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RESEARCH ARTICLE
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THE THERAPEUTIC DOSE OF ANTI-DIABETIC DRUG TOLBUTAMIDE IN HUMAN AND RENAL HISTOKINETIC STUDY IN MICE.

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ABSTRACT

This study was conducted to explore the influence of Tolbutamide on blood glucose levels in human *(Homo sapiens)* diabetes mellitus patients type 2 (NIDDM) and in mice to evaluate the effects of tolbutamide on kidney tissue. Tolbutamide is an exceptionally applied orally in human and in mice. One hundred diabetes patients type 2 (NIDDM) doctors prescribed used to tolbutamide, data was taken from the DHQ Hospital Dera Ghazi khan and 5 mice was collected from the rice filed. From the diabetes mellitus patient's blood sample was taken two times in a trial before use of tolbutamide and after forty days used of tolbutamide and 2 mice will be slaughters after twenty and 3 after the forty days. Dose of tolbutamide in human patients one tablet 500mg/day before eating of food but in mice 10mg/kg. The entire diabetic patient having elation with range from 42 to 58 years old blood sample was taken first day of trial and after the forty day of trial to examine the blood glucose level. Two mice will be slaughters after the twenty days of trial and three after forty days to remove the kidney from each mouse to examine the effects of tolbutamide on the tissue. Like other data our study indicates that in patients NIDDM tolbutamide lower the blood glucose levels direct by releasing of insulin from the beta cells of pancreatic tissue. Tolbutamide also side effects that we examine on the tissue of mice after the twenty and forty days of trial. After the twenty days use of tolbutamide mild damage the kidney tissue but after the forty days severe effects on the kidney tissue like necrosis, blood clot, hemorrhage and inflammation. Some other physical symptom in diabetic patients has been observe like chills, dizziness, dark urine, diarrhea, vomiting of blood, itching, headache, abdominal pain or stomach, in mice dark urine and diarrhea.

INTRODUCTION

Diabetes is the disease of blood in which glucose level increase the normal level due to lack of insulin secretion from the pancreas. Diabetes is not curable disease but the treatment is used to control the sugar level in blood either not the production of insulin from the insulin. Diabetes is a chronic disease associated with the hyperglycemia with end organ damage, dysfunction, kidney, nerve, heart, blood vessel, and retina and failure organ. In 2011 international diabetes federation estimate an over 366 million people are diabetes and in 2030 surge to 552 million *(Whiting.et al.2011*). In majority cases of diabetes mellitus are divided into two broad etiopathogenic categories of type1 and type2 but in some individual this categories are not applicable. This application is applicable only some clinical practice are based on the given variables such as age, the hyperglycemia, presentation of ketosis,

degree of obesity and need of insulin production. The landmark studying type1 diabetes (DCCT) and landmark studying type2 diabetes (Doct, 1995, Ukpds, 1995) Assess the importance of glycemic control in lowering diabetes microvascular and other consequences.(American Diabetes Association, 2010b).
Anti-diabetic drugs are used to treats the polygenic disorder of diabetes mellitus to reduce the aldohexose levels in blood. All area unit administered orally, exenatid, and pramlintid with the exception of endocrine, additionally known as oral antihyperglycemic agents or oral hypoglycemic agents (*Janbon M, Chaptal J, Vedel A, Schaap J, 1942*).

TOLBUTAMIDE

Tolbutamide is a white powdery substances or crystalline powder referred to as N-(4-methyl-benzenesulphonyl) it also known as 1-Butyl-3-(*p*-tolysulfonyl) urea and their Chemical Formula is $C_{12}H_{18}N_2O_3S$. Tobutamide has slightly bitter in taste and practically odorless. When tolbutamide is melted and slowly cooled down then unstable crystallizes form which upon reheating slowly undergone solid-solid phase transformation to stable forms, because the absence of the p-amino group which are common to used against the bacterial sulfonamide and tolbutamide cannot be acetylated (Beyer, W. F., & Jensen, E. H. (1974). Tolbutamide exist in to two form on the basis of shape, one is obtained by the addition of hexane or aqueous ammonia precipitation in benzene solution by the acetic acid addition, 2ne form is metastable and obtained by water addition in ethanolic solution (Ibrahim, S. E., & Al-Badr, A. A. (1984).

Tolbutamide binds to receptor SURI and that receptor may be sub potassium-channel, ultimately ends up in s change of the membrane and these ions initiate the merger of vesicle within the membrane, these vesicles site the endocrine waiting to be free from the cells (E Markworth, C Schwanstecher, M Schwanstecher, 2000).

When the patients metabolisms free from the vesicles that ends up in lowered the glucose levels and this management of high glucose levels in the patient's body helps to stop injury of urinary organ, nerve tissue, sexual operate issue, blindness, loss of limb and kidney failure. Correct medication against polygenic disease of diabetes mellitus also reduces the chances of much disease risk like heart attack and stroke (Ashcroft, F M Ashcroft, 1996). Tolbutamide is anti-diabetic drugs that lowered the glucose levels in blood and their chonic effects were investigated in an animal model of diabetes where patients' ECGs showed impaired heart function. The study showed that both treated and untreated patients with diabetes mellitus had higher left ventricular end diastolic pressure than usual without a discernible stroke response.Triglyceride buildup and acid Schiff staining material accumulation were both shown to increase the stiffness of myocardial infarction by chemical analysis using an electron microscope. *(Wu, C. F. (1977).* The buildup of triglycerides and acid Schiff positive glycoprotein in the myocardium's interstitium were linked to impaired left ventricular function in a chronic animal model of diabetes mellitus, although there was no indication of coronary artery disease.

