A RANDOMISED CONTROLLED STUDY OF EFFICACY AND SAFETY OF SAROGLITAZAR IN TYPE 2 DIABETES MELLITUS

THESIS

Submitted to

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, JODHPUR

In partial fulfilment of the requirement for the degree of

DOCTOR OF MEDICINE (MD)

(PHARMACOLOGY)

JULY 2020

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DECLARATION

I hereby declare that the work reported in the thesis entitled **"A RANDOMISED CONTROLLED STUDY OF EFFICACY AND SAFETY OF SAROGLITAZAR IN TYPE 2 DIABETES MELLITUS"** embodies the result of original research work carried out by me in the Department of Pharmacology and Endocrinology, All India Institute of Medical Sciences, Jodhpur.

I further state that no part of the thesis has been submitted either in part or in full for any other degree of All India Institute of Medical Sciences or any other institution/ University.

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CERTIFICATE

This is to certify that the thesis entitled "**A RANDOMISED CONTROLLED STUDY OF EFFICACY AND SAFETY OF SAROGLITAZAR IN TYPE 2 DIABETES MELLITUS**" is an original work of **Dr Sachin J** carried out under our guidance and supervision, at All India Institute of Medical Sciences, Jodhpur.

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ACKNOWLEDGMENT

I would like to take this opportunity to acknowledge each and every one who has helped me in every stage to successfully complete this dissertation project and I assume myself extremely fortunate to work under many honourable scholars. Only because of guidance and assistance, I was able to do this, and I would not miss a chance to thank them all.

I owe deep sense of gratitude and sincere thanks to my guide, my advisor, my mentor **Dr. Surjit Singh**, Additional Professor, Department of Pharmacology, AIIMS, Jodhpur who provided me with an opportunity to work under his guidance. I am thankful for his continuous support of my dissertation, for his motivation, patience, immense knowledge and enthusiasm. His guidance helped me in all the time of research and writing of the thesis. I am greatly in debt to him for devoting valuable time out of his busy schedule and being concerned for completion of thesis. This thesis work would not have been possible without his valuable advice and critical guidance. I could not have imagined a better advisor and mentor for my whole post-graduation. I am thankful to God for providing such an opportunity.

A special debt of gratitude is owed to my co-guide, great adviser and a truly wonderful person **Dr. Ravindra Shukla**, Associate Professor, Department of Endocrinology, AIIMS, Jodhpur for providing me with an opportunity to carry out the study at their department. He has been generous in sharing his knowledge on various aspects related to my thesis. His invaluable guidance, understanding and insight in the subject helped me in completing my work successfully. Words are not sufficient to express my gratefulness for constant support, encouragement, guidance and help throughout my work.

I am grateful to my co-guide, **Dr. Mithu Banerjee**, Additional Professor, Department of Biochemistry, AIIMS, Jodhpur for her invaluable support.

I am grateful to my co-guide, **Dr. Jaykaran Charan**, additional professor, Department of Pharmacology, AIIMS, Jodhpur for sharing his immense knowledge and supporting me.

I am grateful to my co-guide, **Dr. Shoban Babu Varthya**, Associate Professor, Department of Pharmacology, AIIMS, Jodhpur for his constant guidance.

I am grateful to my HOD, **Dr. Sneha Ambwani**, Professor & Head, Department of Pharmacology, AIIMS, Jodhpur for always nurturing me to grow more and supporting throughout my tenure.

I want to take a moment to express my sincere thanks and gratitude to all the faculty members **Dr. Pradeep Dwivedi**, Additional Professor, **Dr. Rimple Jeet Kaur**, Assistant

Professor, **Dr. Tarun Kumar**, Assistant Professor of Department of Pharmacology, AIIMS, Jodhpur for their kind co-operation.

I am also extremely thankful to my best friends **Dr. Bindiya C Gowda, Dr. Suman SV, Dr. Shanmugapriya Seshatri** and **Dr. Abhishek Kondapalli** for their much-needed help, good wishes and constant moral support. Also thankful to **Dr. Eram, Dr. Shinjan, Dr. Vanishri, Dr. Pradakshina and Dr. Parul**, Senior Resident, Department of Endocrinology, AIIMS, Jodhpur for their invaluable support and motivation.

A special thanks is extended to **Dr. Hina Lal, Dr. Kisna Ram, Dr. Shanmugapriya Seshatri, Dr. Pallavi Jha, Dr. Sakshi Sharma, Dr. Arun S** and **Dr. Sanchi Sukhija**, Senior Residents Department of Pharmacology, AIIMS, Jodhpur for their cooperation and encouragement during the course of this project. A special thanks to my colleagues, **Dr. Anindita Pradhan, Dr Suman SV, Dr Abhishek Kondapalli, Dr. Aswini, Dr. Abhishek Anil, Dr. Pravesh, Dr. Aaqib** and **Dr. Simi** for their generous help during my tenure. A special thanks to all office staff **Mr Manoj, Mr Sunil**, and **Mr Abhishek** of Department of Pharmacology for their kind co-operation during my tenure.

I am thankful to **Director, AIIMS, Jodhpur** for thesis fund and permitting me to avail all the facilities available in the institute for conducting this study.

I'm very thankful to **God**, the supreme power who helped in every step, showing me the right path of life and showering his blessings upon me. This project could not be reality without his grace. My parents, not less than God stood by my side in every aspect. Without them, I would not be here, and I cannot forget to thank them. Caring Dad **Mr. Jagadish MR**, loving Mom **Mrs. Lalitha B** and my devoted brother **Mr. Shashank J**, whom I am greatly indebted for boosted me up morally with continuous support and love.

SPECIAL ACKNOWLEDGEMENTS

My special acknowledgements go to all those people who made possible the difficult task of completing my MD thesis. My warm appreciation is due to all the Pharmacology and Endocrinology staff and technicians who cooperated in my long working hours. At last but not least I am deeply indebted to all the patients in my study without whom it would never have been possible to conduct and complete this study.

Dr Sachin J

Dedicated to

My Parents,

My Guide and

Department of Pharmacology

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1.	T1DM:	Type 1 Diabetes Mellitus
2.	T2DM:	Type 2 Diabetes Mellitus
3.	NCD:	Non-Communicable Disease
4.	CAD:	Coronary Artery Disease
5.	TG:	Triglycerides
6.	CVD:	Cardiovascular Disease
7.	PPAR:	Peroxisome Proliferator Activated Receptor
8.	DCGI:	Drug Controller General of India
9.	HbA1c:	Glycated Hemoglobin
10.	LDL-C:	Low Density Lipoprotein
11.	HDL-C:	High Density Lipoprotein
12.	FPG:	Fasting Plasma Glucose
13.	PPG:	Post Prandial Glucose
14.	BMI:	Body Mass Index
15.	ATP:	Adenosine Tri Phosphate
16.	UPR:	Unfolded Protein Response
17.	SERCA:	Sarco/Endoplasmic Reticulum Ca++ ATPase
18.	ER:	Endoplasmic Reticulum
19.	m-RNA:	Messenger Ribonucleic Acid
20.	HOMA:	Homeostatic Model Assessment
21.	IR:	Insulin Resistance
22.	B%:	Beta cell Function
23.	S%:	Sensitivity
24.	PPRE:	Peroxisome Proliferator Responsive Elements
25.	DQoL:	Diabetes Quality of Life
26.	LPL:	Lipoprotein Lipase
27.	PLTP:	Phospholipid Transfer Protein
28.	TNF:	Tumor Necrosis Factor
29.	AUC:	Area Under Curve
30.	NAFLD:	Non-Alcoholic Fatty Liver Disease
31.	WHO:	World Health Organisation

32. NCEP: National Cholesterol Education Program
33. ATP III: Adult Treatment Panel III
34. AHA: American Heart Association
35. NHLBI: National Heart Lung Blood Institute
36. ADA: American Diabetes Association
37. ALT: Alanine Transaminase
38. FFA: Free Fatty Acid
39. SE: Standard Error
40. ANOVA: Analysis of Variance
41. SD: Standard Deviation
42. PI: Principal Investigator
43. OPD: Outpatient Department
44. NYHA: New York Heart Association
45. AST: Aspartate Transaminase
46. hs-CRP: High Sensitivity C-Reactive Protein
47. MS: Metabolic Syndrome
48. SPSS: Statistical Package of Social Science
49. IEC: Institutional Ethics Committee
50. CTRI: Clinical Trials Registry-India
51. ICH-GCP: International Conference on Harmonization - Good Clinical Practice
52. ICMR: Indian Council of Medical Research
53. BUC: Blood Uric Acid
54. SBP/DBP: Systolic/Diastolic Blood Pressure
55. ITT: Intention to Treat
56. CI: Confidence Interval
57. POC: Proof of Concept
58. NASH: Non-Alcoholic Steatohepatitis
59. OHA: Oral Hypoglycemic Agents

SUMMARY

1 SUMMARY

TITLE: A Randomised Controlled Study of Efficacy and Safety of Saroglitazar in Type 2 Diabetes Mellitus.

BACKGROUND: Saroglitazar is a dual peroxisome proliferator activated receptor (PPAR) alpha/gamma agonist, that regulates lipid and glucose metabolism. This drug is used to treat type 2 diabetes mellitus (T2DM) and dyslipidemia. It was approved for the use in diabetic dyslipidemia since 2013 and as an add on therapy with metformin for diabetes in India by the Drug Controller General of India.

AIM: To evaluate the efficacy and safety of saroglitazar in type 2 diabetes mellitus

METHOD: Participants were included after screening and randomised (1:1) into two groups to receive saroglitazar 4mg (n=28) or placebo (n=27) with the baseline characteristics almost similar. They were followed up for 12 weeks to assess the glycemic parameters including HbA1c, fasting plasma glucose and post prandial glucose. Lipid parameters were also assessed.

RESULTS: We observed a significant decline in HbA1c in saroglitazar group from baseline to 12 weeks ($p<0.001$) and when compared between the groups of mean change in HbA1c (<0.001). Decline in fasting plasma glucose was also significant ($p=0.011$). Among the lipid parameters, significant reduction was seen comparing the groups in triglycerides ($p<0.001$), LDL ($p<0.001$) and significant increase in HDL ($p<0.001$). We also evaluated HOMA model and significant improvement in HOMA-IR and HOMA-B% was seen ($p=0.044$; $p=0.002$ respectively). To see the effect of study drug on quality of life, we evaluated DQoL scores and we found significant improvement ($p=0.001$). We evaluated the metabolic syndrome parameters also and we found the significant reduction in waist circumference ($p<0.001$). There was a drastic decrease in the number of patients with metabolic syndrome in saroglitazar group after the treatment of 12 weeks.

CONCLUSION: We conclude that the study drug saroglitazar 4 mg effectively reduced HbA1c level, improving the lipid parameters when compared to placebo indicating decrease in gluco-lipotoxicity and improving the beta cell function with decrease in insulin resistance through the agonism of dual alpha/gamma peroxisome proliferator activated receptor.

INTRODUCTION

2 INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic non-communicable disease (NCD) characterised by hyperglycemia resulting from either insulin resistance or decreased insulin production. Macrovascular and microvascular complications are caused by a chronic hyperglycemic state (1). People with DM are at higher risk of morbidity and mortality than the general population. There is a rapid increase in the global burden of diabetes mellitus, with an estimated average increase in the prevalence of 3-4% every year (2). India is one of the hotspots in the world for the epidemic of diabetes mellitus. India also has 2nd highest number of people with diabetes in the world.

There are 3 main types of diabetes mellitus; Type 1 DM (5%) also called Juvenile diabetes occurs due to the failure of the pancreas to secrete insulin, Type 2 DM (95%) occurs due to developed insulin resistance and the third main type is Gestational diabetes occurs in a pregnant woman with a raised level of blood sugar without history (3). Classification of diabetes can also be done by the underlying cause. Type 1 diabetes is an autoimmune condition, where the immune system of the body attacks insulin secreting gland, leading to failure of pancreas gland to produce insulin. Type 2 diabetes commonly seen in obese adult individuals. Several underlying factors contribute to hyperglycemic state in these individuals. An important factor is the body's resistance to insulin, basically ignoring its own insulin secretion. The next important factor is the decrease in insulin level production by the pancreas (4).

The critical role is played by genetic background predisposing individuals to type 2 Diabetes mellitus, where a sedentary lifestyle and unhealthy habit of eating may lead to this metabolic condition (5, 6). Although there is relative heterogeneity between type 1 and type 2 diabetes mellitus, they involve varied pathophysiological mechanisms, affecting mainly the pancreas as well as other major organs (7). Thus, treating the condition is more challenging.

Diabetes is not only about high glucose levels in the blood. There are a number of complications seen in diabetic patients, either at the time of the diagnosis or at the time of presentation like diabetic retinopathy (8, 9). In the meanwhile, they can develop it in later

stages too. The vital organs all over the body are involved in dysfunction, mainly the cardiovascular system, renal system, and the nervous system (10, 11).

A study estimated global prevalence in adults aged 20-79 years of 8.8% in 2015 would be increased to 10.4% in 2040. The prevalence of diabetes was found to be higher in high and middle-income countries (2). India has a high prevalence of type 2 diabetes and has a widespread genetic predisposition profoundly supported by studies (12, 13) saying that the increasing incidence of cardiovascular complications is leading to increased morbidity and mortality in India. Insight urgent attention is needed to decrease the prevalence in the upcoming years. For that, one of the measures could be innovation of novel therapies. Dyslipidemia is one of the important risk factors for the development of coronary artery disease (CAD). An increase in the incidence of CAD throws some light on the role played by lipid parameters. They are, increased levels of total cholesterol, plasma triglycerides, low density lipoproteins and decreased levels of high-density lipoprotein and these are major risk factors for stroke, CAD and peripheral vascular diseases (14, 15). 50% of diabetic patients has a prevalence of hypertriglyceridemia (16) and often doesn't respond to statin therapy (17). The epidemiological evidence shows plasma TG level is an excellent marker of cardiovascular diseases (CVD) (18, 19). Along with that, studies also show post prandial TG is also a risk factor for CVD (20). Currently, fibrates, niacin, omega-3 fatty acids or the combination of these drugs with statins are used for the treatment of dyslipidemia (21). Various side effects have limited the use of these drugs and have opened the doors to explore newer drugs.

In this study, we are studying a similar novel therapy, a dual Peroxisome Proliferator Activated Receptors (PPAR) α/γ agonist involving the actions on both lipid as well as glucose profiles (22, 23). The potential of PPAR agonist to decrease the risk of cardiovascular disease in patients with type 2 diabetes (T2DM) needs tenacious attention (24). Many PPAR-α/γ agonists have gone through various stages of clinical development in the past 20 years. Still, due to safety and efficacy concerns, many of those drugs were withheld from development and discontinued from the programs of clinical development before the phase III developmental stage (25, 26). After all these backlashes, the research didn't stop at that moment. PPAR agonist are still being explored, and new drugs are being

developed, considering its greater potential to act on lipid and glucose metabolism. Dual PPAR agonists, which are able to activate both α and γ PPAR receptors, can simultaneously enhance glycemic control as well as normalize abnormal lipid levels, which is generally observed in T2DM patients (27).

Saroglitazar is a monocarboxylic acid [(S)-a-ethoxy-4-{2-[2-methyl-5-(4-methylthio) phenyl)]-1H-pyrrol-1-yl]- ethoxy)-benzenepropanoic acid magnesium salt]. This newer dual PPAR α/γ agonist is synthesized in India by the pharmaceutical company Zydus Cadila (trade name, Lipaglyn). Drug Controller General of India (DGCI) has approved saroglitazar for the treatment of type 2 diabetes mellitus along with dyslipidemia and hypertriglyceridemia, which was unable to manage by statin therapy alone in 2013 (28, 29). It's also claimed that saroglitazar is not accompanying the side effects like edema or weight gain (23) and is thus considered a safer medication for treating diabetes mellitus, although fewer adverse effects were reported such as gastritis, pyrexia and asthenia (30).

There are very few clinical trials on the study drug saroglitazar to assess the efficacy on lipid parameters, glycemic control and the risk for cardiovascular diseases in type 2 diabetes patients. It's found that the values of lipid parameters and glycemic parameters were significantly declined with saroglitazar given along with background metformin therapy showing its favourable potential to decrease the risk of cardiovascular diseases in patients of T2DM (31). Another study shows the effect on insulin sensitivity in T2DM patients with hypertriglyceridemia, and they found the levels of triglycerides, FPG, and HbA1c to be significantly reduced. It also showed the effect on HDL-C to significantly improved levels (32).

Recently two years ago (January 2020), for the treatment of type 2 diabetes mellitus, saroglitazar got the head nod from DGCI as an add-on treatment with metformin. It also got consent from the government for promotion in India for the treatment of Non-cirrhotic Non-alcoholic steatohepatitis two years ago. Since there is lack of studies for the evidence of efficacy and safety of saroglitazar in the treatment of diabetes mellitus as well as dyslipidemia, we planned for this study to evaluate for the same, along with that we also assess the effect on metabolic syndrome parameters.

REVIEW OF LITERATURE

3 REVIEW OF LITERATURE

A literature review is a critical evaluation of the existing research on the related topic or research problem so that a broad understanding of the information available is gained. It also assists the investigator to identify research methods used by others, reveals gaps in the existing literature and offers an opportunity for new research.

3.1 History of Diabetes

In 1550 BC, for the very first-time diabetes' history begins with the introduction of the term polyuria I the book 'Ebers Papyrus'. Honey urine means 'Madhumeha' was the term introduced by Sushrutha for the first time in 400BC. In around 30-50 BC, Celsus recognised diabetes, and it was later given its name (a Siphon means diabetes) by Aretaeus the Cappadocian in 1st century. The description of diabetes as the "melting down of flesh and limbs" was also made by him. Later on various scholars across the globe mentioned sweet and sticky urine a condition of polyuria in 3rd – 5th centuries. Avicenna in 10th century observed increased appetite and gangrene of extremeties, which he mentioned in "The canon of medicine" (33).

Diabetes Mellitus in the era of Ancient Ayurveda:

During the ages of Charaka and Sushrutha (400BC), diabetes mellitus was studied in ayurvedic medicine. Wagbhat discovered the pathophysiology of diabetes in 800 BC. Diabetes was referred as a urinary disease in ancient days by ayurvedic physicians and was narrated as 'Madhumeha'. People thought that madhumeha was incurable and termed it as 'Vat Prameh'. It was observed by Sushrutha that those individuals who lead a sedentary lifestyle, avoid exercise, have bad eating habits, and developing obesity would develop the disease 'Pramah' (Diabetes). The risk factors of diabetes like genetic predisposition and hereditary characteristics of diabetes, were well-known to ayurvedic physicians of ancient times. It's also mentioned by Sushrutha the classification of diabetes into 2 types. The first type was according to the hereditary risk factor present from birth and the second one was due to leading an unhealthy lifestyle (34).

3.2 Epidemiology

Diabetes mellitus has become a popular lifestyle disease gaining a rapid potential of epidemic in our subcontinent India. Currently, in the world there are more than 62 million individuals with the diabetes. In the year 2000, our country (31.7 million) gained the number one spot with a maximum number of people with diabetes mellitus, followed by our neighbour country China (20.8 million) and the United States (17.7 million) in second and third place respectively (35). According to Wild et al. India is going to win the race again with respect to the prevalence of diabetes by 2030 also. Globally the prevalence would double from 171 million patients in 2000 to 366 million in 2030. It's also predicted that the number of diabetic patients in India would be 79.4 million, followed by China and the United States with 42.3 million and 30.3 million, respectively, making the disease burden more worse (36).

The living standards which are raising, urban migration, changes in lifestyle and plenty of reasons make the etiology of diabetes mellitus in India multifactorial. It might also include genetic factors as the contribution. Even though there are very few nationwide or multicentric trials to study the prevalence of diabetes mellitus and the complications caused by it, there is poor management of the disease, screening, and preventive measures. And also, we can face the obstacles such as, lack of proper counselling to the patients, non-adherence to the guidelines of the antidiabetic treatment and travel difficulties with the long distance to the hospitals. Disparity can be seen in the management of diabetes when we compare rural health services to urban health services, which may lead to more diabetic complications. More attention and research is required to address the inequality of the treatment of the rural-urban population.

3.3 Risk factors

There are numerous risk factors contributing to the development of type 2 diabetes mellitus. Among the biological risk factors, above normal body mass index is the major risk factor. Usually, BMI increases with various reasons, which might be sedentary lifestyle and unhealthy eating habits, which are indirectly contributing to risk factor type 2 diabetes

mellitus. Diabetic men are more obese that non-diabetic men in most of the studies. This also shows a stronger association of diabetes risk with an increase in BMI in both sexes (37, 38). Body fat distribution is also an independent risk factor for diabetes. Visceral adipose tissue is an independent predictor of lipid and glucose abnormalities, which is more in males compared to females. Visceral adipose tissue and Subcutaneous adipose tissue ratio is the risk predictor in females (39). Brown adipose tissue is one of the factors that influence energy metabolism, obesity-related type 2 diabetes and insulin resistance. Studies shows that more brown adipose tissue present in the body would reduc the insulin resistance and increase adiponectin level (40). Metabolic syndrome, a cluster of factors, is also a risk factor for diabetes. These risk factors vary between the sexes as well as ethnicities. But the, central obesity and increased waist circumference is predominantly a risk factor in females (41-44). In addition to these, there are certain newer makers for the risk assessment for diabetes. They are copeptin, pronuerotensin, low vitamin D3, increase in gamma glutamyl transferase, low sex hormone binding globulin and others (45-53). Along with the biological risk factors, we can also find the psychosocial risk factors responsible for development of type 2 diabetes mellitus. Socioeconomic status assessed by the level of education, income and position is inversely related to the prevalence of type 2 diabetes and obesity in developed countries (54). It's also confirmed by a meta-analysis of cohort studies and case-control studies, that the risk factor for type 2 diabetes mellitus is higher in the lower socioeconomic classes (55). The impact of psychosocial stress on diabetes couldn't be ruled out, as the risk is higher in working class, people with sleep disturbance and other similar conditions (56-59). Lifestyle plays a major role. For example, unhealthy fast food eating habits, drinking sugar-sweetened beverages and also smoking are risk factors for the type 2 diabetes mellitus. Studies have shown that the risk of developing diabetes is higher in high alcohol drinkers (> 63g/day) compared to non-drinkers. But in mild alcohol drinkers(< 63g/day), the risk was found to be reduced, an observational study says (60, 61). Meta-analysis of cohort studies has shown the risk for diabetes is higher in both passive and active smokers, which has no gender differences. As per the data of metanalysis, 11.7% of cases in type 2 diabetes in men are smokers, and 2.4% are women. Its also seen from the studies, in the past decade, the smoking trend has been changed. Smoking is seen more in females, and it may lead to a higher

incidence of diabetes in females related to smoking. It also increases the risk for myocardial infarction(62-66).

3.4 Pathophysiology

Insulin is synthesized by the beta cells of the pancreas. Pre-proinsulin which is synthesized undergoes various conformational changes, and proinsulin is yielded. Later proinsulin is cleaved into insulin and c-peptide (67-70). Once the glucose concentration increases, ATP is produced by the metabolism of glucose increases. This leads to the closure of ATP-dependent potassium channels,which in turn rises the membrane potential and opens the voltage-gated calcium channels. The increases in the intracellular calcium triggers exocytosis of the insulin (71-73). The basic pathology of developing type 2 diabetes mellitus lies in beta cell dysfunction. The loss of islet integrity under different circumstances like genetic susceptibility, inflammatory stress, inflammation by toxic stress, oxidative/metabolic stress and amyloid stress is the main factor for the progression of diabetes (74, 75).

The apoptotic unfolded protein response pathways (UPR) are activated by the excess of free fatty acids and glucose levels, which results in beta cell dysfunction (76, 77). Glucotoxicity, lipotoxicity and glucolipotoxicity are seen in obesity induced oxidative stress and metabolic stress. This leads to the dysfunction of beta cells. These various stress factors inhibit the sarco/endoplasmic reticulum Ca++ ATPase (SERCA) which impairs ER Ca++ mobilisation. Also, an increase in the biosynthesis of proinsulin accumulation of islet amyloid polypeptides is seen. These conditions result in proinsulin mRNA degradation, favouring apoptotic signals and induction of interleukin - 1–beta. This, in turn, recruits more macrophages and results in local inflammation of islet (78). As so far, we discussed, the regulation of insulin has to be precise to meet the metabolic needs. Hence, the proper integrity of islet is a must, otherwise, poor regulation of insulin ultimately leads to hyperglycemia. Any deviation in the normal steps of production of insulin and its precursors may lead to dysfunction of insulin secretion and is a cause of beta cell failure. Ultimately these are the contributing factors for the pathophysiology of type 2 diabetes mellitus (79, 80).

3.5 Complications of diabetes mellitus

Microvascular as well as macrovascular complications are the pathological hallmark of diabetes mellitus involving the vasculature. The long-term failure and damage of major organs like kidneys, eyes, nerves and hearts is due to the chronic hyperglycemic state of the body. There is no exact demarcation between the pathological mechanism of macrovascular and microvascular complications and clarity is still pending to understand the varying response to the therapeutic interventions. Diabetic microangiopathy, the pathognomic feature of this condition, occurs due to the synthesis of extracellular matrix protein and causes the thickening of the capillary basement membrane (81, 82).

Obesity, which is often called a complex lifestyle disease, is the major risk factor in developing diabetes mellitus, yet the research focussed on this condition is less comparatively (83). Even though Indians have lower rates of obesity and overweight, the prevalence of diabetes is high in India when compared to the countries of west. This is suggesting us that, irrespective of the body mass index (BMI), diabetes can occur in any individual, even in lower BMI individuals (83, 84). Therefore, risk is seen equally even in the relative lean adults with a lower BMI. Furthermore, the genetic predisposition to the development of CAD (coronary artery disease) due to lower level of HDL (high density lipoprotein) and dyslipidemia is seen more in Indians. All these factors contribute to higher risk for the development of diabetic complications early at the age of 20-40 years in Indians compared to Caucasian population, i.e., >50 years. This indicates the screening and monitoring are much needed regardless of the age group in India (85).

Type 2 diabetes mellitus and metabolic syndrome share Insulin resistance as a common feature. Diabetic patients with metabolic syndrome are more prone to myocardial infarction due to its complex metabolic abnormalities. The clinical features of metabolic syndrome includes, hyperglycemia, abdominal obesity, hypertriglyceridemia, hypertension, and low levels of HDL. Any three of the above five features makes the diagnosis of metabolic syndrome (86). It's still unclear whether metabolic syndrome is only a risk factor for the development of coronary artery disease and diabetes mellitus or it is representing the clinical manifestation of insulin resistance and its consequences.

3.6 Homeostatic model assessment (HOMA)

Homeostatic model assessment is a method used in diabetes for evaluating insulin resistance and β cell function from fasting plasma glucose level and fasting insulin level or C-peptide concentrations (87). The balance between baseline glucose and baseline insulin is always well maintained in a healthy individual and this relationship often indicates how good the balance between insulin secretion and hepatic glucose output is maintained (88). This entire process is supported by the feedback loop between beta cells and the liver.

The original HOMA model: HOMA1; Mathews et al, used a very simple mathematical formulae of the original non-linear solution to the iterative equations. The formulae are widely used and simplified to (89):

1. HOMA1-IR= (FPI *FPG)/22.5 for insulin resistance
2. HOMA1-B%= (20 * FPI)/(FPG - 3.5) for βcell function, FPI - fasting plasma insulin concentration (mU/l) and FPG - fasting plasma glucose (mmol/l).
3. HOMA2: the newer updated computer HOMA model
4. HOMA2 has HOMA2-B%, HOMA2-S% AND HOMA2-IR similarly as HOMA1 model for beta cell function, sensitivity and insulin resistance respectively.(89)

3.7 Quality of life

Quality of life assessment is done by a Revised Version of Diabetes Quality of Life (DQoL) Instrument. It was developed to analyse the effect of two different drugs on two different groups of the study on incidence and the development of early complications related to the vascular system. The DQoL instrument was used to assess diabetic patients regarding health-related quality of life. It has three important domains, they are satisfaction, worry and impact. It's been used since 10 years in the research of diabetes mellitus (90). DQoL has been proven to be valid and has strong reliability as a questionnaire to assess the quality of life of diabetic patients (91, 92). The original and older version of DQoL had many limitations. Evaluating a substantial number of elderly diabetic patients with varying severity of complications was cumbersome and difficult at the same time. It was also requiring more time to complete the

questionnaire leading to improper thinking and invalid responses from the patients, which often led to the frustration of the researcher. Then later, researchers came up with an idea to develop a shorter version of the diabetes quality of life. Later Bujang et al, developed a newly revised version of diabetes quality of life, while retaining the three important domains, satisfaction, impact and worry. The requirement of quality of life measures were in line with the initial concept of the domains (93). Whenever it's claimed that the instrument used is less sensitive to measure the QoL (Quality 0f life) among diabetic patients, the revised version of DQoL is much crucial and helpful (94). (ANNEXURE 3)

3.8 Saroglitazar

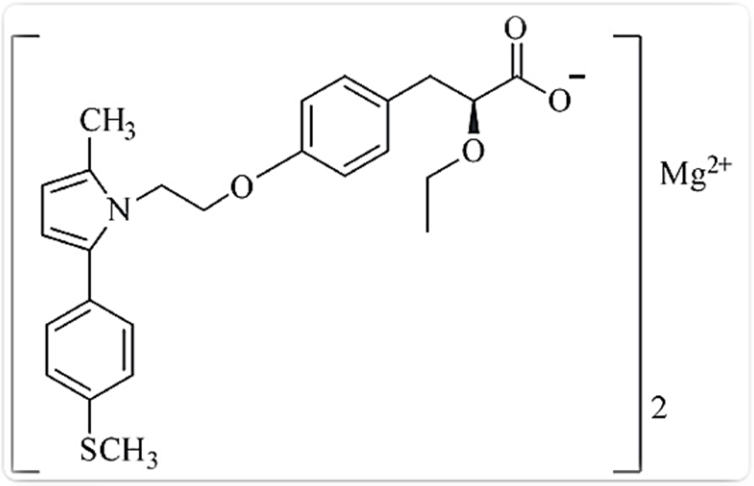
Saroglitazar, a peroxisome proliferator activated receptor (PPAR) agonist, regulates lipid and glucose metabolism. With the trade name lipaglyn this drug is used to treat T2DM and dyslipidemia. It was approved for the use in our country by the Drug Controller General of India. Saroglitazar is indicated for the management of diabetic dyslipidemia and hypertriglyceridemia with T2DM, which is uncontrolled by Statin therapy.(22)

Mechanism of action:

PPARs are lipid receptors and has various lipid-related mechanisms. Agonistic action at PPAR-alpha decreases the triglycerides levels in blood and agonist action on PPAR-gamma improves insulin resistance and accordingly decreases blood pressure. Upon binding to the ligand, in the nucleus PPAR translocation happens. Following this, PPRE (peroxisome proliferator responsive elements) binds with retinoid X receptors to heterodimerize with PPARs. Hence they regulate the transcription of target genes (95). PPAR alpha increases fatty acid catabolism by regulating the expression of lipoprotein lipase (LPL), apolipoprotein genes, fatty acid transport and oxidation genes, as well as genes for High Density Lipoprotein metabolism (PLTP) and ketone body synthesis (96, 97). As a result, hepatic PPAR alpha activation is accompanied with a considerable extent of triglyceride clearance and elevated plasma HDL level, supporting the clinical utilization of PPAR alpha agonists to treat hyperlipidemic condition and cardiovascular disease (CVD). PPAR gamma particularly

enhances lipid uptake and lipogenesis in the adipose tissues, leading to decline in the circulating levels of triglycerides, free fatty acids and decreases insulin resistance (98). Further to add, in the adipocytes, there are certain genes GLUT4, IRS-1, IRS-2, and c-Cbl associated proteins which are responsible for insulin-dependent glucose uptake. Similarly, adipokines are also PPAR γ responsive. They are adiponectin, resistin, leptin and TNF- alpha. Insulin signalling can be influenced by adipokines. Consequently, the activation of PPAR gamma in the adipocytes can enhance the systemic insulin sensitivity sufficiently. Hence, making the potent antidiabetic agents by PPAR gamma agonists (99).

