Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/6xkhrd03

CONCERTED AND SYNCHRONIZED EFFORT TO CURE DIABETES

Mayank Arora[1*]

[*]Asst. Professor In Chemistry, Sd (Pg) College, Panipat, Email Address: - auroramayank@gmail.com

***Corresponding Author:** Mayank Arora
*Asst. Professor In Chemistry, SD (PG) College, Panipat, Email Address:- auroramayank@gmail.com

Abstract:
Therapeutic diabetes cannot be achieved while working in a single direction. Moreover, it requires a multifaceted approach involving diet control, use of α glycosidase inhibitors, insulin therapies, use of drugs, and regular exercise. Further, the human insulin gene (INS) is located on chromosome 11p15.5, between the tyrosine hydroxylase and insulin-like growth factor-2 genes. The INS gene contains three exons and two introns, and the final spliced mRNA transcript is 446 bp in length and codes for the preproinsulin peptide. Glucose is considered the most important stimulant of insulin secretion from the β cell, but amino acids such as arginine also play important roles as physiologic stimulators of insulin secretion. An intact concentration of cC AMP is required for normal functioning of the genetic system to synthesize insulin in β cells of Langerhans.

Key Words: -Genetic Disorder, Environmental factors, Linkage Disequilibrium, Histocompatible locus antigens, ϭ cells of islets, Hyperglycemia

INTRODUCTION: There are two types of diabetes, viz., Type 1 and Type 2. Diabetes 1 is also known as insulin dependent diabetes. Broadly speaking, it generally arises as a genetic disorder caused by certain environmental factors like severe viral disease. Some nutritional and chemical agents lead to linkage disequilibrium between human response genes on chromosome 6 w.r.t. histocompatiblelocus antigens. In this type of diabetes, damage takes place both due to cell mediated and humoral anti-immune responses. In Diabetes 2 there is insulin resistance in muscle as well as fat cells. In insulin resistance, it can not move insulin from the blood into characteristic cells, thereby leading to high levels of glucose even after fasting, i.e. hyperglycemia.

First, dietary therapy concerns not only the type of food but also the timing of taking the food. It rationalizes taking food with a lower glycemic index but also uses adopting sipping overgulp in the sense that this edge not only maintains favorable glucose levels in blood, low levels of insulin reduced concentrations of gastric inhibitory polypeptide but also low concentrations of fatty acids n, LDL Aand uric acid in blood. So the first direction towards control of diabetes is to study various nutrients wrt glycemic index but also find the timing of taking the food. Further diabetes 2 is related to excessive weight loss, disturbed serum lipid profiles, and an increased risk of coronary heart disease. All these risks can be avoided by simple management of a diet chart wherein slow glucose absorption from the small intestine into blood will prove multiplonged targets from a single shot wherein not only glucose concentration is maintained but also optimal levels of triglycerides, uric acid levels, levels of fibrinogen and plasminogen activators and inhibitors, and optimal levels of plasminogen activators. Metabolic effects of absorption rate were studied by taking the first 100 gms of gulucose in solution form in five minutes and then taking the same amount of gulucose

solution distributed over three hours. Comparisons can be made between gulping vs sipping wrt concentration of glucose in blood, serum free fatty acid concentrations, serum insulin concentration, serum Cpeptide, and plasma gastric inhibitory opolypeptide concentration all over time.

POSSIBLE EFFECTS OF PROLONGING ABSORPTION TIME OF CARBOHYDRATE

1. Flatter post-meal glucose profile
2. Lower mean insulin concentrations wrt time
3. Reduced response to gastric inhibitory polypeptide
4. Low release of urinary Cpeptide
5. Suppression of plasma free fatty acids
6. Reduced urinary catecholamine output
7. Reduced blood LDL levels
8. Lower plasma apolipoprotein B level
9. Increased urinary uric acid secretion

Table 1: GULPING 100 GMS GLUCOSE IN 5 MINUTES BY HUMAN VOLUNTEERS AND ITS EFFECTS

SR/NO	TIME	BLOOD GLU (mmol/ lit)	SERUM FFA µmol/Lit	Serum insulin Pmol/Lit	Serum C peptide Pmol/Lit	Plasma GIP Pmol/LIT
1	0	5	600	25	475	65
2	60	8	200	400	1500	200
3	120	6.3	200	25	600	60
4	180	4	400	25	450	50
5	240	4	750	15	420	60

