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## REVIEW

# Novel Dual-ACTING PEROXISOME Proliferator-Activated Receptor Alpha and Gamma Agonists.

SHARMA R

### ABSTRACT

Peroxisome proliferator-activated receptors (PPARs) are nuclear transcription factors, and play a central role in insulin sensitivity, lipid metabolism, and inflammation. PPAR- $\gamma$  appears to improve glycaemic control by increasing peripheral insulin sensitivity and reducing hepatic glucose production, thereby helping to preserve beta-cell function. However, they have modest beneficial effects on lipid parameters. It has been observed that fibrate drugs which activate PPAR- $\alpha$ , produce significant improvements in dyslipidaemia and decrease atherosclerotic lesions, but do not affect glycaemia. Theoretically, a compound targeting both the  $\alpha$  and  $\gamma$  PPARs simultaneously, might combine the benefits of thiazolidinediones (TZDs) and fibrates. Hence, there is a resurgence of interest in the development of new antidiabetic drugs that combine the insulin-sensitizing effects of PPAR $\gamma$  activation with the additional lipid-modifying activity of the other PPAR subtypes. Muraglitazar, Tesaglitazar, Ragaglitazar, Isohumulone, Farglitazar, and Naveglitazar are on the deck in late-stage clinical trials, and may be effective in reducing cardiovascular risk, but their long-term clinical effects are still unknown. The ongoing basic studies have elucidated the cardio protective role of PPAR delta. Therefore, further studies are on the track to develop PPA  $\alpha/\delta$  and PPAR $\gamma/\delta$  dual agonists and PPAR  $\alpha/\gamma/\delta$  pan agonists for the treatment of diabetic cardiovascular complications.

**Key Words:** Muraglitazar, Tesaglitazar, Ragaglitazar, Farglitazar, Naveglitazar

Dr Rashmi Sharma, MD, EX. Senior Demonstrator, Post-graduate Department of Pharmacology and Therapeutics, Govt Medical College, Jammu-J&K (India), Clinical Pharmacologist, J&K Health Services Jammu (India).

Corresponding author:

Dr. Rashmi Sharma, R/O 216-A, Last-Morh Gandhi-Nagar, Near Govt Flats, Jammu (Tawi) J&K (India), Pin 180004. Email: rashmichams@yahoo.com, drrashmi@india.com

### Introduction

Peroxisome proliferator-activated receptors (PPARs) are nuclear transcription factors, and play a central role in insulin sensitivity, lipid metabolism, and inflammation. They help in the regulation of storage and catabolism of dietary fats and glucose, adipocyte differentiation, inflammatory responses, and cancer. Each PPAR

consists of three functional domains;- The N-terminal, and DNA binding and ligand binding domains. PPAR forms a heterodimer with the retinoid X receptor, which recognizes DNA sequences in the promoter region of their target genes.<sup>[1]</sup> Four forms of PPARs have been described to exist, namely; PPAR- $\alpha$ , PPAR- $\beta$ , PPAR- $\gamma$  and PPAR- $\delta$  (Table-1). [1-3]

Thiazolidinediones (TZDs) or glitazones like rosiglitazone and pioglitazone are higher affinity PPAR- $\gamma$  agonists for type 2 diabetes.[4,5] Glitazones cause an increase in insulin sensitivity and produce hypoglycaemic effects by increasing fatty acid extraction by adipose tissues, shifting the energy metabolism of myocytes towards glucose consumption, up-regulating or activating molecules involved in insulin signaling and glucose uptake,

producing a protective effect on pancreatic beta-cells, and inhibiting tumor necrosis factor(TNF)- $\alpha$ . [2] The TZDs have also been shown to have antiproliferative, anti-inflammatory, and immunomodulatory effects, with a potential role in the treatment of diabetic complications, inflammatory-proliferative diseases in non-insulin-resistant euglycaemic individuals, autoimmune, atopic and inflammatory diseases, sepsis, and reperfusion injury. [6,7] Patients with diabetes have an increased risk for cardiovascular disease that contributes to a decreased life expectancy. Various observational and interventional studies have indicated that some insulin sensitizers appear to reduce the incidence of cardiovascular events, and improve survival. [8,9] A randomized clinical trial in patients with advanced atherosclerosis indicates that addition of pioglitazone to therapy for hyperglycaemia, may reduce the incidence of cardiovascular events such as myocardial infarction and stroke. [8,9]

### Novel peroxisome proliferator-activated receptor alpha and gamma agonists:

**Search Methodology:** Prominent general/internal medicine journals (MEDLINE, EMBASE, PUBMED between 2000 and 2007) were searched for review papers, and pre-clinical and clinical trials published on dual PPAR  $\alpha$  /  $\gamma$  agonists. All the data was collected, and important evidences regarding therapeutic uses and pharmacology of dual PPAR  $\alpha$  /  $\gamma$  agonists are summarized in the present article.