Molecular structure of saroglitazar (95, 100):



Saroglitazar, [(S)-alpha-ethoxy-4-(39))-benzene propanoic acid magnesium salt]

There have been many clinical trials to study the effects of saroglitazar on glycemic and lipid parameters on Indian patients with T2DM. PPARs are the transcription factors included in the superfamily of nuclear receptors. Three isoforms of PPAR i.e., alpha, gamma, and delta have been described. The act on DNA response elements as heterodimers with the nuclear retinoic acid receptors. Their natural activating ligands are fatty acids and lipid derived substrates.(101)

Effect of food on pharmacokinetics on saroglitazar in healthy individuals seen in a study conducted which had a minor effect. While food has reduced Cmax by 30%, the extent of absorption as measured by AUC was not influenced (102)

Indications: Diabetic dyslipidemia

Dose: Available in two doses, 2mg and 4mg (22)

Side effects: stomach ache, nausea, vomiting, chest pain, fever and dizziness.(100)

3.9 Diabetic dyslipidemia

Diabetic dyslipidemia is cluster of abnormalities of metabolism, includes hypertriglyceridemia, low HDL-C level, high LDL-C level, postprandial hyperglycemia with lipidemia and also insulin resistance leading to increased risk of cardiovascular diseases (103-106). Even though statins are used successfully to treat the dyslipidemic conditions, patients with dyslipidemia remained at higher risk for the cardiovascular disease (CVD). Hence treating the high TGs, LDL, and low HDL conditions would decrease the future residual risk for cardiovascular diseases(28, 107, 108). For this condition a dual PPAR agonist has got all the attention from the world as a promising new therapeutic option for both type 2 diabetes mellitus and dyslipidemia(109) with its unique mechanism as we discussed earlier. Preclinical studies as well as phase 1 and 2 studies of saroglitazar has shown the promising favourable effects on both glycemic and lipid parameters(22, 110).

Upendra Kaul et al, conducted an integrated analysis on saroglitazar in diabetic dyslipidemia in real world clinical studies conducted after authorization of drug in India. Authors considered 18 studies with saroglitazar 4mg given once daily for diabetic patients with dyslipidemia for at least 12 weeks. There was a total of 5824 diabetic patients with the mean age ranged from 49.6 to 59.1 years. Authors saw the consistent mean decrease in triglycerides (approx. 45% to 62%), LDL-C (approx. 11% to 27%), Total Cholesterol (approx. 17% to 26%), and glycated haemoglobin level (approx. 0.7% to 1.6%). The mean increase in HDL was approx. up to 9% from the baseline values to the end of the studies. Saroglitazar had also proved its efficacy in improving the level of alanine aminotransferase and also fatty liver in NAFLD (non-alcoholic fatty liver disease) with diabetic dyslipidemia. They concluded with saroglitazar have a very good effect on both glycemic and lipid parameters without any adverse events in real world clinical studies of duration 58 weeks.(23)

3.10 Metabolic syndrome

Metabolic syndrome is a bunch of clinical findings constituting the disorder of metabolism. Grundy and colleagues introduced the term metabolic syndrome in 2001 and in the recent years there are more than 57000 literatures available on metabolic syndrome (111, 112). It's also known by various other names, such as, syndrome X, reaven syndrome, plurimetabolic syndrome, dysmetabolic syndrome, insulin resistance syndrome and the deadly quartet (113). Various authors defined metabolic syndrome with various risk factors. Haller and Singer included diabetes, obesity, hyperproteinemia, hypertension, fatty liver and gout in the syndrome (114-117). It was Gerald Reaven in 1988, explained the role of insulin resistance in pathology of metabolic syndrome and also the risk for cardiovascular disease and diabetes (118). According to WHO, the prevalence for obesity is increasing and in parallel, this increases the risk for metabolic syndrome too. Studies says, nearly quarter of the heart disease burden and half of the diabetes burden are mainly related to obese and overweight (113, 119).

National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) defined metabolic syndrome with the following components, 1) impaired glucose metabolism, 2) abdominal obesity or indicator of insulin resistance, 3) hypertension, 4) atherogenic dyslipidemia(112). NCEP/ATPIII criteria says, 3 out of 5 criteria need to be satisfied to diagnose the metabolic syndrome: abdominal obesity, which is specific to sex waist circumference, low high-density cholesterol level, high triglycerides, increased fasting glucose level and hypertension. American heart association (AHA) and National heart lung blood institute (NHLBI) in 2004, reduced the threshold for fasting glucose from 110mg/dl to 100mg/dl as per American diabetes association (ADA)(120). Right now, in our trial we are using modified criteria for metabolic syndrome, which was made for Indian population(121). The list of criteria is being discussed in the methodology part (also ANNEXURE 2).

Metabolic syndrome has high prevalence in western countries as well as Asian countries. It's seen that in Asian Indians, the prevalence in the rural population was observed 5% and increases to more than one third in the urban population. It's also directly proportional to ageing (122). Framingham heart study offspring study has shown that, the age adjusted

relative risk of cardiovascular disease in the participants with metabolic syndrome was 2.88 for men and in women (> 8 years) it was found to be 2.25(123, 124).

Non-alcoholic fatty liver disease (NAFLD) has an association with metabolic syndrome. The prevalence of NAFLD is increasing along with the increasing prevalence of obesity, which is the main cause of chronic liver disease (125). Sometimes NAFLD is also referred as metabolic syndrome of liver and thoughts were given to include as one of the components of metabolic syndrome (126). Our study drug Saroglitazar has been studied on NAFLD for its efficacy. Samer Gawrieh et al. conducted a randomised trial for the efficacy of saroglitazar in NAFLD, which was a phase 2 trial. 106 patients with NAFLD, body mass index of >25kg/m^2 and alanine aminotransferase (ALT) >50U/L were included in the trial. They were randomised into 1:1:1:1 ratio i.e., placebo and saroglitazar 1mg, 2mg, and 4 mg groups. The endpoints were change in ALT level from baseline to after 16 weeks and change in liver fat content from baseline to after 16 weeks. The results of this study shows significant improvement in both the endpoints. The least squares mean change of ALT was −25.5% (5.8), −27.7% (5.9), and −45.8% (5.7), with saroglitazar 1 mg, 2 mg, and 4 mg, respectively when compared to placebo 3.4% (5.6) ($P < 0.001$). The improvement in the liver fat content was seen only with 4mg group i.e., -19.7% (5.6) vs placebo 4% ((%(5.9). There was change in homeostatic model assessment - insulin resistance -6.3% (1.7), triglycerides -68.7mg/dl (10.3), $p<0.05$ were seen in all parameters. Overall saroglitazar 4mg significantly improved ALT, insulin resistance, liver fat content and dyslipidemia in NAFLD patients (127).

With the series of events from increasing the level of free fatty acid inhibits signalling for insulin. Gluconeogenesis is increased by insulin resistance and increase in FFA substrates, which contributes to hyperglycemia and later type 2 diabetes mellitus (128-131). Hypertension is caused due to the endothelial dysfunction. Also, renin angiotensin hyperactivity is seen in obesity (132). The target of this condition is mainly decreasing the risk of type 2 diabetes and cardiovascular disease. Hence, change in the lifestyle is a must, and treatment for dyslipidemia and hypertension is necessary. For abdominal obesity, patients are encouraged to lose the weight and increase the resistant training exercise at least 2 days per week. Regarding diet, it should be low in unhealthy fat and avoid simple sugars. If the

triglyceride level is >500mg/dl, fibrates or nicotinic acid should be started. Blood pressure can be controlled by lifestyle modification if the BP is >120/80mmHg, whereas medication should be started if BP is >140/90mmHg. Lifestyle changes can delay the progression of increased fasting glucose to type 2 diabetes mellitus(86).

There has been very less data and literature in the treatment of metabolic syndrome with our study drug saroglitazar. Hence, we have the secondary endpoints of our study to see the effect of saroglitazar on the parameters of metabolic syndrome.

3.11 Studies of saroglitazar in T2DM

Nimisha Jain et al. studied the efficacy of saroglitazar on insulin sensitivity in patients of type 2 diabetes mellitus with high levels of triglycerides. 30 participants were randomised into 1:1 ratio, placebo and saroglitazar 4mg group for 4 months. The primary endpoints were change in insulin sensitivity, glucose metabolism and HOMA-beta at 4 months from baseline. Secondary endpoints were change in fasting plasma glucose, postprandial glucose, body weight, HbA1c, lipid profile and c-peptide levels. At the end of the trial, saroglitazar group showed improvement in glucose metabolism ($p=0.025$) and SI-clamp ($p=0.011$) which was statistically significant. There was significant reduction in triglycerides ($p=0.001$), fasting plasma glucose ($p=0.019$), increase in HDL level ($p<0.01$) and HbA1c (0.019). authors say, saroglitazar overall improves dyslipidemia by effectively decreasing triglycerides and increasing insulin sensitivity along with the functioning of beta cells(32).

Jani RH et al. studied the efficacy and safety of saroglitazar in type 2 diabetes patients with uncontrolled hypertriglyceridemia with atorvastatin treatment in a multicentric, prospective, randomised, placebo-controlled study. A total of 302 patients were recruited and randomised into saroglitazar 2 mg (n=101), 4mg (n=99) and placebo group (n=102). The primary efficacy endpoint was change in triglyceride level from baseline to 12 weeks and secondary end points were change in lipid profile parameters and fasting plasma glucose from baseline to 12 weeks. After the completion of the study, results revealed a significant reduction in triglyceride levels by -45.5±3.03% in 2mg group and -46.7±3.02% (mean±SE) in 4mg group when compared to placebo ($p=0.001$). Along with that, saroglitazar 2mg decreased the level

of non-HDLC levels, total cholesterol and FPG significantly. Saroglitazar 4mg group reduced LDL-C level and apolipoprotein level significantly. There were no side effects found by the study drug and authors concluded the drug to be safe and effective in type 2 diabetes patients with hypertriglyceridemia (110).

Krishnappa et al. studied the effect of saroglitazar on glycemic control, cardiovascular disease risk and lipid profile parameters in type 2 diabetes mellitus. It was a multicentric, phase 3, randomised controlled study. Total of 1155 patients were randomised into 3 groups saroglitazar 2mg, 4mg and pioglitazone 30mg into 1:1:1 ratio. The primary efficacy endpoint was mean change in HbA1c from baseline to 24 weeks in all three groups. The secondary efficacy endpoints were comparison of HbA1c of all 3 groups at 12 weeks, 24weeks and 56 weeks, mean change in HbA1c from baseline to 12 weeks and 56weeks, mean change in fasting plasma glucose, post prandial glucose, lipid profile parameters from baseline to all time points i.e., 12weeks, 24weeks and 56weeks. Safety was also evaluated throughout the study. Paired t test and ANCOVA test was applied for the statistical analysis. Across 3 groups, the baseline characteristics were similar and there was significant difference. The mean change (±SD) in HbA1c within the group from baseline to 24 weeks were saroglitazar 2mg is − 1.38 ±1.99; saroglitazar 4 mg is −1.47 ± 1.92; and − 1.41 ±1.86 for pioglitazone 30mg group, which was statistically significant in each group ($p<0.016$). Authors also claim the significant reduction in lipid profile parameters and increase in HDL-C from baseline($p<0.016$). The adverse effects were mild to moderate and were reported to DCGI, India. Overall saroglitazar significantly improved the glycemic control and lipid profile in type 2 diabetes patients (31).

AIMS AND OBJECTIVES

4 AIMS AND OBJECTIVES

4.1 Aim

To analyse the efficacy and safety of Saroglitazar in Type 2 Diabetes Mellitus

4.2 Objectives of study

We have primary and secondary objectives as follows

4.2.1 Primary Objective

To compare the effect of Saroglitazar versus placebo on HbA1c in T2 DM

4.2.2 Secondary objective

- To evaluate the effect on lipid profile parameters of Saroglitazar versus placebo in T2 DM
- To evaluate the effect on the HOMA index of Saroglitazar versus placebo in T2 DM
- To evaluate the effect on Metabolic syndrome parameters of Saroglitazar versus placebo in T2 DM
- To evaluate the effect on the QOL score of Saroglitazar versus placebo in T2 DM
- To evaluate the safety of Saroglitazar versus placebo in T2 DM

MATERIALS AND METHODS

5 MATERIAL AND METHODS

5.1 Study setting

This study was conducted by the Department of pharmacology in collaboration with the Department of Endocrinology at All India Institute of Medical Sciences, Jodhpur (AIIMS, JDH). Diabetic patients were recruited in the Outpatient Division of the Department of Endocrinology, AIIMS, which is a tertiary healthcare centre located in Jodhpur city, Rajasthan state of India. The enrolment of patients was done between February 2021 to June 2022. Rajasthan is a northern state of India with a diabetes prevalence of 15.6% (2014)(133).

5.2 Study design

This study design was planned to be randomised placebo-controlled open-label trial, involving 50 patients with Type 2 Diabetes Mellitus. All the patients who met eligibility criteria were randomised in 1:1 into two treatment groups. One group was given saroglitazar 4mg once daily orally and the control arm was given a placebo. Placebo was prepared in the pharmacy lab with gelatin capsules and vitamin C as the ingredient. All the patients were on stable Metformin 500 mg BD daily dose along with vildagliptin 50 mg.

Randomisation was done by variable block randomisation, as per the randomisation sequence generated by R software. Concealment of randomisation was done by storage of the randomisation sequence in opaque sealed envelopes at a central place with the principal investigator (PI) or by randomization sequence stored with Investigator and telephonically confirming the random number from the PI by the investigator assigned for treatment allocation at the time of enrolment of patients.

5.3 Study population

Diabetic patients of age limit 18 to 65 years were enrolled in the OPD of Department of Endocrinology as per Inclusion and Exclusion criteria. All the patients were diagnosed type 2 diabetes mellitus according to ADA criteria. We enrolled the patients who were on stable glycemic control with the lifestyle modification. They were also motivated to do regular exercise and have low calorie diet intake in the course of the study. Patients were from various places in the Rajasthan state, majority were from Jodhpur itself.

5.4 Eligibility criteria

5.4.1 Inclusion Criteria:

1. Age 18 – 65yr
2. Type 2 diabetes mellitus to be made as per ADA criteria
3. On lifestyle modifications and metformin and vildagliptin medications for 3 months or newly diagnosed T2DM
4. HbA1C >7%

5.4.2 Exclusion Criteria:

1. Patient who had any clinically significant or unstable medical or Psychiatric illness
2. History of cardiac diseases (NYHA grade 3 – 4) or cardiac anomalies
3. Patient on other PPAR agonistic drugs for > 30 days
4. History of Renal insufficiency - serum creatinine ≥1.8mg/dl
5. Patient with a history of significant thyroid dysfunction and hepatic impairment (serum bilirubin >2 times, AST, ALT and alkaline phosphatase >3 times the upper limit of normal
6. Patient has a history of uncontrolled hypertension
7. Patient having any malignancy
8. Patient has any substance abuse (alcohol/drugs)
9. Pregnant & Lactating Woman
10. Patient with a known history of allergy/intolerance to study medication

5.5 Study endpoints assessment

Patients were assessed for various parameters required for the study regularly during the follow up visits. Height, weight and waist circumference were measured using standard methods in standard units. For the fasting sample parameters like, fasting plasma glucose, fasting insulin and lipid profile, patients were asked to come early in the morning to the OPD without eating any food or drinking beverages. Venous blood samples were taken for the assessment. Patients from far distance used to send the report by doing the test from nearby laboratory.

For fasting insulin, the blood sample was collected in the yellow cap vacutainer and was preserved in the refrigerator at -80C in the biochemistry lab, AIIMS Jodhpur. After the follow up of all the patients, all the samples collected, were analysed for fasting insulin levels (Chemiluminescence, Diasorin Liaison XL). For post prandial glucose, patients were asked to have breakfast and come back after 2 hours. Later, venous blood samples were collected for the same. HbA1c (HPLC, Biorad Variant II), Blood Uric acid (uricase, Beckman Coulter AU680) and hsCRP (Immunoturbidimetry, Beckman Coulter AU680) evaluation was also done at the same time. FPG, PPG were analysed by Hexokinase method, using Beckman Coulter AU680 instrument and lipid profile was analysed by Oxidase peroxidase method, using Beckman Coulter AU680 instrument.

For the assessment of the diabetes quality of life, the standard questionnaire was used which has three domains satisfaction, impact and worry. The scores of DQoL were added within the domain as well as counted in total also.

5.6 Criteria and models

Metabolic syndrome

Metabolic syndrome evaluation was done as per **Modified NCEP ATP III** (121). (Minimum of 3 out of 5 parameters)

1. Waist circumference >90cms in men and >80 cm in women
2. Hypertriglyceridemia ≥150 mg/dl
3. High-density lipoprotein (HDL) cholesterol <40 mg/dl in males and <50 mg/dl in females
4. Blood pressure (BP) ≥130/85 mmHg, and
5. Fasting plasma glucose (FPG) ≥110 mg/dl

Both original as well as revised criteria for the evaluation of metabolic syndrome were also used and analysis was done in all three criteria. Abdominal obesity criteria in the original NCEP ATP III is of waist circumference >102cmin men and in women was >88cm, rest all the parameters were similar to modified criteria (134). In revised NCEPATP III criteria the fasting blood sugar level cut off is >100mg/dl and rest of the parameters of criteria is similar to original criteria (120). All the parameters were evaluated at baseline and after 3 months. Mean change in parameters were compared after 12 weeks, saroglitazar versus placebo.

HOMA Index:

Homeostatic model assessment (HOMA) is a tool to evaluate β cell function and insulin resistance (IR) using fasting glucose level values and fasting insulin level values or C-peptide concentrations. HOMA model has been utilized in more than 500 studies for the estimation of beta cell function as well as insulin resistance. (89)

The equations for estimation of HOMA- IR and β cell function, respectively are given below:

1. HOMA1-IR = (FPI*FPG)/22.5
2. HOMA1-β cell function = (20 * FPI)/ (FPG - 3.5)

where FPI is fasting plasma insulin concentration (mU/l) and FPG is fasting plasma glucose (mmol/l).

5.7 Sample size

The sample size for our study was calculated on the basis of previously published study done by Jain et al.(32). Assuming a standard deviation of 1 in the study group and 0.7 in the control group with an effect size of 0.98 and a clinically meaningful mean difference of 0.84 in HbA1c in two treatment groups, with 90 per cent power and alpha error of 5%, the sample size is estimated to be 22 per treatment group. Taking into account, the 10% dropout, we planned to recruit 25 patients per treatment group. For a total of two groups, 50 patients would be recruited. At end of study, we enrolled 55 patients.

5.8 Study duration

The study duration was of 2 years. All the patients were followed up for 12 weeks and were assessed every 4 weeks.

5.9 Compliance

The patient compliance was evaluated by pill count from the blister packs returned by the patients, and it was found to be compliant in both the groups.

5.10 Statistical analysis

Data were expressed as mean ± standard error. An Independent Student t-test was used for the comparison of numerical variables between the two groups. The Chi-square test was used to compare categorical variables. Intragroup comparison of mean changes in outcomes was evaluated by Paired t-test. Analysis was done in both Intention to treat principle as well as per protocol principle. A two-sided p-value <0.05 was considered as statistically significant. Analysis was done using SPSS version 23 (IBM Corp. Ltd, Newark, USA).

5.11 Efficacy and Safety Endpoints

Patients were assessed for efficacy and safety as per the study flowchart.

Efficacy primary endpoints:

1. To compare the mean change in HbA1c after 12 weeks of placebo versus Saroglitazar in T2 DM.

Efficacy secondary endpoints:

1. To compare the mean change after 12 weeks on lipid profile parameters of Saroglitazar versus placebo in T2 DM
2. To compare the mean change after 12 weeks on HOMA index (HOMA- beta cell function and HOMA- Insulin resistance) of Saroglitazar versus placebo in T2 DM
3. To compare the effect on Metabolic syndrome parameters after 12 weeks of Saroglitazar versus placebo in T2 DM
4. To compare the effect on the QOL score after 12 weeks of Saroglitazar versus placebo in T2 DM

Safety endpoints were evaluated by taking the information of any adverse drug events that occurred during the course of treatment of 12 weeks of Saroglitazar versus placebo in T2 DM.

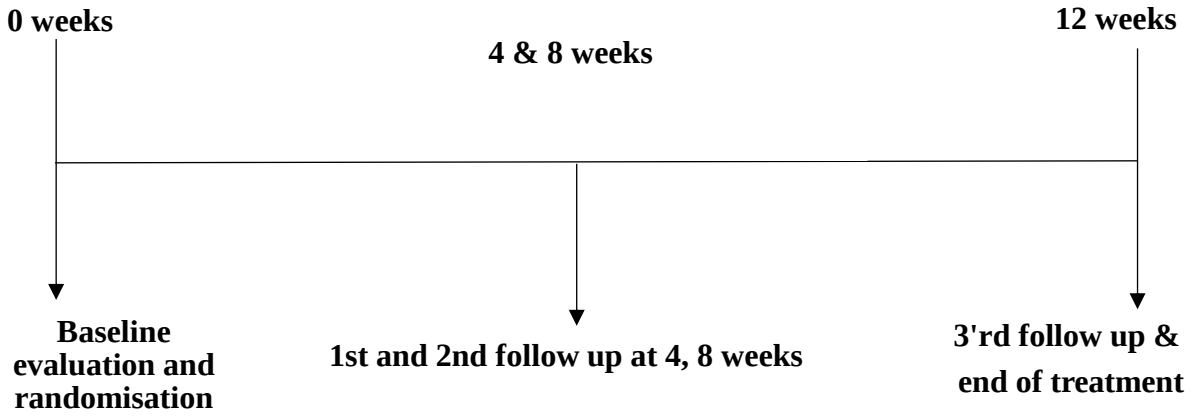
Efficacy assessments including laboratory parameters, were done at baseline and the end of the treatment. FBG and PPBG were done at 4 and 8 weeks also. Safety assessments were done throughout the study.

HOMA index – HOMA- β cell function and HOMA-IR were assessed at baseline and 12 weeks.

Quality of life: Quality of life assessment was done by A Revised Version of Diabetes Quality of Life Instrument (ANNEXURE 3)

Rescue medication: Patients not controlled were treated with glimepiride. In the saroglitazar group, patients were up titrated to 4 mg BD if not controlled with saroglitazar 4 mg once daily. All patients were on stable metformin 500mg BD daily dose and vildagliptin 50 mg BD throughout the study.

5.12 Study plan



5.13 Safety monitoring

All patients who received at least one dose of the study drug were included in the safety analysis. Safety data were obtained through patient interviews and examinations at all study visits. All adverse drug events were monitored at each post-randomization visit by open and closed questions.

Hypoglycaemia was meant to be recorded and graded as per ADA recommendation. However, there were no hypoglycemic episodes were reported.

5.14 Safety reporting

All adverse events were classified as mild, moderate and severe and also as serious and non-serious. “A serious adverse event or reaction is any toward occurrence that at any dose resulting in death, life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, causing teratogenicity or intervention demanding to prevent permanent disability”.

All serious adverse drug events were planned to report to the ethics committee within 24 hours and to DCGI within 7 days. If required, Data Safety Monitoring Board would be constituted of persons not involved in the trial. But there were no Serious Adverse events were seen.

5.15 Ethical consideration

The study was approved by Institutional Ethics Committee (IEC) – AIIMS/IEC/2021/3299 dated 12th March 2021. The study was registered with the Clinical Trial Registry of India (CTRI) with registration number CTRI/2021/04/032550.

The study was conducted as per Good Clinical Practice (ICH-GCP), ICMR guidelines, after getting approval from Institutional Ethics Committee, AIIMS, Jodhpur. The aims and objectives were explained to the respondent and participants were asked to participate in the study willingly on their own and got signed the informed consent form for the study.

5.16 Funding

Fund was provided by the institute AIIMS, Jodhpur, as per thesis grant.

5.17 Confidentiality

Confidentiality and respect for personal privacy were maintained, and respondents had the opportunity to withdraw from the study.

Patient medical records and identity were treated as confidential documents. They were only revealed to other doctors/scientists/monitors/auditors of the study. The results of the study would be published in a scientific journal, but patients would not be identified by name and consent for the same has been taken.

5.18 Clinical implication

Knowing the efficacy, potency and safety of the drugs helps to care for the patients for more personalised treatment.

RESULTS

6 RESULTS

6.1 Participants flow

A total of 133 patients were screened for enrolment to the study. Out of which 16 patients were not eligible for the criteria. 5 patients were not willing to participate in the study and 57 patients were enrolled in other study. A total of 78 patients were excluded from the study. A total of 55 patients were enrolled after the screening based on eligibility criteria. After randomisation, 27 patients were enrolled in the placebo group and 28 patients were enrolled in the saroglitazar 4mg group by the end of the study. Follow-up was done every month to check the efficacy and patients were contacted by phone to assess the safety. A total of 5 patients were lost to follow-up in the placebo group.

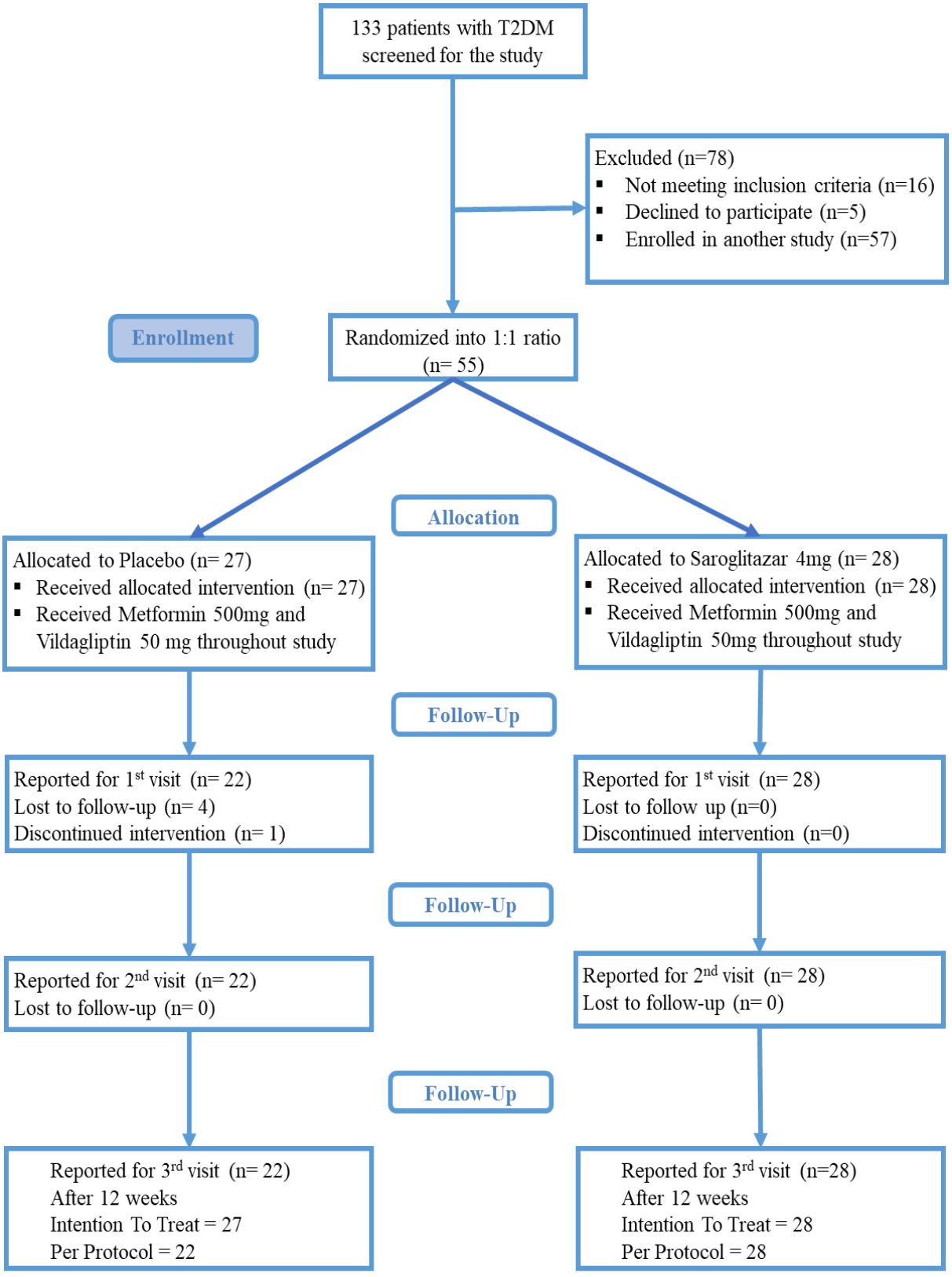


Figure 1: CONSORT flow chart

6.2 Comparison of baseline parameters between the groups

6.2.1 Demographic data

The mean age of the patients enrolled in the placebo group was 52±6.94 (mean age in years ± standard deviation (SD)); while in the saroglitazar group was 45.11±9.92. There was a significant difference in the mean age between these groups (p = 0.004), though the patients were randomized into two groups (Table 1).

