818 | 0.681 | 5.317655 | |
| 12 | Within Groups | 4.4 | 8 | 0.55 | | | | |
| 13 | | | | | | | | |
| 14 | Total | 4.5 | 9 | | | | | |
| 15 | | | | | | | | |

Figure:13 Result of ANOVA : single factor for HbA1C GROUP 1.

8. ANOVA test result for Group 2 HbA1c p-value =0.601. ANOVA test to be considered variation between the group should be p<0.01 but here higher value states that Single factor ANOVA was very insignificant.

| | A | B | C | D | E | F | G | H |
|---|---|---|---|---|---|---|---|---|
| 1 | Anova: Single Factor | | | | | | | |
| 2 | | | | | | | | |
| 3 | SUMMARY | | | | | | | |
| 4 | *Groups* | *Count* | *Sum* | *Average* | *Variance* | | | |
| 5 | Column 1 | 5 | 42.6 | 8.52 | 1.312 | | | |
| 6 | Column 2 | 5 | 40.6 | 8.12 | 1.392 | | | |
| 7 | | | | | | | | |
| 8 | | | | | | | | |
| 9 | ANOVA | | | | | | | |
| 10 | *Source of Variation* | *SS* | *df* | *MS* | *F* | *P-value* | *F crit* | |
| 11 | Between Groups | 0.4 | 1 | 0.4 | 0.295858 | 0.601 | 5.317655 | |
| 12 | Within Groups | 10.816 | 8 | 1.352 | | | | |
| 13 | | | | | | | | |
| 14 | Total | 11.216 | 9 | | | | | |
| 15 | | | | | | | | |

Figure:14 Result of ANOVA : single factor for HbA1C GROUP 2.

9. ANOVA test result for Group 3 HbA1c p-value =0.570. ANOVA test to be considered variation between the group should be p<0.01 but here higher value states that Single factor ANOVA was very insignificant.

| | A | B | C | D | E | F | G | H |
|---|---|---|---|---|---|---|---|---|
| 1 | Anova: Single Factor | | | | | | | |
| 2 | | | | | | | | |
| 3 | SUMMARY | | | | | | | |
| 4 | *Groups* | *Count* | *Sum* | *Average* | *Variance* | | | |
| 5 | Column 1 | 5 | 48.7 | 9.74 | 11.993 | | | |
| 6 | Column 2 | 5 | 43.6 | 8.72 | 2.827 | | | |
| 7 | | | | | | | | |
| 8 | | | | | | | | |
| 9 | ANOVA | | | | | | | |
| 10 | *Source of Variation* | *SS* | *df* | *MS* | *F* | *P-value* | *F crit* | |
| 11 | Between Groups | 2.601 | 1 | 2.601 | 0.351012 | 0.570 | 5.317655 | |
| 12 | Within Groups | 59.28 | 8 | 7.41 | | | | |
| 13 | | | | | | | | |
| 14 | Total | 61.881 | 9 | | | | | |
| 15 | | | | | | | | |

Figure:15 Result of ANOVA : single factor for HbA1C GROUP 3.

From the above calculation it was interpreted that p value in all the case were >0.01 so Subject variation is insignificant.

## 6.2 Paired –t- test result

- To ensure the result to be accurate p value <0.01.
- High p value signifies the acceptance of hypothesis that was taken.
- If the P value is large, the data do not give you any reason to conclude that the overall means differ. Even if the true means were equal.it don't have convincing evidence that they differ**.**

1. GROUP 1 PAIRED –t- TEST.

| t-Test: Paired Two Sample for Means | | |
|---|---|---|
| | *Variable 1* | *Variable 2* |
| Mean | 162.6 | 156 |
| Variance | 481.3 | 30 |
| Observations | 5 | 5 |
| Pearson Correlation | 0.836368184 | |
| Hypothesized Mean Differe | 36.6 | |
| df | 4 | |
| t Stat | -3.808161597 | |
| P(T<=t) one-tail | 0.009 | |
| t Critical one-tail | 2.131846786 | |
| P(T<=t) two-tail | 0.018970077 | |
| t Critical two-tail | 2.776445105 | |