Table 2 SIPPING 100 GMS OF GLUCOSE OVER A PERIOD OF 3 HOURS

Sr/No	TIME	BLOOD GLUCOSE (mmol/Lit)	SERUM FFA (µmol/Lit)	SERUM PEPTIDE (Pmol/Lit)	SERUM C PEPTIDE (Pmol/Lit)	PLASMA GIP (Pmol/Lit)
1	0	4.3	450	20	400	70
2	60	5	220	40	510	75
3	120	5.1	210	40	520	80
4	180	5	205	45	525	85
5	240	3.9	203	40	490	60

Thus from the comparision of tables it is clear that on sipping glucose levels declined progressively over time. Mean insulin levels and total urinary glucose output were reduced and also with sipping respiratory quotient rose progressively

SECOND MEAL EFFECT:- This effect was observed on human volunteers as effect of one meal on the next.It was found that one carbohydrate load facilitate the disposal of next in the sense that 80 gms glucose tolerance test (GTT) was conducted and it was found that absorption of glucose continues at a high rate over a 3 hours period but hyperglycemia lasts only for 90 minutes period in normal human being as after this 90 minutes period rate of absorption of glucose becomes the same as rate of uptake of it by the tissues. Thus by interference i.e. the glucose rise following second meal while glucose is still being absorbed from the first meal meets less resistance or in other words more tolerance. But simultaneously it was found that the above fact proves true only when first meal has low fat diet or low serum free fatty acid concentration. Furthur it was found that

viscous fibre like guar gum which was used to prolong carbohydrate absorption also demonstrated the second meal glucose tolerance with prolonged suppression of 3 hydroxybutyrate and to flatten post meal hyperglycemia and serum insulin response. These fibers have also been shown to reduce LDL, blood cholesterol and apolipoprotein B levels.

TABL E 3 :VARIATION OF SERUM BLOOD GLUCOSE, SERUM FFA, SERUM INSULIN, SERUM C PEPTIDE AND PLKASMA GIP WITH TIME AFTER TAKING 5 GMS INTRAVENOUS GLUCOSE, POST GLUCOSE BOLUS

Sr/No	TIME (MINUTES)	SERUM GLUCOSE (mmol/Lit)	SERUM FFA (µmol/Lit)	SERUM INSULIN (Pmol/Lit)	SERUM C PEPTIDE (Pmol/Lit)	PLASMA GIP (Pmol/Lit)
1	240	4.2	720	30	220	50
2	250	6.0	740	50	600	50
3	260	5.8	680	55	600	52
4	270	5.8	350	55	580	50

TABLE 4: VARIATION OF SERUM BLOOD GLUCOSE, SERUM FFA, SERUM INSULIN, SERUM C PEPTIDE AND PLKASMA GIP WITH TIME AFTER TAKING 5 GMS INTRAVENOUS GLUCOSE, POST SIPPING

Sr/ No	TIME MINUTES	SERUM GLUCOSE (mmol/Lit	SERUM FFA (µmol/Lit)	SERUM INSULIN (Pmol/Lit)	SERUM C PEPTIDE (Pmol/Lit)	PLASMA GIP (Pmol/Lit)
1	240	4.2	250	30	550	75
2	250	5.8	300	50	725	70
3	260	5.6	300	55	480	70
4	270	5.6	310	55	480	75

SECOND THEREPUTIC MODEL:

