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Therapeutic Potential of the Dual Peroxisome Proliferator Activated Receptor (PPAR)/ Agonist Aleglitazar in Attenuating TNF-mediated Inflammation and Insulin Resistance in Human Adipocytes: A Review

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

Aleglitazar, is a novel promising drug, that related to peroxisome proliferator-activated receptor (PPARα&γ) agonists which shows an ant-diabetic and anti-inflammatory characteristics. The goal of this study is to evaluate anti-inflammatory and anti-arthritic properties of Aleglitazar in arthritis models induced in experimental animals and to conclude the comparative ulcerogenic potential of diclofenac in type 2 diabetes animals. The anti-inflammatory characteristics of Aleglitazar will be investigated in Carrageenan-induced hind paw edema as acute inflammation.

The Aim of the review: This study aims to assess anti-inflammatory and anti-arthritic activities of aleglitazar in arthritis models induced in experimental animals. It is to determine comparative ulcerogenic potential diclofenac in type 2 diabetic animals on gastric mucosa in rats.

Keywords: PPAR; Aleglitazar; TNF; inflammation insulin resistance; adipocytes.

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ABBREVIATIONS

ANG	:	*Angiotensin*
BMI	:	*Body mass index*
COX1	:	*Cyclooxygenase-1 enzyme*
COX2	:	*Cyclooxygenase-2 enzyme*
CRP	:	*C-reactive protein*
FFA	:	*Free fatty acids*
GCF	:	*Gingival crevicular fluid*
GDM	:	*Gestational diabetes mellitus*
GFR	:	*Glomerular filtration rate*
1GIR	:	*Glucose-insulin rate*
HbA1c	:	*Glycated haemoglobin*
HDL	:	*High-density lipoprotein cholesterol*
IL-1β	:	*Interleukin 1β*
LDL	:	*Low-density lipoprotein cholesterol*
NO	:	*Nitric oxide*
NO/ONOO	:	*Nitric oxide/peroxynitrite ratio*
NSAIDS	:	*Nonsteroidal anti-inflammatory class of drugs*
PGE2	:	*Prostaglandin E2*
PGs	:	*Prostaglandins*
PAI-1	:	*Plasminogen activator inhibitor-1*
PPAR α & γ	:	*Peroxisome proliferator activated receptor α & γ*
SC	:	*Serum creatinine*
STZ	:	*Streptozotocin*
TG	:	*Triglycerides*
TNF- α	:	*Tumor necrosis factor alpha*
T2DM	:	*Type 2 diabetes mellitus*

1. INTRODUCTION

Obesity is frequently associated with insulin resistance, and highly responsible for developing type 2 diabetes (T2D) [1,2], T2D is a metabolic disease that causes sugar to increase in blood circulation results from insulin resistance and the primary risk factor of T2D is inflammation [3].

Diclofenac is a proven, commonly used non-steroidal anti-inflammatory and anti-pyritic drug. Diclofenac exerts its activity by inhibiting cyclooxygenase-1 (COX1) and cyclooxygenase-2 (COX2) leading to inhibit prostaglandin synthases [4].

Aleglitazar is a new drug that used as an anti-inflammatory drug that improved insulin sensitivity, and dyslipidemia. Aleglitazar is a single novel molecule that contains the both active synthetic peroxisome proliferator activated receptors (PPARs α&γ) has potent and dual agonist action on PPARs α&γ [5].

2. OBESITY

Is a pathological condition result from an accumulation of excesses adipose tissue in a different site of the body including liver and skeletal muscle, and it's considered as a neurochemical imbalance can be measured by the body mass index (BMI), which is a ratio of weight to high. Normal range of BMI (18.5-24.9 kg/m^2), overweight range (25-29.9 kg/m^2), obesity BMI 30 kg/m^2 and more [6] (Fig. 1).

Weight gain and increased adipocyte, result in hypertrophic and loss of function of adipocyte [8]. Free fatty acid (FFA) in this condition released in blood circulation, pro-inflammatory cytokines as tumor necrosis factor alpha (TNF-α), Plasminogen activator inhibitor (PAI)-1, and angiotensin (ANG)), and adiponectin which is a specific protein in adipocyte that play a role in insulin resistance and atherosclerosis [9].