Figure: 16 Result of Paired t test for FBS.

| t-Test: Paired Two Sample for Means | | |
|---|---|---|
| | *Variable 1* | *Variable 2* |
| Mean | 218 | 208.4 |
| Variance | 2470 | 430.3 |
| Observations | 5 | 5 |
| Pearson Correlation | 0.900632798 | |
| Hypothesized Mean Difference | 18 | |
| df | 4 | |
| t Stat | -0.581513343 | |
| P(T<=t) one-tail | 0.296 | |
| t Critical one-tail | 2.131846786 | |
| P(T<=t) two-tail | 0.592089658 | |
| t Critical two-tail | 2.776445105 | |

Figure: 17 Result of Paired t test for PPBS.

| | A | B | C | D |
|---|---|---|---|---|
| 1 | t-Test: Paired Two Sample for Means | | | |
| 2 | | | | |
| 3 | | *Variable 1* | *Variable 2* | |
| 4 | Mean | 8.6 | 8.4 | |
| 5 | Variance | 0.8 | 0.3 | |
| 6 | Observations | 5 | 5 | |
| 7 | Pearson Correlation | 0.40824829 | | |
| 8 | Hypothesized Mean Difference | 1.6 | | |
| 9 | df | 4 | | |
| 10 | t Stat | -3.74165739 | | |
| 11 | P(T<=t) one-tail | 0.01 | | |
| 12 | t Critical one-tail | 2.131846786 | | |
| 13 | P(T<=t) two-tail | 0.020092107 | | |
| 14 | t Critical two-tail | 2.776445105 | | |
| 15 | | | | |

Figure: 18 Result of Paired t test for HbA1c.

- From Group 1 paired –t- test its been noticed that for FBS and HbA1c value of P(T<=t) was very significant. And for PPBS P value came to be very high so it's not significant.

2. GROUP 2 PAIRED –t- TEST.

| | A | B | C |
|---|---|---|---|
| 1 | t-Test: Paired Two Sample for Means | | |
| 2 | | | |
| 3 | | *Variable 1* | *Variable 2* |
| 4 | Mean | 155.6 | 141.4 |
| 5 | Variance | 839.3 | 197.3 |
| 6 | Observations | 5 | 5 |
| 7 | Pearson Correlation | 0.547879843 | |
| 8 | Hypothesized Mean Differenc | 29.6 | |
| 9 | df | 4 | |
| 10 | t Stat | -1.41684466 | |
| 11 | P(T<=t) one-tail | 0.115 | |
| 12 | t Critical one-tail | 2.131846786 | |
| 13 | P(T<=t) two-tail | 0.229484656 | |
| 14 | t Critical two-tail | 2.776445105 | |

Figure: 19 Result of Paired t test for FBS.

B2

| | A | B | C |
|---|---|---|---|
| 1 | t-Test: Paired Two Sample for Means | | |
| 2 | | | |
| 3 | | *Variable 1* | *Variable 2* |
| 4 | Mean | 212 | 194 |
| 5 | Variance | 1382.5 | 1242.5 |
| 6 | Observations | 5 | 5 |
| 7 | Pearson Correlation | 0.693367778 | |
| 8 | Hypothesized Mean Difference | 12 | |
| 9 | df | 4 | |
| 10 | t Stat | 0.472133685 | |
| 11 | P(T<=t) one-tail | 0.331 | |
| 12 | t Critical one-tail | 2.131846786 | |
| 13 | P(T<=t) two-tail | 0.661436021 | |
| 14 | t Critical two-tail | 2.776445105 | |
| 15 | | | |

Figure: 20 Result of Paired t test for PPBS.

B11 0.00634786324777201

| | A | B | C | D |
|---|---|---|---|---|
| 1 | t-Test: Paired Two Sample for Means | | | |
| 2 | | | | |
| 3 | | *Variable 1* | *Variable 2* | |
| 4 | Mean | 8.52 | 8.12 | |
| 5 | Variance | 1.312 | 1.392 | |
| 6 | Observations | 5 | 5 | |
| 7 | Pearson Correlation | 0.874643235 | | |
| 8 | Hypothesized Mean Difference | 1.52 | | |
| 9 | df | 4 | | |
| 10 | t Stat | -4.295003938 | | |
| 11 | P(T<=t) one-tail | 0.006 | | |
| 12 | t Critical one-tail | 2.131846786 | | |
| 13 | P(T<=t) two-tail | 0.012695726 | | |
| 14 | t Critical two-tail | 2.776445105 | | |
| 15 | | | | |

Figure: 21 Result of Paired t test for HbA1c.