Glucose homeostasis is maintained in humans by reciprocal regulation of insulin secretion by β cells and glucagon secretion by α cells of islets of Langerhans. A favorable ATP/ADP ratio is required for the release of insulin from β cells. This favorable ratio sequentially leads to closure of K + ATP channels, thus leading to depolarization of the plasma membrane and thus opening voltage sensitive L type Ca++ ion channels and eventual exocytosis of insulin containing granules. Enzyme glucokinase plays a very important role in maintaining a favorable ATP/ADP ratio in β cells as it is (a) a rate-limiting enzyme for the process of secretion of insulin, i.e., the rate of glucose oxidation depends on the phosphorylation reaction of glucose catalyzed by this enzyme, and now because of the lower affinity for this enzyme for glucose as compared to other hexakinases, it picks up glucose at a much lower rate but does it consistently for a long duration of time and thus maintains optimal concentration of glucose with time. Secondly, it is not inhibited by its end product. This feature allows its continued activity despite a high glucose load.Genetics impairments related to glucokinase activity are related to allosteric inhibition of it by the end product, i.e. glucose 6 phosphate. Thus, a favorable ATP/ADP ratio can not be maintained. It was proposed in any order that somehow the allosteric site of the enzyme gets masked so that the end product can not inhibit the enzyme, and we have a revived system that can meet a heavy glucose load. These masking agents were identified in the form of polar L-selenocysteine (Sec) and l pyrrolysine (Pyl) α amino acids. Diabetic volunteers with impaired glucokionase are fed with Sec and Pyl when we find flattening of blood glucose levels over prolonged periods of time.

VARIATION OF BLOOD GLUCOSE LEVELS WITH TIME AFTER CONSUMMING 20 gms OF IT IN SINGLE BOLUS IN DIABETIC VOLUNTEERS

SUBJECT	30 MINUTES	60 MINUTES	90 MINUTES	120 MINUTES	150 MINUTES	180 MINUTES
DIABETICVOLUNTEERS WITH DOSAGE OF 20 gms GLUCOSE IN SINGLE BOLUS (mgm/100ml)	350	324	316	299	279	260
DIABETIC VOLUNTEERS WITH DOSAGE OF 20 GMS GLUCO PACKED WITH 2 GMS SEC AND PLY AMINO ACIDS (mgm/100ml)	260	235	189	145	136	130

An explanation for the masking effect w.r.t. amino acid diet lies in the fact that the latter contains multiple exposed functional groups that somehow block allosteric sites responsible for end product inhibition, and further, as these amino acids are polar and hence are soluble in the blood. So they can access their target sites easily.

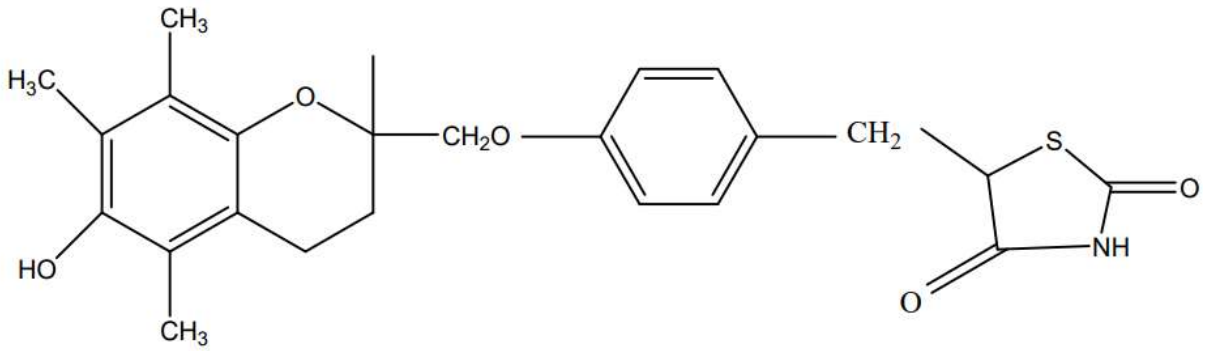
DIABETIC THEREPUTIC MODEL3:-α GLUCOSIDASE INHIBITORS IN THE TREATMENT OF DIABETES