When tolbutamide was given to the livers, the dihydroxyacetone, rate of hepatic glycolysis from fructose, and glycerol were likewise boosted by 40, 250, and 100%, respectively, and reduced by 30% by the endogenous rate of hepatic ketogenesis. The cessation of tolbutamide use from perfusion reversed all of the mediated changes in hepatic metabolism. When tolbutamide is present, the tricarboxylic acid cycle decreases pyruvate and hepatic gluconeogenesis from lactate rather than increasing pyuvate oxidation through triglyceride or pyruvate dehydrogenase complex (Patel, T. B. (1986).

The patients of diabetes mellitus are risk of early decline renal function and kidney function monitoring at least once per year.The pharmacokinetics of anti-diabetic drugs may be altered the glymerular filtration rate (GFR) is less than 60ml/min. Glinide and Sulfonylurea therapies are associated with the risk of hypoglycemia and increased in renal impairment when tolbutamide discontinued once glomerular filtration rate <60ml/min (Zanchi, A., Lehmann, R., & Philippe, J. (2012).

Most inactive compound prior to excretion metabolized rather than being excreted unchanged for such drugs metabolism pathway "rout of elimination" since this biotransformation of the drugs molecules remove from the body by pharmacologic activity. The chemical reaction of the drugs subsequent excretion of inert metabolites is less pharmacologic importance (Reidenberg, M. M. (1974).

Because sulfonylureas impair insulin metabolism or hepatic glucose production, they increase the risk of hypoglycemia consequences and can worsen and prolong liver and kidney disease. The pharmacokinetics of the majority of sulfonylureas have not been thoroughly studied in patients with renal and liver disease. Most sulfonylureas are excreted by the kidneys as metabolites, some of which have pharmacological activity similar to the parent medications, such as tolbutamide, glibenclamide, and chloropamide (Rosenkranz, B. (1996).

The proximal tubule of the kidney was isolated in one of the studies to assess if sulfonylureas medications can prevent hypoxia damage in a whole kidney preparation. .Glibenclamide (10Mmin) and Tolbutamide (200Mμ) were applied to isolated rat kidney damaging gassing from the oxygen to nitrogen for 30. Several drugs that are used against different kind of disease impart the effects on different structure of body organ, cells, tissue and their function **(**Engbersen, R.(2000).

Apart from their glycemic effects, next to nothing is known about the physiological actions of sulfonylurea molecules. In the recent investigation it was found that both tolbutamide and insulin produce compound depress the phosphate excretion from the kidney and also depress the liver function in the dog was also observed in people with cirrhosis and normal diabetes. This study demonstrates that in both normal and diabetic patients, tolbutamide has no effect on peripheral glucose utilization.The utilization of glucose is increased by the insulin levels in peripheral tissue and this was investigating those 13 normal and 6 diabetic patients (Elrick, H., & Purnell, R. (1957).

In diabetic patients tolbutamide receiving 500mg led to increase the concentration of tolbutamide in the blood fall the sugar levels and four senior diabetics were given dicoumarol together with tolbutamide. It takes an average of 4.9 hours for the blood's tolbutamide concentration to build up to 17.5 hours. The rise caused by tolbutamide may be due to dicoumarol's suppression of hepatic metabolism. This buildup may potentially raise the risk of hyperglycemia in diabetic patients receiving tolbutamide after sulfaphenazole is administered. (Kristensen, M., & Hansen, J. M. (1967).

In the experiments Sprague-Dawley to study the models of kidney functions: severe kidney function, moderate kidney function, and normal kidney function in which rat were subjected to surgical procedure in three generation. 42 days after the surgery rats were scarified and hepatic CYP2C and CYP3A expression was determined. In addition to used the tobutamide(CYP2C11), testosterone (CYPA3 and CYP2C) and midazolam to evaluate the enzymatic activity in liver microsomes. Both severe and moderate kidney disease was reduction in CYP2C11 and CYP3A2 expression ($p < 0.05$) (Velenosi, et al (2012).Patients with non-insulin-dependent diabetes mellitus are given sulfonylureas such glibenclamide, chlorpropamide, and tolbutamide to test the effects of the medications by causing insulin to be produced by blocking the ATP-sensitive K+ channel in pancreatic β-cells. (Babenko et al.1998).

In clinical trial sulfaphenazole and many other combine drugs that induce the hypoglycemia side effects when the concentration increases from the normal levels in blood (Hansen and Christensen, 1977). Another organic compound probenecid a potent of organic anion inhibitor is including the drugs. The renal secretion of sulfaphenazole by the organic anion transport system could be reduced by their interaction of combined drugs and probenecid (Petitpierre et al., 1972).

In pancreatic β-cell membrane Sulfonylureas stimulate the insulin secretion in non insulin dependent diabetes mellitus patients by blocking ATP sensitive K^+ channel. This effect is induced due to the binding action of sulfaphenazole receptor of the channel. K_{ATP} channels are present in many tissue and cells but contain different types of sulfaphenazole subunit like SUR2B in smooth muscle, SUR2A in heart and SUR1 in β-cells. K_{ATP} channels sensitivity is different to Sulfonylureas is variable tolbutamide and gliclazid not effects on the cardiac and smooth muscles type and also block the β-cell (Ashcroft et al (2000).