The number of males and females in the placebo group was 18 and 9 respectively (66.6%/33.3%); while in the saroglitazar group were 19 and 9 respectively (67.9%/32.1%). There was no significant difference between the groups (p>0.05) (Table 1).

6.2.2 Clinical symptoms and comorbidities

In the placebo group, the number of patients having polyuria were 33.3% (n=9), polydipsia were 44.1% (n=12), polyphagia were 22.2% (n=6), visual symptoms were 44.4% (n=12). Paraesthesia/ hyperesthesia was present in 22.2% (n=6), but none of the patients had ulcer or wounds or gangrene. Family history of DM was present in 29.6% of patients (n=8), history of smoking in 23.1% (n=6), alcohol consumption in 11.1% (n=3). Non-vegetarians were 14.8% (n=4), history of chronic drug intake was observed in 18 (66.7%), hypertension in 37% (n=10), coronary artery disease (CAD) in 7.4% (n=2), hypothyroidism in 3.7% (n=1) and past surgeries were seen in 22.2% (n=6) (Table 1).

In the saroglitazar group, the number of patients with Polyuria were 50% (n=14), Polydipsia were 53.6% (n=15), Polyphagia were 60.7% (n=17), Visual symptoms were 57.1% (n=16). Paraesthesia/ hyperesthesia was present in 39.3% (n=11), Ulcer/wounds and gangrene were seen in none of the patients. Family history of DM was present in 32.1% (n=9), history of smoking in 17.9% (n=5), Alcohol consumption history was there in 10.7% (n=3), Non-vegetarians were 21.4% (n=6), history of chronic drug intake was observed in 57.1% (n=16), Hypertension in 17.9% (n=5), Coronary artery disease (CAD) was present in was 3.6% (n=1), Hypothyroidism in 17.9% (n=5) and past surgeries in 17.9% (n=5) (Table 1).

There was no significant difference in any of the clinical symptoms and comorbidities (p > 0.05), except polyphagia, which was seen more in the saroglitazar group (p=0.006)

6.2.3 Anthropometry

Weight:

The mean weight in the placebo group was 73.17±12.31 kg (mean ± SD) and in the saroglitazar group was 71.35±11.39 kg. There was no significant difference between the groups (p = 0.572) (Table 1).

Waist circumference:

The mean waist circumference in the placebo group was 84±8.12 cm and in the saroglitazar group was 84.18±6.97 cm. There was no significant difference between the groups (p=0.932) (Table 1).

Body Mass Index:

The mean BMI in the placebo group was 27.31±3.54 kg/m^2 and in the saroglitazar group was 26.27±4.19 kg/m^2. There was no significant difference between the groups (p=0.324) (Table 1).

6.2.4 Blood pressure

There was significant higher mean systolic blood pressure in placebo group (139.04±16.14 mmHg) as compared to saroglitazar group (128.32±12.75 mmHg) (p=0.008), which might be because of younger age group in saroglitazar group. However, no difference was observed in mean diastolic blood pressure in placebo (85.22±9.53 mmHg) and saroglitazar groups (80.21±9.44 mmHg) (p-value = 0.056) (Table 1).

6.2.5 Glycemic parameters

Glycated Haemoglobin (HbA1C):

The mean HbA1C in the placebo group was 8.29±1.2 and in the saroglitazar group was 8.51±1.4. There was no significant difference between the groups (p=0.536) (Table 1).

Fasting Plasma Glucose:

The mean FPG in the placebo group was 136.19±52.82 mg/dl and in the saroglitazar group was 156.04±51.50 mg/dl. There was no significant difference between the groups (p=0.164) (Table 1).

Post Prandial Glucose:

The mean PPG in the placebo group was 226.3±87.82 mg/dl and in the saroglitazar group was 233.71±77.69 mg/dl. There was no significant difference between the groups (p=0.741) (Table 1).

6.2.6 Lipid parameters

Triglycerides:

The mean triglycerides in the placebo group was 179.11±60.08 mg/dl (mean ± SD) and in the saroglitazar group was 190.14±89.73 mg/dl. There was no significant difference between the groups (p=0.596) (Table 1).

Total Cholesterol:

The mean total cholesterol in the placebo group was 191±44.03 mg/dl and in the saroglitazar group was 191.64±41.97 mg/dl. There was no significant difference between the groups (p=0.956) (Table 1).

High Density Lipoprotein (HDL):

The mean HDL in the placebo group was 37.73±7.71 mg/dl and in the saroglitazar group was 37.57±8.99 mg/dl. There was no significant difference between the groups (p = 0.943) (Table 1).

Low Density Lipoprotein (LDL):

The mean LDL in the placebo group was 122.56±44.71 mg/dl and in the saroglitazar group was 127.07±36.89 mg/dl. There was no significant difference between the groups (p=0.684) (Table 1).

6.2.7 Blood Uric Acid and High sensitive C-Reactive Protein (hsCRP)

Blood Uric Acid:

The mean B. Uric acid in the placebo group was 5.31±1.14 mg/dl and in the saroglitazar group was 5.37±1.3 mg/dl. There was no significant difference between the groups (p=0.867) (Table 1).

hsCRP:

The mean hsCRP in the placebo group was 3.42±2.64mg/L and in the saroglitazar group was 4.4±4.01 mg/L. There was no significant difference between the groups (p=293) (Table 1).

6.2.8 Fasting Insulin, HOMA-IR and HOMA-B%

Fasting insulin:

The mean fasting insulin in the placebo group was 11.39±3.77mIU/L and in the saroglitazar group was 11.92±3.51 mIU/L. There was no significant difference between the groups (p=0.592) (Table 1).

HOMA-IR:

The mean HOMA-IR in the placebo group was 3.91±2.27 and in the saroglitazar group was 4.47±1.65. There was no significant difference between the groups (p=319) (Table 1).

HOMA-B%:

The mean HOMA-B% in the placebo group was 74.31±43.71 and in the saroglitazar group was 63.4±48.95. There was no significant difference between the groups (p=0.88) (Table 1).

6.2.9 Diabetes quality of life (DQoL)

Satisfaction:

The mean DQoL score for the Satisfaction domain in placebo group is 7.67±2.49 (minimum score = 6, maximum score = 30) and in the saroglitazar group is 11.57±5.82. There was a significant difference between the groups in the satisfaction domain, p = 0.002 (Table 1).

Impact:

The mean DQoL score for the Impact domain in placebo group is 5.22±1.55 (minimum score = 4, maximum score = 20) and in the saroglitazar group is 7.18±3.61. There was a significant difference between the groups in the Impact domain, p = 0.012 (Table 1).

Worry:

The mean DQoL score for the Worry domain in placebo group is 3.81±1.66 (minimum score = 3, maximum score = 15) and in the saroglitazar group is 5.39±2.88. There was a significant difference between the groups in the Worry domain, p = 0.017 (Table 1).

Total DQoL score:

The mean total DQoL score in the placebo group is 16.7±4.93 (minimum score = 13, maximum score = 65) and in the saroglitazar group is 24.14±12.05. There was a significant difference in the total DQoL score between the groups, p = 0.004 (Table 1).

Table 1: Baseline characteristics of participants in placebo and saroglitazar groups

Baseline characteristics of two treatment groups			
Baseline characteristics	**Placebo** Mean±SD or n=27 (%)	**Saroglitazar 4mg** Mean±SD or n=28 (%)	***p-value*** **(Two sided)**
Age (years), mean±SD	52±6.94	45.11±9.92	0.004*
Male/female, n (%)	18/9 (66.6/33.3)	19/9 (67.9/32.1)	1.00
Polyuria, n (%)	9 (33.3)	14 (50)	0.277
Polydipsia, n (%)	12 (44.1)	15 (53.6)	0.593
Polyphagia, n (%)	6 (22.2)	17 (60.7)	0.006*
Visual symptoms, n (%)	12 (44.4)	16 (57.1)	0.423
Paraesthesia/hyperesthesia, n (%)	6 (22.2)	11 (39.3)	0.245
Ulcer/wounds, n (%)	0	0	0
Gangrene, n (%)	0	0	0
Family history of DM, n (%)	8 (29.6)	9 (32.1)	1.00
Smoking, n (%)	6 (23.1)	5 (17.9)	0.741
Alcohol, n (%)	3 (11.1)	3 (10.7)	1.00
Non vegetarian, n (%)	4 (14.8)	6 (21.4)	0.729
Chronic drug intake, n (%)	18 (66.7)	16 (57.1)	0.582
Hypertension, n (%)	10 (37)	5 (17.9)	0.138
Coronary artery disease (CAD), n (%)	2 (7.4)	1 (3.6)	0.611
Hypothyroidism, n (%)	1 (3.7)	5 (17.9)	0.193
Any past surgeries, n (%)	6 (22.2)	5 (17.9)	0.746

Baseline characteristics	**Placebo** Mean±SD or n=27 (%)	**Saroglitazar 4mg** Mean±SD or n=28 (%)	***p-value*** **(Two sided)**
Weight (Kg)	73.17±12.31	71.35±11.39	0.572
Height (cm)	163.47±9.92	165.01±8.89	0.529
Body mass index (BMI) (kg/m^2)	27.31±3.54	26.27±4.19	0.324
SBP (mmHg)	139.04±16.14	128.32±12.75	0.008*
DBP (mmHg)	85.22±9.53	80.21±9.44	0.056
Waist circumference (cm)	84±8.12	84.18±6.97	0.932
HbA1C (%)	8.29±1.2	8.51±1.4	0.536
FPG (mg/dl)	136.19±52.82	156.04±51.50	0.164
PPG (mg/dl)	226.3±87.82	233.71±77.69	0.741
Triglycerides (mg/dl)	179.11±60.08	190.14±89.73	0.596
Total cholesterol (mg/dl)	191±44.03	191.64±41.97	0.956
HDL (mg/dl)	37.73±7.71	37.57±8.99	0.943
LDL (mg/dl)	122.56±44.71	127.07±36.89	0.684
HsCRP (mg/L)	3.42±2.64	4.4±4.01	0.293
Blood uric acid (mg/dl)	5.31±1.14	5.37±1.3	0.867
Fasting insulin (mIU/L)	11.39±3.77	11.92±3.51	0.592
HOMA-IR	3.91±2.27	4.47±1.65	0.319
HOMA-B%	74.31±43.71	63.4±48.95	0.880

Baseline characteristics	**Placebo** Mean±SD or n=27 (%)	**Saroglitazar 4mg** Mean±SD or n=28 (%)	***p-value*** **(Two sided)**
Diabetes Quality of Life (DQoL)			
1. Satisfaction	7.67±2.49	11.57±5.82	0.002*
2. Impact	5.22±1.55	7.18±3.61	0.012*
3. Worry	3.81±1.66	5.39±2.88	0.017*
Total DQoL score	16.7±4.93	24.14±12.05	0.004*
** Asterisk mark indicating statistically significant difference between the groups*			

6.3 Change in efficacy parameters in placebo and saroglitazar groups at 12 weeks

Analysis was done both in the intention to treat principle as well as per protocol principles.

6.3.1 Weight, Waist circumference and Body Mass Index

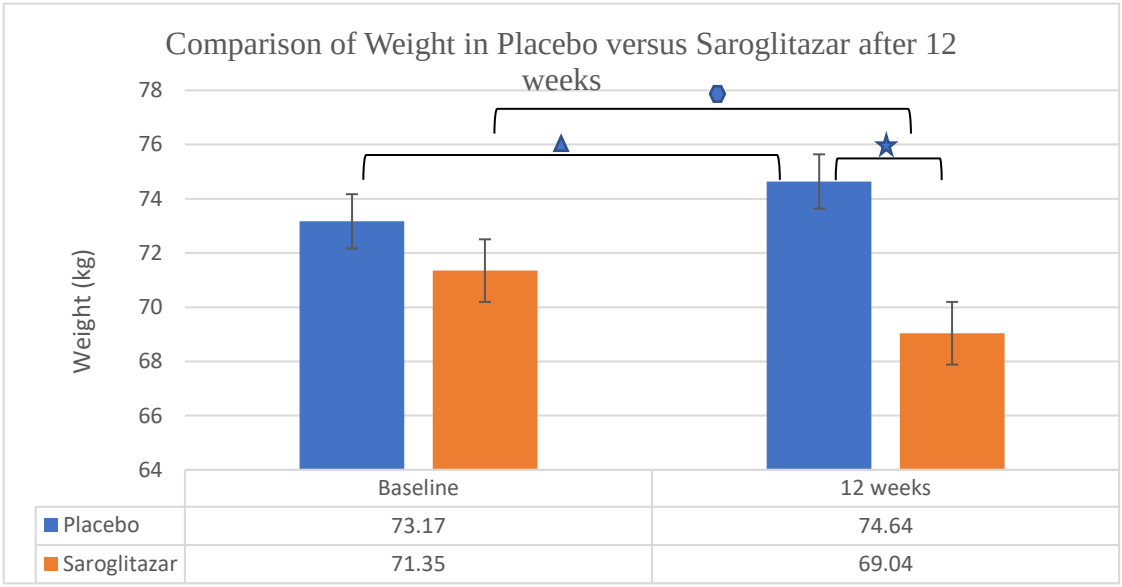


Figure 2: Comparison of Weight

▲ *Significant change (increase) in weight in placebo from baseline to 12 weeks ($p<0.05$)*

⬣ *Significant change (decrease) in weight in saroglitazar from baseline to 12 weeks ($p<0.05$)*

★ *Significant difference of change in weight in placebo versus saroglitazar after 12 weeks ($p<0.05$)*

Weight:

There was a significant change in mean weight after 12 weeks in either of the groups. Though mean weight increases significantly by 0.97 ± 1.57 kg in the placebo group ($p = 0.003$), patient in saroglitazar group observed significant decrease in mean weight by -2.31±1.97 kg ($p < 0.001$). (Table 2; Figure 2)

Statistically significant decline in weight was observed in saroglitazar group as compared to placebo (Mean difference (95%CI) = 3.29 (2.32 to 4.26), p-value <0.001). Per protocol results (Table 3) were similar to ITT analysis.

Waist circumference:

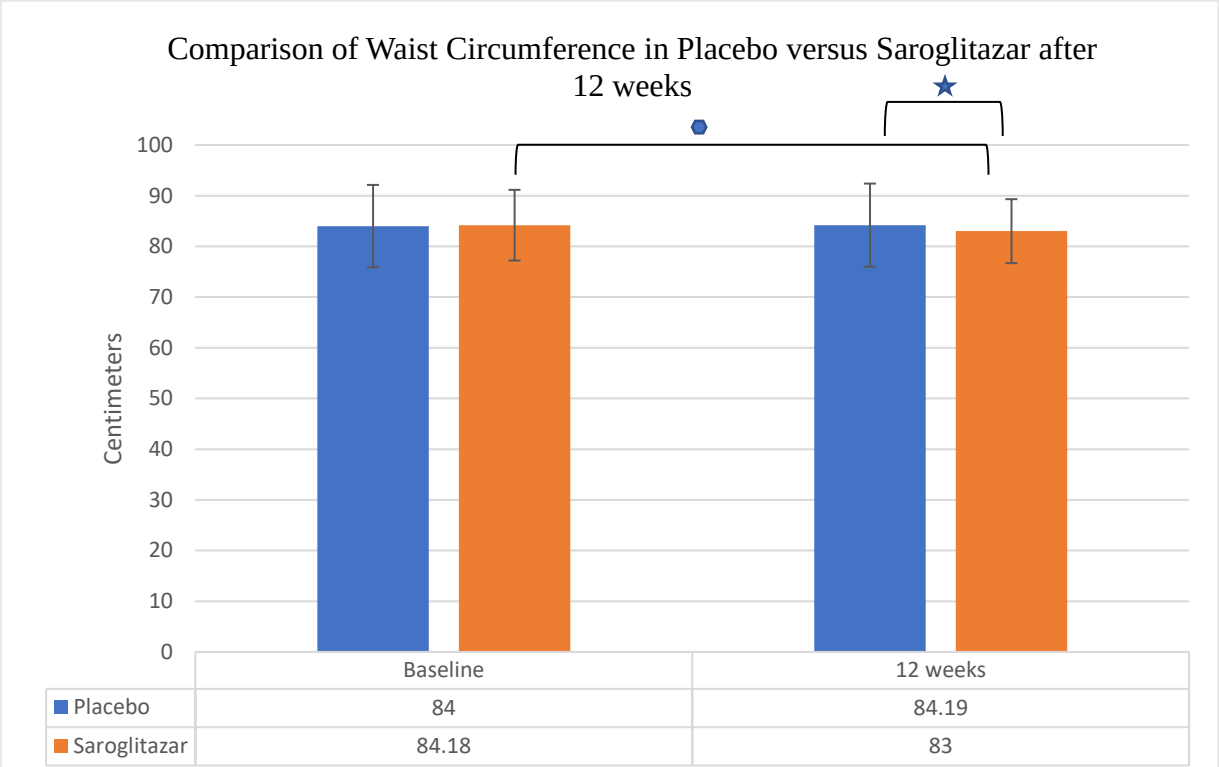


Figure 3: Comparison of waist circumference

⬣ *Significant change in waist circumference in saroglitazar from baseline to 12 weeks ($p<0.05$)*

★ *Significant difference of change in waist circumference in placebo versus saroglitazar after 12 weeks ($p<0.05$)*

There was a significant change in mean waist circumference after 12 weeks in the saroglitazar group. The mean waist circumference increased by 0.18 ± 0.84 cm in the placebo group ($p = 0.256$), patients in saroglitazar group observed significant decrease in mean waist circumference by -1.17±1.19 cm ($p<0.001$). (Table 2; Figure 3)

Statistically significant decline in waist circumference was observed in saroglitazar group as compared to placebo (Mean difference (95%CI) = 1.36(0.8 to 1.92), p-value <0.001). Per protocol results (Table 3) were similar to ITT analysis.

Body Mass Index:

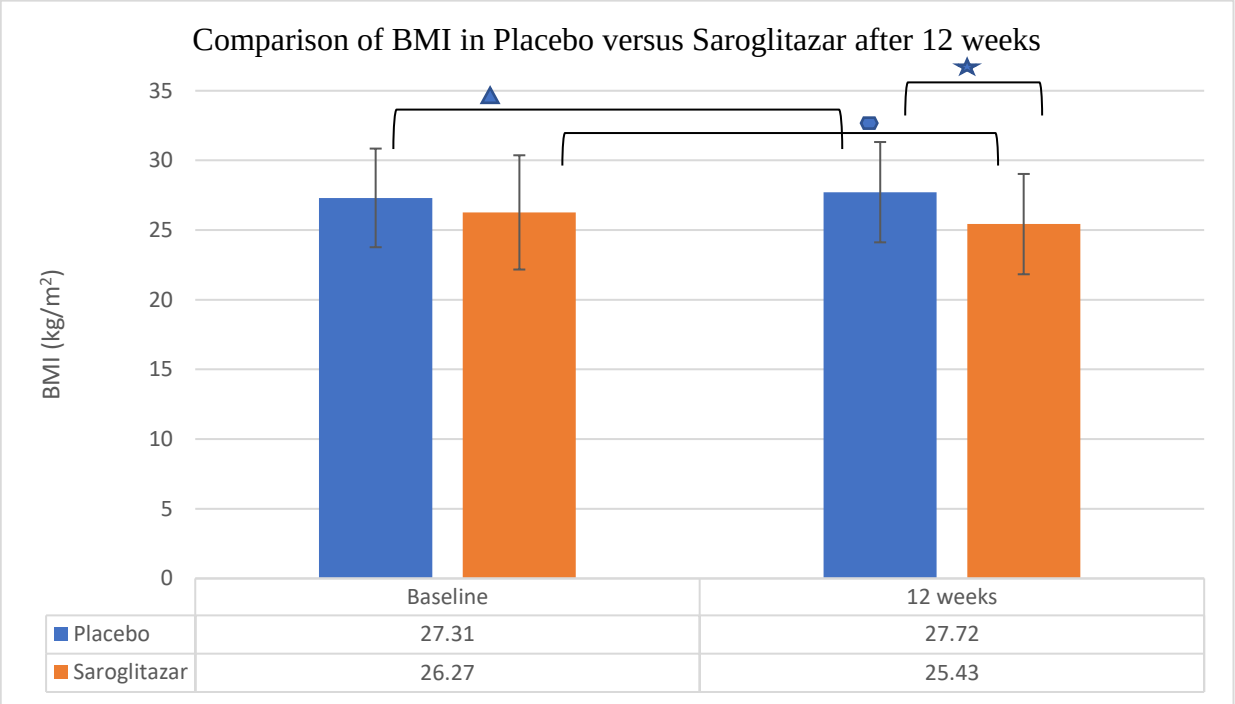


Figure 4: Comparison of BMI

▲ *Significant change (increase) in BMI in placebo from baseline to 12 weeks ($p<0.05$)*

⬢ *Significant change (decrease) in BMI in saroglitazar from baseline to 12 weeks ($p<0.05$)*

★ *Significant difference of change in BMI in placebo versus saroglitazar after 12 weeks ($p<0.05$)*

There was significant change in mean BMI after 12 weeks in either of the groups. Though mean BMI increased significantly by 0.406 ± 0.604 kg/m^2 (p=0.002) in the placebo group, patients in saroglitazar group observed significant decrease in mean BMI by -0.84±0.75 kg/m^2 (p<0.001). (Table 2; Figure 4)

Statistically significant decline in BMI was observed in saroglitazar group as compared to placebo (Mean difference (95%CI) = 1.24 kg/m^2 (0.87 to 1.61), p-value <0.001). Per protocol results (Table 3) were similar to ITT analysis.

6.3.2 Blood pressure

Systolic blood pressure:

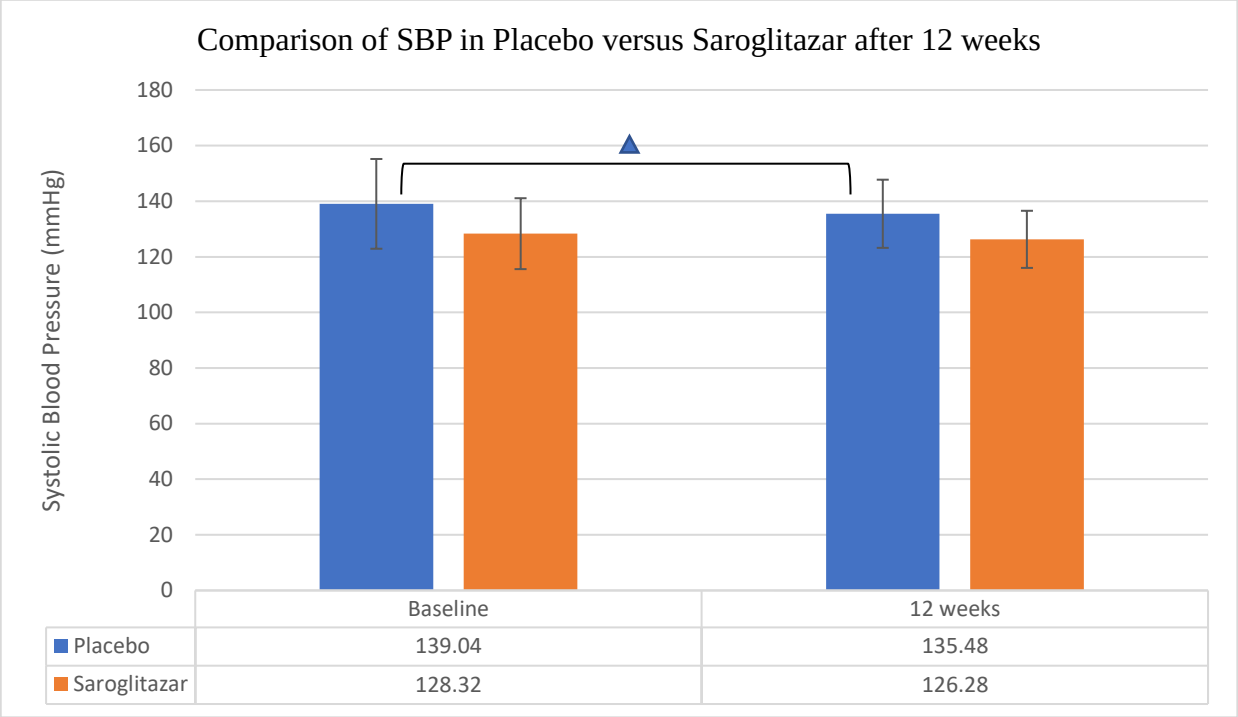


Figure 5: Comparison of SBP

▲ *Significant change in SBP in placebo from baseline to 12 weeks ($p<0.05$)*

There was significant change in mean SBP after 12 weeks in the placebo group. The mean SBP decreased significantly by -3.56±8.68 mmHg (p=0.043) in the placebo group, patient in saroglitazar group observed no significant decrease in mean SBP, -1.64 ±6.8 mmHg (p=0.212). (Table 2; Figure 5)

No statistically significant decline in SBP was observed in saroglitazar group as compared to placebo (Mean difference (95%CI) = -1.91 mmHg (-6.12 to 2.29), p-value =0.36). Per protocol results (Table 3) were similar to ITT analysis.

Diastolic blood pressure:

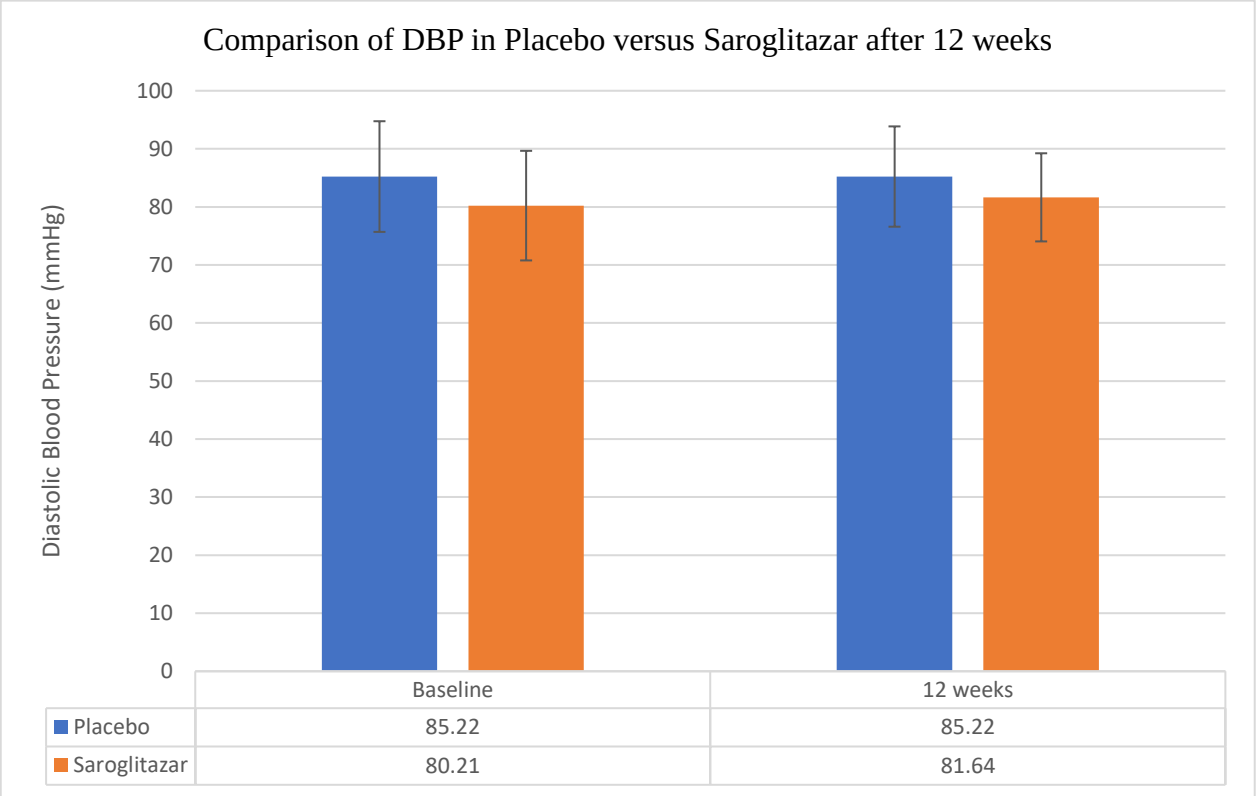


Figure 6: Comparison of DBP

There was no significant change in mean DBP after 12 weeks in either of the groups. The mean DBP increased by 0.001± 6.21 mmHg (p = 1.0) in the placebo group, patients in saroglitazar group observed increase in mean DBP, 1.43±7.59 mmHg (p=0.328). (Table 2; Figure 6)

No statistically significant change in DBP was observed in saroglitazar group as compared to placebo (Mean difference (95%CI) = -1.42 mmHg (-5.18 to 2.32), p-value =0.44). Per protocol results (Table 3) were similar to ITT analysis.