Increased level of FFA and pro-inflammatory cytokines will lead to deposition in non-adipose tissues and decrease systemic inflammatory grade, resulting in activating the mechanism of insulin resistance in tissues (Fig. 2) [8].

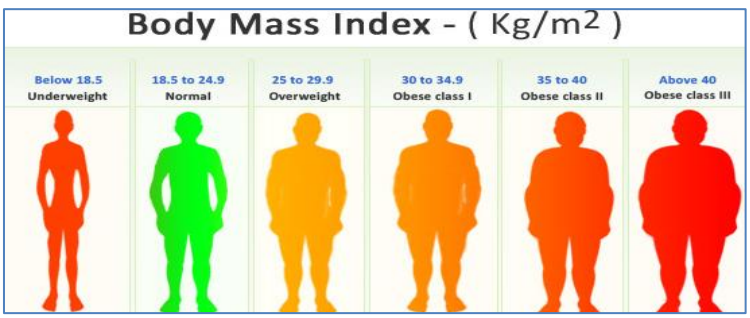

Fig. 1. BMI: It is a method use for determination if a person weight within the normal range or at high risk for obesity [7]

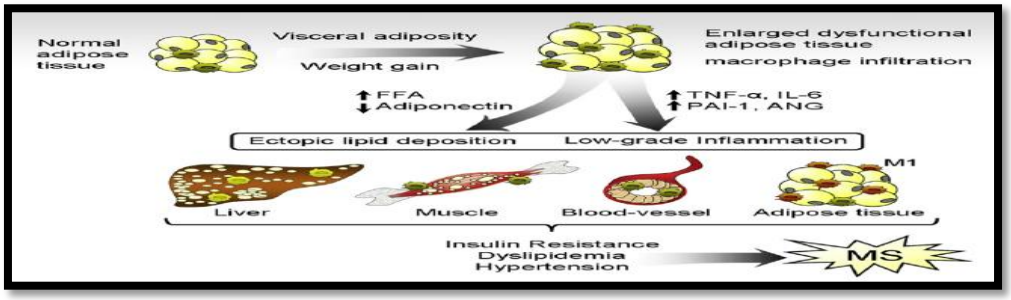

Fig. 2. Adipose tissue expansion, insulin resistance, and the metabolic syndrome. Macrophages are conducted, infiltrate and contributing further to pro-inflammatory M1 phenotype in the hypertrophic adipose tissue [8]

3. DIABETES MELLITUS

Is a silent metabolic syndrome characteristic by hyperglycemia resulting from lowering or impaired insulin secretion or increase insulin resistance by the body tissue [6].

3.1 Types of Diabetes

Insulin treatment is required at any type. Most important types are:

1- Gestational diabetes mellitus (GDM) is known as any degree of glucose intolerance with onset or first recognition during pregnancy. Diet modification is applied or insulin for treatment, this condition may not persistence after pregnancy [10].
2- Type 1 diabetes (Autoimmune diabetes mellitus): Is an absolute insulin deficiency resulting from absolute destruction of β cells [11].
3- Type 2 Diabetes mellitus: Is a relative insulin reduction that resists the action of insulin [11]. People suffers from obesity are more threatened to develop T2D, and metabolic syndrome [6].

3.2 Complications

Patients with T2D may present with characteristic symptoms such as thirst, polyuria, a defect of vision, and weight loss. In sever form, ketoacidosis or a non-ketotic hyperosmolar state may lead to loss of conscious. T2D can cause pathological and functional changes in the organ may be present for a long time before the diagnosis is made. The long-term effects of T2D lead to a gradual increase of the specific complications of retinopathy with a loss of vision, and nephropathy that may lead to renal failure [12].