By the sulfaphenazole binding of tolbutamide in blood plasma protein while the binding of tolbutamide caused a similar shift in tissue and plasma protein, which resulted in no change in Kp, the displacement of plasma protein in both blood plasma and tissue, which was bigger than that tissue binding, was the primary cause of the Kp increase (Sugita et al (1984).

The combination of tolbutamide and phenformin medication caused the release of fatty acids and glycerol from the rat epidermal adipose tissue incubated Krebs Ringer phosphate or bicarbonate medium that did not include lipolytic hormone or glucose. The concentration secretion from the rat epidermal adipose tissue fatty acid and glycerol significantly decrease by the action of tolbutamide and phenformin have no significantly decrease the fatty acid and glycerol secretion. This observation indicates that the tolbutamide has direct action on the adipose tissue of rat epidermis to reduce the concentration of fatty acid and glycerol secretion (Stone et al (1966).

We examined the mechanism of benzamido-derivative meglitinide, glibenclamide and sulfonylureas tolbutamide under lying the specificity of the tissue using cardiac (Kir6.2/SUR2A) K (ATP) and cloned beta-cells channel expressed in xenopus oocytes (Gribble et al (1998).

In which one of the study to evaluate that the sulphonylureas may regulate the levels of cyclic AMP in Kidney, lung, heart and brain but not merely in islet cells.The methylxanthines inhibit the activity of cyclic AMP phosphodiester which hydrolyses cyclic AMP into 5-AMP and their effects show the same results by use of sulphonylureas which stimulate the greater effects in the pancreas and elsewhere (Goldfine et al (1971).

Tolbutamide administration lowered the blood glucose levels in diabetic animals and not imparts their effects on the glucose value in diabetic animals. The administration of tolbutamide significantly did not alter of any tissue enzymatic activities measure in mildly, severely or moderately in diabetic animals (MURPHY, E. D., & ANDERSON, J. W. (1974).

In which one of the study tolbutamide in rat heart profused with 5 mM glucose and 5 mM acetate to tolbutamide that chronically utilization of glucose and glycolytic flux. Their effects of tolbutamide can be increase with increase the concentration then utilization of glucose is also increase like concentration of 0.6 mM. The analysis of the tissue to revealed that the higher concentration of tolbutamide also enhance the glycogenolysis indicating that increase the glycolysis was caused both glucose consumption and glycogen metabolization (Lopez-Quijada, C. (1962). The mechanism of tolbutamide is antilipolytic and able to increase the concentration of cyclic AMP is unknown. When

the concentration of cyclic AMP increase the tolbutamide inhibits lipolysis and activated the enzyme that involve in the formation of cyclic AMP (BROWN et al (1972).

Since the fat cells from animals given tolbutamide convert substantially more glucose to lipid when insulin is present than those from the control group, the insulin improves the responsiveness of adipose tissue. Large doses of tolbutamide were found to argue for the insulin binding site by lowering serum insulin levels, isolated pancreatic secretory response, and pancreatic output (Joost et al (1982).

Through an unidentified mechanism involving a beta cell's sulfonylurea receptor, sulfonylureas in individuals with non-insulin-dependent diabetes mellitus (NIDDM) lower blood glucose levels by directly boosting the release of insulin from the islet of pancreatic tissue's functional beta cells. By blocking the beta cell membrane's ATP potassium channels and potassium efflux, which causes depolarization, calcium inflow, kinase activation, calcium calmodium, and the exocytosis of insulin-containing granules, the impact is comparable to that of glucose. Tolbutamide is a medication that may have unintended side effects. Even while not all of these adverse effects are possible, if they do, medical help may be necessary. Rare side effects include chills, lightheadedness, dark urine, diarrhea, and blood in the vomit.

Incidence not known
Bleeding gums**,** bloody, black, or tarry stools**,** Agitation**,** back or leg pains**,** chest pain**,** confusion**,** convulsions**,** convulsions**,** depression**,** decreased urine output**,** fatigue**,** cough or hoarsenes and fluid-filled skin blisters.

MATERIAL AND MEHOD

Experimental design

During experimental periods total 100 human (Homo sapiens) that are the patients of diabetes mellitus are type 2 NIDDM and 5 mice. All the patients are normally mature and age range from 42 to 58 years. The total 100 diabetes patients are divided into 10 groups on the base of age because the entire 10 group is different from each other at 2year age. The data of diabetes mellitus patients was obtained from the DHQ Hospital Dera Ghazi khan and mice are collected from the rice field. In this study mice are used to evaluate the effects of tolbutamide on the tissue of kidney and in human to evaluate the glucose levels.

Therapeutic dose

The therapeutics dose of the tolbutamid has only one tablet of 500mg before eating of any food in every morning. The mice dose depend upon the body weight, 10mg/kg tolbutamide are used in mice. The dose should be given the mice tablet put into water to form solution and administered in their mouth with help of syringe.

Clinical and behavioral observation

The clinical symptom such are notice on all the diabetes mellitus type2 such as a chills, dizziness, dark urine, diarrhea, vomiting of blood, itching, headache, Pain in the stomach or abdomen, clay-colored feces, fever, appetite loss, nausea, rash, foul breath, and unusual weakness or exhaustion.

Sample collection and processing

The samples are collect from the human diabetes patients and 5 mice. From the human blood sample are collect to evaluate the blood sugar level and kidney function. After the forty days trial mice are slaughters and collect the kidney sample to analysis the effect of tolbutamide on tissue. 10% formalin was used to preserve the specimens' representative tissues for histological analysis. The tissue was

sliced into sections that were 5–6 µm thick after being preserved and embedded using a standard paraffin procedure. Hematoxylin and eosin staining was then applied to the slides.