The goal of anti-diabetic therapy is to approximate the blood glucose fluctuations as well as possible while avoiding serious hypoglycemia. Use of sulphonylureas is related to a serious hypoglycemic agent, but is also related to weight gain and hyperinsulinemia. The latter is associated with problems of atherosclerosis in patients with diabetes. The use of metFORMIN is also limited as it is associated with lactic acidosis in patients with impaired renal function and in patients with cardiac disease. So, the urgent need was felt to have a therapeutic agent which can regulate blood glucose levels in the blood without causing serious hypoglycemia and hyperinsulinemia or weight gain, which is related to the use of sulfonylureas insulin therapy. Reduction of postprandial glucose through use of soluble fiber as an alternative has not been widely prevailed as its large amounts are required, its lack of palatability, the unpredictable effects and unpleasant side effects. New alternatives are α glucosidase inhibitors such as acrabose, deoxynojirimycin derivatives such as miglitol, voglibose and emiglitate. Acrabose lowers postprandial glucose and insulin by retarding the digestion of carbohydrates in the small intestine, thereby delaying glucose absorption and flattening blood glucose levels. Starch is digested to oligosaccharides by amylase and further digestion of oligosaccharides takes place in the presence of enzyme α glucosidases such as maltase, isomaltase, and sucrase to carbohydrate monosaccharide, with the major bulk carried by glucose. Acrabose is the first commercially available α glucosidase inhibitor. It is a pseudotetrasaccharide of microbial origin that competitively inhibits both amylase and membrane bound α glucosidase with approximately equal affinity. Ingestion of acrabose with meals causes carbohydrate digestion to be delayed, resulting in a significant decrease in postprandial blood glucose levels. Carbohydrates are not digested in the upper part of the small intestine and reach the ileum as a small bowel, where further digestion and absorption occur. Further, acrabose does not block the sodium dependent glucose transporter nor does it inhibit β glucosidases, so digestion and absorption of lactose take place normally. In the absence of acrobose, there is little α glucosidase activity in the ileum and colon. But with its use, there takes place induction of α glucosidase activity in these regions, leading to delayed digestion and absorption of carbohydrate meal with smoothening of blood glucose and

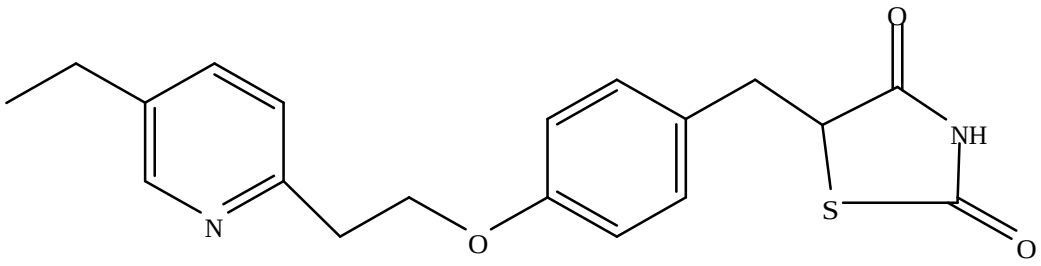
insulin levels. Unlike sulfonylureas and insulin therapy, acrabose does not cause weight gain, an increase in concentration of insulin in the blood. Further, unlike sulfonyl ureas, the use of acrabose is associated with decreased lipogenesis in hepatic and adipose tissue. The effects of acrabose include decrease in glycated hemoglobin, decreased glycated glomerular basement membranes, decreased glycosylation end product formation in connective tissue, prevention of renal hypertrophy, decreased immunoglobulin deposition, decreased glomerular sclerosis, decreased cataract formation, prevention of neuropathy and retinopathy and increased concentrations of GLUT 4 in muscles.