3.3 Induction of T2D Mellitus in Experimental Animals

T2D induced by streptozotocin (STZ), which is a molecule that produces a selective toxic effect in experimental animal [13]. Doses should be

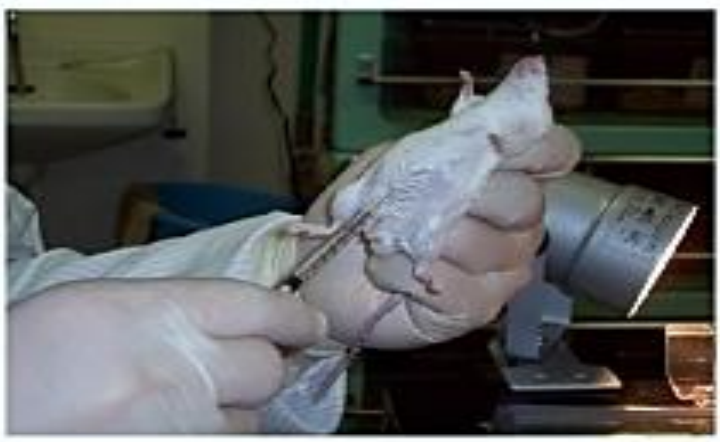

Fig. 3. Induction of STZ. Intraperitoneally in rat model to induce T2DM [17]

calculated to perform a partial destruction of β cell mass to produce a non-ketotic and a mild insulin deficient state of T2D [14]. Animals will be injected with a single dose of streptozotocin 65 mg/kg intraperitoneally (Fig. 3) [15].

Here are other ways to induce diabetes in a model rat by consuming of unbalanced high-fat diets that result in accumulation of fat in adipose tissue and increase body weight. The accumulation of fat will affect the releasing of deferent protein from the adipose tissue called adipokines, that plays an important role in insulin sensitivity and inflammation, which can be developed into some obesity-related disorder like type 2 diabetes [16].

4. INFLAMMATION

Is a host response reflection to tissue injury, and indicates the occurrence by four signs (Cardinal signs): redness, swelling, heat, and pain [18].

4.1 Carrageenan-induced Hind Paw Edema in the Mouse

Carrageenan induced inflammation by subcutaneous injunction in the right hind paw 100 µL (suspended in 1.5% vichele) of carrageenan that results in acute, non-immune, well reached, and highly reproducible inflammation, the action of pro-inflammatory agents, histamine, complement, and reactive oxygen will produce cardinal signs of inflammation develop subsequently to the injection. The traditional method to measure inflammatory response is quantified by increasing the size of paw oedema [18], which represent the magnitude of inflammation response effectively [19].

Hind paw size can be measured either by plethysmometer's caliper which is a rough method (Fig. 4) or by new The new technology to asses induced acute paw inflammation in the rats by epifluorescence imaging, a Fluorescence intensity in the saline and carrageenan-treated hindpaw (Fig. 5).

Carrageenan-induced hind paw edema as acute inflammation model in mice [18]. In addition, cotton pellet-induced granuloma as chronic inflammation model in rats [20].

100 µl of l carrageenan suspended in normal saline 1.5% concentration will be subcutaneously injected into a hind paw of the animals on one side. 100 µl of saline will be injected into the contralateral hind paw and used as a control. Using plethysmometer, the hind paw volumes will be measured before and after six hours of carrageenan injection. Oedema is expressed as the variation between the change in carrageenan-treated hind paw volume and the control saline-treated (Fig. 6) [18].

The results will be expressed as percentage of puffiness calculated as following the formula:

> Alteration = (width of the hind paw at the end day of experiment− width of the hind paw prior carrageenan/width of the hind paw prior carrageenan × 100%) [21].

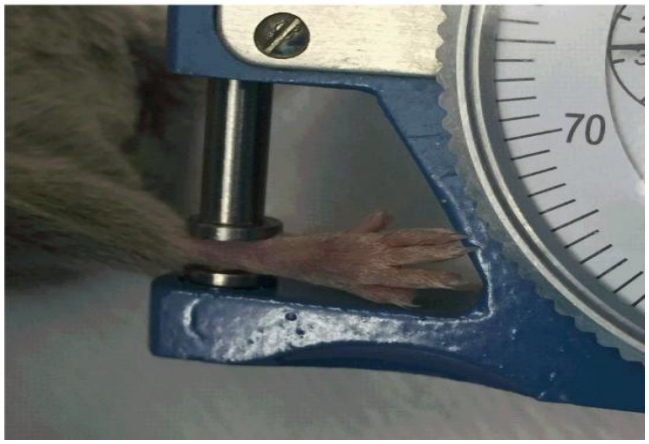

Fig. 4. Hind paw measurement by caliper. The paw measure by placing the paw in the caliper paw touch either side of the caliper, measurements read in mm [19]