Histopathology

Grassing

A spot in the laboratory where the organ is cut into one-centimeter pieces.The reagent is not used clearly in the tissue if the organ fragments are greater than 1 cm. The specimens are one inch in length and one centimeter in width. The advantages of this method include being able to see the tumors, colors, and shapes of the specimens. Following the organ's chopping into tiny pieces, the tissue cassette is placed inside and labeled.

Tissue fixation

Various types of fixatives, such as formaldehyde, picric acid, and ethylene, are employed. Formaldehyde is the most often utilized fixative in this situation. Formaldehyde is inexpensive and widely accessible. Additional advantages include its easy absorption by specimens. In order to create formaldehyde solution, 37% concentrated formaldehyde must be mixed with 63% water to create a diluted solution. Following this, take out 10% use it for fixation after mixing it with 90% water. Soak the tissue in formaldehyde for at least two hours and up to sixteen hours.

Dehydration

Removing excess water from the tissue is the first step in the dehydration process. through a sequence of consistently raising the alcohol levels. The tissue was placed in 30% alcohol for two hours, and then in 70% alcohol for two hours.

•The tissue was exposed to 95% alcohol for one hour.

•The tissue was exposed to 95% alcohol for two hours.

Clearing

In order to employ xylene, which is inexpensive and readily available, excess water and alcohol must be removed. Clove oil is one such chemical that is occasionally utilized.

• For two hours, transfer the tissue in pure xylene.

• For one hour, move the tissue in absolute xylene.

Infiltration

Tissues are submerged in melted paraffin wax during this procedure. Give the tissue several hours to rest. It should be stored in measured paraffin at 60°C for a few days, or at the very least, for a day.

Embedding

Melting wax is poured over the tissue and allowed to cool to 45°C. Paraffin is inexpensive and widely accessible. Blocks made of paraffin are softer and easier to carve.

Cutting Microtome

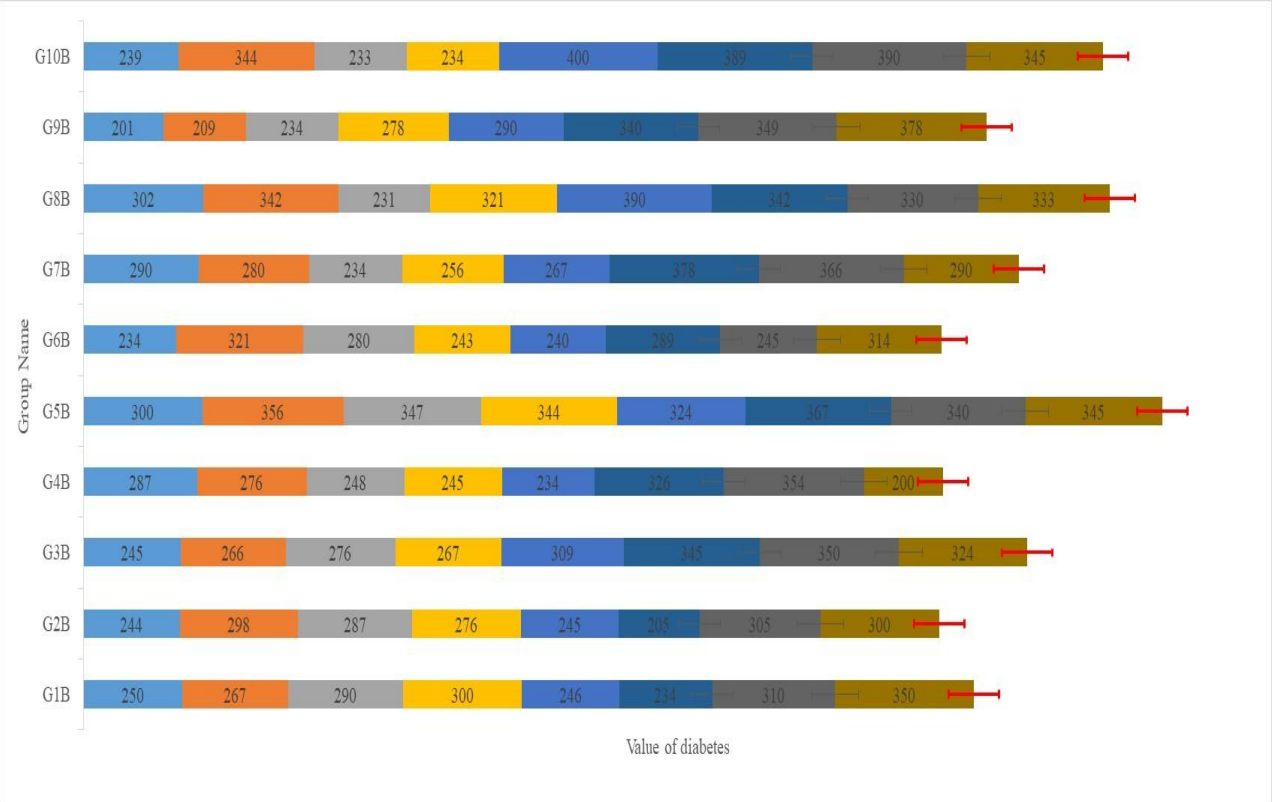
To cut tissue, a device known as a microtome is used. There are several varieties of microtome, but the one used here is a rotary microtome, which is heavy and fixed in place by its weight. It has three parts: a holder for the tissue, a cutter that uses knives, and a wheel for assistance. After the tissue is cut, the section is placed in hot water that is between 50° and 60°C.