**Muraglitazar (BMS-298585):** Muraglitazar is a non-TZDs, oxybenzylglycine dual PPAR  $\alpha$  /  $\gamma$  agonist, that is in advanced clinical development for the treatment of type 2 diabetes and its associated dyslipidemia. [8,9] It shows potent activity in vitro at human PPAR  $\alpha$  ( effective concentration (EC50) = 320 nM) and PPAR  $\gamma$  (EC50) = 110 nM). [11], [12] Various animal studies have documented the beneficial effect of muraglitazar on plasma lipids, glucose metabolism, and insulin resistance.

In obese diabetic db/db mice muraglitazar treatment (0.03-50 mg/ kg/ day) for 2 weeks resulted in dose-dependent reductions of glucose, insulin, triglycerides (TG), free fatty acids (FFA), and cholesterol levels. [13] In older hyperglycaemic db/db mice, longer-term muraglitazar treatment (30 mg/kg/ day for 4 weeks) prevented time-dependent deterioration of glycaemic control and development of insulin deficiency. [14] In severely hyperglycaemic db/db mice, muraglitazar treatment (10 mg/kg/day for 2 weeks) improved oral glucose

tolerance and reduced plasma glucose and insulin levels. [13] It has been reported that muraglitazar results in an increase in insulin content (in the pancreas), plasma adiponectin levels, high-molecular weight adiponectin complex levels, and reduces elevated plasma corticosterone levels and elevated liver lipid content in db/db mice. [13]

This first dual-PPAR agonist was reviewed by a US Food and Drug Administration (FDA) advisory committee on September 9, 2005, resulting in a vote of 8:1, recommending approval for its use as monotherapy for type 2 diabetes, and as combination therapy in patients with blood glucose inadequately controlled by metformin. [14], [15] However, various prospective, randomized, double-blind, multicenter studies (phase 2 and 3 clinical trials released under public disclosure laws for the FDA advisory committee meeting) enrolling patients (3725) with type 2 diabetes and haemoglobin A(1c) levels between 7% and 10%, showed occurrence of death, MI (myocardial infarction), or stroke in 1.47% patients on muraglitazar treatment, compared with 0.67% patients in the combined placebo and pioglitazone treatment groups ( P = 0 .03). [14] Transient ischemic attack and congestive cardiac failure were reported in 2.11% of patients in the muraglitazar group, and in 0.81% of patients in controls group (P = .004). [14] Compared with placebo or pioglitazone, muraglitazar was associated with an excess incidence of the composite end point of death and major adverse cardiovascular events. [14] The toxicity of muraglitazar was evaluated in a comprehensive nonclinical toxicology program that included single-dose and repeat-dose oral toxicity studies in mice, rats, and monkeys. [16] In the above study, subcutaneous oedema, haematologic/haematopoietic and serum chemistry alterations, and morphologic findings in the heart and adipose tissue in rats and monkeys, were observed after chronic use of muraglitazar, as observed with PPAR gamma agonists. Muraglitazar was found to be nongenotoxic, in the standard battery of genotoxicity studies. [16] However, gallbladder adenomas in male mice and adipocyte neoplasms in male and female rats were seen at suprapharmacologic doses, whereas urinary bladder tumours occurred in male rats at lower exposures. Subsequent investigative studies established that the urinary bladder carcinogenic effect was mediated by urolithiasis, rather than a direct pharmacological effect on the urothelium. Muraglitazar had no effect on reproductive functions, it had no teratogenic effect, and demonstrated no selective developmental toxicity. [16]