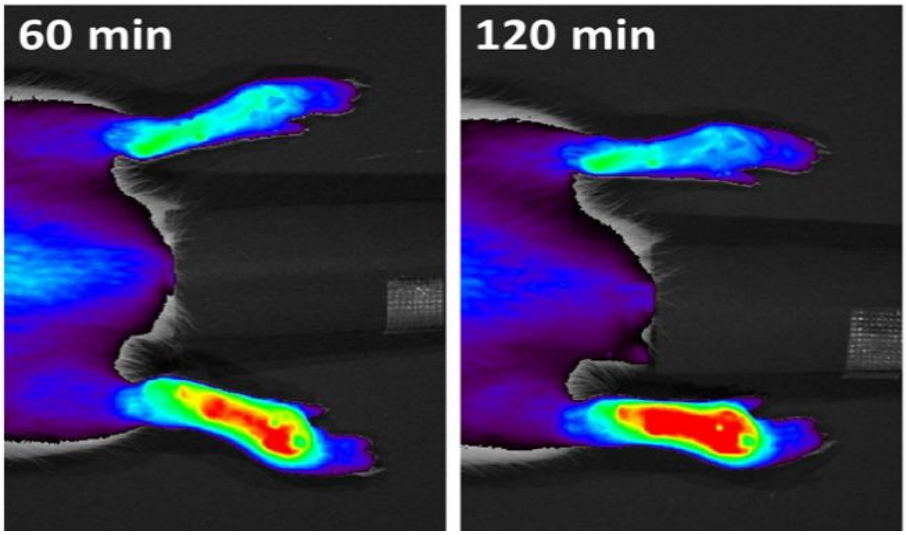

Fig. 5. Carrageenan-induced acute paw inflammation in the rat (Fluorescence intensity in the saline and carrageenan) measured after injection by epifluorescence imaging 60 and 120 min [22]

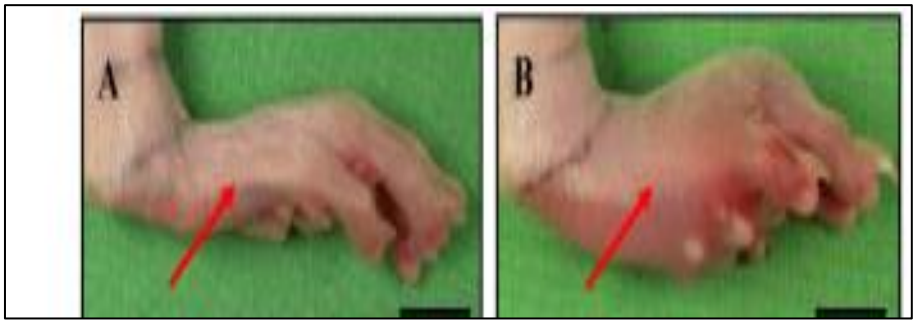

Fig. 6. Carrageenan control and injected hind paw (A) control hind paw, (B) injected hind paw by carrageenan 100 µL suspended in 1.5% vichele, show an edema and redness [23]

5. ANTI-INFLAMMATORY DRUGS

5.1 Diclofenac

Diclofenac sodium is a nonsteroidal anti-inflammatory class of drugs (NSAIDS), that used as anti-inflammatory and painkiller drug. Diclofenac interposed by inhibiting the release ofcyclooxygenase-1 (COX1) and cyclooxygenase-2 (COX2), that convert arachidonic acid into prostaglandins (PGs). Diclofenac should be used in minimal dose due to its toxicity. Diclofenac at 5 mg/kg dose started to show an inhibition in hind paw edema after 2 hours [24]. Diclofenac can increase the risk of heart attack, strokes, blood clots and gastroduodenal ulceration [25]. Gastroduodenal ulceration and bleeding are the major limitations to the use of NSAIDs. It's lead to damage to the gastroduodenal mucosa via several mechanisms, including the topical irritant effect of these drugs on the epithelium, weakness of the barrier properties of the mucosa, inhibition synthesis of the gastric prostaglandin, decrees blood flow through the gastric mucosa and interference with the repair of superficial injury. The presence of acid in the lumen of the stomach also help in increase rate of the pathogenesis of NSAIDs induced ulcers and bleeding, through impairing the restitution process, interfering with haemostasis and inactivating several growth factors that are important in mucosal defence and repair [26] (Fig. 7).