Staining

After extracting the paraffin wax from the tissues, they are immersed in xylene for three minutes. After that, the tissues are immersed in pure alcohol for three minutes in order to remove the xylene. The tissues are exposed to alcohol at decreasing concentrations—from 95% to 30%—for two minutes.

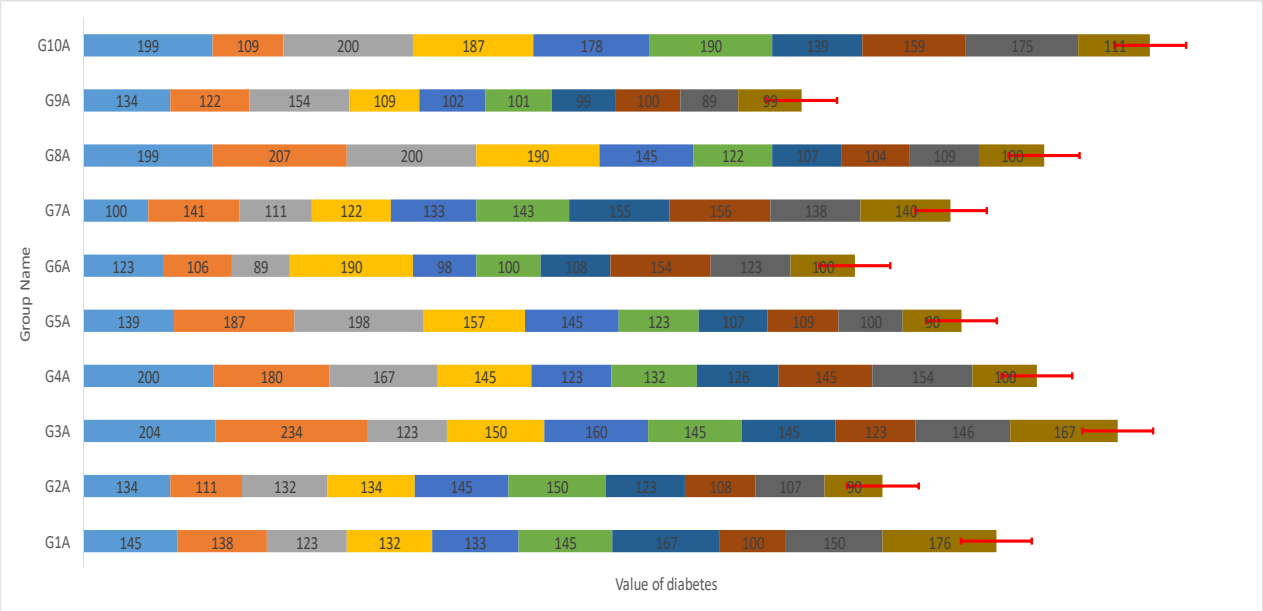
After the alcohol, the tissues are immersed in water for five minutes. For decolorization, escalating alcohol grades are used in 4–10 dips. During the next one and a half to two minutes, eosine is used. After three minutes, the picture was cleaned with xylene after the tissue had been dried to eliminate the alcohol. A dollop of from Canada balsam added to the slide. They fixed the slide permanently by adding a cover slip.

Results



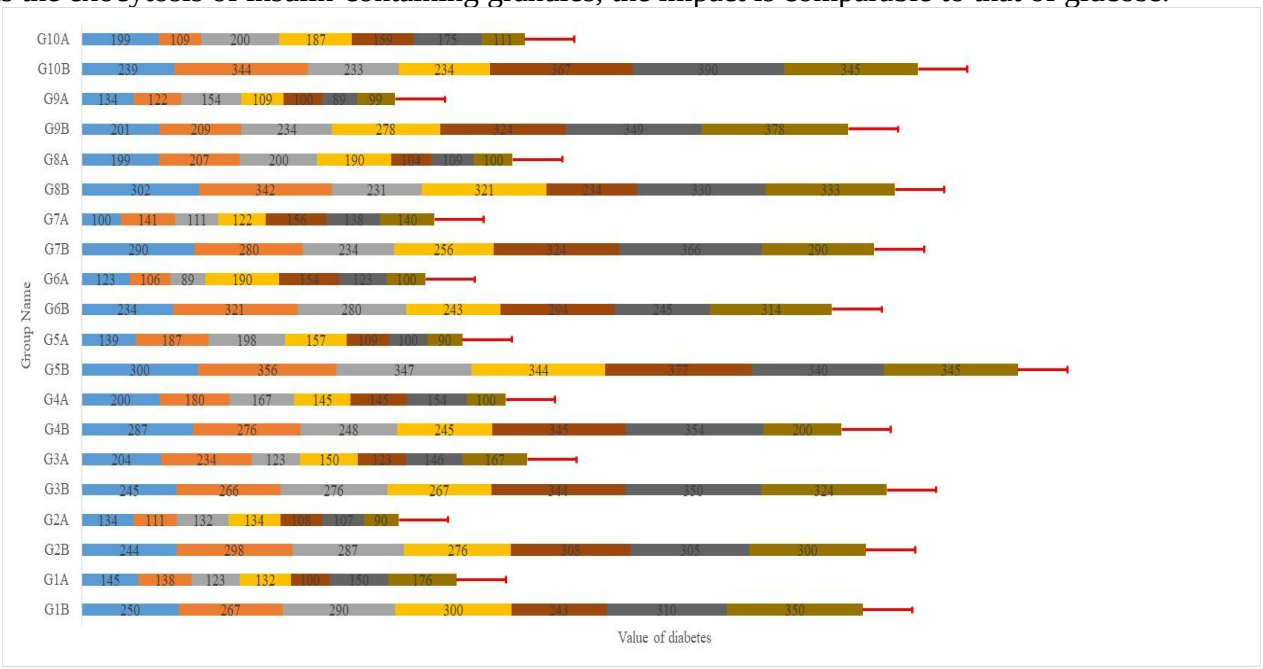
Graph-1: Show the high level of blood glucose concentration in 100 patients of diabetes mellitus type 2 (NIDDM).