**Tesaglitazar:** The biologically active form of tesaglitazar is the (S)-enantiomer, whereas, the (R)-enantiomer is approximately 100 times less potent than its antipode.[17,18] In a pharmacokinetics study on eight healthy male subjects after a single oral or intravenous (i.v.) dose of 1 mg of tesaglitazar, the maximum plasma concentration ( $C_{max}$ ) was achieved at a  $\approx$ 1 hour post dose with 100% bioavailability (no or negligible first-pass metabolism).[18] It has a mean plasma clearance of 0.16 litre /hour, the volume of distribution at a steady state of 9.1 liters, and an elimination half-life of  $\approx$ 45 hours. Tesaglitazar was mainly metabolized before excretion, and about 20% of it was excreted unchanged, resulting in a renal clearance of 0.030 l/h.[17] Plasma protein binding of tesaglitazar was high ( $\approx$ 99.9%), and the mean blood-plasma partitioning ratio was 0.66 ( low affinity for red blood cells). There was no indication of partial inversion of the (S)-enantiomer to the corresponding (R)-form. Tesaglitazar was well tolerated. [17]

In a dose-escalation study in healthy males, oral tesaglitazar demonstrated an increase in concentration time curve (AUC) and the  $C_{max}$  proportionally, with increasing doses, indicating linear pharmacokinetics.[17] Food had no effect on the extent of its absorption, although the rate of absorption was reduced in the fed state. <sup>[19]</sup> In animal studies, tesaglitazar has been shown to lower circulating TG, glucose, and insulin levels in mice models with type 2 diabetes, and has been shown to lower circulating triglyceride and insulin levels in obese Zucker rat models of insulin resistance. [18] Also, clinical evaluation has shown that tesaglitazar improves lipid and glucose metabolism, increases insulin sensitivity, and improves the atherogenic lipoprotein profile in patients with dyslipidaemia associated with insulin resistance. [20] Both PPAR  $\alpha$  and  $\gamma$  are expressed in the kidney, and their agonists exhibit renoprotective effects in type 2 diabetes.[21] In various animal studies, treatment of db/db mice with tesaglitazar for 3 months, significantly lowered fasting plasma glucose and the homeostasis model assessment of insulin resistance levels, but had little effect on body weight, adiposity, or cardiac function. [21] It was observed that treatment with tesaglitazar was associated with reduced plasma insulin and total TG levels, and increased plasma adiponectin levels. Tesaglitazar markedly attenuated albuminuria and significantly lowered glomerulofibrosis, collagen deposition, and transforming growth factor-beta1 expression in renal tissues of db/db mice.

Moreover, in cultured mesangial cells and proximal tubule cells, where both PPARs  $\alpha$  and  $\gamma$  were expressed, tesaglitazar treatment abolished high glucose-induced total collagen protein production and type I and IV collagen gene expression. Thus, tesaglitazar is found to have a reno-protective effect in diabetic patients. [21]

**Ragaglitazar (NNC 61-0029 or (-) DRF2725):** Ragaglitazar has high affinity for the hPPAR- $\alpha$  and  $\gamma$  receptors with IC(50) values of 0.98 and 0.092 microM, respectively.[22]

In pharmacokinetic studies, ragaglitazar showed rapid absorption with  $t_{max}$ : 1.5-1.7 h,  $t_{1/2}$  of 80 hours, following a single dose (1-120 mg) and 104 hours in healthy subjects, and 122 hours in patients after multiple dosing [a loading dose and thereafter once-daily doses (0.5-16 mg)]. [23] It has been observed that 4 mg ragaglitazar daily for 21 days resulted in decrease in fasting levels of plasma glucose (18%), C-peptide (18%), fructosamine (6%), TG (36%), FFA (49%), total cholesterol (11%), low-density lipoprotein (LDL) cholesterol (21%), and very low-density lipoprotein (VLDL) cholesterol (15%), as well as an increase in HDL cholesterol (33%).[24] Ragaglitazar was well tolerated; however, peripheral oedema and anaemia were reported at the highest dose level (16 mg). [23]

In a study on early and late diabetes stages in Zucker diabetic fatty (ZDF) rats, ragaglitazar treatment resulted in overall reduced circulating insulin, and improved insulin sensitivity to a greater extent than after treatment with rosiglitazone. In late-intervention therapy, ragaglitazar was found to reduce Hb A<sub>1c</sub> by 2.3%, as compared to 1.1% reduction by rosiglitazone. [24]