6.3.3 Glycemic parameters

Glycated Haemoglobin (HbA1c):

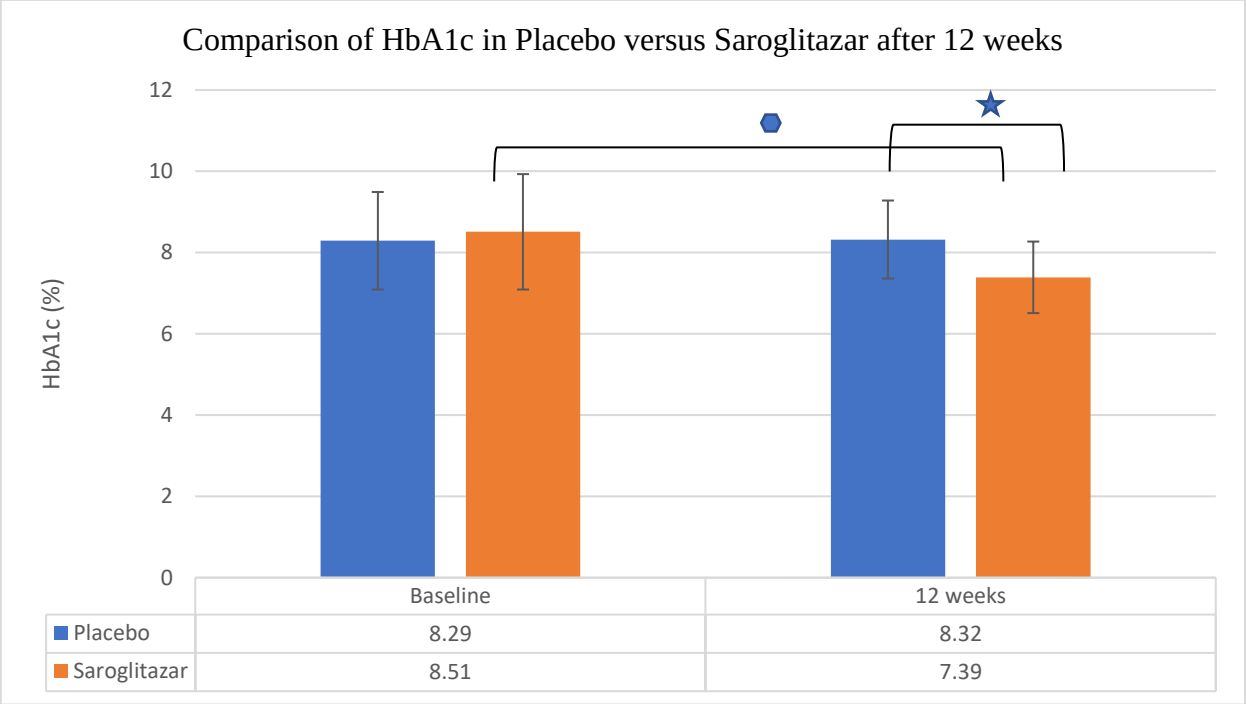


Figure 7: Comparison of HbA1c

- *Significant change (decrease) in HbA1ct in saroglitazar from baseline to 12 weeks ($p<0.05$)*
- *Significant difference of change in HbA1c in placebo versus saroglitazar after 12 weeks ($p<0.05$)*

There was significant change in mean HbA1C after 12 weeks in the saroglitazar group. The mean HbA1C increases by 0.029 ±0.79 ($p = 0.847$) in the placebo group, patient in saroglitazar group observed significant decrease in mean HbA1C by -1.12±0.78 ($p < 0.001$). (Table 2; Figure 7)

Statistically significant decline in HbA1C was observed in saroglitazar group as compared to placebo (Mean difference (95%CI) = 1.15(0.72 to 1.57), p-value <0.001). Per protocol results (Table 3) were similar to ITT analysis.

Fasting plasma glucose (FPG):

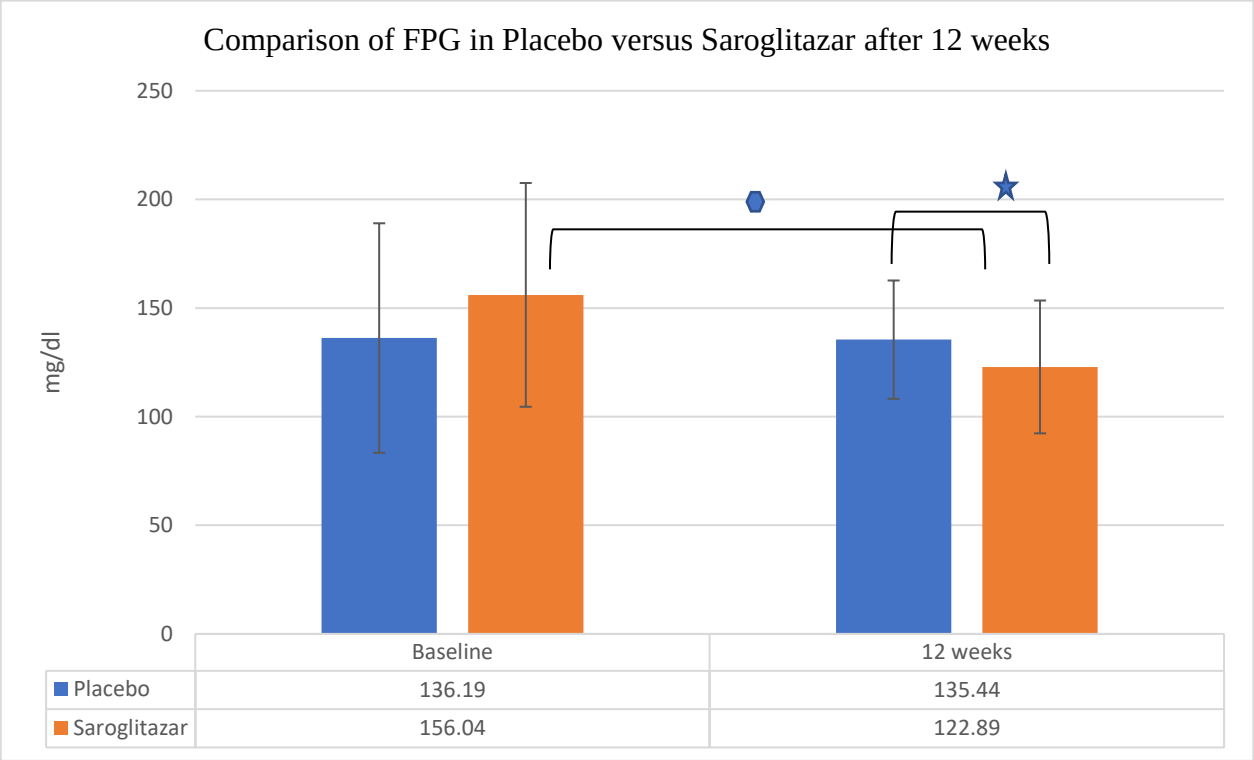


Figure 8: Comparison of FPG

⬢ *Significant change (decrease) in FPG in saroglitazar from baseline to 12 weeks ($p<0.05$)*

★ *Significant difference of change in FPG in placebo versus saroglitazar after 12 weeks ($p<0.05$)*

There was a significant change in mean fasting plasma glucose after 12 weeks in the saroglitazar group. The mean FPG decreased by -0.74 ±52.46 mg/dl (p = 0.942) in the placebo group, patients in the saroglitazar group observed a significant decrease in mean FPG by -33.14± 38.36 mg/dl (p < 0.001). (Table 2; Figure 8)

A statistically significant decline in FPG was observed in the saroglitazar group as compared to placebo (Mean difference (95%CI) = 32.42(7.6 to 57.19), p-value = 0.011). Per protocol results (Table 3) were different to ITT analysis and was not statistically significant (p = 0.23)

Post Prandial Glucose (PPG):

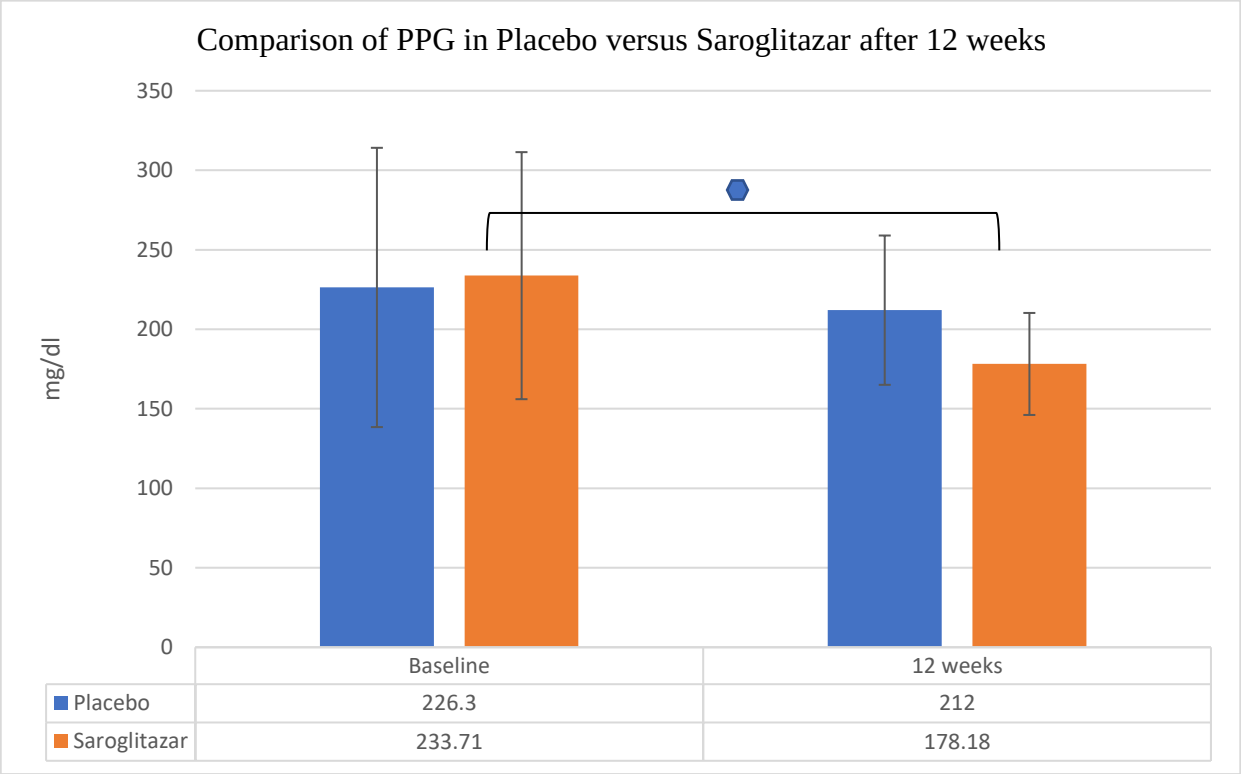


Figure 9: Comparison of PPG

⬢ *Significant change (decrease) in PPG in saroglitazar from baseline to 12 weeks ($p<0.05$)*

There was significant change in mean postprandial glucose after 12 weeks in the saroglitazar group. Though mean PPG decreases by -14.30± 87.24 mg/dl ($p = 0.402$) in the placebo group, patients in the saroglitazar group observed significant decrease in mean PPG by -55.54± 66.44 mg/dl ($p<0.001$). (Table 2; Figure 9)

No statistically significant decline in PPG was observed in the saroglitazar group as compared to placebo (Mean difference (95%CI) = 41.23(-0.6 to 83.08), p-value = 0.053). Per protocol results (Table 3) were similar to ITT analysis.

6.3.4 Lipid parameters

Triglycerides:

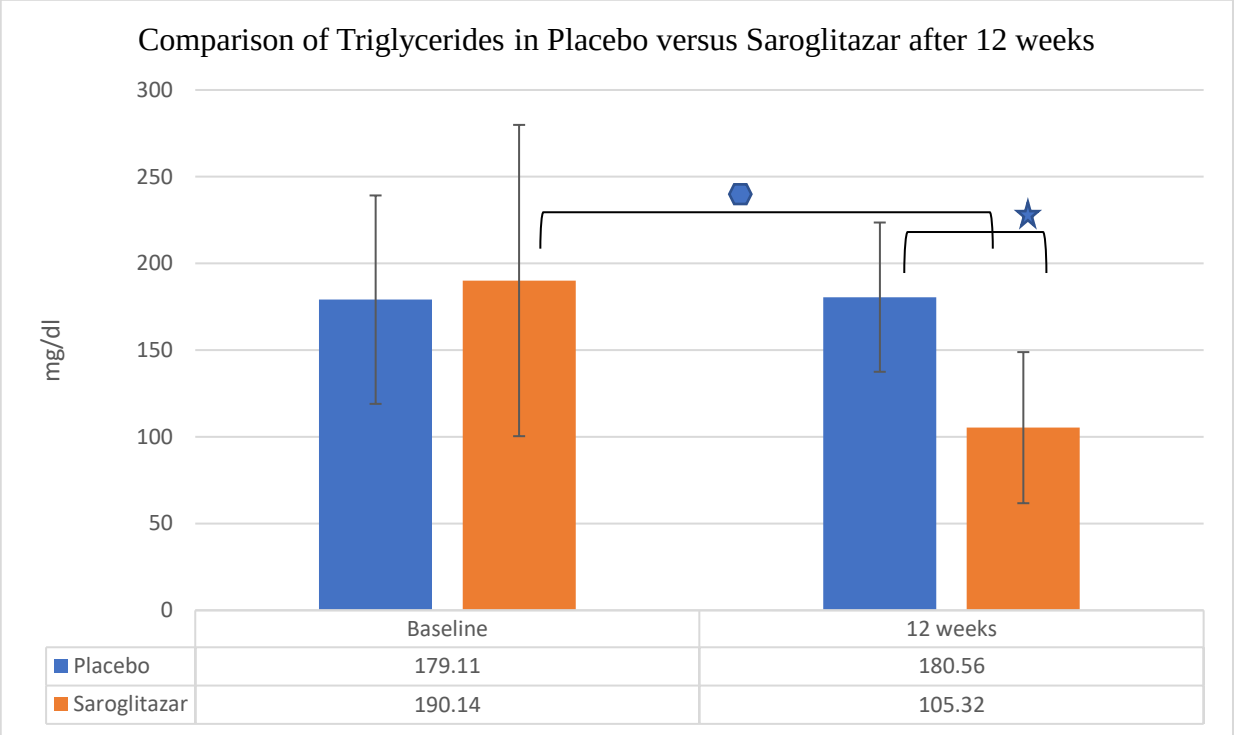


Figure 10: Comparison of Triglycerides

- *Significant change (decrease) in Triglycerides in saroglitazar from baseline to 12 weeks ($p<0.05$)*
- *Significant difference of change in Triglycerides in placebo versus saroglitazar after 12 weeks ($p<0.05$)*

There was a significant change in mean triglycerides after 12 weeks in the saroglitazar group. The mean triglycerides increased by 1.44±41.0 mg/dl (0.856) in the placebo group, patients in the saroglitazar group observed significant decrease in mean triglycerides by -84.82± 63.71 mg/dl ($p<0.001$). (Table 2; Figure 10)

A statistically significant decline in triglycerides was observed in the saroglitazar group as compared to placebo (Mean difference (95%CI) = 86.26 (57.16 to 115.36), p-value <0.001). Per protocol results (Table 3) were similar to ITT analysis.

Total cholesterol:

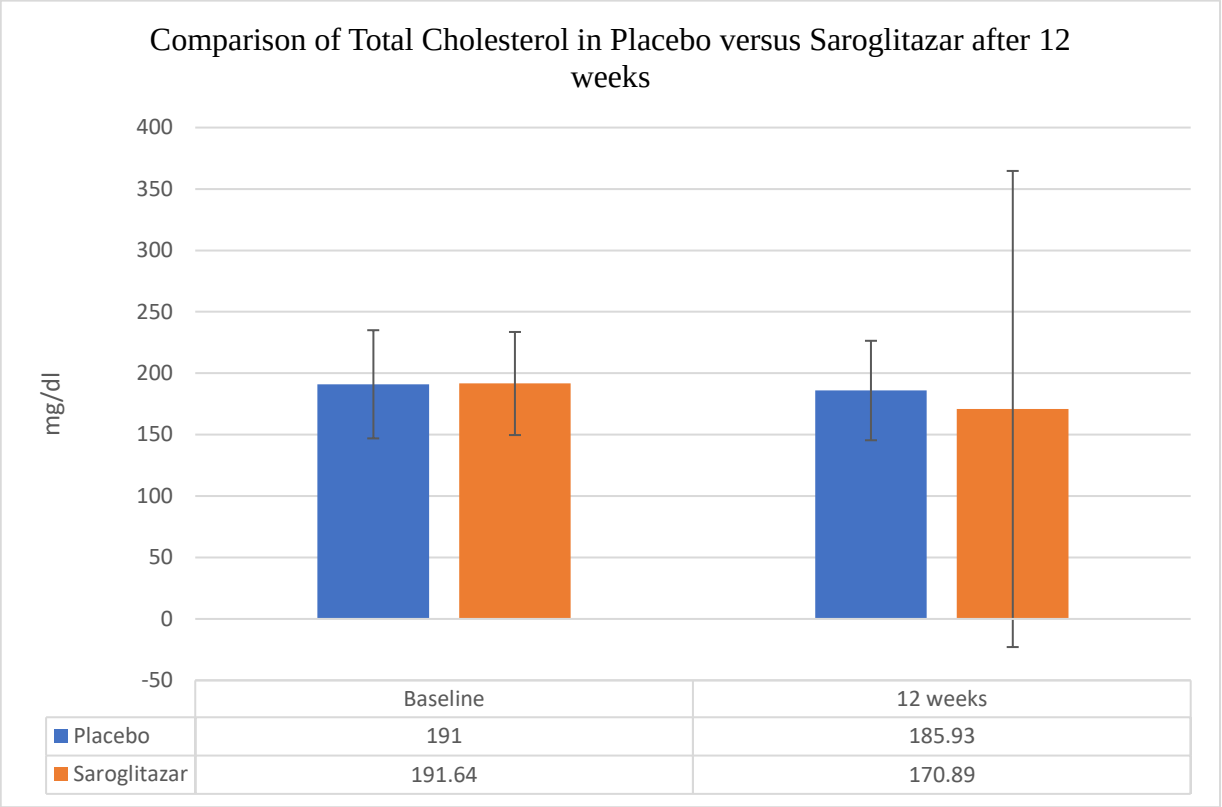


Figure 11: Comparison of Total Cholesterol

There was a no significant change in mean total cholesterol after 12 weeks in either of the groups. The mean total cholesterol decreased by -5.07± 35.83 mg/dl (p = 0.468)) in the placebo group, patients in the saroglitazar group observed decrease in mean total cholesterol by -20±194.35 mg/dl (p = 0.57). (Table 2; Figure 11)

No statistically significant decline in total cholesterol was observed in the saroglitazar group as compared to placebo (Mean difference (95%CI) = 15.67(-60.59 to 91.93), p-value = 0.68). Per protocol results (Table 3) were similar to ITT analysis.

High density lipoprotein:

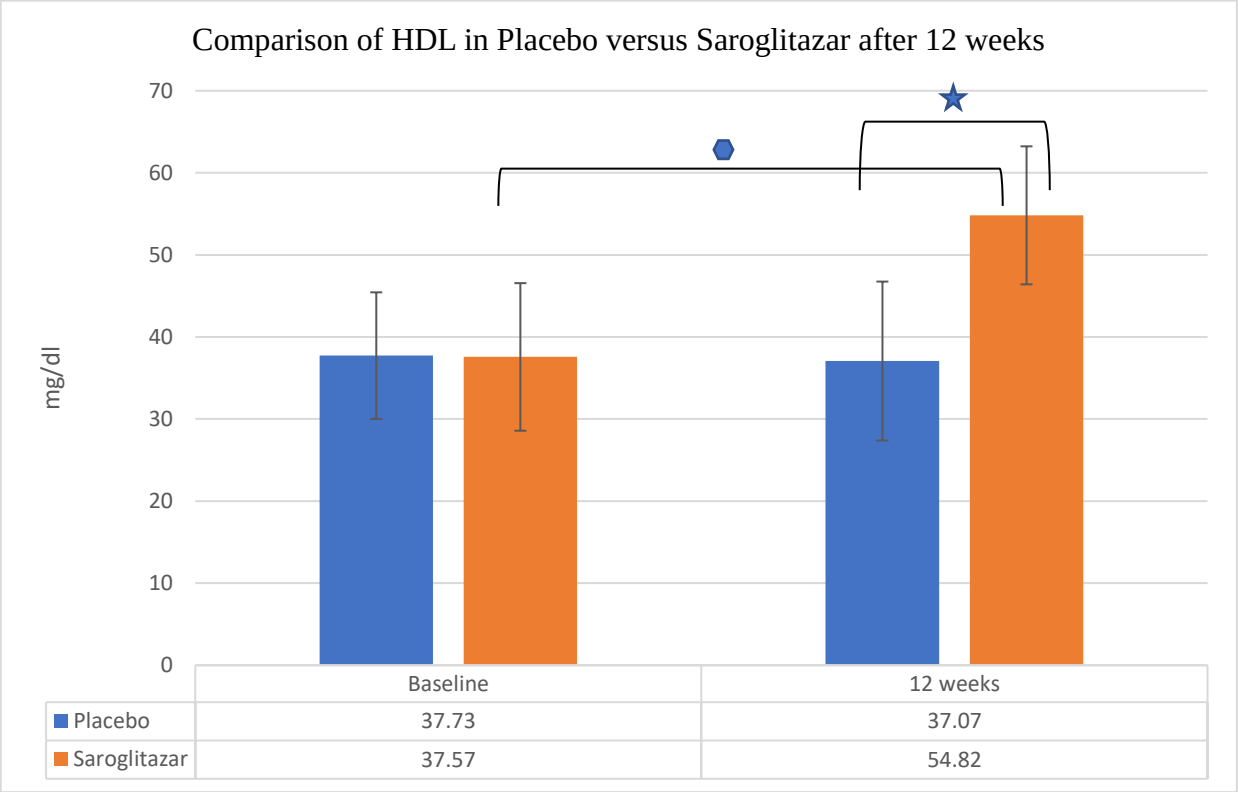


Figure 12: Comparison of HDL

- ⬣ *Significant change (increase) in HDL in saroglitazar from baseline to 12 weeks ($p<0.05$)*
- ★ *Significant difference of change in HDL in placebo versus saroglitazar after 12 weeks ($p<0.05$)*

There was a significant change in mean HDL after 12 weeks in the saroglitazar group. The mean HDL decreased by -0.659 ±7.82 ($p = 0.665$) in the placebo group, patients in the saroglitazar group observed significant increase in mean HDL by 17.25±8.91 ($p < 0.001$)). (Table 2; Figure 12)

A statistically significant increase in HDL was observed in the saroglitazar group as compared to placebo (Mean difference (95%CI) = -17.9(-22.4 to -13.36)), p-value <0.001). Per protocol results (Table 3) were similar to ITT analysis.

Low density lipoprotein:

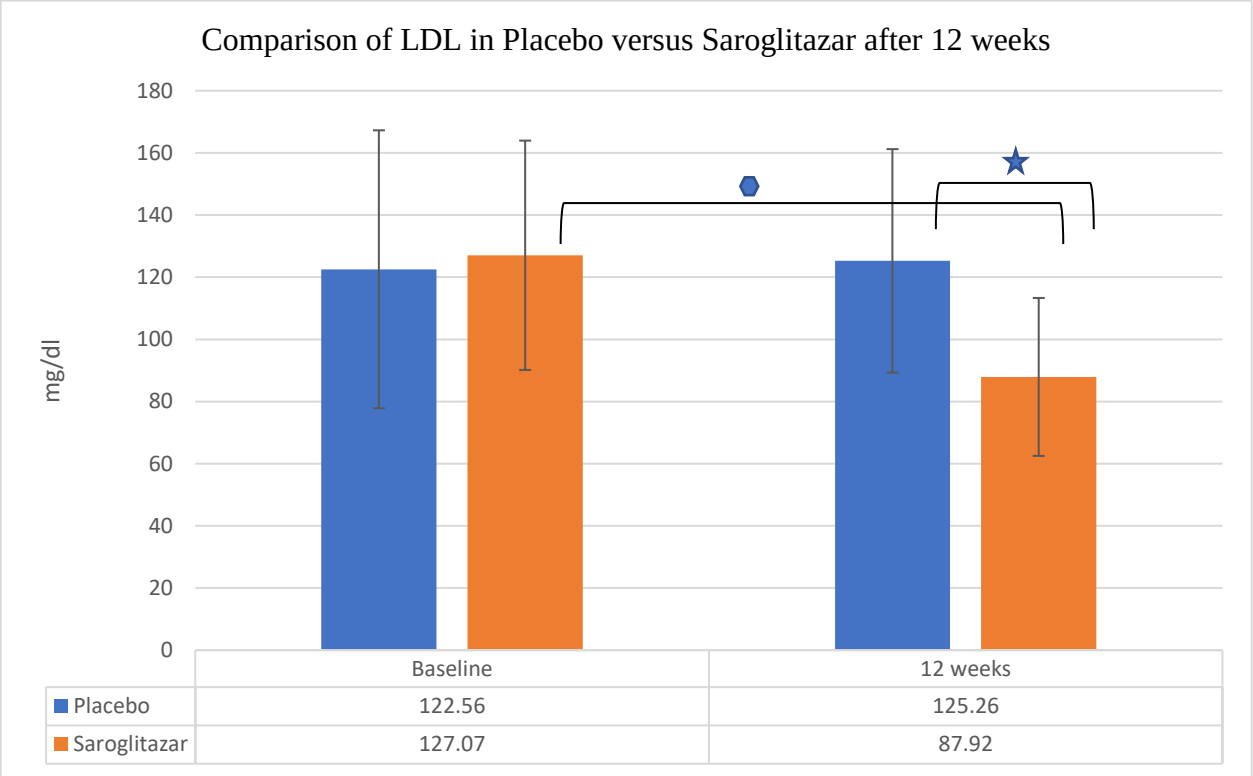


Figure 13:Comparison of LDL

⬢ *Significant change (decrease) in LDL in saroglitazar from baseline to 12 weeks (p<0.05)*

★ *Significant difference of change in LDL in placebo versus saroglitazar after 12 weeks (p<0.05)*

There was a significant change in mean LDL after 12 weeks in the saroglitazar group. The mean LDL increased by 2.7±39.14 (0.723) in the placebo group, patients in the saroglitazar group observed significant decrease in mean triglycerides by -39.25± 27.06 (<0.001). (Table 2; Figure 13)

A statistically significant decline in triglycerides was observed in the saroglitazar group as compared to placebo (Mean difference (95%CI) = 41.95(23.8 to 60), p-value <0.001). Per protocol results (Table 3) were similar to ITT analysis.

6.3.5 Blood uric acid and HsCRP

Blood uric acid:

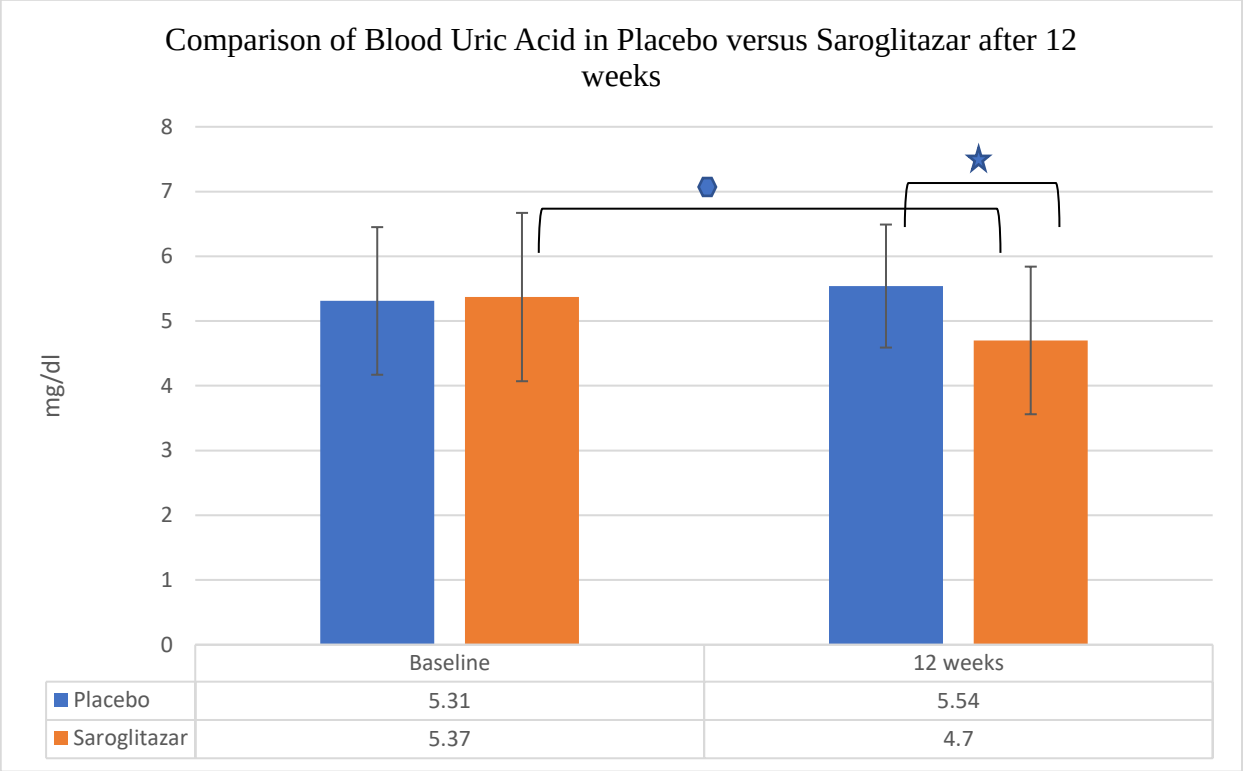


Figure 14: Comparison of Blood Uric Acid

⬣ *Significant change (decrease) in Blood uric acid in saroglitazar from baseline to 12 weeks ($p<0.05$)*

★ *Significant difference of change in Blood uric acid in placebo versus saroglitazar after 12 weeks ($p<0.05$)*

There was a significant change in mean blood uric acid after 12 weeks in the saroglitazar group. The mean blood uric acid increased by 0.22±0.85 (p = 0.188) in the placebo group, patients in the saroglitazar group observed significant decrease in mean triglycerides -0.66±0.8 (p < 0.001). (Table 2; Figure 14)

A statistically significant decline in blood uric acid was observed in the saroglitazar group as compared to placebo (Mean difference (95%CI) = 0.88(0.43 to 1.33)), p-value <0.001). Per protocol results (Table 3) were similar to ITT analysis.