In our study to investigate that the tolbutamide controls the blood glucose levels to stimulate the beta cells of pancreas for the production of insulin and also involve stop the glyconeogensis and convert the glucose into glycogen. One hundred diabetic patients' type 2 data were obtained from the Hospital and doctor prescribed the tolbutamide to control the sugar levels. Blood sample collected from each of the patients and evaluate the blood glucose level range of glucose concentration in all patients from 201mg/dl to 367mg/dl (graph-1). Each patient used tolbutamide tablet 500mg each days. The glucose concentration is very high in all patients. All the patients of diabetic are subdivided into ten groups on the base of their age. Many symptoms have been observed in mostly patients like abdominal pain, vomiting, fatigue, dizziness and black urine. With passage of time high blood glucose levels can damage the organ including blood vessel, heart attack, stroke, and problem with kidneys, eyes, gums, feet and nerves. Neutrophils one of the most important members of the innate immune system has be found to defective due to high blood glucose levels. Due to the high glucose levels in blood cause the osteoarthritis is the degenerative disease of bone and cartilage. High levels of glucose can also impair of much protein function and then cause much disease in diabetic patients. Dysfunction of protein like enzyme involve in the metabolism to catalyze many reaction then all the process in cells will be disturbed due the abnormal function of protein, so the need is that to control the glucose concentration in normal range.



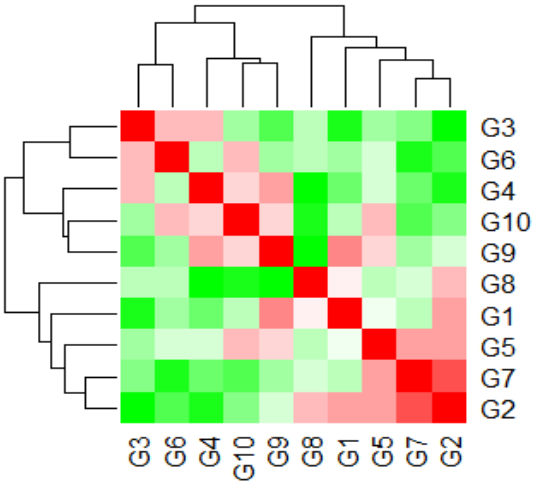
Graph-2: **Show the control blood glucose concentration in 100 patients of diabetes mellitus type 2 (NIDDM).**

After the forty days used of tolbutamide blood samples of all patients taken and examine the glucose concentration. Significantly decrease the glucose the concentration in most of the patients (Graph-2) from 150mgldl to 200mg/dl. Tolbutamide is a powerful drug for the reduction of glucose act upon the liver to transform glucose into glycogen, which the muscles and liver can store. Through an unidentified mechanism involving a tolbutamide receptor on the beta cell, tolbutamide lowers blood glucose levels directly while promoting the release of insulin from the islet of pancreas tissue's functional beta cells. By blocking the beta cell membrane's ATP potassium channels and potassium efflux, which causes depolarization, calcium inflow, kinas activation, and calcium calmodium, as well as the exocytosis of insulin-containing granules, the impact is comparable to that of glucose.



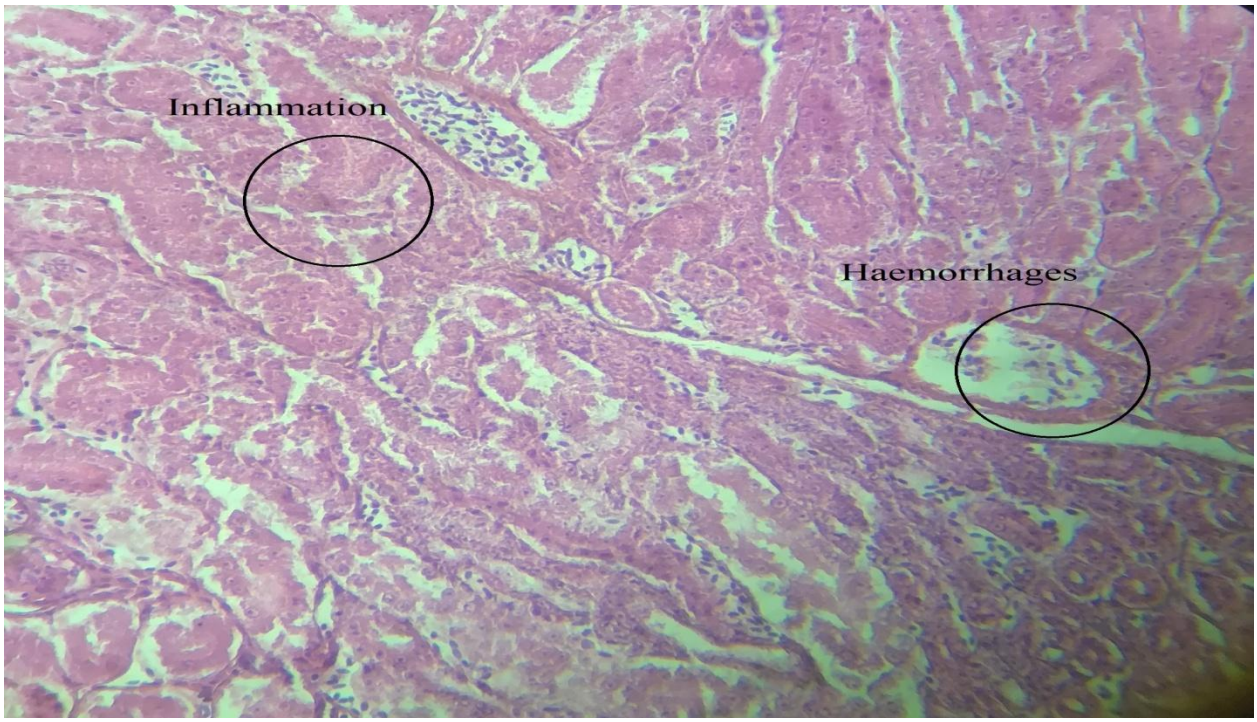
Graph-3: Show the comparison of diabetes mellitus type 2 (NIDDM) before and after use of drug tolbutamide in forty days trial.