- From Group 2 paired –t- test its been noticed that for FBS ,PPBS, HbA1c value of P(T<=t) was very in significant.

3. GROUP 3 PAIRED –t- TEST

B11 $f_x$ 0.219919112015313

| | A | B | C | D |
|---|---|---|---|---|
| 1 | t-Test: Paired Two Sample for Means | | | |
| 2 | | | | |
| 3 | | *Variable 1* | *Variable 2* | |
| 4 | Mean | 170.8 | 149.6 | |
| 5 | Variance | 3760.7 | 953.3 | |
| 6 | Observations | 5 | 5 | |
| 7 | Pearson Correlation | 0.243156662 | | |
| 8 | Hypothesized Mean Differe | 44.8 | | |
| 9 | df | 4 | | |
| 10 | t Stat | -0.856828955 | | |
| 11 | P(T<=t) one-tail | 0.220 | | |
| 12 | t Critical one-tail | 2.131846786 | | |
| 13 | P(T<=t) two-tail | 0.439838224 | | |
| 14 | t Critical two-tail | 2.776445105 | | |
| 15 | | | | |

Figure: 22 Result of Paired t test for FBS.

B2 $f_x$

| | A | B | C |
|---|---|---|---|
| 1 | t-Test: Paired Two Sample for Means | | |
| 2 | | | |
| 3 | | *Variable 1* | *Variable 2* |
| 4 | Mean | 242 | 222.6 |
| 5 | Variance | 2932.5 | 1806.3 |
| 6 | Observations | 5 | 5 |
| 7 | Pearson Correlation | 0.608729269 | |
| 8 | Hypothesized Mean D | 42 | |
| 9 | df | 4 | |
| 10 | t Stat | -1.1482886 | |
| 11 | P(T<=t) one-tail | 0.157 | |
| 12 | t Critical one-tail | 2.131846786 | |
| 13 | P(T<=t) two-tail | 0.314850772 | |
| 14 | t Critical two-tail | 2.776445105 | |
| 15 | | | |

Figure: 23 Result of Paired t test for PPBS..

A2

| | A | B | C | D |
|---|---|---|---|---|
| 1 | t-Test: Paired Two Sample for Means | | | |
| 2 | | | | |
| 3 | | *Variable 1* | *Variable 2* | |
| 4 | Mean | 9.74 | 8.72 | |
| 5 | Variance | 11.993 | 2.827 | |
| 6 | Observations | 5 | 5 | |
| 7 | Pearson Correlation | 0.2883526 | | |
| 8 | Hypothesized Mean Difference | 2.74 | | |
| 9 | df | 4 | | |
| 10 | t Stat | -1.13601286 | | |
| 11 | P(T<=t) one-tail | 0.160 | | |
| 12 | t Critical one-tail | 2.13184679 | | |
| 13 | P(T<=t) two-tail | 0.31939697 | | |
| 14 | t Critical two-tail | 2.77644511 | | |
| 15 | | | | |

Figure: 24 Result of Paired t test for HbA1c.

- From Group 3 paired –t- test its been noticed that for FBS ,PPBS, HbA1c value of P(T<=t) was very in significant.

# 7. Conclusion

HbA1c indicates intrinsic control that mean how glycated hemoglobin disappears ; which was found be significant in Group 1> Group 2 > Group 3.

However FBS was not significant in Group 2 and Group 3 but found to be in Group 1. Biguanide(Metformin) is usually the 1st line of drug in all the group it's been there since it was prescribed for long. Other groups were added subsequently. Since the time gap is 6 months. We may get the significant difference in Group 2 and Group 3, if prolonged longitudinal study is conducted.