It has been observed that ragaglitazar and pioglitazar equally improve metabolic profile and insulin sensitivity in ZDF rats, particularly when they are administered early in the course of diabetes. Ragaglitazar improves  $\beta$ -cell function (HOMA- $\beta$ ) more than three-fold with prevention and intervention therapies, whereas pioglitazar showed improvement only in intervention therapy. <sup>[25]</sup> In a 12-week, double-blind, parallel, randomized, placebo-controlled dose-ranging study on 177 hypertriglyceridaemic type 2 diabetic subjects, ragaglitazar, in doses of 1, 4 and 10 mg, resulted in a significant decrease in fasting plasma glucose, TG, FFA, apolipoprotein B, LDL cholesterol, and total cholesterol, and also resulted in a significant increase in HDL cholesterol. <sup>[26]</sup>

Common adverse events were oedema, weight increase, leukopaenia, and anaemia. [26]

**Farglitazar (GI262570):** It is the L-tyrosine analogue, and has high affinity for the human PPAR $\gamma$  nuclear receptor, and a low but possibly important activity for the PPAR $\alpha$  receptor (1,000 times less potent on PPAR $\alpha$ ). [1,3] It has robust effects on glucose, high-density lipoprotein (HDL), and triglycerides (TG), in diabetic patients. Its blood glucose and lipid lowering activity have been demonstrated in patients of Type 2 diabetes. [27] The blood pressure (BP) lowering effect of farglitazar has also been reported in various studies. [27] A 4-week randomized, double-blind, parallel-group study on 304 hypertensive type-2 diabetics, showed dose-dependent (0.5, 1, 2, 5, or 10 mg daily) reductions in a mean 24-hour ambulatory BP with farglitazar, in comparison to placebo. [27] Farglitazar 10 mg resulted in a statistically and clinically significant lowering of mean seated trough, diastolic and systolic BP, with smaller non-significant decreases at lower doses. Farglitazar was well tolerated, with no clinically significant increase in heart rate. Dose-related oedema was seen (up to 13% at 10 mg after 4 weeks). The 10 mg dose is not being developed in Phase III. [17]

**Naveglitazar :** Naveglitazar [LY519818; benzenepropanoic acid, alpha-methoxy-4-[3-(4-phenoxyphenoxy)propoxy], (alpha-S)-] is a nonthiazolidinedione PPAR  $\alpha / \gamma$  dual,  $\alpha$  dominant agonist. [28] After oral administration, naveglitazar is well absorbed and moderately metabolized in mice, rats, and monkeys. [28] The most prominent metabolite observed in circulation is the R-enantiomer of naveglitazar, LY591026, which is formed via enzymatic chiral inversion. Para-Hydroxy naveglitazar and the sulfate conjugate of para-hydroxy naveglitazar, are also observed in circulation in most species, especially in the monkey. [28] It is metabolized by enzymatic chiral inversion, aromatic hydroxylation, oxidative dehydrogenation, and/or various phase II conjugation pathways. Naveglitazar is highly bound to plasma proteins among the species examined (>99%). [28]

Arylthiazolidinedione (TZD 18), Isoxazolidinedione (JTT-501) and KRP\_297 are other dual PPAR  $\alpha$  and  $\gamma$  agonists under development. [1,3]

**Isohumulones:** [29] These are the bitter compounds derived from hops, that are present in beer. Hops, the female inflorescences of the hop

plant (*Humulus lupulus* L.), are used as a preservative and flavouring agent in beer. Isohumulones, called iso-  $\alpha$  acids, are the compounds that impart the bitter flavour to beer. Previously, humulone was shown to inhibit angiogenesis by suppressing cyclooxygenase-2, and to have antibacterial properties. Recently, among the three major isohumulone homologs, isohumulone and isocohumulone are found to activate PPAR  $\alpha$  and  $\gamma$ . In an animal study on diabetic KK-A $^y$  mice, isohumulones (isohumulone and isocohumulone) were found to reduce plasma glucose, TG and FFA (65.3, 62.6, and 73.1%, respectively, for isohumulone), as seen with pioglitazone. However, unlike pioglitazone, isohumulone treatment did not result in significant body weight gain. Moreover, C57BL/6N mice which were fed a high fat diet that were treated with isohumulones, showed improved glucose tolerance, reduced insulin resistance, increased liver fatty acid oxidation, a decrease in size, and an increase in apoptosis of their hypertrophic adipocytes. A double-blind, placebo-controlled pilot study on diabetic patients, have demonstrated a significant decrease in blood glucose and haemoglobin A1c levels after 8 weeks of therapy with isohumulones (by 10.1 and 6.4%, respectively, versus week 0). Hence, isohumulones have the potential to be a therapeutic option in type 2 diabetes and metabolic syndrome.