DIABETIC THEREPUTIC MODEL 4:- USE OF THIAZOLIDINEDIONES AS DRUGS TO CONTROL INSULIN RESISTANCE

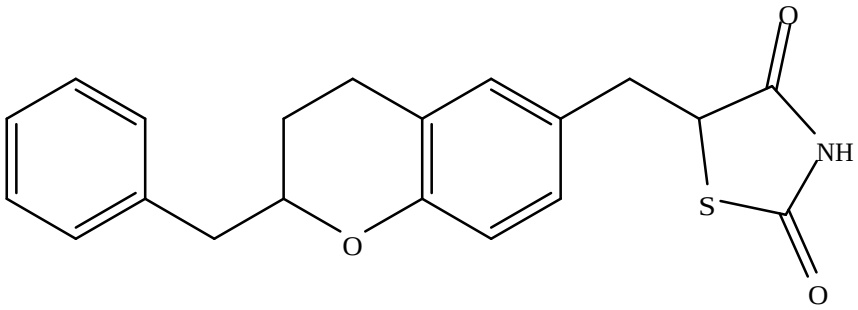
As far as drug therapy is concerned, sulphonylures are associated with hypoglycemia, weight gain and hyperinsulinemia. Further, metFORMIN has a known association with lactic acidosis and its restriction on use for patients with cardiac history. Besides, all these do not directly deal with the pathology of insulin resistance. On the contrary, the thiazolidinediones are a novel drug class that decreases insulin resistance by enhancing insulin action in skeletal muscles, liver, and adipose tissue. They do not stimulate insulin secretion in pancreatic β cells. Rather, they act by lowering insulin resistance and markedly decreasing the concentration of blood glucose, insulin, and triglycerides. These drugs not only act through insulin mediated glucose uptake by tissues but also through glycogen synthesis in the liver and an increased rate of glycolysis in cells. As far as the mechanism of insulin sensitization by these drugs is concerned, it was found that insulin sensitivity induced by these drugs requires several days of treatment, suggesting transcriptional modifications are involved in the actions of these drugs. One of the prominent symptoms associated with insulin resistance is hypertension, which may also be due to sodium retention in the blood.Insulin resistance leads to hypertension through increased glomerular filtration rate, increased renal sodium excretion or through inhibition of renal arterial smooth muscle cells. Thiazolidinediones have profound effects on lowering blood pressure. Thiazolidinediones induced glucose uptake by cells in diabetic patients with insulin resistance is probably accounted for enhanced expression of transporters such as GLUT 1 and GLUT 4. Cellular effects of thiazolidinediones are likely to manifest in earlier transcriptional events in fat cell differentiation that requires a target already present in preadipocytes. This target is identified as a fatty acid activator receptor belonging to the steroid / thyroid hormone super family that interacts with fatty acids to regulate transcription. The drugs classified under Dithizolidinediones are as under