Comparison between the glucose concentration before and after use of tolbutamide in diabetic patients show significantly decreases the glucose concentration in blood from 150mg/d to 200mg/dl. This study indicates that the tolbutamide has greatly decreased the glucose concentration.



Graph-3: Show the relation in age of all 100 patients diabetes mellitus type 2 (NIDDM).

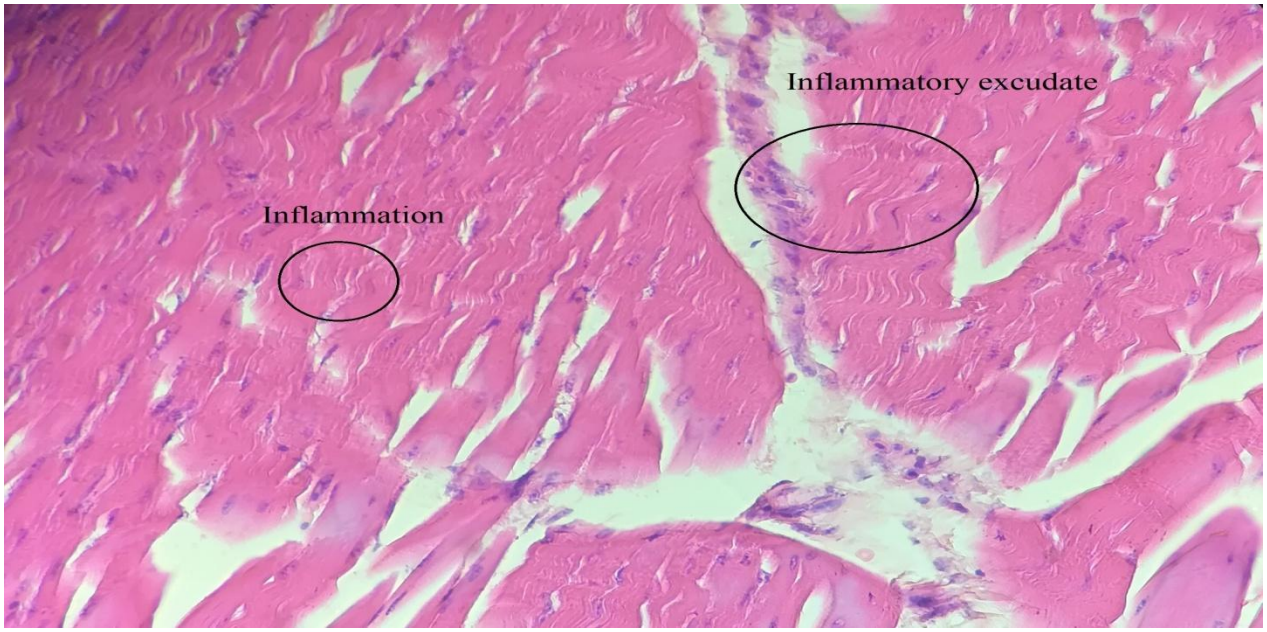
NIDDM occur in age above the forty years and 90% of the people are the patients of this disease.
2 to 5% of this disease occur before forty years age and called maturity onset diabetes of young (MODY). This type of disease occur mutation in enzyme glucokinase that convert glucose into glucose-6-phosphate. The conversion of glucose into glucose-6-phosphate occurs in glycolysis mean breakdown of glucose into pyruvic acid.