High sensitive C- reactive protein:

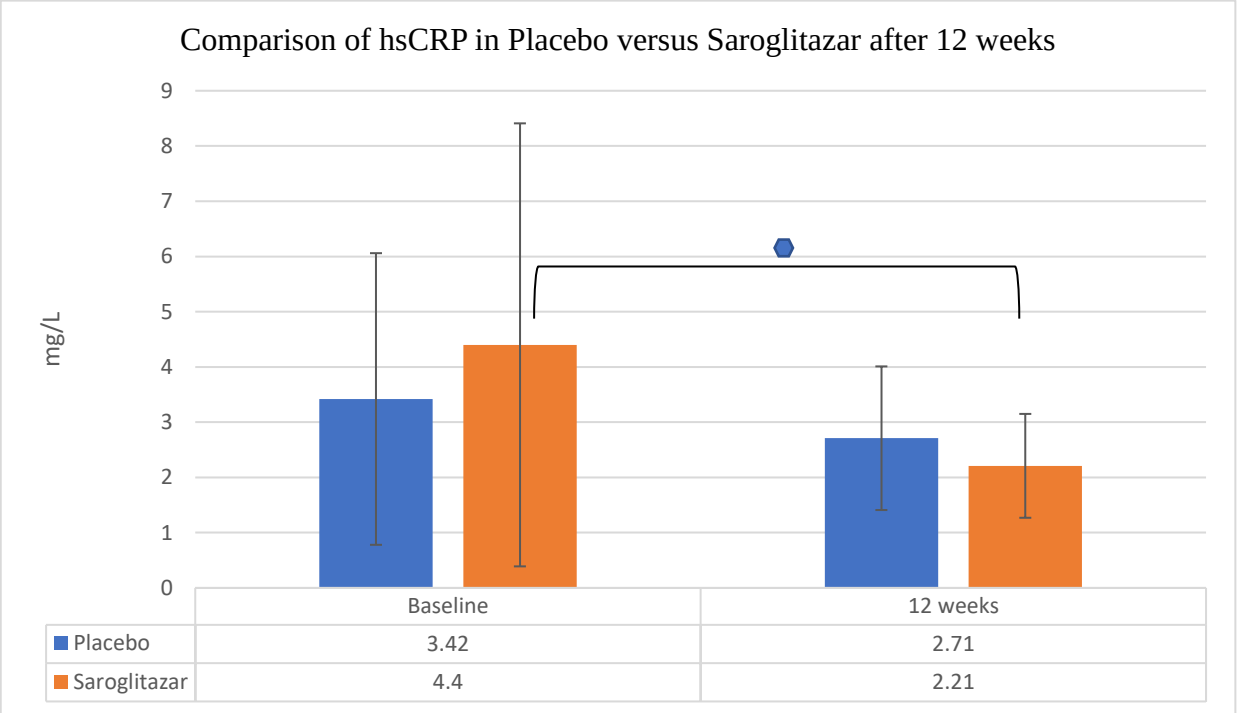


Figure 15: Comparison of hsCRP

⬢ *Significant change (decrease) in hsCRP in saroglitazar from baseline to 12 weeks ($p<0.05$)*

There was a significant change in mean hsCRP after 12 weeks in the saroglitazar group. The mean hsCRP decreased by -0.71±2.19 (0.103) in the placebo group, patients in the saroglitazar group observed significant decrease in mean hsCRP by -2.1±3.47 (0.002). (Table 2; Figure 15)

No statistically significant decline in hsCRP was observed in the saroglitazar group as compared to placebo (Mean difference (95%CI) = 1.47(-0.09 to 3.05), p-value = 0.065). Per protocol results (Table 3) were similar to ITT analysis.

6.3.6 Fasting insulin, HOMA-IR and HOMA-B%

Fasting Insulin:

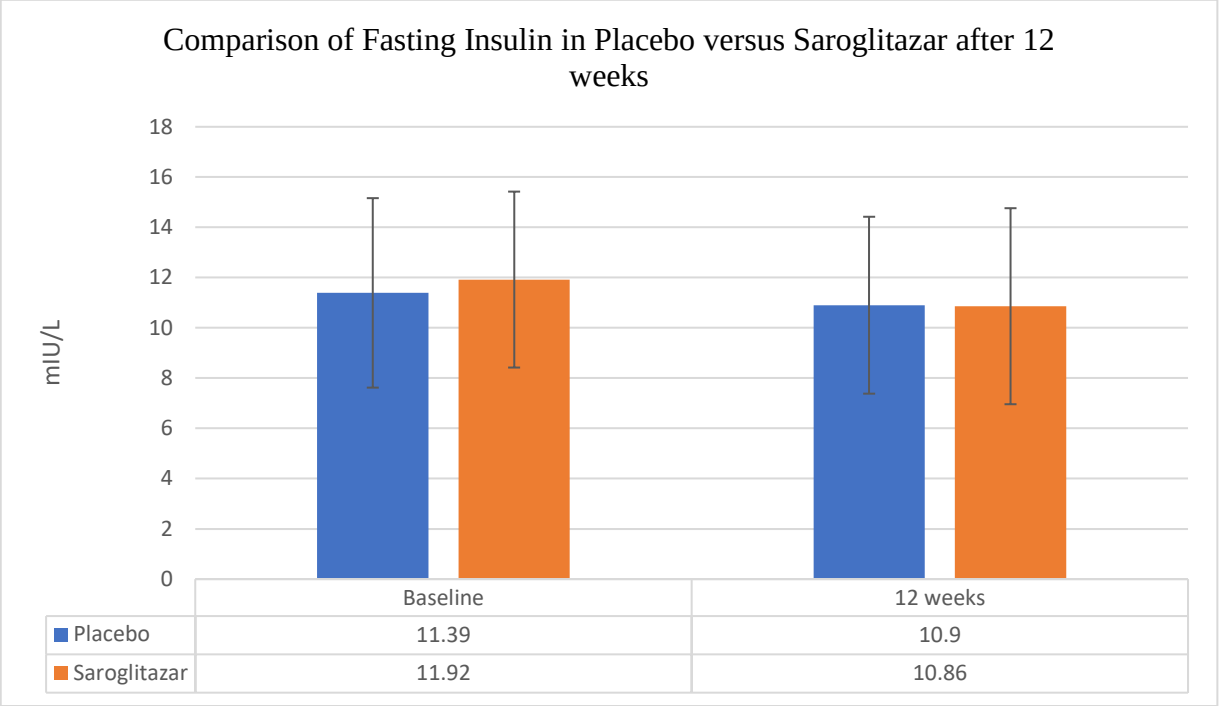


Figure 16: Comparison of Fasting Insulin

There was a no significant change in mean fasting insulin after 12 weeks in either of the groups. The mean fasting insulin decreased by -0.49±2.18 (p = 0.253) in the placebo group, patients in the saroglitazar group observed decrease in mean fasting insulin by -1.06±3.68 (p = 0.139). (Table 2; Figure 16)

No difference in fasting insulin was observed in the saroglitazar group as compared to placebo (Mean difference (95%CI) = 0.56(-1.07 to 2.21), p-value = 0.49). Per protocol results (Table 3) were similar to ITT analysis.

HOMA-IR:

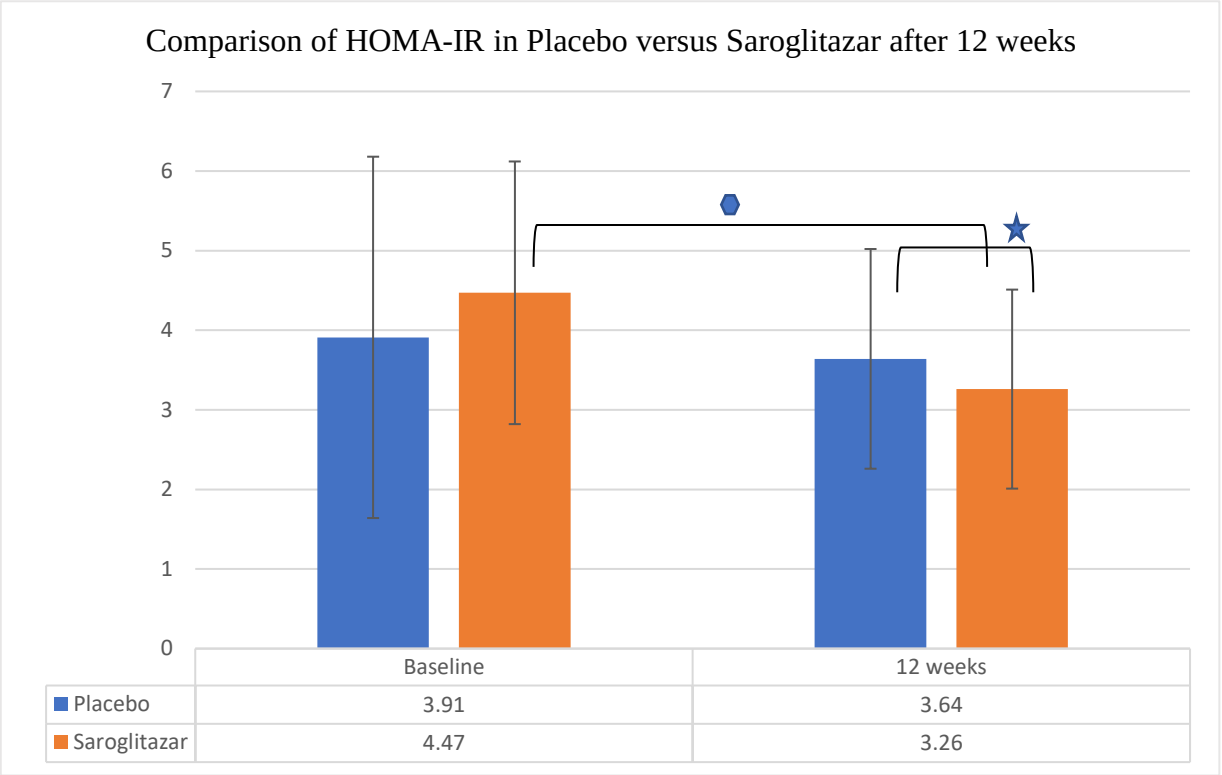


Figure 17: Comparison of HOMA-IR

⬢ *Significant change (decrease) in HOMA-IR in saroglitazar from baseline to 12 weeks ($p<0.05$)*

★ *Significant difference of change in HOMA-IR in placebo versus saroglitazar after 12 weeks ($p<0.05$)*

There was a significant change in mean HOMA-IR after 12 weeks in the saroglitazar group. The mean HOMA-IR decreased by -0.26±1.65 (p = 0.417) in the placebo group, patients in the saroglitazar group observed decrease in mean HOMA-IR by -1.2±1.72 (p = 0.001). (Table 2; Figure 17)

A statistically significant decline in HOMA-IR was observed in the saroglitazar group as compared to placebo (Mean difference (95%CI) = 0.94(0.028 to 1.86), p-value = 0.044). Per protocol results (Table 3) were different to ITT analysis, p = 0.087

HOMA-B%:

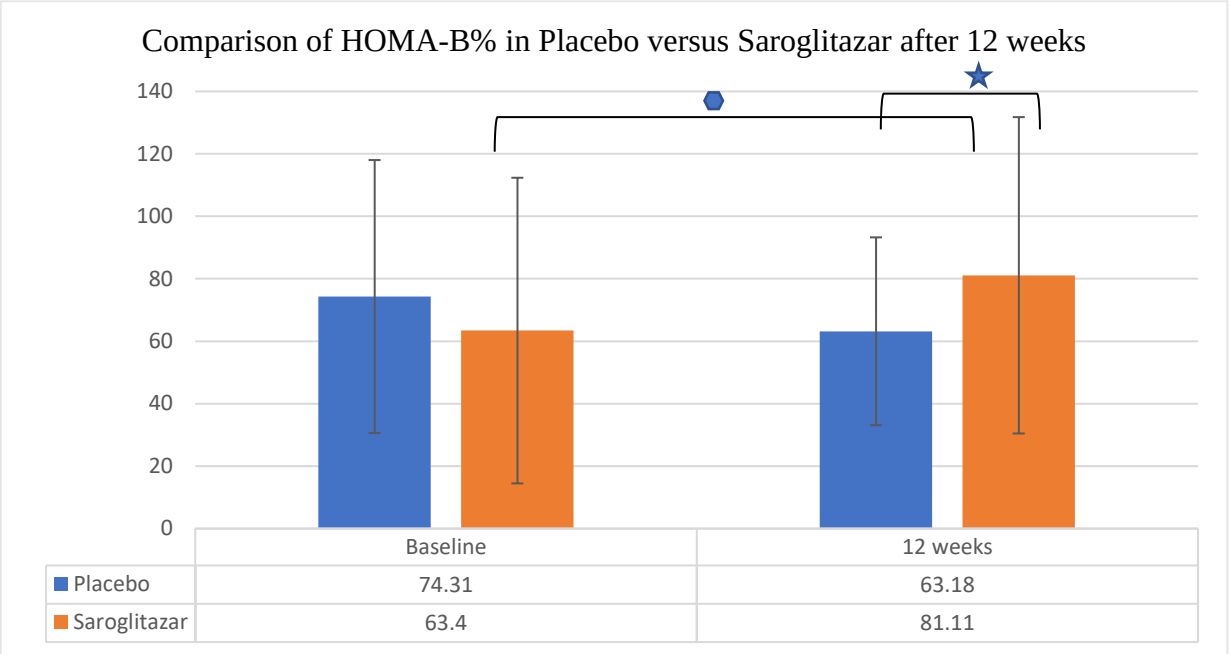


Figure 18: Comparison of HOMA-B%

- *Significant change (increase) in HOMA-B% in saroglitazar from baseline to 12 weeks ($p<0.05$)*
- *Significant difference of change in HOMA-B% in placebo versus saroglitazar after 12 weeks ($p<0.05$)*

There was a significant change in mean HOMA-B% after 12 weeks in the saroglitazar group. The mean HOMA-B% decreased by -11.13± 35.38 (0.114) in the placebo group, patients in the saroglitazar group observed an increase in mean HOMA-B% by 17.71± 28.83 (0.003). (Table 2; Figure 18)

Statistically significant improvement in HOMA-B% was observed in the saroglitazar group as compared to placebo (Mean difference (95%CI) = -28.85(-46.36 to -11.33), p-value = 0.002). Per protocol results (Table 3) were similar to ITT analysis.

In Per Protocol Analysis, the significant change across the groups were almost similar and statistically significant with p-value <0.05; except fasting plasma glucose value and HOMA-IR. The mean difference of FPG is 32.23 (CI 4.64 to 59.81), with the p value 0.23, which was statistically not significant. The means difference of HOMA-IR is 0.88 (CI -0.13 to 1.9), with the p value 0.087, which was statistically not significant

6.3.7 Diabetes Quality of Life (DQoL)

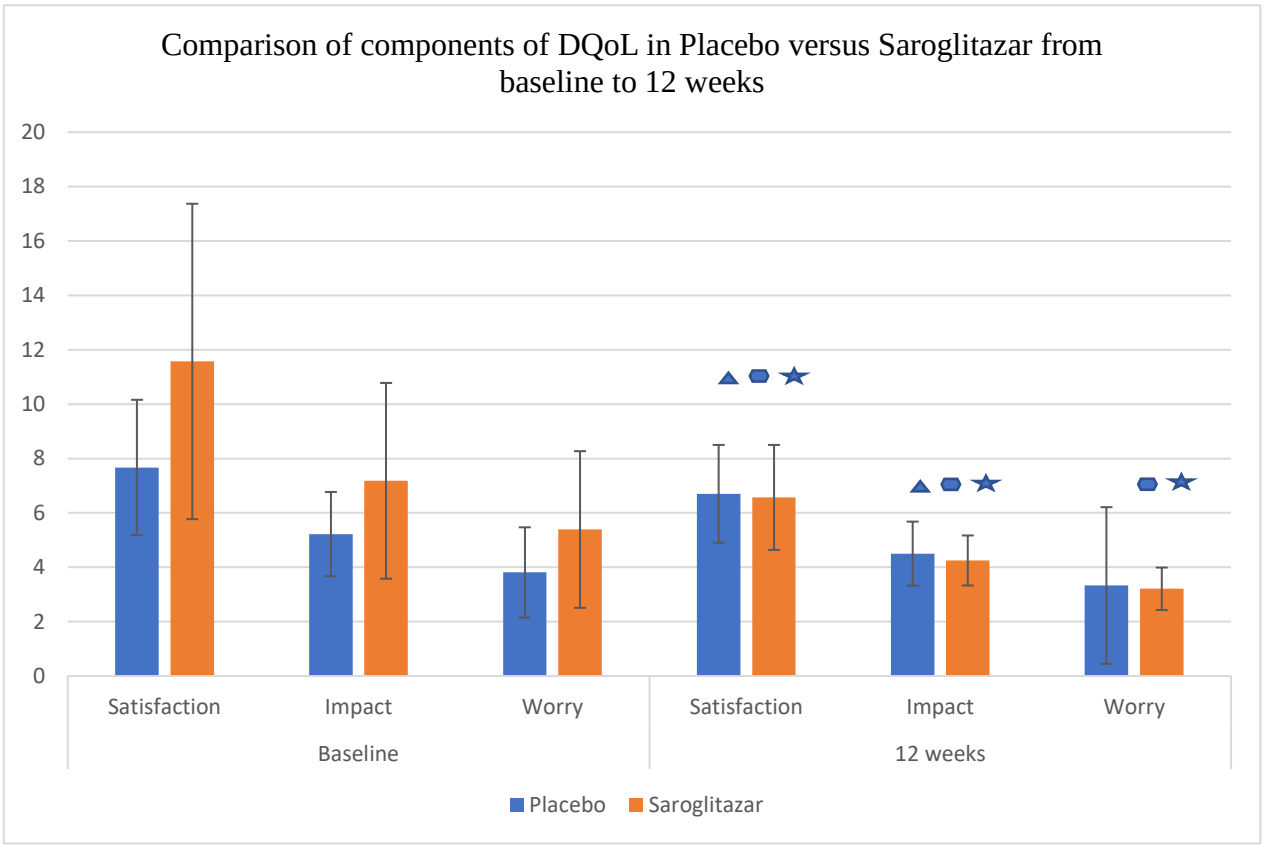


Figure 19:Comparison of components of DQoL

- ▲ *Significant change (decrease) in all the components of DQoL except Worry in placebo from baseline to 12 weeks ($p<0.05$)*
- ⬢ *Significant change (decrease) in all the components of DQoL in saroglitazar from baseline to 12 weeks ($p<0.05$)*
- ★ *Significant difference of change in all the components of DQoL in placebo versus saroglitazar after 12 weeks ($p<0.05$)*

Satisfaction:

There was a significant change in mean satisfaction domain scores after 12 weeks in either of the groups. The mean satisfaction scores decreased by -0.96±2.1 (p = 0.025) in the placebo group, patients in the saroglitazar group observed a decrease in mean satisfaction scores by -4.82±5.22 ($p<0.001$). (Table 2; Figure 19)

Statistically significant improvement (decrease) in satisfaction scores were observed in the saroglitazar group as compared to placebo (Mean difference (95%CI) = 3.85 (1.69 to 6.02), p-value = 0.001). Per protocol results (Table 3) were similar to ITT analysis.

Impact:

There was a significant change in mean Impact domain scores after 12 weeks in either of the groups. The mean Impact scores decreased by -0.67±1.3 (p = 0.013) in the placebo group, patients in the saroglitazar group observed a decrease in mean Impact scores by -2.93±3.4 (p<0.001). (Table 2; Figure 19)

Statistically significant improvement (decrease) in Impact scores were observed in the saroglitazar group as compared to placebo (Mean difference (95%CI) = 2.26 (0.85 to 3.6), p-value = 0.002). Per protocol results (Table 3) were similar to ITT analysis.

Worry:

There was a significant change in mean Worry domain scores after 12 weeks in the saroglitazar group. The mean Worry scores decreased by -0.48±1.22 (0.051) in the placebo group, patients in the saroglitazar group observed a decrease in mean Worry scores by -2.18±2.5 (p<0.001). (Table 2; Figure 19)

Statistically significant improvement (decrease) in Worry scores were observed in the saroglitazar group as compared to placebo (Mean difference (95%CI) = 1.69 (0.59 to 2.79), p-value = 0.003). Per protocol results (Table 3) were different to ITT analysis, p = 0.12.

Total DQoL score:

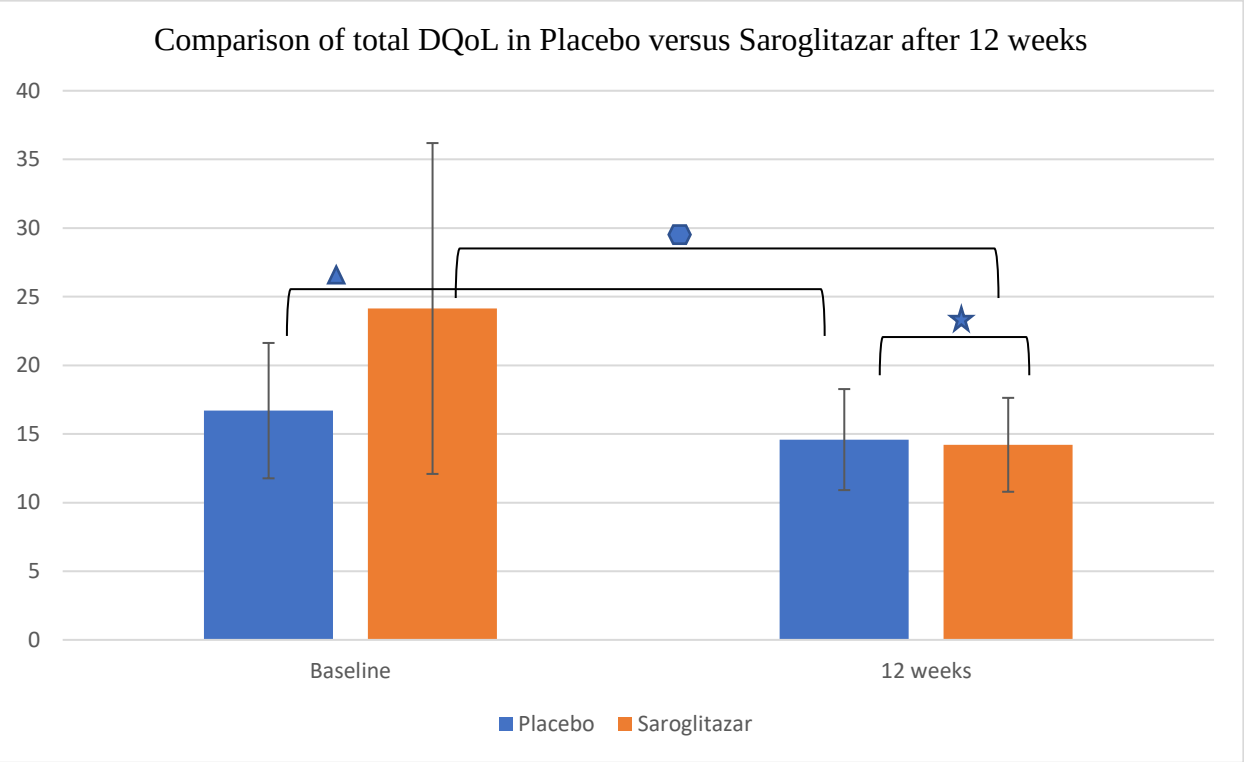


Figure 20:Comparison of DQoL

- ▲ *Significant change (decrease) in Total DQoL score in placebo from baseline to 12 weeks ($p<0.05$)*
- ⬢ *Significant change (decrease) in Total DQoL score in saroglitazar from baseline to 12 weeks ($p<0.05$)*
- ★ *Significant difference of change in Total DQoL score in placebo versus saroglitazar after 12 weeks ($p<0.05$)*

There was a significant change in mean total DQoL score after 12 weeks in either of the groups. The mean total DQoL scores decreased by -2.11±3.95 (p = 0.01) in the placebo group, patients in the saroglitazar group observed a decrease in mean total DQoL scores by -9.93±11.03 (p < 0.001). (Table 2; Figure 20)

Statistically significant improvement (decrease) in total DQoL scores were observed in the saroglitazar group as compared to placebo (Mean difference (95%CI) = 7.81 (3.3 to 12.33), p-value = 0.001). Per protocol results (Table 3) were similar to ITT analysis.

Table 2:Change in Efficacy Parameters (ITT) after the treatment for 12 weeks in both the groups

Mean change in efficacy parameters after treatment for 12 weeks (ITT analysis)								
Parameters	**Treatment**						**T-test**	
	Placebo			**Saroglitazar 4mg**				
	0 weeks	**12 weeks**	**Mean change (mean±SD)(p)**	**0 weeks**	**12 weeks**	**Mean change (mean±SD)(p)**	**Mean difference (95% Confidence Interval)**	**p-value (two-sided)**
Weight (Kg)	73.17±12.31	74.64 ± 12.78	0.97±1.57 (0.003) #	71.35±11.39	69.04±9.91	-2.31±1.97 (<0.001) ##	3.29 (2.32 to 4.26)	<0.001*
BMI (Kg/m^2)	27.31±3.54	27.72±3.6	0.406±0.604 (0.002) #	26.27±4.19	25.43±3.69	-0.84±0.75 (<0.001) ##	1.24 (0.87 to 1.61)	<0.001*
SBP (mmHg)	139.04±16.14	135.48±12.26	-3.56±8.68 (0.043)	128.32±12.75	126.28±10.27	-1.64±6.8 (0.212)	-1.91 (-6.12 to 2.29)	0.36
DBP (mmHg)	85.22±9.53	85.22± 8.64	0.001±6.21 (1.0)	80.21±9.44	81.64±4.53	1.43±7.59 (0.328)	-1.42 (-5.18 to 2.32)	0.44
Waist-circumference (cm)	84±8.12	84.19±8.2	0.18±0.84 (0.256)	84.18±6.97	83±6.31	-1.17±1.19 (<0.001) ##	1.36 (0.8 to 1.92)	<0.001*
HbA1C (%)	8.29±1.2	8.32±0.96	0.029±0.79 (0.847)	8.51±1.42	7.39±0.88	-1.12±0.78 (<0.001) ##	1.15 (0.72 to 1.57)	<0.001*
FPG (mg/dl)	136.19±52.82	135.44±27.23	-0.74±52.46 (0.942)	156.04±51.5	122.89±30.57	-33.14±38.36 (<0.001) ##	32.42 (7.6 to 57.19)	0.011*
PPG (mg/dl)	226.3±87.82	212± 46.96	-14.30±87.24 (0.402)	233.71±77.69	178.18±32.07	-55.54±66.44 (<0.001) ##	41.23 (-0.6 to 83.08)	0.053

Mean change in efficacy parameters after treatment for 12 weeks (ITT analysis)								
Parameters	**Treatment**						**T-test**	
	Placebo			**Saroglitazar 4mg**				
	0 weeks	**12 weeks**	**Mean change (mean±SD)(p)**	**0 weeks**	**12 weeks**	**Mean change (mean±SD) (p)**	**Mean difference (95% Confidence Interval)**	**p-value (two-sided)**
Triglycerides (mg/dl)	179.11±60.08	180.56±43.03	1.44±41.0 (0.856)	190.14±89.73	105.32±43.56	-84.82±63.71 (<0.001)##	86.26 (57.16 to 115.36)	<0.001*
Total cholesterol (mg/dl)	191.0±44.03	185.93±40.49	-5.07±35.83 (0.468)	191.64±41.97	170.89±193.8	-20±194.35 (0.57)	15.67 (-60.59 to 91.93)	0.68
HDL (mg/dl)	37.73±7.71	37.07±9.68	-0.659 ±7.82 (0.665)	37.57±8.99	54.82±8.41	17.25±8.91 (<0.001) ##	-17.9 (-22.4 to -13.36)	<0.001*
LDL (mg/dl)	122.56±44.71	125.26±35.96	2.7±39.14 (0.723)	127.07±36.89	87.92±25.41	-39.25±27.06 (<0.001) ##	41.95 (23.8 to 60)	<0.001*
hsCRP (mg/L)	3.42±2.64	2.71±1.3	-0.71±2.19 (0.103)	4.4±4.01	2.21±0.94	-2.1±3.47 (0.002) ##	1.47 (-0.09 to 3.05)	0.065
Blood uric acid (mg/dl)	5.31±1.14	5.54±0.95	0.22±0.85 (0.188)	5.37±1.3	4.7± 1.14	-0.66±0.8 (<0.001) ##	0.88 (0.43 to 1.33)	<0.001*
Fasting Insulin (mIU/L)	11.39±3.77	10.9±3.52	-0.49±2.18 (0.253)	11.92±3.51	10.86±3.92	-1.06±3.68 (0.139)	0.56 (-1.07 to 2.21)	0.49
HOMA-IR	3.91±2.27	3.64±1.38	-0.26±1.65 (0.417)	4.47±1.65	3.26±1.25	-1.2±1.72 (0.001) ##	0.94 (0.028 to 1.86)	0.044*
HOMA-B%	74.31± 43.71	63.18± 30.08	-11.13±35.38 (0.114)	63.40±48.95	81.11±50.66	17.71±28.83 (0.003) ##	-28.85 (-46.36 to -11.33)	0.002*

Mean change in efficacy parameters after treatment for 12 weeks (ITT analysis)								
Parameters	**Treatment**						**T-test**	
	Placebo			**Saroglitazar 4mg**				
	0 weeks	**12 weeks**	**Mean change (mean ± SD) (p)**	**0 weeks**	**12 weeks**	**Mean change (mean ± SD) (p)**	**Mean difference (95% Confidence Interval)**	**p-value (two-sided)**
Diabetes Quality of Life (DQoL) 1. Satisfaction	7.67±2.49	6.7±1.8	-0.96±2.1 (0.025) #	11.57±5.8	6.75±1.93	-4.82±5.22 (<0.001) ##	3.85 (1.69 to 6.02)	0.001*
2. Impact	5.22±1.55	4.5±1.18	-0.67±1.3 (0.013) #	7.18±3.6	4.25±0.928	-2.93±3.4 (<0.001) ##	2.26 (0.85 to 3.6)	0.002*
3. Worry	3.81±1.66	3.33±0.87	-0.48±1.22 (0.051)	5.39±2.88	3.21±0.78	-2.18±2.5 (<0.001) ##	1.69 (0.59 to 2.79)	0.003*
Total DQoL score	16.7±4.93	14.59±3.68	-2.11±3.95 (0.01) #	24.14±12.05	14.21±3.42	-9.93±11.03 (<0.001) ##	7.81 (3.3 to 12.33)	0.001*

 # Hash mark indicates significant difference in placebo group from baseline to 12 weeks
Double hash mark indicates significant difference in Saroglitazar group from baseline to 12 weeks
** Asterisk mark indicates significant difference in mean change between the groups after treatment of 12 weeks*

Table 3: Change in Efficacy parameters after the treatment for 12 weeks in both the groups with per protocol analysis