Before 6 months at the point of 1st test call all the patients were getting Biguanide ,from that point the Group 1 were not taken any additional medication. Group2 was added with Thiazolidinedion and Group 3 was added with Sulfonylurea and DPP-4.

# 8. Reference


1. Nichols GA, Alexander CM, Girman CJ, Kamal-Bahl SJ, Brown JB. Treatment escalation and rise in $HbA_{1c}$following successful initial metformin therapy. *Diabetes Care* 29(3), 504–509 (2006).

2. Rodbard HW, Jellinger PS, Davidson JA *et al.* Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on Type 2 diabetes mellitus: an algorithm for glycemic control. *Endocr. Pract.* 15(6), 540–559 (2009).

3. Hundal RS, Krssak M, Dufour S *et al.* Mechanism by which metformin reduces glucose production in

4. Rao AD, Kuhadiya N, Reynolds K, Fonseca VA. Is the combination of sulfonylureas and metformin associated with an increased risk of cardiovascular disease or all-cause mortality?: a meta-analysis of observational studies.*Diabetes Care* 31(8), 1672–1678 (2008).

5. 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). *JAMA* 281(21), 2005–2012 (1999).

6. Del PS, Bianchi C, Marchetti P. β-cell function and anti-diabetic pharmacotherapy. *Diabetes Metab. Res. Rev.*23(7), 518–527 (2007).

7. Raskin P. Oral combination therapy: repaglinide plus metformin for treatment of Type 2 diabetes. *Diabetes Obes. Metab.* 10(12), 1167–1177 (2008).

8. Johansen OE, Birkeland KI. Defining the role of repaglinide in the management of Type 2 diabetes mellitus: a review. *Am. J. Cardiovasc. Drugs* 7(5), 319–335 (2007).

9. Krentz AJ, Bailey CJ. Oral antidiabetic agents: current role in Type 2 diabetes mellitus. *Drugs* 65(3), 385–411 (2005).

10. 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). *JAMA* 281(21), 2005–2012 (1999).

11. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with Type 2 diabetes (UKPDS 34). *Lancet* 352(9131), 854–865 (1998).

12. Raskin P. Oral combination therapy: repaglinide plus metformin for treatment of Type 2 diabetes. *Diabetes Obes. Metab.* 10(12), 1167–1177 (2008).

13. Del PS, Bianchi C, Marchetti P. β-cell function and anti-diabetic pharmacotherapy. *Diabetes Metab. Res. Rev.*23(7), 518–527 (2007).

14. Bailey CJ, Day C. Antidiabetic drugs. *Br. J. Cardiol.* 10, 128–136 (2003).

15. van de Laar FA. α-glucosidase inhibitors in the early treatment of Type 2 diabetes. *Vasc. Health Risk Manag.* 4(6), 1189–1195 (2008).

16. Krentz AJ, Bailey CJ. Oral antidiabetic agents: current role in Type 2 diabetes mellitus. *Drugs* 65(3), 385–411 (2005).

17. Derosa G, Salvadeo SA, D'Angelo A *et al.* Metabolic effect of repaglinide or acarbose when added to a double oral antidiabetic treatment with sulphonylureas and metformin: a double-blind, cross-over, clinical trial. *Curr. Med. Res. Opin.* 25(3), 607–615 (2009).

***Websites***

18. http://packageinserts.bms.com/pi/pi_glucophage.pdfhttp://www.medicalnewstoday.com/info/diabetes/