**Conclusion:** The new generation of dual-action glitazars are on deck in late-stage clinical trials, and may be effective in reducing cardiovascular risk, but their long-term clinical effects are still unknown (table-2 and 3). The novel PPAR $\gamma$  modulating drugs like Gw0072, Mcc-555, and NC-2100, with efficacious insulin sensitizing properties and minimum potential side-effects, are also under development. [1] The ongoing basic studies have elucidated the cardio protective role of PPAR  $\delta$ . [35] Therefore, further studies are on the track to develop PPAR  $\alpha / \delta$  and PPAR  $\gamma / \delta$  dual agonists and PPAR  $\alpha / \gamma / \delta$  pan agonists for the treatment of diabetic cardiovascular complications. More powerful new compounds with pan-PPAR activity and proven long-term safety should be highly effective in a clinical setting of patients, with coexisting relevant lipid and glucose metabolism disorders. These discoveries pave the way for the development of drugs for treating chronic multigenic cardiovascular and metabolic diseases, for which therapy is presently insufficient or non-existent.

**Table/Fig 1**

**Peroxisome Proliferator Activated Receptors and their clinical implications.**

<b>PPAR RECEPTOR</b>	<b>LOCATION</b>	<b>FUNCTION</b>	<b>DRUGS AS AGONISTS</b>
<b>PPAR-<math>\alpha</math></b> <sup>[1,2]</sup>  It has three distinct N-terminal isoforms:- PPARr1, PPARr2 and PPARr3.	Skeletal muscle, liver, kidney, and vascular endothelial cells.	Controls LP metabolism, FA oxidation and cellular uptake of fat.  Regulation of adipocyte gene expression and differentiation  Regulation of target genes involved in glucose and lipid metabolism	Fibrate class of lipid-lowering agents (ie, clofibrate, fenofibrate, and gemfibrozil).
<b>PPARs-<math>\beta</math></b> <sup>[3]</sup>	Oligodendrocytes and spermatocytes.	Oligodendrocyte differentiation and spermatogenesis	-
<b>PPAR-<math>\gamma</math></b> <sup>[3,6]</sup>	Adipocytes, skeletal muscle, and cardiac muscle.	Improvements in insulin sensitivity and glycemic control.  Adipocyte differentiation and fat deposition.  Antihypertensive angiotensin II Type 1 receptor antagonists has selective PPAR- $\gamma$ -modulating activity.	Oral hypoglycemics like, pioglitazone and rosiglitazone.
<b>PPAR-<math>\delta</math></b> <sup>[3]</sup>	Muscle, adipocytes, macrophages, etc	Increases FA oxidation and serves as an anti-inflammatory factor.	-
<b>PPAR-<math>\alpha</math>+ PPAR-<math>\gamma</math></b> <sup>[1-6]</sup>	-	Combined treatments with PPAR gamma and alpha agonists improve insulin resistance and alleviate atherogenic dyslipidemia.	The new generation of dual-action PPARs--the glitazars:- muraglitazar, tesaglitazar, ragaglitazar.

PPARs= Peroxisome Proliferator Activated Receptors, LP=lipoprotein, FA= fatty acid