Mean change in efficacy parameters after treatment for 12 weeks (PP analysis)								
Parameters	**Treatment**						**T-test**	
	Placebo			**Saroglitazar 4mg**				
	0 weeks	**12 weeks**	**Mean change (mean ± SD) (p)**	**0 weeks**	**12 weeks**	**Mean change (mean ± SD) (p)**	**Mean difference (Confidence Interval)**	**p-value (two-sided)**
Weight (Kg)	73.43 ± 13.22	74.64±12.78	1.2±1.67 (0.003) #	71.35±11.39	69.04±9.91	-2.31±1.97 (<0.001) ##	3.51(2.45 to 4.57)	<0.001 *
BMI (Kg/m^2)	27.28±3.75	27.78±3.82	0.49±0.63 (0.001) #	26.27±4.19	25.43±3.69	-0.84±0.75 (<0.001) ##	1.33(0.2 to 0.93)	<0.001 *
SBP (mmHg)	138.05±16.41	133.68±10.96	-4.36±9.4 (0.042) #	128.32±12.75	126.68±10.27	-1.64±6.8 (0.212)	-2.72(-7.3 to 1.9)	0.24
DBP (mmHg)	84.09±9.72	84.09±6.51	0.001±6.91 (1.0)	80.21±9.44	81.64±4.53	1.43±7.59 (0.328)	-1.42(-5.6 to 2.7)	0.49
Waist circumference (cm)	84.16±8.34	84.39±8.43	0.23±0.93 (0.257)	84.18±6.97	83±6.31	-1.17±1.19 (<0.001) ##	1.41(0.78 to 2.03)	<0.001 *
HbA1C (%)	8.35±1.28	8.39±1.0	0.036±0.88 (0.848)	8.51±1.42	7.39±0.88	-1.12±0.78 (<0.001) ##	1.15(0.68 to 1.63)	<0.001 *
FPG (mg/dl)	137.09±58.49	136.18±29.78	-0.91± 58.37 (0.942)	156.04±51.5	122.89±30.57	-33.14± 38.36 (<0.001) ##	32.23(4.64 to 59.81)	0.23
PPG (mg/dl)	232.36±96.29	214.82±51.14	-17.55± 96.76 (0.405)	233.71±77.69	178.18±32.07	-55.54± 66.44 (<0.001) ##	37.99(-8.47 to 84.45)	0.107

Mean change in efficacy parameters after treatment for 12 weeks (PP analysis)								
Parameters	**Treatment**						**T-test**	
	Placebo			**Saroglitazar 4mg**				
	0 weeks	**12 weeks**	**Mean change (mean±SD)(p)**	**0 weeks**	**12 weeks**	**Mean change (mean±SD)(p)**	**Mean difference (Confidence Interval)**	**p-value (two-sided)**
Triglycerides (mg/dl)	185.64±62.79	187.41±41.73	1.77±45.62 (0.857)	190.14±89.73	105.32±43.56	-84.82± 63.71 (<0.001) ##	86.59(54.22 to 118.96)	<0.001*
Total cholesterol (mg/dl)	191.73±46.5	185.5±42.36	-6.23± 39.77 (0.471)	191.64±41.97	170.89±193.8	-20±194.35 (0.57)	14.51(-70.33 to 99.36)	0.732
HDL (mg/dl)	38.12±8.28	37.32±10.57	-0.8±8.7 (0.667)	37.57±8.99	54.82±8.41	17.25±8.91 (<0.001) ##	-18.05(-23.11 to -13)	<0.001*
LDL (mg/dl)	128.05±46.35	131.36±35.12	3.32±43.53 (0.724)	127.07±36.89	87.82±25.41	-39.25± 27.06 (<0.001) ##	42.56(22.38 to 62.74)	<0.001*
hsCRP (mg/L)	3.48±2.89	2.6±1.32	-0.87±2.4 (0.103)	4.4±4.01	2.21±0.94	-2.1±3.47 (0.002) ##	1.31(-0.43 to 3.06)	0.136
Blood uric acid (mg/dl)	5.37±1.14	5.64±0.88	0.27±0.94 (0.189)	5.37±1.3	4.71±1.14	-0.66±0.8 (<0.001) ##	0.936(0.44 to 1.43)	<0.001*
Fasting Insulin (mIU/L)	11.34±3.49	10.74±3.14	-0.6±2.41 (0.255)	11.92±3.51	10.86±3.92	-1.06±3.68 (0.139)	0.45(-1.3 to 2.2)	0.61
HOMA-IR	3.95±2.44	3.63±1.4	-0.32±1.83 (0.419)	4.47±1.67	3.26±1.25	-1.2±1.72 (0.001) ##	0.88(-0.13 to 1.9)	0.087
HOMA-B%	76.55±45.4	62.88±29.04	-13.66±38.91 (0.114)	63.4± 48.95	81.11±50.66	17.71± 28.83 (0.003) ##	-31.38(-50.63 to -12.12)	0.002*

Mean change in efficacy parameters after treatment for 12 weeks (PP analysis)								
Parameters	**Treatment**						**T-test**	
	Placebo			**Saroglitazar 4mg**				
	0 weeks	**12 weeks**	**Mean change (mean ± SD) (p)**	**0 weeks**	**12 weeks**	**Mean change (mean ± SD) (p)**	**Mean difference (Confidence Interval)**	**p-value (two-sided)**
Diabetes Quality of Life (DQoL) 1. Satisfaction	7.41±2.21	6.23±0.68	-1.18±2.28 (0.24)	11.57±5.8	6.75±1.93	-4.82±5.22 (<0.001) ##	3.64 (1.23 to 6.04)	0.004*
2. Impact	4.95±1.43	4.14±0.46	-0.82±1.4 (0.12)	7.18±3.6	4.25±0.928	-2.93±3.4 (<0.001) ##	2.11 (0.54 to 3.6)	0.009*
3. Worry	3.73±1.69	3.14±0.46	-0.59±1.33 (0.05)	5.39±2.88	3.21±0.78	-2.18±2.5 (<0.001) ##	1.58 (0.36 to 2.8)	0.12
Total DQoL score	16.09±4.42	13.5±1.26	-2.59±4.25 (0.009) #	24.14±12.05	14.21±3.42	-9.93±11.03 (<0.001) ##	7.33 (2.49 to 12.34)	0.005*

 # Hash mark indicates significant difference in placebo group from baseline to 12 weeks
Double hash indicates significant difference in Saroglitazar group from baseline to 12 weeks
** Asterisk mark indicates significant difference in mean change between the groups after treatment of 12 weeks*

Table 4: Effect of Saroglitazar versus placebo on metabolic syndrome after 12 weeks

Effect on Metabolic syndrome			
	Placebo (n)	Saroglitazar 4mg (n)	p-value
Modified NCEP ATP III baseline	13	17	0.422
Modified NCEP ATP III after 3 months	17	1	<0.001
Original NCEP ATP III baseline	13	16	0.593
Original NCEP ATP III after 3 months	17	0	<0.001
Revised NCEP ATP III baseline	13	15	0.79
Revised NCEP ATP III after 3 months	18	0	<0.001
*Asterisk mark indicates significant decrease in number of patients			

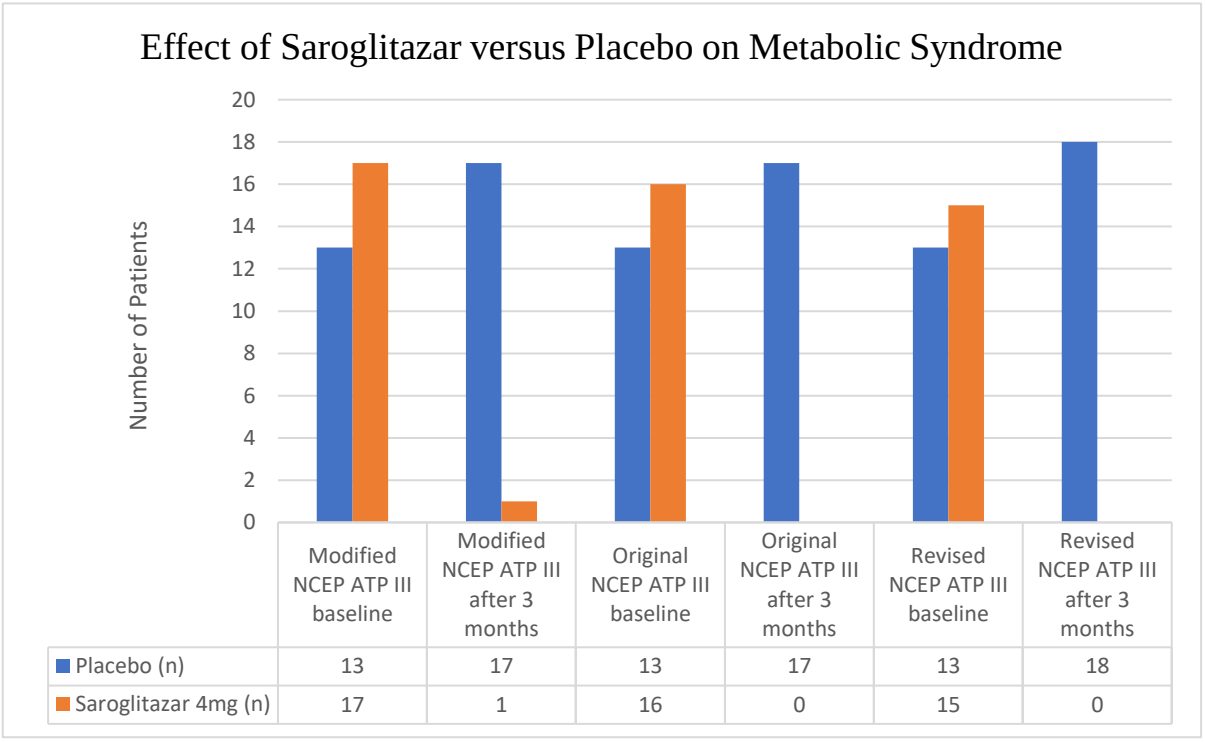


Figure 21: Effect of Treatment on Metabolic Syndrome

Metabolic syndrome parameters were assessed at the baseline and at the end of the study after 12 weeks. As per Modified NCEP ATP III criteria at baseline, there were 13 patients satisfying the criteria in placebo group and 17 patients were satisfying the criteria in saroglitazar group. There was no statistically significant difference between the groups ($p=0.422$). After 3 months, the number of patients with metabolic syndrome increased to 17 in placebo group and there was only one patient with metabolic syndrome in saroglitazar group. There was statistically significant decrease in number of patients with metabolic syndrome in saroglitazar group as compared to placebo ($p<0.001$) (Table 4; Figure 21).

As per Original NCEP ATP III criteria at baseline, there were 13 patients satisfying the criteria in placebo group and 16 patients were satisfying the criteria in saroglitazar group. There was no statistically significant difference between the groups ($p=0.593$). After 3 months, statistically significant decrease in number of patients with metabolic syndrome in saroglitazar group as compared to placebo ($p<0.001$) (Table 4; Figure 21).

As per Revised NCEP ATP III criteria at baseline, there were 13 patients satisfying the criteria in placebo group and 15 patients were satisfying the criteria in saroglitazar group. There was no statistically significant difference between the groups ($p=0.79$). After 3 months, statistically significant decrease in number of patients with metabolic syndrome in saroglitazar group as compared to placebo ($p<0.001$) (Table 4; Figure 21).

Therefore, it was observed as per all three criteria for NCEP ATP III, statistically significant decrease was observed in number of patients having metabolic syndrome in saroglitazar as compared to placebo.

6.4 Adverse Drug Effects

There was one case of adverse effect was seen in placebo group. The patient reported allergic skin rashes on the skin and the intervention was discontinued. Later, it was found to be unrelated to the intervention and was considered not a serious adverse effect. There were no adverse effects found in the saroglitazar group.

DISCUSSION

7 DISCUSSION

Our study was planned to fill the gap of knowledge with respect to the efficacy and safety of saroglitazar in the treatment of type 2 diabetes mellitus. Along with that, to evaluate its efficacy on the metabolic syndrome parameters also. Placebo was used as the control arm. Baseline antidiabetic therapy was given to all patients in both groups. The Randomised Controlled study was conducted from January 2021 to June 2022, in Department of Pharmacology in collaboration with Department of Endocrinology at AIIMS, Jodhpur.

Several studies have been conducted to evaluate the effects of a dual PPAR α/γ agonist, saroglitazar. We are here evaluating the effect of this drug in the treatment of type 2 diabetes mellitus, metabolic syndrome parameters, lipid parameters and also on the quality of life. Our study shows the significant reduction in glycated hemoglobin, fasting plasma glucose, increase in HDL and decrease in LDL and triglycerides as well as significant improvement in HOMA index.

In our study, saroglitazar significantly reduced HbA1C level when compared with the placebo group. A significant mean reduction of -1.12±0.78 ($p<0.001$) was observed in the saroglitazar group at 3 months as compared to baseline. In comparison to placebo, there was significant higher reduction in HbA1c levels of 1.15 (CI 0.72 to 1.57); $p<0.001$. The result obtained are consistent with results of the previous studies (Table 5) (22, 31, 32, 135-137).

Krishnappa et al, study was done to see the effect of saroglitazar 2mg and 4 mg compared with pioglitazone, on glycemic and lipid parameters along with the cardiovascular disease risk in type 2 diabetes mellitus patients. It was the multicentric RCT and patients were randomisation in 1:1:1 ratio to saroglitazar 2mg, 4 mg, and pioglitazone 30 mg, and primary endpoint was reduction in HbA1C levels at 24 weeks. Krishnappa et al. found significant reduction in HbA1c levels with saroglitazar 2 mg (1.38 ± 1.99) and 4 mg (1.47 ± 1.92) and pioglitazone 30 mg (1.41 ± 1.86) (p value <0.016) (31). Jain et al. observed significant reduction in HbA1c levels with saroglitazar 4 mg as compared to placebo (p=0.001) (Table 5).

Similarly, significant reduction in HbA1c levels was observed with the use of other PPAR agonist like muraglitazar (10), tesaglitazar (11, 138) and aleglitazar (139). Saroglitazar is one

such drug that has seen greater mean reduction in the HbA1C level. The effect of saroglitazar is also enhanced on adipose tissue in rodent model by adipocyte hypertrophy, adipocyte dysfunction induced by limited diet, cellular damage of adipocytes and extracellular matrix deposition in conditions like obesity(140). Saroglitazar doesn't cause drug-drug interactions which are clinically relevant (as per the data of pharmacokinetics of diverse CYP2C8)(141).

In our study, there was significant reduction in fasting plasma glucose within saroglitazar at 12 weeks (-33.14± 38.36) ($p<0.001$) as well as in comparison to placebo ($p=0.011$). However, there was no difference in the post prandial glucose (PPG) between the groups. Even though mean change in PPG was trending towards the significance ($p=0.053$). These results are consistent with the results of the Krishnappa et al. where FPG was significantly reduced p-value <0.016 (31). Commenting on the lipid profile parameters, it was observed that there was a significant reduction in the triglycerides within saroglitazar group at 12 weeks i.e., -84.82± 63.71 ($p<0.001$). There was statistically significant higher reduction in triglycerides in saroglitazar as compared to placebo, ($p<0.001$). In addition, significant reduction in the low-density lipoprotein (LDL) levels within saroglitazar at 12 weeks (-39.25± 27.06) ($p<0.001$) as well as in comparison to placebo ($p<0.001$). Also, there was significant increase in HDL levels within saroglitazar group i.e., 17.25±8.91 (<0.001) and in comparison to placebo ($p<0.001$). However, there was no much difference in the total cholesterol levels. Krishnappa et al. observed significant decrease in levels of LDL, VLDL, TG, TC and significant increase in HDL levels ($p<0.016$), consistent with results of our study(31). This shows that saroglitazar is a promising drug in reducing the risk of cardiovascular diseases by reducing the lipid biomarkers(22).

In our study, saroglitazar has great impact on anthropometric parameters. Within saroglitazar group statistically significant reduction in weight (-2.31±1.97, (kg)) ($p<0.001$) was observed at 3 months of treatment and also when compared to placebo, there was a statistically significant difference ($p<0.001$). The similar reduction was observed with respect to the waist circumference (-1.17±1.19, (cm)) ($p<0.001$) within saroglitazar group and when compared to placebo there was statistically significant change($p<0.001$). We found the significant decrease in body mass index within saroglitazar group (-0.84±0.75) (kg/m^2) ($p<0.001$) and when compared with placebo, there was a significant decrease in BMI ($p<0.001$). Blood uric acid was significantly reduced ($p<0.001$) when compared to placebo and significantly reduced within saroglitazar group. Some of the studies in epidemiology predicted that increase in uric

acid would increase the risk of cardiovascular disease (142, 143). This also increases the risk of metabolic syndrome(144). In an unadjusted observational study, it was found that 65% increased risk of metabolic syndrome is seen in high blood uric acid level patients (145). Targeting and finding the significant changes in the lipid profile parameters, waist circumference, blood uric acid and fasting plasma glucose, saroglitazar is found to be a promising drug in the treatment of metabolic syndrome.

Saroglitazar was found to have the significant effect on the HOMA index. In our study, it significantly reduced the mean HOMA-IR (insulin resistance) by -1.2±1.72 ($p = 0.001$) and when compared with placebo it was statistically significant reduction ($p = 0.044$), indicating the reduction in insulin resistance. Saroglitazar was found to increase the mean HOMA-B% significantly after 12 weeks by 17.71± 28.83 ($p = 0.003$) indicating the improvement in beta cell function. When compared to placebo there was a significant difference between the groups ($p = 0.002$). The results were found to be consistent with the Jain et al., where significant increase in HOMA-B% ($p=0.01$) was observed (32). One of the important mechanisms in insulin resistance was found to be lipotoxicity and triglycerides was the key metabolite in the induction of lipotoxicity. Deranged metabolism of triglycerides in muscles and liver further produces various noxious metabolites like, fatty acyl coenzyme A, diacylglycerol and ceramides, contributing to lipotoxicity. This can be prevented by PPAR-alpha agonist, which decreases the triglycerides and increases the insulin sensitivity(146). As our study drug saroglitazar is a dual PPAR alpha/gamma agonist, it significantly reduces the gluco-lipotoxicity by reducing both the non-HDL lipids and HbA1c.

Jain et al. conducted a similar study to evaluate the efficacy of saroglitazar on insulin sensitivity and they found the significant reduction in HbA1c, non-HDL lipids, fasting plasma glucose and significant improvement in insulin sensitivity as well as HDL. But they didn't find the significant change in fasting insulin level and C-peptide level. This was also correlating with our results as we didn't observe any significant change in fasting insulin. Significant decrease in fasting glucose contributed to reduction in HOMA-IR. Increasing insulin sensitivity towards the reduced glycemic profile might have contributed to reduction in HOMA-IR(32). As observed in our study, the significant decrease in FPG is correlating with improved insulin sensitivity in liver, due to predominant expression of PPAR-alpha receptors in liver. It's also an important target of our study drug. We have also seen the significant improvement in the beta cell function by increase in HOMA-B% which can be the

result of improvement in insulin sensitivity. Kim et al. expressed that, since saroglitazar has activity on PPAR-alpha/gamma which are expressed on beta cells abundantly, might have resulted in significant improvement in insulin sensitivity. (147). In addition, PPAR-gamma has been shown to act directly on β cell genes involved in glucose sensing, insulin secretion and insulin gene transcription. PPAR-γ activation by saroglitazar might play a protective role against glucose, lipid, cytokine and islet amyloid polypeptide (IAPP) induced triggering of stress pathways.

No significant effect was found on blood pressure with the use of saroglitazar. Also, there was no significant change in total cholesterol, HsCRP and fasting insulin levels after 12 weeks. Similar results were seen in the previous study by Jain et al., in which no difference was observed in PPG (p=0.07), fasting insulin (p=0.624), total cholesterol (p=0.3) levels with saroglitazar (32). There was significant improvement in Diabetes Quality of Life (DQoL) in our study overall as well as in individual domains. At baseline, DQoL was higher in saroglitazar group. This might be due to younger patients enrolled in saroglitazar, who are more worried with regard to early onset of DM and its progression. In the satisfaction domain, there was a significant improvement in either of the groups (placebo, p=0.025; saroglitazar, p=<0.001). Also, when compared between the 2 groups, there was significant improvement (satisfaction domain - p=0.001) in saroglitazar as compared to placebo. In the Impact domain, statistically significant improvement was observed in either of the groups (placebo, p=0.013; saroglitazar, p<0.001) and when compared between the groups, saroglitazar group significantly reduced the scores. In worry domain, there was no significant change in placebo group (p=0.051), but in the saroglitazar group there was significant improvement (p=<0.001). Also, when compared between the 2 groups, there was a significant decrease in worry domain (p=0.003) in saroglitazar. Except worry domain, significant improvement was seen in both groups with respect to timeline, as well as scores were significantly improved with use of saroglitazar when compared between the groups. The quality of life of the patients increased because there was a standard of care taken in both the groups. Along with the regular follow ups, personal care given to the patients might have contributed to the overall improvement in the scores of the both the groups.

In our study we also found the significant change in metabolic syndrome parameters. As we discussed earlier, there are 5 parameters in the modified NCEP ATP III criteria, out of which any 3 parameters would satisfy the criteria to diagnose metabolic syndrome. We found except

blood pressure, other four parameters were significantly changed and number of patients with metabolic syndrome at the end of the study reduced drastically. There was no significant change in systolic blood pressure as well as diastolic blood pressure in either groups over time, neither when compared between the groups (p=0.36, p=0.44, respectively). Waist circumference was significantly reduced within saroglitazar group over time (-1.17±1.19 cm) (p<0.001). Also, significant improvement was observed in comparison with placebo over time (p<0.001). Fasting plasma glucose and triglycerides was reduced significantly as discussed earlier. There was significant increase in HDL levels too. There are no previous studies to see the effect of saroglitazar in metabolic syndrome. However, some of the studies have established that, PPAR-alpha agonism increases the gene transcription of apoA-1, which in turn increases the level of high-density lipoprotein (HDL)(148). High levels of HDL-C and apoA-1 are established protective factors for cardiovascular diseases(149). As per modified NCEP ATP III criteria, there were 13 patients in placebo group and 17 patients in saroglitazar group diagnosed with metabolic syndrome. After the completion of the trial, the number of patients increased to 17 in placebo group and reduced to 1 in saroglitazar group. There was a significant decrease in number of patients with metabolic syndrome in saroglitazar group as compared to placebo group (p<0.001). This shows that saroglitazar is a promising drug in the treatment of metabolic syndrome. However, Further exploration in the treatment of metabolic syndrome with saroglitazar is needed.

The other drugs of this category like muraglitazar and tesaglitazar had a serious safety concerns breech and they were discontinued from the clinical development in May 2006(150). Myocardial infarction, heart failure, stroke are the serious cardiovascular adverse events of muraglitazar(28, 150). Elevated serum creatinine and decreased glomerular filtration rate was the reason for the discontinuation of teglitazar(28, 138, 151). Literature also says saroglitazar is the drug which has the combination effects on both PPAR α and γ. This has an added advantage to improve the lipid profile as well as glycemic profile. Hence can be used in the treatment of diabetic dyslipidemia in the clinical practice.(22, 100, 152). Saroglitazar has got the authorization for the marketing in India since 2013 for the treatment of diabetic dyslipidemia and as an add on therapy to metformin in the treatment of T2DM in January 2020. Non-cirrhotic Non-alcoholic steatohepatitis is the condition with hypertriglyceridemia, also got the approval for the treatment with saroglitazar in March 2020(31).

It has been reported that PPAR agonist has the effect on the vascular smooth muscle. It inhibits the proliferation of the same and decreases the risk of thrombotic events and also suppresses atherosclerosis (153-156). PPAR agonist showed the potential in decreasing the cardiovascular diseases and also the risk factors associated with it (157, 158). In one of the study, authors used PPAR agonist and adipose tissue derived regenerative cells on a rat model of ischemic cardiomyopathy. The enhancement of adiponectin paracrine effect and improvement in cardiac functions were appreciated with PPAR agonist.(159)

Saroglitazar 2mg and 4 mg has significant effect in reducing the lipid parameters at 12 and 24 weeks as proved by earlier study. This might also indicate that lipid biomarker of cardiovascular diseases might be reduced(31). In another study, authors said the possible association of HbA1C with cardiovascular disease and diabetes mellitus risk. They found out that increase in one percent of HbA1C would be related to cardiovascular disease risk which includes events of cardiovascular disease, coronary artery disease and other cause of mortality(160). Most antidiabetic drugs would reduce the level of HbA1C by 0.5 to 1.5% in the clinical trials. This might often depends on the baseline HbA1C, study population and study designs(161). According to the renowned associations like American Diabetes Association and the European Association for the Study of Diabetes, personalised treatment can be given after the entire clinical picture study. This may not only include HbA1C reduction, but also, safety, frequency, tolerability and the easiness of administering the drug(162)

Table 5: Comparison of different studies on Saroglitazar

Study ID (Study design)	Institution/ country of study conduct and Study population observed(N)/ Regimens	Study control(N)/ Regimen and Study population characteristics	Study outcomes
Krishnappa et al (31), on glycemic parameters, lipid profile parameters and cardiovascular risk; Randomised (3 groups), double-blind, phase 3 study	Multicentric, 39 sites in India, 1155 patients were enrolled (Saroglitazar 2mg - 380; saroglitazar 4mg – 386)	Pioglitazone 30mg – 389 patients, T2DM, Age 18-75years lifestyle modification of 6 weeks, HbA1C≥7.5%, H/O stable metformin dose for 6 weeks, along with diet and exercise, FPG≤270 mg/dL	At 24 weeks, there was significant reduction in HbA1c in all the groups ($p<0.016$); the levels of LDL, VLDL, TG, TC and Non-HDL found significant decrease and HDL levels significant increase ($p<0.016$); within group mean change in HbA1C ± SD in saroglitazar 2mg group was -1.38±1.99, saroglitazar 4mg group -1.47±1.92 and pioglitazone group -1.41±1.86. FPG was significantly decreased $p<0.016$.
Siddiqui et al (163), on Non-alcoholic steatohepatitis; phase 2 double-blind RCT (Proof of Concept study)	16 adult patients; saroglitazar 2mg, saroglitazar 4mg	Placebo – 3 patients, Mean age 52±14 years; Definite NASH on liver biopsy within last 90days, NAFLD activity score at least 4,	Primary efficacy end point (change in NAFLD Activity Score) was not statistically significant in saroglitazar 4mg group (-1.9±1.57, p=0.60); saroglitazar 2mg group (-1.5±0.84, p=0.77) and placebo (-1.3±0.58). Saroglitazar 4mg, reduced triglycerides (-17±44mg/dL), total cholesterol (-16±31mg/dL), and LDL-C (-13±28mg/dL). No change in glycemic parameters was seen. Steatohepatitis was resolved and fibrosis didn't worsen in 3 patients in saroglitazar 4mg and 4 patients in saroglitazar 2mg treatment groups, none in the placebo group.

Jain et al (32), on insulin sensitivity; randomised double-blind placebo-controlled trial	Department of Endocrinology, PGIMER, Chandigarh, India, Newly diagnosed T2DM patients; 61 patients screened; 30 patients randomised; 15 in saroglitazar 4mg group	15 in the placebo group, Patients aged 30-60years, disease since last 5years, HbA1c 7-9, S.TGL >150mg/dl, BMI 23-35Kg/m^2	Saroglitazar significantly reduced (saroglitazar 4mg vs placebo) triglyceride (p=0.001), HbA1c −1.34 ± 1 vs −0.5 ± 0.7 mg/dl (p=0.019), FPG (p=0.019), improved insulin sensitivity, HDL-C (p<0.01) and also beta cell function (HOMA-beta; p<0.01)
Ghosh et al (136), on diabetic dyslipidaemia; randomised open-label parallel-group phase 4 clinical trial	Department of endocrinology of a tertiary care teaching hospital, 19 patients, Metformin 1000mg/day and saroglitazar 4mg/day	18 patients, Metformin 1000mg/day and fenofibrate 160mg/day, Either sex adults; aged 18-70years; newly diagnosed T2DM; TGL >150mg/dl; HbA1C 6.5-8	Saroglitazar with metformin showed a significant reduction in HbA1C, TG, FPG, and PPG (p<0.001) levels when compared to metformin and fenofibrate group
Pai et al (22), on safety and efficacy; multicentre, prospective, randomised, double-blind PRESS 5 study	14 sites all over India, Saroglitazar 2mg n=37; saroglitazar 4mg n= 39	Pioglitazone 45mg n=33, 353 patients were screened; 122 were enrolled; Patients aged 18-65years with T2DM with hypertriglyceridemia 200-400mg/dl, BMI>23kg/m^2, HbA1C 7-9 and received either sulfonylureas, metformin or both for at least 3months.	Saroglitazar 2mg and 4 mg reduced triglycerides significantly(p<0.001) whereas pioglitazone also reduced, but when compared to saroglitazar it was less. After 24 weeks saroglitazar 4 mg, significantly reduced LDL-C (−12.0 ± 39.38 mg/dL), VLDL-C (−23.9 ± 15.26 mg/dL), TC (−18.5 ± 40.62 mg/dL), FPG (−22.6 ± 66.30 mg/dL), and HbA1C (−03 ± 0.60%) compared to baseline. FPG and HDL showed decrease in both groups.

Jani et al (110), on safety and efficacy in T2DM with hypertriglyceridemia not controlled with atorvastatin; multicentre randomised double-blind PRESS 4 study	Multiple hospital clinics, Saroglitazar 2mg n=101, saroglitazar 4mg n= 99	Placebo n=102, Total n=302; aged 18-65years with T2DM, on max 2 OHAs; LDL>100mg/dl; TG level 200-500mg/dl and BMI >23 kg/m2; and on treatment with atorvastatin 10 mg for at least 4 weeks	Saroglitazar 2mg and 4mg significantly reduced (primary EP) TGL - 45.5±3.03 and -46.7±3.02, respectively ($p<0.001$) compared with placebo. Saroglitazar 2 mg and 4 mg observed statistical decrease in levels (secondary EP) of non-HDL-C, LDL-C, total cholesterol, and fasting plasma glucose. HDL was increased in both groups significantly after 12 weeks though HbA1c showed trend to be decreasing.
Gutierrez et al (137), on triglycerides levels. Multicentre, randomised, double-blind, double-dummy and active-controlled study	10 medical centres in Mexico, Saroglitazar 4mg n=48	Fenofibrate 160mg n=46, A total of 445 patients were screened and 94 eligible patients were randomised; Aged > 18 years, fasting TG >500- 1500mg/dl at 2 visits before enrolment	Significant reduction in TG levels at 12 weeks from baseline in the saroglitazar group (LSM=-55.3% compared to fenofibrate group (LSM =-41.1%, $p=0.048$. authors concluded saroglitazar 4mg is non inferior to fenofibrate 160mg Decrease in HbA1c level was statistically significant from baseline in saroglitazar group (−0.39%) when compared to fenofibrate group increase in HbA1c levels in (4.28%) ($p = 0.023$).

8 STRENGTH AND LIMITATIONS

Our study was a randomised controlled study which helps to remove the major bias. Objectives and eligibility criteria were clearly stated which helped to choose the target population. It's the first study in western Rajasthan to see the effect of saroglitazar on metabolic syndrome which fills the knowledge gap as well as helps physicians about the available treatment options.