19. http://www.evalued.bcu.ac.uk/tutorial/4d.htm

20. http://www.medscape.com/viewarticle/745225_4

21. http://www.sciencedirect.com/science/article/pii/S0149291800800788

22. http://www.nejm.org/doi/full/10.1056/nejm199803263381303#t=articleDiscussion

23. http://europepmc.org/abstract/med/10926309

24. http://www.ncbi.nlm.nih.gov/pubmed/25652751

25. http://www.ncbi.nlm.nih.gov/pubmed/25644093

26. http://www.ncbi.nlm.nih.gov/pubmed/25597711

# 9. Appendix-I

**Paper Survey Consent Paragraph**

You are being invited to participate in a research study titled **"Comparison and Evaluation of Oral Hypoglycemic Drugs Combination Therapy for Control of T2DM"**. This study is being done by **Mr. Ranjan Kumar Prajapati under supervision of Dr. Bibhukalyan Prasad Nayak** from the National Institute of Technology, Rourkela. You were selected to participate in this study because the study needs the participation of volunteers suffering from Type-2 DM (T2DM). During the course of this questionnaire based survey, the participants need to give information about **FBS (Fasting blood sugar), PPBS(Post Prandial blood sugar), HbA1c(Hemoglobin A1c ) level along with Diabetic medication would be taken for research purpose**. The purpose of this research study is to validate and compare the effect of hypoglycemic drugs alone or in combination in controlling T2DM. The participants would be grouped based on drug/drugs combination. The prognosis of therapy would be obtained from FBS, PPBS and/or HbA1 concentration. The participant has to give information on these blood parameters measured recently. The outcome will be measured by statistical analysis. If you agree to take part in this study, you will be asked to complete the survey/questionnaire on the next page. This survey/questionnaire will ask about **medication, dosage, FBS, PPBS, HbA1c and medical complication history (no sensitive issues will be asked i.e. – alcohol/drug use, suicide, child abuse, etc.**. It will take you approximately **5 minutes** to complete. You may not directly benefit from this research; however, we hope that your participation in the study may help the physicians to understand the best combination therapy for T2DM that can give better and durable control of T2DM without frequent change of drugs/dosage due to drug resistance. To the best of our ability your answers in this study will remain confidential. We will minimize any risks to breach of confidentiality by confining the data in **an EXCEL sheet, no information would be taken into consideration about participant's personal data.** The filled questionnaire forms would be retained to the researchers only.

**Your participation in this study is completely voluntary and you can withdraw at any time. You are free to skip any question you choose.**

If you have questions about this project or if you have a research-related problem, you may contact the researcher(s) i.e. **Dr. Bibhukalyan Prasad Nayak (9438284064) and Ranjan Kumar Prajapati (8763721758)**. If you have any questions concerning your rights as a research subject, you may contact the National Institute of Technology, Rourkela Department of Biotechnology and Medical engineering, at (0661)-2462287 or bibhukalyan@nitrkl.ac.in.

By proceeding to the survey/questionnaire on the next page you are indicating that you are at least 18 years old, have read and understood this consent form and agree to participate in this research study. Please keep this page for your records and return the survey/questionnaire to the researchers.

# Diabetes Questionnaire

Date

| | | | | |
|---|---|---|---|---|
| **Name** | | | | |
| **Age** | | **Sex** | Male ☐ | Female ☐ |
| **Phone** | | | | |

## Diabetes History

| | | | | |
|---|---|---|---|---|
| **Year/Age of Diabetes Diagnosis:** | | | | |
| **What type of diabetes you have:** | type 1 ☐ | type 2 ☐ | Pre-diabetes ☐ | gestational ☐ |
| **Relatives with diabetes:** | | | | |
| **Any weight changes (up or down)?** | Yes ☐ | | No ☐ | |

## Blood Glucose Report

| | | | |
|---|---|---|---|
| **Do you check your blood sugars:** | Yes ☐ | No ☐ | Blood sugar range: _____ to_____ |
| **What was your last hemoglobin A1c?** | | | Don't know ☐ |
| **Do you exercise regularly?** | Yes ☐ | | No ☐ |

## Medications

| | | | |
|---|---|---|---|
| **Do you take diabetes medications:** | Yes (check all that apply below) ☐ | | No ☐ |
| **Diabetes Pills** | Insulin injections ☐ | Only Pills ☐ | Combination of pills and injections ☐ |
| **Dosage** | **Trade name** | | |
| **Do you take any over the counter medications, vitamins, or supplements?** | Yes ☐ | No ☐ | |

## Medical Concerns

| | | | |
|---|---|---|---|
| Heart ☐ | Kidney ☐ | Eye ☐ | Foot ☐ |
| Remark | | | |

**Dr.Bibhukalyan Prasad Nayak** .....

**(Project Guide).** (Signature)

Ranjan Kumar Prajapati

(Student 4th year) B.Tech, Biotechnology.