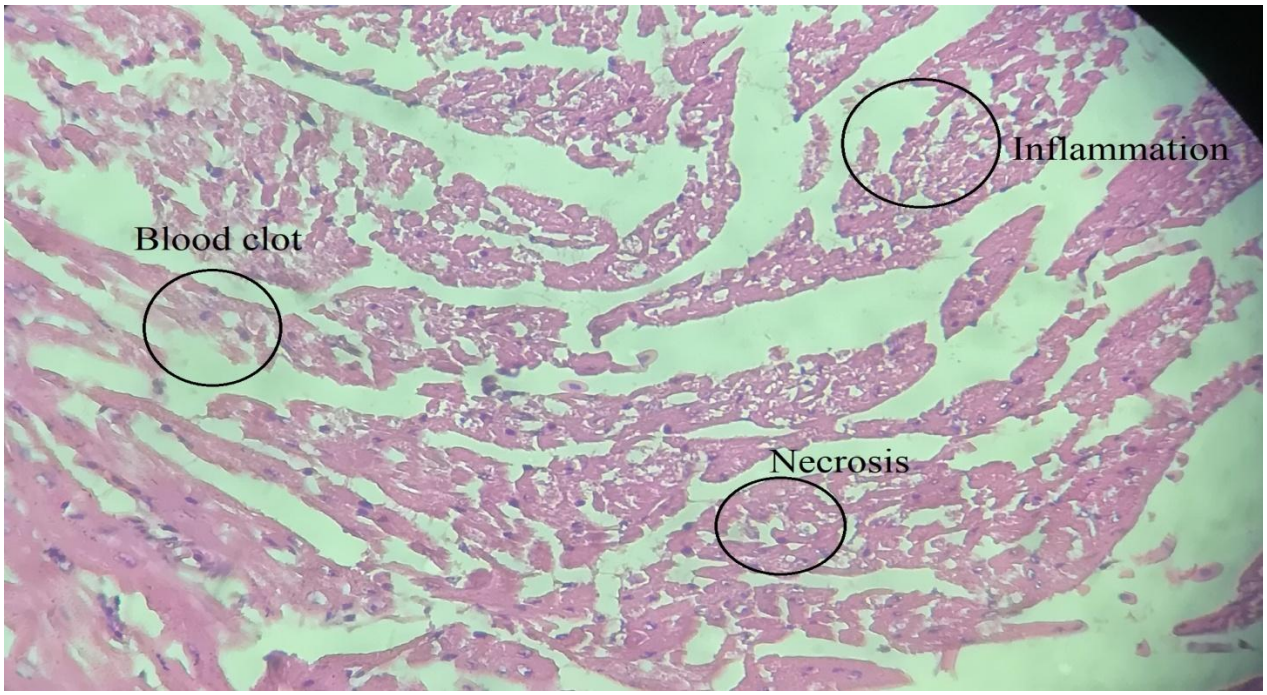
Picture-1 Show the effect of tolbutamide on kidneys tissue of mice after the 20 days trial.

Tolbutamide is anti-diabetic drugs used against the high level of glucose in blood to decrease the glucose concentration to normal. To evaluate the effects of tolbutamide on the body tissue perform

experiment on mice tolbutamide was given by 10mg/kg body weight. After the twenty, dose of tolbutamide given to mice will be slaughtered and kidney sample used for histologic study. Many clinical symptoms are shown on tissue like hemorrhages and inflammation.



Picture-2 Show the effect of tolbutamide on kidneys tissue of mice after the 20 days trial.



Picture-3 Show the effect of tolbutamide on kidneys tissue of mice after the 40 days trial.

Many other clinical symptoms were also observed on the kidneys tissue of the inflammatory excudate, blood clot and necrosis. The use of tolbutamide in whole world to reduce the blood glucose levels also show damaging effects on the different types of tissue.

DISCUSSION

Blood sample collected from each of the patients and evaluate the blood glucose level range of glucose concentration in all patients from 201mg/dl to 367mg/dl (graph-1). Each patient used tolbutamide

tablet 500mg each days. The glucose concentration is very high in all patients. All the patients of diabetic are subdivided into ten groups on the base of their age. Many symptoms have been observed in mostly patients like abdominal pain, vomiting, fatigue, dizziness and black urine. With passage of time high blood glucose levels can damage the organ including blood vessel, heart attack, stroke, and problem with kidneys, eyes, gums, feet and nerves. Neutrophils one of the most important members of the innate immune system has be found to defective due to high blood glucose levels.

Tolbutamide administration lowered the blood glucose levels in diabetic animals and not imparts their effects on the glucose value in diabetic animals. The administration of tolbutamide significantly did not alter of any tissue enzymatic activities measure in mildly, severely or moderately in diabetic animals (MURPHY, E. D., & ANDERSON, J. W. (1974).

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The patients of diabetes mellitus are risk of early decline renal function and kidney function monitoring at least once per year.The pharmacokinetics of anti-diabetic drugs may be altered the glymerular filtration rate (GFR) is less than 60ml/min. Glinide and Sulfonylurea therapies are associated with the risk of hypoglycemia and increased in renal impairment when tolbutamide discontinued once glomerular filtration rate <60ml/min (Zanchi, A., Lehmann, R., & Philippe, J. (2012). Tolbutamide is a powerful drug for the reduction of glucose act upon the liver to convert the glucose into glycogen to store in liver and in muscles. In patients non insulin dependent diabetes mellitus type 2 (NIDDM) tolbutamide lower the blood glucose levels directly stimulating the release of insulin from the functioning beta cells of the islet of pancreas tissue by unknown process that involves a tolbutamide receptor on the beta cell.

Comparison between the glucose concentration before and after use of tolbutamide in diabetic patients show significantly decreases the glucose concentration in blood from 150mg/d to 200mg/dl. This study indicates that the tolbutamide has greatly decreased the glucose concentration.

CONCLUSION

Our study indicate that use of tolbutamide drugs to patients of diabetes to reduces glucose concentration 150mg/dl to 200mg/dl in forty days but also impair the tissue structure of many organ like kidneys. Many clinical signs are observed on the kidney tissue like inflammation, necrosis and blood clot

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