Talking about our limitations, the sample size was small which could impact on the final result. Lack of supporting studies on efficacy of saroglitazar in metabolic syndrome is also might be the drawback. It was an open label study; hence it would influence the outcome. Generalisability is limited since it was a single centre study. Confounding factors might play a role since we had a difference in the baseline characteristics of few parameters.

9 Future Direction:

Further exploration for the efficacy of saroglitazar in treatment of type 2 Diabetes Mellitus with metabolic syndrome in larger population is needed.

CONCLUSION

10 CONCLUSION

Saroglitazar a dual PPAR alpha/gamma agonist 4mg given once daily has significantly reduced glycemic (HbA1c and FPG) and lipid parameters (HDL and non-HDL). Results were consistent with the previous studies proving its efficacy in treating type 2 diabetes mellitus. It significantly reduced insulin resistance and improved beta cell function as evident from significant decrease in HOMA-IR and significant increase in HOMA-B%, respectively. There was a significant reduction in number of patients having metabolic syndrome in saroglitazar treated group as per original, revised and modified NCEP ATP III criteria as compared to placebo. It had significant impact on central obesity decreasing the waist circumference as well as weight significantly.

Taking into consideration the significant improvement in glycaemic and lipid parameters, futuristically saroglitazar has a promising potential in the management of T2DM associated with dyslipidaemia and metabolic syndrome. As observed in the results, there was no improvement in the fasting insulin levels, indicating the improvement in the insulin sensitivity by saroglitazar could have been contributed by decreasing the insulin resistance and enhancing beta cell function.

All the parameters of the metabolic syndrome were significantly improved after the treatment with saroglitazar for 12 weeks. However, no change was observed in blood pressure. Hence, it’s undeniable that our study drug might be used in the treatment of metabolic syndrome and further exploration in the efficacy in the same is needed.

With evidence from our study, we thereby conclude that saroglitazar 4mg is efficient as well as safe to be used in the management of type 2 diabetes mellitus associated with metabolic syndrome or dyslipidaemia.

BIBLIOGRAPHY

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1. Haris B, Saraswathi S, Al-Khawaga S, Hasnah R, Saeed A, Mundekkadan S, et al. Epidemiology, genetic landscape and classification of childhood diabetes mellitus in the State of Qatar. Journal of diabetes investigation. 2021;12(12):2141-8.
2. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes research and clinical practice. 2017;128:40-50.
3. Alanazi NH, Alsharif MM, Rasool G, Alruwaili ABH, Alrowaili AMZ, Aldaghmi AS, et al. Prevalence of diabetes and its relation with age and sex in Turaif city, northern Saudi Arabia in 2016-2017. Electron Physician. 2017;9(9):5294-7.
4. Ripsin CM, Kang H, Urban RJ. Management of blood glucose in type 2 diabetes mellitus. Am Fam Physician. 2009;79(1):29-36.
5. Udler MS, McCarthy MI, Florez JC, Mahajan A. Genetic Risk Scores for Diabetes Diagnosis and Precision Medicine. Endocrine reviews. 2019;40(6):1500-20.
6. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nature reviews Endocrinology. 2018;14(2):88-98.
7. Demir S, Nawroth PP, Herzig S, Ekim Üstünel B. Emerging Targets in Type 2 Diabetes and Diabetic Complications. Advanced science (Weinheim, Baden-Wurttemberg, Germany). 2021;8(18):e2100275.
8. Spijkerman AM, Dekker JM, Nijpels G, Adriaanse MC, Kostense PJ, Ruwaard D, et al. Microvascular complications at time of diagnosis of type 2 diabetes are similar among diabetic patients detected by targeted screening and patients newly diagnosed in general practice: the hoorn screening study. Diabetes Care. 2003;26(9):2604-8.
9. Selvin E, Ning Y, Steffes MW, Bash LD, Klein R, Wong TY, et al. Glycated hemoglobin and the risk of kidney disease and retinopathy in adults with and without diabetes. Diabetes. 2011;60(1):298-305.
10. Kendall DM, Rubin CJ, Mohideen P, Ledeine JM, Belder R, Gross J, et al. Improvement of glycemic control, triglycerides, and HDL cholesterol levels with muraglitazar, a dual (alpha/gamma) peroxisome proliferator-activated receptor activator, in patients with type 2 diabetes inadequately controlled with metformin monotherapy: A double-blind, randomized, pioglitazone-comparative study. Diabetes Care. 2006;29(5):1016-23.
11. Bays H, McElhattan J, Bryzinski BS. A double-blind, randomised trial of tesaglitazar versus pioglitazone in patients with type 2 diabetes mellitus. Diabetes & vascular disease research. 2007;4(3):181-93.
12. Unoki H, Takahashi A, Kawaguchi T, Hara K, Horikoshi M, Andersen G, et al. SNPs in KCNQ1 are associated with susceptibility to type 2 diabetes in East Asian and European populations. Nat Genet. 2008;40(9):1098-102.
13. Tabassum R, Chauhan G, Dwivedi OP, Mahajan A, Jaiswal A, Kaur I, et al. Genome-wide association study for type 2 diabetes in Indians identifies a new susceptibility locus at 2q21. Diabetes. 2013;62(3):977-86.
14. Wild SH, Byrne CD, Tzoulaki I, Lee AJ, Rumley A, Lowe GD, et al. Metabolic syndrome, haemostatic and inflammatory markers, cerebrovascular and peripheral arterial disease: The Edinburgh Artery Study. Atherosclerosis. 2009;203(2):604-9.

15. Rodriguez-Colon SM, Mo J, Duan Y, Liu J, Caulfield JE, Jin X, et al. Metabolic syndrome clusters and the risk of incident stroke: the atherosclerosis risk in communities (ARIC) study. Stroke. 2009;40(1):200-5.
16. Murad MH, Hazem A, Coto-Yglesias F, Dzyubak S, Gupta S, Bancos I, et al. The association of hypertriglyceridemia with cardiovascular events and pancreatitis: a systematic review and meta-analysis. BMC endocrine disorders. 2012;12:2.
17. Feher M, Greener M, Munro N. Persistent hypertriglyceridemia in statin-treated patients with type 2 diabetes mellitus. Diabetes Metab Syndr Obes. 2013;6:11-5.
18. Harchaoui KE, Visser ME, Kastelein JJ, Stroes ES, Dallinga-Thie GM. Triglycerides and cardiovascular risk. Current cardiology reviews. 2009;5(3):216-22.
19. Jeppesen J, Hein HO, Suadicani P, Gyntelberg F. Triglyceride concentration and ischemic heart disease: an eight-year follow-up in the Copenhagen Male Study. Circulation. 1998;97(11):1029-36.
20. Kolovou GD, Mikhailidis DP, Kovar J, Lairon D, Nordestgaard BG, Ooi TC, et al. Assessment and clinical relevance of non-fasting and postprandial triglycerides: an expert panel statement. Current vascular pharmacology. 2011;9(3):258-70.
21. Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). European heart journal. 2011;32(14):1769-818.
22. Pai V, Paneerselvam A, Mukhopadhyay S, Bhansali A, Kamath D, Shankar V, et al. A Multicenter, Prospective, Randomized, Double-blind Study to Evaluate the Safety and Efficacy of Saroglitazar 2 and 4 mg Compared to Pioglitazone 45 mg in Diabetic Dyslipidemia (PRESS V). J Diabetes Sci Technol. 2014;8(1):132-41.
23. Kaul U, Parmar D, Manjunath K, Shah M, Parmar K, Patil KP, et al. New dual peroxisome proliferator activated receptor agonist-Saroglitazar in diabetic dyslipidemia and non-alcoholic fatty liver disease: integrated analysis of the real world evidence. Cardiovasc Diabetol. 2019;18(1):80.
24. Bermudez V, Finol F, Parra N, Parra M, Perez A, Penaranda L, et al. PPAR-gamma agonists and their role in type 2 diabetes mellitus management. Am J Ther. 2010;17(3):274-83.
25. Balachandran K. Dual PPAR alpha/gamma Agonists: Continuing Cardiac Concerns. Indian J Endocrinol Metab. 2019;23(5):586-7.
26. Henry RR, Lincoff AM, Mudaliar S, Rabbia M, Chognot C, Herz M. Effect of the dual peroxisome proliferator-activated receptor-alpha/gamma agonist aleglitazar on risk of cardiovascular disease in patients with type 2 diabetes (SYNCHRONY): a phase II, randomised, dose-ranging study. Lancet. 2009;374(9684):126-35.
27. Boden G, Laakso M. Lipids and glucose in type 2 diabetes: what is the cause and effect? Diabetes Care. 2004;27(9):2253-9.
28. Sosale A, Saboo B, Sosale B. Saroglitazar for the treatment of hypertrig-lyceridemia in patients with type 2 diabetes: current evidence. Diabetes Metab Syndr Obes. 2015;8:189-96.
29. Agrawal R. The first approved agent in the Glitazar's Class: Saroglitazar. Curr Drug Targets. 2014;15(2):151-5.
30. Chhabra M, Vidyasagar K, Gudi SK, Sharma J, Sharma R, Rashid M. Efficacy and safety of saroglitazar for the management of dyslipidemia: A systematic review and meta-analysis of interventional studies. PLoS One. 2022;17(7):e0269531.

31. Krishnappa M, Patil K, Parmar K, Trivedi P, Mody N, Shah C, et al. Effect of saroglitazar 2 mg and 4 mg on glycemic control, lipid profile and cardiovascular disease risk in patients with type 2 diabetes mellitus: a 56-week, randomized, double blind, phase 3 study (PRESS XII study). Cardiovasc Diabetol. 2020;19(1):93.
32. Jain N, Bhansali S, Kurpad AV, Hawkins M, Sharma A, Kaur S, et al. Effect of a Dual PPAR alpha/gamma agonist on Insulin Sensitivity in Patients of Type 2 Diabetes with Hypertriglyceridemia- Randomized double-blind placebo-controlled trial. Sci Rep. 2019;9(1):19017.
33. Lakhtakia R. The history of diabetes mellitus. Sultan Qaboos Univ Med J. 2013;13(3):368-70.
34. Rastogi S, Singh N, Gutch M, Bhattacharya A. Predicting and preventing diabetes: Translational potential of Ayurveda information on pre-diabetes. Journal of Ayurveda and integrative medicine. 2021;12(4):733-8.
35. Joshi SR, Parikh RM. India--diabetes capital of the world: now heading towards hypertension. J Assoc Physicians India. 2007;55:323-4.
36. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27(5):1047-53.
37. Bray GA. Medical consequences of obesity. The Journal of clinical endocrinology and metabolism. 2004;89(6):2583-9.
38. Kautzky-Willer A, Harreiter J, Pacini G. Sex and Gender Differences in Risk, Pathophysiology and Complications of Type 2 Diabetes Mellitus. Endocrine reviews. 2016;37(3):278-316.
39. He H, Ni Y, Chen J, Zhao Z, Zhong J, Liu D, et al. Sex difference in cardiometabolic risk profile and adiponectin expression in subjects with visceral fat obesity. Translational research : the journal of laboratory and clinical medicine. 2010;155(2):71-7.
40. Liu X, Wang S, You Y, Meng M, Zheng Z, Dong M, et al. Brown Adipose Tissue Transplantation Reverses Obesity in Ob/Ob Mice. Endocrinology. 2015;156(7):2461-9.
41. Wannamethee SG, Papacosta O, Lawlor DA, Whincup PH, Lowe GD, Ebrahim S, et al. Do women exhibit greater differences in established and novel risk factors between diabetes and non-diabetes than men? The British Regional Heart Study and British Women's Heart Health Study. Diabetologia. 2012;55(1):80-7.
42. Xu S, Gao B, Xing Y, Ming J, Bao J, Zhang Q, et al. Gender differences in the prevalence and development of metabolic syndrome in Chinese population with abdominal obesity. PLoS One. 2013;8(10):e78270.
43. Relimpio F, Martinez-Brocca MA, Leal-Cerro A, Losada F, Mangas MA, Pumar A, et al. Variability in the presence of the metabolic syndrome in Type 2 diabetic patients attending a diabetes clinic. Influences of age and gender. Diabetes research and clinical practice. 2004;65(2):135-42.
44. Kuk JL, Ardern CI. Age and sex differences in the clustering of metabolic syndrome factors: association with mortality risk. Diabetes Care. 2010;33(11):2457-61.
45. Abbasi A, Corpeleijn E, Meijer E, Postmus D, Gansevoort RT, Gans RO, et al. Sex differences in the association between plasma copeptin and incident type 2 diabetes: the Prevention of Renal and Vascular Endstage Disease (PREVEND) study. Diabetologia. 2012;55(7):1963-70.
46. Melander O, Maisel AS, Almgren P, Manjer J, Belting M, Hedblad B, et al. Plasma proneurotensin and incidence of diabetes, cardiovascular disease, breast cancer, and mortality. Jama. 2012;308(14):1469-75.

47. Stadlmayr A, Aigner E, Huber-Schönauer U, Niederseer D, Zwerina J, Husar-Memmer E, et al. Relations of vitamin D status, gender and type 2 diabetes in middle-aged Caucasians. Acta Diabetol. 2015;52(1):39-46.
48. Song Y, Wang L, Pittas AG, Del Gobbo LC, Zhang C, Manson JE, et al. Blood 25-hydroxy vitamin D levels and incident type 2 diabetes: a meta-analysis of prospective studies. Diabetes Care. 2013;36(5):1422-8.
49. Lee BK, Park S, Kim Y. Age- and gender-specific associations between low serum 25-hydroxyvitamin D level and type 2 diabetes in the Korean general population: analysis of 2008-2009 Korean National Health and Nutrition Examination Survey data. Asia Pacific journal of clinical nutrition. 2012;21(4):536-46.
50. Maestro B, Campión J, Dávila N, Calle C. Stimulation by 1,25-dihydroxyvitamin D3 of insulin receptor expression and insulin responsiveness for glucose transport in U-937 human promonocytic cells. Endocrine journal. 2000;47(4):383-91.
51. Schneider AL, Lazo M, Ndumele CE, Pankow JS, Coresh J, Clark JM, et al. Liver enzymes, race, gender and diabetes risk: the Atherosclerosis Risk in Communities (ARIC) Study. Diabetic medicine : a journal of the British Diabetic Association. 2013;30(8):926-33.
52. Ding EL, Song Y, Manson JE, Hunter DJ, Lee CC, Rifai N, et al. Sex hormone-binding globulin and risk of type 2 diabetes in women and men. N Engl J Med. 2009;361(12):1152-63.
53. Peter A, Kantartzis K, Machann J, Schick F, Staiger H, Machicao F, et al. Relationships of circulating sex hormone-binding globulin with metabolic traits in humans. Diabetes. 2010;59(12):3167-73.
54. Tang M, Chen Y, Krewski D. Gender-related differences in the association between socioeconomic status and self-reported diabetes. International journal of epidemiology. 2003;32(3):381-5.
55. Agardh E, Allebeck P, Hallqvist J, Moradi T, Sidorchuk A. Type 2 diabetes incidence and socio-economic position: a systematic review and meta-analysis. International journal of epidemiology. 2011;40(3):804-18.
56. Krajnak KM. Potential Contribution of Work-Related Psychosocial Stress to the Development of Cardiovascular Disease and Type II Diabetes: A Brief Review. Environmental health insights. 2014;8(Suppl 1):41-5.
57. Eriksson AK, van den Donk M, Hilding A, Östenson CG. Work stress, sense of coherence, and risk of type 2 diabetes in a prospective study of middle-aged Swedish men and women. Diabetes Care. 2013;36(9):2683-9.
58. Norberg M, Stenlund H, Lindahl B, Andersson C, Eriksson JW, Weinehall L. Work stress and low emotional support is associated with increased risk of future type 2 diabetes in women. Diabetes research and clinical practice. 2007;76(3):368-77.
59. Heraclides AM, Chandola T, Witte DR, Brunner EJ. Work stress, obesity and the risk of type 2 diabetes: gender-specific bidirectional effect in the Whitehall II study. Obesity (Silver Spring, Md). 2012;20(2):428-33.
60. Knott C, Bell S, Britton A. Alcohol Consumption and the Risk of Type 2 Diabetes: A Systematic Review and Dose-Response Meta-analysis of More Than 1.9 Million Individuals From 38 Observational Studies. Diabetes Care. 2015;38(9):1804-12.
61. Schrieks IC, Heil AL, Hendriks HF, Mukamal KJ, Beulens JW. The effect of alcohol consumption on insulin sensitivity and glycemic status: a systematic review and meta-analysis of intervention studies. Diabetes Care. 2015;38(4):723-32.

62. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. Jama. 2007;298(22):2654-64.
63. Spijkerman AM, van der AD, Nilsson PM, Ardanaz E, Gavrila D, Agudo A, et al. Smoking and long-term risk of type 2 diabetes: the EPIC-InterAct study in European populations. Diabetes Care. 2014;37(12):3164-71.
64. Pan A, Wang Y, Talaei M, Hu FB, Wu T. Relation of active, passive, and quitting smoking with incident type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2015;3(12):958-67.
65. Raho E, van Oostrom SH, Visser M, Huisman M, Zantinge EM, Smit HA, et al. Generation shifts in smoking over 20 years in two Dutch population-based cohorts aged 20-100 years. BMC public health. 2015;15:142.
66. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. Lancet. 2011;378(9799):1297-305.
67. Cerf ME. Beta cell dysfunction and insulin resistance. Frontiers in endocrinology. 2013;4:37.
68. Bunney PE, Zink AN, Holm AA, Billington CJ, Kotz CM. Orexin activation counteracts decreases in nonexercise activity thermogenesis (NEAT) caused by high-fat diet. Physiology & behavior. 2017;176:139-48.
69. Fu Z, Gilbert ER, Liu D. Regulation of insulin synthesis and secretion and pancreatic Beta-cell dysfunction in diabetes. Current diabetes reviews. 2013;9(1):25-53.
70. Halban PA. Proinsulin processing in the regulated and the constitutive secretory pathway. Diabetologia. 1994;37 Suppl 2:S65-72.
71. Boland BB, Rhodes CJ, Grimsby JS. The dynamic plasticity of insulin production in β-cells. Molecular metabolism. 2017;6(9):958-73.
72. Rorsman P, Ashcroft FM. Pancreatic β-Cell Electrical Activity and Insulin Secretion: Of Mice and Men. Physiological reviews. 2018;98(1):117-214.
73. Seino S, Shibasaki T, Minami K. Dynamics of insulin secretion and the clinical implications for obesity and diabetes. The Journal of clinical investigation. 2011;121(6):2118-25.
74. Christensen AA, Gannon M. The Beta Cell in Type 2 Diabetes. Current diabetes reports. 2019;19(9):81.
75. Halban PA, Polonsky KS, Bowden DW, Hawkins MA, Ling C, Mather KJ, et al. β-cell failure in type 2 diabetes: postulated mechanisms and prospects for prevention and treatment. J Clin Endocrinol Metab. 2014;99(6):1983-92.
76. Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circulation research. 2010;107(9):1058-70.
77. Graciano MF, Valle MM, Kowluru A, Curi R, Carpinelli AR. Regulation of insulin secretion and reactive oxygen species production by free fatty acids in pancreatic islets. Islets. 2011;3(5):213-23.
78. Yamamoto WR, Bone RN, Sohn P, Syed F, Reissaus CA, Mosley AL, et al. Endoplasmic reticulum stress alters ryanodine receptor function in the murine pancreatic β cell. The Journal of biological chemistry. 2019;294(1):168-81.
79. Hoang Do O, Thorn P. Insulin secretion from beta cells within intact islets: location matters. Clinical and experimental pharmacology & physiology. 2015;42(4):406-14.
80. Liu M, Weiss MA, Arunagiri A, Yong J, Rege N, Sun J, et al. Biosynthesis, structure, and folding of the insulin precursor protein. Diabetes, obesity & metabolism. 2018;20 Suppl 2(Suppl 2):28-50.

81. Orasanu G, Plutzky J. The pathologic continuum of diabetic vascular disease. J Am Coll Cardiol. 2009;53(5 Suppl):S35-42.
82. Group AC, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358(24):2560-72.
83. Rao CR, Kamath VG, Shetty A, Kamath A. A cross-sectional analysis of obesity among a rural population in coastal Southern Karnataka, India. Australas Med J. 2011;4(1):53-7.
84. Mohan V, Deepa R. Obesity and abdominal obesity in Asian Indians. Indian J Med Res. 2006;123(5):593-6.
85. Misra A, Khurana L. Obesity-related non-communicable diseases: South Asians vs White Caucasians. Int J Obes (Lond). 2011;35(2):167-87.
86. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005;112(17):2735-52.
87. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412-9.
88. Bergman RN, Ider YZ, Bowden CR, Cobelli C. Quantitative estimation of insulin sensitivity. The American journal of physiology. 1979;236(6):E667-77.
89. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care. 2004;27(6):1487-95.
90. Bujang MA, Adnan TH, Mohd Hatta NKB, Ismail M, Lim CJ. A Revised Version of Diabetes Quality of Life Instrument Maintaining Domains for Satisfaction, Impact, and Worry. Journal of diabetes research. 2018;2018:5804687.
91. Reliability and validity of a diabetes quality-of-life measure for the diabetes control and complications trial (DCCT). The DCCT Research Group. Diabetes Care. 1988;11(9):725-32.
92. Influence of intensive diabetes treatment on quality-of-life outcomes in the diabetes control and complications trial. Diabetes Care. 1996;19(3):195-203.
93. Testa MA, Simonson DC. Assessment of quality-of-life outcomes. N Engl J Med. 1996;334(13):835-40.
94. Bott U, Mühlhauser I, Overmann H, Berger M. Validation of a diabetes-specific quality-of-life scale for patients with type 1 diabetes. Diabetes Care. 1998;21(5):757-69.
95. Chan LS, Wells RA. Cross-Talk between PPARs and the Partners of RXR: A Molecular Perspective. PPAR research. 2009;2009:925309.
96. Auwerx J, Schoonjans K, Fruchart JC, Staels B. Regulation of triglyceride metabolism by PPARs: fibrates and thiazolidinediones have distinct effects. J Atheroscler Thromb. 1996;3(2):81-9.
97. Contreras AV, Torres N, Tovar AR. PPAR-alpha as a key nutritional and environmental sensor for metabolic adaptation. Adv Nutr. 2013;4(4):439-52.
98. Ahmadian M, Suh JM, Hah N, Liddle C, Atkins AR, Downes M, et al. PPARgamma signaling and metabolism: the good, the bad and the future. Nat Med. 2013;19(5):557-66.
99. Sugii S, Olson P, Sears DD, Saberi M, Atkins AR, Barish GD, et al. PPARgamma activation in adipocytes is sufficient for systemic insulin sensitization. Proc Natl Acad Sci U S A. 2009;106(52):22504-9.

100. Jain MR, Giri SR, Trivedi C, Bhoi B, Rath A, Vanage G, et al. Saroglitazar, a novel PPARalpha/gamma agonist with predominant PPARalpha activity, shows lipid-lowering and insulin-sensitizing effects in preclinical models. Pharmacol Res Perspect. 2015;3(3):e00136.
101. Chatterjee S, Majumder A, Ray S. Observational study of effects of Saroglitazar on glycaemic and lipid parameters on Indian patients with type 2 diabetes. Sci Rep. 2015;5:7706.
102. Patel MR, Kansagra KA, Parikh DP, Parmar DV, Patel HB, Soni MM, et al. Effect of Food on the Pharmacokinetics of Saroglitazar Magnesium, a Novel Dual PPARalphagamma Agonist, in Healthy Adult Subjects. Clin Drug Investig. 2018;38(1):57-65.
103. Goldberg IJ. Lipoprotein lipase and lipolysis: central roles in lipoprotein metabolism and atherogenesis. J Lipid Res. 1996;37(4):693-707.
104. Taskinen MR. Diabetic dyslipidemia. Atherosclerosis Supplements. 2002;3(1):47-51.
105. Boullart AC, de Graaf J, Stalenhoef AF. Serum triglycerides and risk of cardiovascular disease. Biochimica et biophysica acta. 2012;1821(5):867-75.
106. Mooradian AD. Dyslipidemia in type 2 diabetes mellitus. Nature clinical practice Endocrinology & metabolism. 2009;5(3):150-9.
107. Reiner Z. Managing the residual cardiovascular disease risk associated with HDL-cholesterol and triglycerides in statin-treated patients: a clinical update. Nutrition, metabolism, and cardiovascular diseases : NMCD. 2013;23(9):799-807.
108. Virani SS. Non-HDL cholesterol as a metric of good quality of care: opportunities and challenges. Texas Heart Institute journal. 2011;38(2):160-2.
109. Balakumar P, Mahadevan N, Sambathkumar R. A Contemporary Overview of PPARalpha/gamma Dual Agonists for the Management of Diabetic Dyslipidemia. Curr Mol Pharmacol. 2019;12(3):195-201.
110. Jani RH, Pai V, Jha P, Jariwala G, Mukhopadhyay S, Bhansali A, et al. A multicenter, prospective, randomized, double-blind study to evaluate the safety and efficacy of Saroglitazar 2 and 4 mg compared with placebo in type 2 diabetes mellitus patients having hypertriglyceridemia not controlled with atorvastatin therapy (PRESS VI). Diabetes Technol Ther. 2014;16(2):63-71.
111. Lemieux I, Després JP. Metabolic Syndrome: Past, Present and Future. Nutrients. 2020;12(11).
112. Expert Panel on Detection E, Adults ToHBCi. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486-97.
113. Samson SL, Garber AJ. Metabolic syndrome. Endocrinology and metabolism clinics of North America. 2014;43(1):1-23.
114. Vague J. The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout, and uric calculous disease. The American journal of clinical nutrition. 1956;4(1):20-34.
115. Oda E. Metabolic syndrome: its history, mechanisms, and limitations. Acta Diabetol. 2012;49(2):89-95.
116. Haller H. [Epidermiology and associated risk factors of hyperlipoproteinemia]. Zeitschrift fur die gesamte innere Medizin und ihre Grenzgebiete. 1977;32(8):124-8.
117. Singer P. [Diagnosis of primary hyperlipoproteinemias]. Zeitschrift fur die gesamte innere Medizin und ihre Grenzgebiete. 1977;32(9):129-33 concl.
118. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes. 1988;37(12):1595-607.

119. Hossain P, Kawar B, El Nahas M. Obesity and diabetes in the developing world--a growing challenge. N Engl J Med. 2007;356(3):213-5.
120. Grundy SM, Brewer HB, Jr., Cleeman JI, Smith SC, Jr., Lenfant C, American Heart A, et al. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation. 2004;109(3):433-8.
121. Misra A, Wasir JS, Pandey RM. An evaluation of candidate definitions of the metabolic syndrome in adult Asian Indians. Diabetes Care. 2005;28(2):398-403.
122. Pandit K, Goswami S, Ghosh S, Mukhopadhyay P, Chowdhury S. Metabolic syndrome in South Asians. Indian J Endocrinol Metab. 2012;16(1):44-55.
123. Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation. 2005;112(20):3066-72.
124. Wilson PW, Meigs JB. Cardiometabolic risk: a Framingham perspective. Int J Obes (Lond). 2008;32 Suppl 2:S17-20.
125. Krawczyk M, Bonfrate L, Portincasa P. Nonalcoholic fatty liver disease. Best practice & research Clinical gastroenterology. 2010;24(5):695-708.
126. Smits MM, Ioannou GN, Boyko EJ, Utzschneider KM. Non-alcoholic fatty liver disease as an independent manifestation of the metabolic syndrome: results of a US national survey in three ethnic groups. Journal of gastroenterology and hepatology. 2013;28(4):664-70.
127. Gawrieh S, Noureddin M, Loo N, Mohseni R, Awasty V, Cusi K, et al. Saroglitazar, a PPAR-alpha/gamma Agonist, for Treatment of NAFLD: A Randomized Controlled Double-Blind Phase 2 Trial. Hepatology. 2021;74(4):1809-24.
128. Bergman RN, Kim SP, Hsu IR, Catalano KJ, Chiu JD, Kabir M, et al. Abdominal obesity: role in the pathophysiology of metabolic disease and cardiovascular risk. The American journal of medicine. 2007;120(2 Suppl 1):S3-8; discussion S29-32.
129. Gupta A, Gupta V. Metabolic syndrome: what are the risks for humans? Bioscience trends. 2010;4(5):204-12.
130. Reaven GM. Relationships among insulin resistance, type 2 diabetes, essential hypertension, and cardiovascular disease: similarities and differences. Journal of clinical hypertension (Greenwich, Conn). 2011;13(4):238-43.
131. Andreassi MG. Metabolic syndrome, diabetes and atherosclerosis: influence of gene-environment interaction. Mutation research. 2009;667(1-2):35-43.
132. Landsberg L, Aronne LJ, Beilin LJ, Burke V, Igel LI, Lloyd-Jones D, et al. Obesity-related hypertension: pathogenesis, cardiovascular risk, and treatment: a position paper of The Obesity Society and the American Society of Hypertension. Journal of clinical hypertension (Greenwich, Conn). 2013;15(1):14-33.
133. Gupta A, Gupta R, Sharma KK, Lodha S, Achari V, Asirvatham AJ, et al. Prevalence of diabetes and cardiovascular risk factors in middle-class urban participants in India. BMJ open diabetes research & care. 2014;2(1):e000048.
134. Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486-97.
135. Einhorn D, Rendell M, Rosenzweig J, Egan JW, Mathisen AL, Schneider RL. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a

randomized, placebo-controlled study. The Pioglitazone 027 Study Group. Clinical therapeutics. 2000;22(12):1395-409.