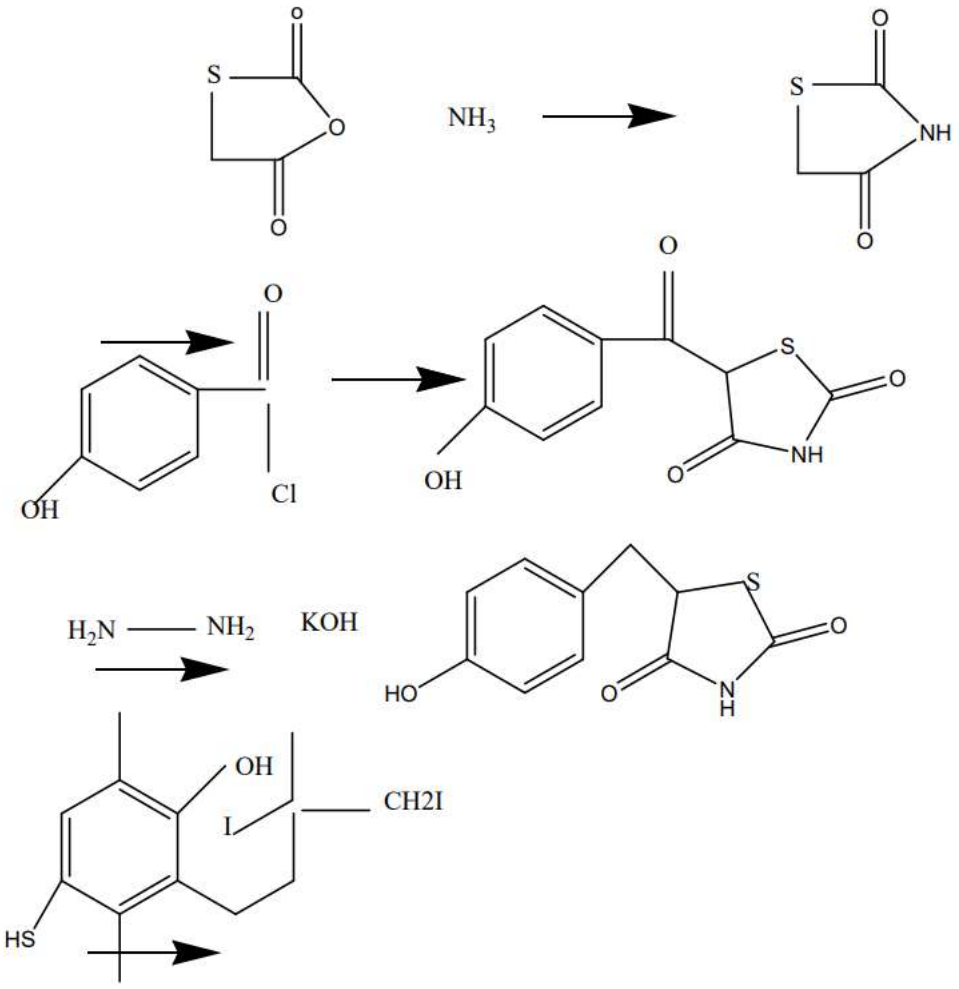
Troglitazone

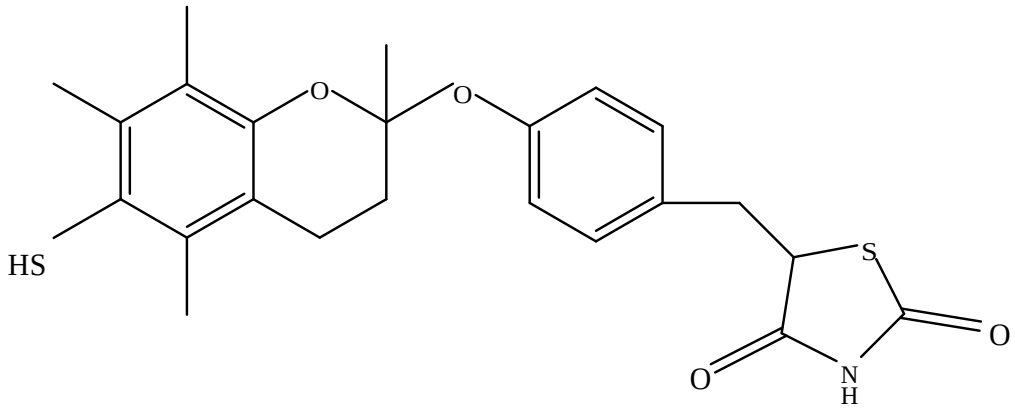


Pioglitazone



Englitazone





Then I prepared thiotroglitazone with tolerance towards insulin resistance many times more, as compared to Troglitazone, as the former hydroxyl group, Troglitazone was replaced by the thiol group. This is so since sulfur is a soft ligand and its high polarizability serves to play far different roles w.r.t. Bonding with metal ions as cofactors for the enzymes. Its diagrammatic synthesis with reagents and mechanism is as shown above.

CONCLUSION: Diabetes is the mother of all diseases as it convolutes into coronary disease, renal malfunction, nephropathy, neuropathy, and retinopathy, and this figure continues to score without any end. So a multifaceted approach involving a balanced diet, adaptation to sipping, taking food with a lower glycemic index, use of nutrient agents with α glucosidase inhibitor properties, and last but not least, proper drug therapy. All these segments are discussed in great detail in this paper.

REFERENCES

1. FUJITA T, Taketomi S, et al. Reduction of insulin resistance in obese diabetic animals by 3-[-4(1methylcyclohexylmethoxy)benzyl]-thiazolidine-2,4 dione
2. Fujiwara T, Yoshioka S, Yoshioka T et al. Characterization of new antidiabetic agent, CS-405 IN Zucker fatty rats
3. Lee MK, Miles PDG, Khoursheed M. et al. Metabolic effects of Triglitazone on fructose induced insulin resistance in the rat Diabetes
4. Oakes ND, Kennedy CJ, Jenkins AB et al. A new antidiabetic agent, BRL, 49653, Reduces lipid availability and improves insulin action and glucoregulation in rat diabetes
5. Castle CK, Colca JR, Melchior GW Lipoprotein profile characterization of KKA mouse before and after treatment with Pioglitazone
6. Klein R, Klein BEK, Mors SE, Epidemiology of proliferative diabetic retinopathy
7. Hanefeld M, Fischer S, Schulze J, et al. Therapeutic potentials of acrabose as first line drug in NIDDM insufficiently treated with diet alone
8. Hollander P Safety profile of acrabose, an α glucosidase inhibitor
9. Golay A, et al. Effect of weight loss on glucose disposal in obese and nonobese diabetic patients
10. Jenkins DJA, et al. Improved glucose tolerance four hours after taking guar with glucose