**Table/Fig 2:**  
**New generation of dual-action glitazars. [1,3,8,9,14,17,23,27,34].**

Drug	Structure	Dose	Pharmaco-kinetics	Adverse drug reactions
Muraglitazar	N-[(4-methoxyphenoxy)carbonyl]-N-[[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]methyl]glycine.	1.5-20 mg	T <sub>max</sub> = 1-6 h  T <sub>1/2</sub> =19 to 27 h	Risk of MI, TIA, CHF, Stroke
Tesaglitazar	(S)-2-ethoxy-3-[4-({4-[methylsulphonyloxy]phenethyl}oxy)phenyl] propanoic acid	1 mg	T <sub>max</sub> =1h  T <sub>1/2</sub> =45h	Well tolerated
Ragaglitazar	(-)-3-(4-(2-(phenoxazin-10-yl)ethoxy)phenyl)-2-ethoxypropanoic acid	0.5-16 mg	T <sub>max</sub> = 1.5-1.7h  T <sub>1/2</sub> 8h *  104-122h**	Oedema  Anemia
Isohumulone	R: -CH <sub>3</sub> CH-(CH <sub>3</sub> ) <sub>2</sub> ; 2-(3-methylbutanoyl)-5-(3-methyl-2-butenyl)-3,4-dihydroxy-4-(4-methyl-3-pentenoyl)-2-cyclopentenone)	-	-	-
Isocohumulone	R: -CH(CH <sub>3</sub> ) <sub>2</sub> ; 2-(2-methylpropanoyl)-5-(3-methyl-2-butenyl)-3,4-dihydroxy-4-(4-methyl-3-pentenoyl)-2-cyclopentenone 3-pentenoyl)-2-cyclopentenone.	-	-	-
Farglitazar	[(S)-2-(2-benzoylphenylamino)-3-[4-[2-(5-methyl-2-phenyl-2-oxazol-4-yl)ethoxy]phenyl]propionic acid]	0.5-5mg	-	Oedema
Naveglitazar	benzenepropanoic acid, alpha-methoxy-4-[3-(4-phenoxyphenoxy)propoxy], (alpha-S)-	-	Well absorbed	-

\*after single dose, \*\*after multiple dose, T<sub>max</sub>= time to achieve maximum concentration, T<sub>1/2</sub>= half life, h= hours, MI=myocardial infarction, TIA= transient ischemic attack, CHF=congestive heart failure.

**Table/Fig – 3**  
**Clinical and Pre-clinical studies of dual-action glitazars.**

<b>Drug</b>	<b>Study</b>	<b>Observations</b>
<b>Muraglitazar</b>	Preclinical study on obese diabetic db/db mice	0.03-50 mg/ kg/ day for 2 weeks resulted in dose-dependent reductions of glucose, insulin, TG, FFA and cholesterol levels. [13]
<b>Muraglitazar</b>	comprehensive nonclinical toxicology program	no effects on reproductive function, no teratogenic effect and no selective developmental toxicity. [16]
<b>Tesaglitazar</b>	dose-escalation study in healthy males	an increase in AUC and C <sub>max</sub> proportionally with increasing doses, indicating linear pharmacokinetics. [17]
<b>Tesaglitazar</b>	mice models of type 2 diabetes	lower circulating TG, glucose and insulin levels. [18]
<b>Tesaglitazar</b>	various animal studies treatment of db/db mice	reno-protective effect in diabetic patients. [21]
<b>Ragaglitazar</b>	Zucker diabetic fatty (ZDF) rats	reduce circulating insulin and improved insulin sensitivity to a greater extent than after treatment with rosiglitazone. [24]
<b>Ragaglitazar</b>	12-week double-blind parallel randomized placebo-controlled	significant decrease in fasting plasma glucose, TG, FFA, apolipoprotein B, LDL cholesterol and total cholesterol and a significant increase in HDL cholesterol. [26]
<b>Farglitazar</b>	4-week randomized, double-blind, parallel-group study on 304 hypertensive type-2 diabetics	dose-dependent (0.5, 1, 2, 5, or 10 mg daily) reductions in mean 24-hour ambulatory BP. [27]
<b>Naveglitazar</b>	Preclinical study on mice, rats, and monkeys	a nonthiozolidinedione PPAR $\alpha$ / $\gamma$ dual, $\alpha$ dominant agonist, well absorbed and moderately metabolized. [28]
<b>Isohumulones</b>	C57BL/6N mice fed a high fat diet	improve glucose tolerance, reduced insulin resistance, increased liver fatty acid oxidation, a decrease in size and an increase in apoptosis of their hypertrophic adipocytes. [29]
<b>Isohumulones</b>	A double-blind, placebo-controlled pilot study	significant decrease in blood glucose and hemoglobin A1c levels after 8 weeks of therapy. [29]

TG= triglycerides, FFA= free fatty acids, AUC =concentration time curve, Cmax= maximum concentration, A1c= glycosylated haemoglobin.

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