136. Ghosh A, Sahana PK, Das C, Mandal A, Sengupta N. Comparison of Effectiveness and Safety of Add-on Therapy of Saroglitazar and Fenofibrate with Metformin in Indian Patients with Diabetic Dyslipidaemia. J Clin Diagn Res. 2016;10(3):FC01-4.
137. Rodriguez-Gutierrez R, Gonzalez JG, Parmar D, Shaikh F, Cruz-Lopez P. Saroglitazar is noninferior to fenofibrate in reducing triglyceride levels in hypertriglyceridemic patients in a randomized clinical trial. J Lipid Res. 2022;63(7):100233.
138. Goldstein BJ, Rosenstock J, Anzalone D, Tou C, Ohman KP. Effect of tesaglitazar, a dual PPAR alpha/gamma agonist, on glucose and lipid abnormalities in patients with type 2 diabetes: a 12-week dose-ranging trial. Curr Med Res Opin. 2006;22(12):2575-90.
139. Stirban AO, Andjelkovic M, Heise T, Nosek L, Fischer A, Gastaldelli A, et al. Aleglitazar, a dual peroxisome proliferator-activated receptor-α/γ agonist, improves insulin sensitivity, glucose control and lipid levels in people with type 2 diabetes: findings from a randomized, double-blind trial. Diabetes Obes Metab. 2016;18(7):711-5.
140. Kumar DP, Caffrey R, Marioneaux J, Santhekadur PK, Bhat M, Alonso C, et al. The PPAR alpha/gamma Agonist Saroglitazar Improves Insulin Resistance and Steatohepatitis in a Diet Induced Animal Model of Nonalcoholic Fatty Liver Disease. Sci Rep. 2020;10(1):9330.
141. Giri P, Delvadia P, Ladani MK, Prajapati N, Gupta L, Patel N, et al. Lack of inhibition of CYP2C8 by saroglitazar magnesium: In vivo assessment using montelukast, rosiglitazone, pioglitazone, repaglinide and paclitaxel as victim drugs in Wistar rats. Eur J Pharm Sci. 2019;130:107-13.
142. Kanbay M, Segal M, Afsar B, Kang DH, Rodriguez-Iturbe B, Johnson RJ. The role of uric acid in the pathogenesis of human cardiovascular disease. Heart (British Cardiac Society). 2013;99(11):759-66.
143. Borghi C, Rosei EA, Bardin T, Dawson J, Dominiczak A, Kielstein JT, et al. Serum uric acid and the risk of cardiovascular and renal disease. Journal of hypertension. 2015;33(9):1729-41; discussion 41.
144. DeBoer MD, Dong L, Gurka MJ. Racial/ethnic and sex differences in the relationship between uric acid and metabolic syndrome in adolescents: an analysis of National Health and Nutrition Survey 1999-2006. Metabolism: clinical and experimental. 2012;61(4):554-61.
145. Wang L, Zhang T, Liu Y, Tang F, Xue F. Association of Serum Uric Acid with Metabolic Syndrome and Its Components: A Mendelian Randomization Analysis. Biomed Res Int. 2020;2020:6238693.
146. Lalloyer F, Vandewalle B, Percevault F, Torpier G, Kerr-Conte J, Oosterveer M, et al. Peroxisome proliferator-activated receptor alpha improves pancreatic adaptation to insulin resistance in obese mice and reduces lipotoxicity in human islets. Diabetes. 2006;55(6):1605-13.
147. Kim HI, Ahn YH. Role of peroxisome proliferator-activated receptor-gamma in the glucose-sensing apparatus of liver and beta-cells. Diabetes. 2004;53 Suppl 1:S60-5.
148. Millar JS, Duffy D, Gadi R, Bloedon LT, Dunbar RL, Wolfe ML, et al. Potent and selective PPAR-alpha agonist LY518674 upregulates both ApoA-I production and catabolism in human subjects with the metabolic syndrome. Arteriosclerosis, thrombosis, and vascular biology. 2009;29(1):140-6.

149. Boden WE. High-density lipoprotein cholesterol as an independent risk factor in cardiovascular disease: assessing the data from Framingham to the Veterans Affairs High--Density Lipoprotein Intervention Trial. Am J Cardiol. 2000;86(12a):19l-22l.
150. Nissen SE, Wolski K, Topol EJ. Effect of Muraglitazar on Death and Major Adverse Cardiovascular Events in Patients With Type 2 Diabetes Mellitus. JAMA. 2005;294(20):2581-6.
151. Lincoff AM, Tardif JC, Schwartz GG, Nicholls SJ, Rydén L, Neal B, et al. Effect of aleglitazar on cardiovascular outcomes after acute coronary syndrome in patients with type 2 diabetes mellitus: the AleCardio randomized clinical trial. Jama. 2014;311(15):1515-25.
152. Jani RH, Kansagra K, Jain MR, Patel H. Pharmacokinetics, safety, and tolerability of saroglitazar (ZYH1), a predominantly PPARalpha agonist with moderate PPARgamma agonist activity in healthy human subjects. Clin Drug Investig. 2013;33(11):809-16.
153. Gizard F, Amant C, Barbier O, Bellosta S, Robillard R, Percevault F, et al. PPAR alpha inhibits vascular smooth muscle cell proliferation underlying intimal hyperplasia by inducing the tumor suppressor p16INK4a. The Journal of clinical investigation. 2005;115(11):3228-38.
154. Ringseis R, Müller A, Herter C, Gahler S, Steinhart H, Eder K. CLA isomers inhibit TNFalpha-induced eicosanoid release from human vascular smooth muscle cells via a PPARgamma ligand-like action. Biochimica et biophysica acta. 2006;1760(2):290-300.
155. Xiong C, Mou Y, Zhang J, Fu M, Chen YE, Akinbami MA, et al. Impaired expression of PPAR gamma protein contributes to the exaggerated growth of vascular smooth muscle cells in spontaneously hypertensive rats. Life Sci. 2005;77(24):3037-48.
156. Gervois P, Vu-Dac N, Kleemann R, Kockx M, Dubois G, Laine B, et al. Negative regulation of human fibrinogen gene expression by peroxisome proliferator-activated receptor alpha agonists via inhibition of CCAAT box/enhancer-binding protein beta. The Journal of biological chemistry. 2001;276(36):33471-7.
157. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005;366(9493):1279-89.
158. Woo MH, Lee HS, Kim J. Effect of pioglitazone in acute ischemic stroke patients with diabetes mellitus: a nested case-control study. Cardiovasc Diabetol. 2019;18(1):67.
159. Mori D, Miyagawa S, Matsuura R, Sougawa N, Fukushima S, Ueno T, et al. Pioglitazone strengthen therapeutic effect of adipose-derived regenerative cells against ischemic cardiomyopathy through enhanced expression of adiponectin and modulation of macrophage phenotype. Cardiovasc Diabetol. 2019;18(1):39.
160. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. Annals of internal medicine. 2004;141(6):413-20.
161. Little RR, Rohlfing CL. The long and winding road to optimal HbA1c measurement. Clinica chimica acta; international journal of clinical chemistry. 2013;418:63-71.
162. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S13-s27.
163. Siddiqui MS, Idowu MO, Parmar D, Borg BB, Denham D, Loo NM, et al. A Phase 2 Double Blinded, Randomized Controlled Trial of Saroglitazar in Patients With Nonalcoholic Steatohepatitis. Clin Gastroenterol Hepatol. 2021;19(12):2670-2.
164. Standards of medical care in diabetes--2011. Diabetes Care. 2011;34 Suppl 1(Suppl 1):S11-61.

ANNEXURES

12 ANNEXURES

Annexure 1: Case Record Form

Case Record Form (clinical trial)

Sr. No.	Clinic No.
Name	CR No.
Address and contact number	Age/Sex
Occupation	Date:

Randomization Code:

Inclusion criteria

1. Patients of either sex with Type 2 DM, aged 18 -65 years. Y/N
2. Newly diagnosed T2DM patients as per ADA criteria. Y/N
3. Patient who are on lifestyle modification and on medication metformin, vildagliptin or both for 3 months. Y/N

Exclusion criteria

1. Patient who had any clinically significant or unstable medical or Psychiatric illnesses. Y/N
2. History of cardiac diseases (NYHA grade 3 – 4) or cardiac anomalies. Y/N
3. Patient on glitazone/glitazar therapy for >30days. Y/N
4. History of Renal insufficiency - serum creatinine ≥1.8mg/dl. Y/N
5. Patient with history of significant hepatic impairment (serum bilirubin >2times, AST, ALT and alkaline phosphatase >3 times the upper limit of normal). Y/N
6. Patient has uncontrolled hypertension. Y/N
7. Patient has any malignancy. Y/N
8. Patient has any substance abuse(alcohol/drugs). Y/N
9. Pregnant & Lactating Woman. Y/N
10. Those being treated with any investigational drug within last 30 days. Y/N
11. Patient is with myopathies/ severe illness/ infections. Y/N
12. Patient with allergy/intolerance. Y/N

Patient- Included/Excluded

Chief complaints

1.
2.

Total duration Age of onset:

EVALUATION

SYMPTOMS	**YES**	**NO**
Polyurea		
Polydipsia		
Polyphagia		
Visual symptoms		
Paraesthesia and hyperesthesia		
Wounds/ ulcers		
Gangrene		

PAST HISTORY - HTN / CAD / Any H/o of any chronic drug intake /Any past surgeries etc.

FAMILY HISTORY:

PERSONAL HISTORY - Smoker/Alcoholic/Veg/non-veg

TREATMENT HISTORY

Drug	Dose	duration	Response

GENERAL PHYSICAL EXAMINATION

Anaemia Cyanosis Jaundice
Edema Lymphadenopathy
Baseline characteristics
Weight Pulse B.P. – BMI
Waist circumference - Hip Cir - Height

SYSTEMIC EXAMINATION

RS -
CVS -
P/A -
CNS-

Efficacy parameters

Parameters	0 weeks	4 weeks	8 weeks	12 weeks
Fasting Glucose				
Blood glucose -PP				
HbA1c				
LDL-C				
HDL-C				
Total Cholesterol				
Triglycerides				
Fasting Insulin				
Hs-CRP				
Blood uric acid				

Safety Parameters

Adverse Events	**1st visit**	**2nd visit**	**3rd visit**
Abdominal distension and flatulence			
Allergic reaction			
Cough			
Diarrhoea and abdominal pain			
Dysgeusia			
Flu like symptoms			
Nasopharyngitis			
Headache			
Hypoglycemia			
Hyperchlorhydria			
Hyperpyrexia			
Impairment of LFT			
Lactic acidosis			
Nausea and vomiting			
Pain			
Vitamin B12 deficiency			
weakness			
Weight gain			

Grading of hypoglycemia

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
ADA grading					
Clinical grading					

Grading of hyperpyrexia

	Low 38–39°C (100.4–102.2°F)	**Moderate** 39–40°C (102.2–104.0°F)	**High** 40–42°C (104.0–107.6°F)	**Hyperpyrexia** >42°C (107.6°F)
Fever grading				

Grading of headache

	0 (no pain)	**1 (minimal unpleasantness)**	**2 (heaviness/ discomfort)**	**3 (mild)**	**4 (moderate)**	**5 (severe)**	**6 (excrucia-tingly severe)**
IHS grading							

Annexure 2: Criteria and Grading used in the study

American Diabetes Association (ADA) criteria

ADA criteria for the diagnosis of Diabetes mellitus

1. HbA1c ≥6.5%. NGSP certified lab test and standardized to the DCCT assay. (or)
2. FPG ≥126 mg/dL (7 mmol/L). At least 8 hours of fasting. (or)
3. 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) after OGTT. As per WHO, 75g anhydrous glucose must be used. (or)
4. RBS≥200 mg/dL (11.1 mmol/L), In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.

(NGSP: National Glycohemoglobin Standardization Program; DCCT: Diabetes Control and Complications Trial, RBS: random plasma glucose)

Original NCEP ATP III criteria:

1. Waist circumference >102cms in men and >88 cm in women
2. Hypertriglyceridemia ≥150 mg/dl
3. High-density lipoprotein (HDL) cholesterol <40 mg/dl in males and <50 mg/dl in females
4. Blood pressure (BP) ≥130/85 mmHg, and
5. Fasting plasma glucose (FPG) ≥110 mg/dl

Revised NCEP ATP III criteria:

1. Waist circumference >102cms in men and >88 cm in women
2. Hypertriglyceridemia ≥150 mg/dl
3. High-density lipoprotein (HDL) cholesterol <40 mg/dl in males and <50 mg/dl in females
4. Blood pressure (BP) ≥130/85 mmHg, and
5. Fasting plasma glucose (FPG) ≥100 mg/dl

The ADA grading(164)

1. Grade 1- Relative hypoglycemia (typical symptoms but with a glucose level > 3.9 mmol/L)
2. Grade 2- Probable symptomatic hypoglycemia (typical symptoms but without confirmation of glucose determination)
3. Grade 3- Asymptomatic hypoglycemia (glucose level ≤ 3.9 mmol/L but without typical symptoms)
4. Grade 4- Documented symptomatic hypoglycemia (typical symptoms and a confirmed glucose level ≤ 3.9 mmol/L)
5. Grade 5- Severe hypoglycemia (an event requiring the assistance of another person regardless of glucose levels)

Annexure 3: Revised version of Diabetes Quality of Life (DQoL)

	Questions	1	2	3	4	5
S1	How satisfied are you with the amount of time it takes to manage your diabetes?					
S2	How satisfied are you with the amount of time you spend getting check-ups?					
S3	How satisfied are you with the time it takes to determine your sugar level?					
S4	How satisfied are you with your current treatment?					
S5	How satisfied are you with your knowledge about your diabetes?					
S6	How satisfied are you with life in general?					
I1	How often do you feel pain associated with the treatment for your diabetes?					
I2	How often do you feel physically ill?					
I3	How often does your diabetes interfere with your family life?					
I4	How often do you find your diabetes limiting your social relationships and friendships?					
W1	How often do you worry about whether you will pass out?					
W2	How often do you worry that your body looks different because you have diabetes?					
W3	How often do your worry that you will get complications from your diabetes?					

Domain: satisfaction
(1 = very satisfied; 2 = moderately satisfied; 3 = neither; 4 = moderately dissatisfied; 5 = very dissatisfied)
Domain: impact
(1 =never; 2 = very seldom; 3 = sometimes; 4 = often; 5 = all the time)
Domain: worry
(0 = does not apply; 1 = never; 2 = very seldom; 3 = sometimes; 4 = often; 5 = all the time)

Annexure 4: Informed Consent Form (English)

All India Institute of Medical Sciences, Jodhpur

Informed Consent Form

Title of the project: **A randomised controlled study of efficacy and safety of saroglitazar in T2DM**

Name of the Principal Investigator: **Dr. Surjit Singh/** Dr. Sachin J

Tel. No. (Mobile): - **9417492229 /** 9019821161

Patient OPD No: _____

I, _____S/o or D/o_____R/o _____give my full, free, voluntary consent to be a part of the study "**A randomised controlled study of efficacy and safety of saroglitazar in T2DM**", the procedure and nature of which has been explained to me in my own language to my full satisfaction. I confirm that I have had the opportunity to ask questions.

I understand that my participation is voluntary, and I am aware of my right to opt out of the study at any time without giving any reason.

I understand that the information collected about me and any of my medical records may be looked at by responsible individual from AIIMS Jodhpur or from regulatory authorities. I give permission for these individuals to have access to my records.

Date: _____ _____

Place: _____ Signature/Left thumb impression (Patient) (Caregiver)

This to certify that the above consent has been obtained in my presence.

Date: _____ _____

Place: _____ Signature of Principal Investigator

1. Witness 1

_____

Signature

Name: _____

Address: _____

_____

2. Witness 2

_____

Signature

Name: _____

Address: _____

_____

Annexure 5: Informed Consent Form (Hindi)

<u>सूचित सहमति</u> प्रपत्र

परियोजना का शीर्षक: ए राँडोमिसेड कंट्रोल्ड स्टडी ऑफ़ एफ्फिकास्यी एंड सेफ्टी ऑफ़ सरॉलिट्ज़ार इन टाइप २ डायबिटीज मेलिटस

प्रधान अन्वेषक: **डॉ. सुरजीत सिंह/ डॉ. सचिन जे**

फोन नंबर: 9417492229/ 9019821161

रोगी / स्वयंसेवी पहचान संख्या:

मैं, _____एस / ओ या डी / ओ _____

आर ओ /_____ देने मेरा पूरा, मुक्त, स्वैच्छिक सहमति अध्ययन " ए राँडोमिसेड कंट्रोल्ड स्टडी ऑफ़ एफ्फिकास्यी एंड सेफ्टी ऑफ़ सरॉलिट्ज़ार इन टाइप २ डायबिटीज मेलिट' का एक हिस्सा है, जो की मेरी खुद की भाषा में मुझे समझाया गया है प्रक्रिया और प्रकृति होने के लिए मेरी पूर्ण संतुष्टि के लिए। मुझे लगता है मैं सवाल पूछने का अवसर मिला है कि इस बात की पुष्टि।

मैं मेरी भागीदारी स्वैच्छिक है कि समझते हैं और बिना कोई कारण बताए किसी भी समय इस अध्ययन से बाहर निकलने का मेरा अधिकार के बारे में पता कर रहा हूँ।

मैं मेरे और मेरे मेडिकल रिकॉर्ड से किसी के बारे एकत्र जानकारी अखिल भारतीय आयुर्विज्ञान संस्थान जोधपुर से या नियामक अधिकारियों से जिम्मेदार व्यक्ति द्वारा देखा जा सकता है। मैं इन व्यक्तियों मेरा रिकॉर्ड और फोटोग्राफ लिए उपयोग किया है और प्रकाशन के लिए इस्तेमाल किया जा सकता है के लिए अनुमति देते हैं।

दिनांक:

प्लेस: हस्ताक्षर / बाएं अंगूठे छाप

इस संस्करण की सहमति मेरी उपस्थिति में प्राप्त किया गया है कि प्रमाणित करने के लिए।

दिनांक:

प्लेस: प्रधान अन्वेषक के हस्ताक्षर

1. गवाह

हस्ताक्षर:

नाम:

पता:

2. गवाह

हस्ताक्षर:

नाम:

पता:

Annexure 6: Patient Information Leaflet (English)

PATIENT INFORMATION LEAFLET

You are being invited to willing fully participate in the study entitled "A Randomised controlled study of efficacy and safety of Saroglitazar in the treatment of T2DM".

Purpose of research

Diabetes mellitus is characterized by abnormally high levels of sugar (glucose) in the blood. Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease. To study the efficacy and safety of Saroglitazar in T2DM.

Study Design

Saroglitazar

- Saroglitazar is a peroxisome proliferator activated receptor (PPAR) agonist, regulates lipid and glucose metabolism.
- Saroglitazar is indicated for the treatment of diabetic dyslipidemia and hypertriglyceridemia with T2DM not controlled by Statin therapy.

Precautions you should take:

- Women: to use reliable contraception while on treatment and for 1 month after completion/stopping of treatment.
- Avoid alcohol while on treatment.

G**eneral instructions:**

- **If side effects occur**, you are advised to contact anyone of the investigators whose contact number is given below.
- **In case of serious side effect,** we will treat you as per the standard treatment practices and you need not have to bear the cost of treatment.
- **Be sure to keep all of your appointments** so that your progress can be checked. Some blood, liver function and other tests may have to be done from time to time to check on your progress and detect any unwanted side effects.
- **After taking the medicines:**
    - Ensure that you take them as instructed.
    - Bring the container with the medicines back at your next visit. You should bring all the medicines which are left in the container.
    - In case you need to take any additional medicine on account of fever, sore throat or any minor illness, please feel free to contact the study doctor.

Confidentiality

Your medical records and identity will be treated as confidential documents. They will only be revealed to other doctors/scientists/monitors/auditors of the study if required. The results of the study may be published in a scientific journal but you will not be identified by name.

Ethics committee approval has been obtained for the study.

Your participation and rights

Your participation in the study is fully voluntary and you may withdraw from the study anytime without having to give reasons for the same. In any case, you will receive the appropriate treatment for your condition. You will not be paid any amount for the participation in the study. You will have to pay for the routine investigations that will be done.

For further queries/questions or help in emergency please contact.

1. **Dr. Sachin J - 09019821161**
2. **Dr. Surjit Singh – 09417492229**

Annexure 7:Patient Information Leaflet (Hindi)

रोगी सूचना पत्र

आप को तैयार करने के लिए आमंत्रित किया जा रहा है पूरी तरह से हकदार अध्ययन में भाग लेने
": ए रॉंडोमिसेड कंट्रोल्ड स्टडी ऑफ़ एफ्फिकास्यी एंड सेफ्टी ऑफ़ सरॉलिट्ज़ार इन टाइप २ डायबिटीज मेलिटस "।

शोध का उद्देश्य

मधुमेह मेलेटस रक्त में शर्करा (ग्लूकोज) के असामान्य रूप से उच्च स्तर की विशेषता है। मधुमेह तेजी से भारत में एक संभावित महामारी की स्थिति प्राप्त कर रहा है, वर्तमान में 62 मिलियन से अधिक मधुमेह रोगियों में इस बीमारी का पता चला है। टाइप २ डायबिटीज मेलिटस में **सरोग्लिटज़ार** की प्रभावकारिता और सुरक्षा का अध्ययन करना।

अध्ययन के डिजाइन

सरोग्लिटज़ार

- **सरोग्लिटज़ार एक पेरोक्सीसम प्रोलिफ़रेटर सक्रिय रिसेप्टर (पीपीएआर) एगोनिस्ट है, जो लिपिड और ग्लूकोज चयापचय को नियंत्रित करता है|**
- **सरोग्लिटज़ार को डायबिटिक डिस्लिपिडेमिया और हाइपर-ट्राइग्लिसराइडिमिया के उपचार के लिए संकेत दिया जाता है, जिसमें टी 2 डीएम स्टैटिन थेरेपी द्वारा नियंत्रित नहीं होता है।**

इस अध्ययन के डीएम के लिए नैदानिक मानदंडों को संतोषजनक डीएम या विषयों के सभी ज्ञात मामलों में शामिल है। आप त्वचा असामान्यताएं और मधुमेह की उपस्थिति के संबंध में प्रश्न पूछा जाएगा

चीजें आप ऐसा नहीं होना चाहिए: लंबे समय तक उपवास

गोपनीयता

अपने मेडिकल रिकॉर्ड और पहचान गोपनीय दस्तावेज के रूप में इलाज किया जाएगा। यदि जरूरी हुआ तो वे केवल अध्ययन के अन्य डॉक्टरों / वैज्ञानिकों / मॉनिटर / लेखा परीक्षकों को पता चल जाएगा। अध्ययन के परिणामों के एक वैज्ञानिक पत्रिका में प्रकाशित किया जा सकता है लेकिन आप नाम से पहचान नहीं की जाएगी।

आचार समिति के अनुमोदन के अध्ययन के लिए प्राप्त किया गया है।

आपकी भागीदारी और अधिकार

अध्ययन में आपकी भागीदारी पूरी तरह स्वैच्छिक है और आप कभी भी उसी के लिए कारण देने के लिए बिना अध्ययन से वापस ले सकते हैं। किसी भी मामले में, आप अपनी हालत के लिए उचित उपचार प्राप्त होगा। इस अध्ययन में भाग लेने के लिए किसी भी राशि का भुगतान नहीं किया जाएगा। आप से किया जाएगा कि दिनचर्या जांच के लिए भुगतान करना होगा।

आपात स्थिति में आगे प्रश्नों / सवाल या मदद के लिए संपर्क करें।

1. **डॉ सुरजीत सिंह** – 9417492229
2. **डॉ. सचिन जे** - 9019821161

Annexure 8: Clinical Trial Details

CLINICAL TRIALS REGISTRY - INDIA
ICMR - National Institute of Medical Statistics

PDF of Trial
CTRI Website URL - http://ctri.nic.in

Clinical Trial Details (PDF Generation Date :- Wed, 07 Apr 2021 04:50:44 GMT)

CTRI Number	CTRI/2021/04/032550 [Registered on: 05/04/2021] - **Trial Registered Prospectively**
Last Modified On	05/04/2021
Post Graduate Thesis	Yes
Type of Trial	Interventional
Type of Study	Drug
Study Design	Randomized, Parallel Group, Placebo Controlled Trial
Public Title of Study	Study of Saroglitazar in Type 2 Diabetis Mellitus
Scientific Title of Study	A Randomised Controlled study of efficacy and safety of Saroglitazar in Type 2 Diabetis Mellitus

Secondary IDs if Any

Secondary ID	Identifier
NIL	NIL

Details of Principal Investigator or overall Trial Coordinator (multi-center study)

Details of Principal Investigator	
Name	Dr Surjit Singh
Designation	Additional Professor
Affiliation	AIIMS, Jodhpur
Address	Department of Pharmacology, Basni 2, AIIMS Jodhpur, Rajashtan, 342005, India Jodhpur RAJASTHAN 342005 India
Phone	9873519558
Fax	
Email	sehmby_ss@yahoo.com

Details Contact Person (Scientific Query)

Details Contact Person (Scientific Query)	
Name	Sachin J
Designation	Junior Resident
Affiliation	AIIMS Jodhpur
Address	Department of Pharmacology, Basni2, AIIMS Jodhpur, Rajasthan, 342005, India Jodhpur RAJASTHAN 342005 India
Phone	9019821161
Fax	
Email	sachin.j.suru@gmail.com

Details Contact Person (Public Query)

Details Contact Person (Public Query)	
Name	Sachin J
Designation	Junior Resident
Affiliation	AIIMS Jodhpur
Address	Department of Pharmacology, Basni2, AIIMS Jodhpur, Rajasthan, 342005, India Jodhpur RAJASTHAN 342005 India
Phone	9019821161

Annexure 9: Ethical clearance certificate

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2021/3464 **Date: 12/03/2021**

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2021/3299**

Project title: **"A Randomised Controlled Study of Efficacy and Safety of Saroglitazar on Type 2 Diabetes Mellitus"**

Nature of Project:	**Research Project Submitted for Expedited Review**
Submitted as:	**M.D. Dissertation**
Student Name:	**Dr. Sachin J**
Guide:	**Dr. Surjit Singh**
Co-Guide:	**Dr. Mithu Banerjee, Dr. Ravindra Shukla, Dr. Jayakaran Charan & Dr. Shoban Babu Varthya**

Institutional Ethics Committee after thorough consideration accorded its approval on above project.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

Please Note that this approval will be rectified whenever it is possible to hold a meeting in person of the Institutional Ethics Committee. It is possible that the PI may be asked to give more clarifications or the Institutional Ethics Committee may withhold the project. The Institutional Ethics Committee is adopting this procedure due to COVID-19 (Corona Virus) situation.

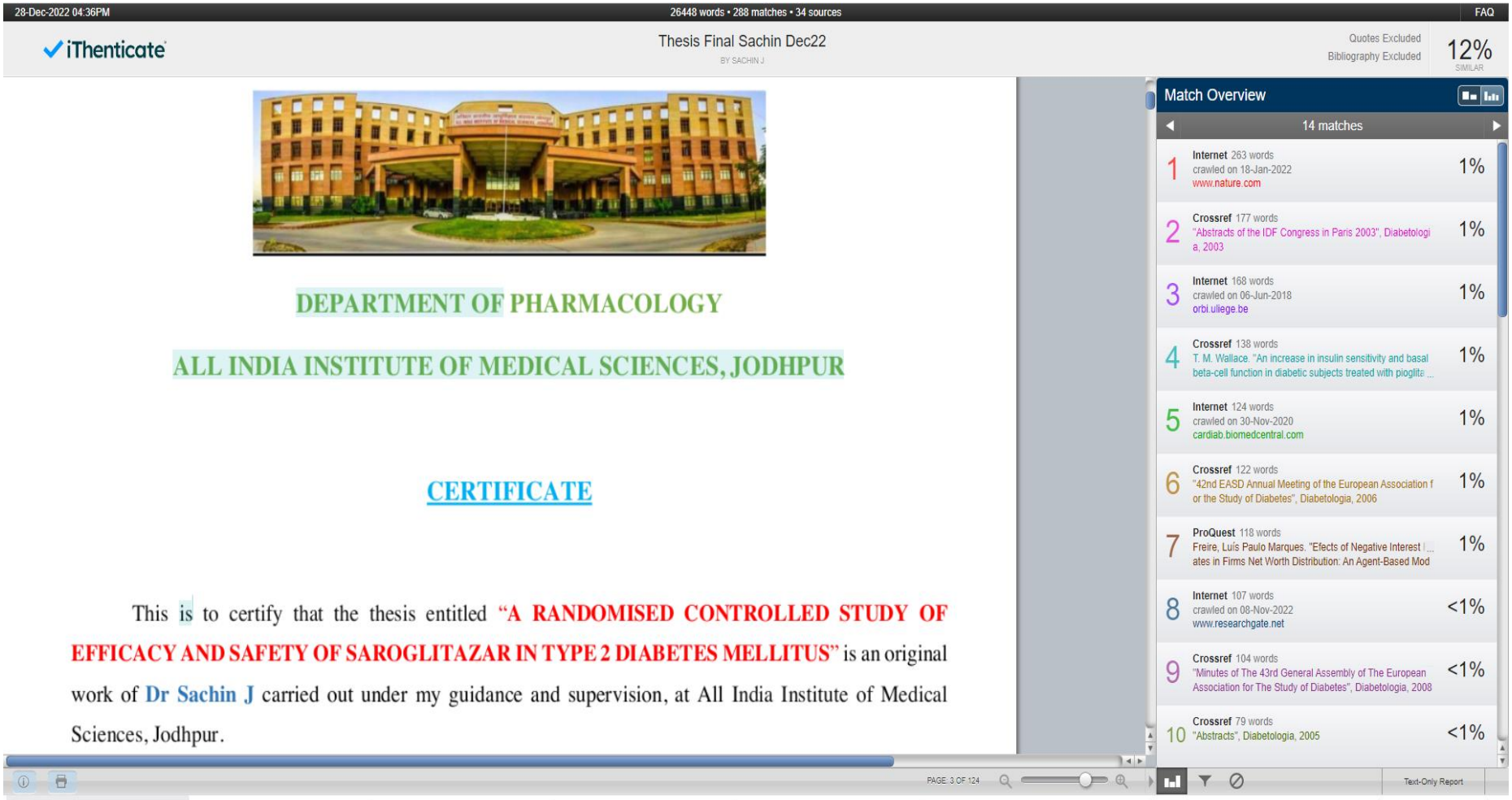
If the Institutional Ethics Committee does not get back to you, this means your project has been cleared by the IEC.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary
Member secretary
Institutional Ethics Committee
AIIMS,Jodhpur

Basni Phase-2, Jodhpur, Rajasthan-342005; **Website:** www.aiimsjodhpur.edu.in; **Phone:** 0291-2740741 Extn. 3109
E-mail : ethicscommittee@aiimsjodhpur.edu.in; ethicscommitteeaiimsjdh@gmail.com

Annexure 10: Plagiarism certificate



Annexure 11: CONSORT checklist

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	2
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	22
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	24
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	25
	4b	Settings and locations where the data were collected	24
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	24
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	26
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	28
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	24
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	24

Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	24
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	24
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	-
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	28
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	34
	13b	For each group, losses and exclusions after randomisation, together with reasons	33
Recruitment	14a	Dates defining the periods of recruitment and follow-up	33
	14b	Why the trial ended or was stopped	33
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	40
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	34
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	43
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted	69

		analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	70
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	81
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	81
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	72
Other information			
Registration	23	Registration number and name of trial registry	31
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	31

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.