5.2 Aleglitazar

Aleglitazar is a combination of PPARα and γ agonist and designed to stimulate both α and γ receptors at minimum concentrations. PPARs

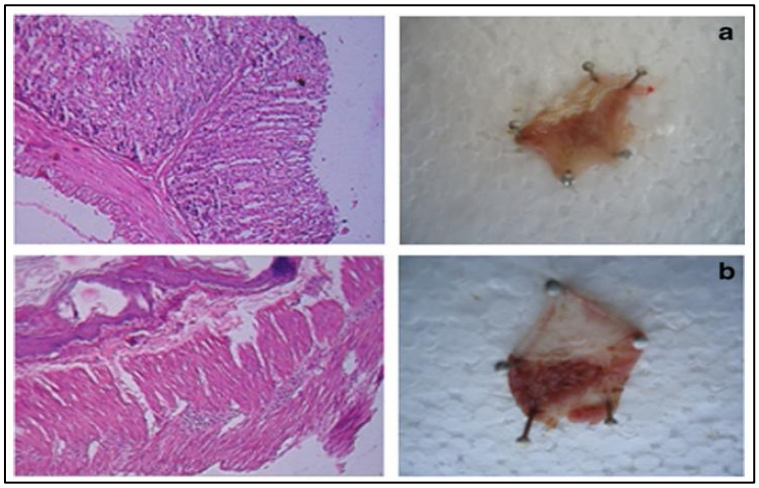

Fig. 7. Morphological and histological examination of rats gastric mucosa in diclofenac-induced ulcer model (section was stained with Haematoxylin and Eosin and magnified by 20×). A. Stomach of control rat; B. Stomach of diclofenac-induced ulcer rat at a dose of (100 mg/kg) [27]

are one of nuclear receptor superfamily, which participated in the transcriptional control of genes contributing in lipid and carbohydrate metabolism, and inflammation, especially in the setting of obesity, hypercholesterolemia, insulin resistance, and atherosclerosis. PPARs are divided into 3 subtypes: PPARα, PPARγ, and PPAR δ. PPAR α found at high concentration in liver, kidney and the skeletal muscle and PPAR γ found at high concentration in adipocytes, muscle cells, the liver and the kidney [5]. The synthetic agonists of PPAR α e.g. fibrate used for lowering triglycerides (TG) and raising high-density lipoprotein cholesterol (HDL) in plasma, while the synthetic PPAR γ agonists e.g. thiazolidinediones pioglitazone used as antidiabetics [1].

5.3 Mechanism of Action

Aleglitazar prepared to be an agonist for both PPAR α&γ.PPARα the agonistic action is controlled lipid levels, thus improving dyslipidemia. In addition, PPARγ controls glucose level and resulting in reduce insulin resistance in diabetic patients [28].

5.4 Optimal Dose

Aleglitazar (150 ug/kg/day) for 16 weeks was selected to explore any potential association of this dual PPAR α/γ agonist with anti-arthritic and anti-inflammatory properties [29].

Supratherapeutic dose (600 µg) of aleglitazar for 26 weeks in patients with normal to borderline impaired renal function with glomerular filtration rate (eGFR 60 mL/min per 1.73 m2), raised serum creatinine by a mean 22% to a plateau after 4 weeks. Then, serum creatinine resumed to baseline after 4 to 8 weeks of drug cessation [29].

5.5 Side Effect

In increase the incidence of the expected dose, will lead to increase in serum creatinine, decrease glomerular filtration rate, progressive nephropathy and bilateral oedema [29].

5.6 Ulcergenic Effect

Aaleglitazar with a dose of (150 µg/kg) shows pharmacological effects on the 8th day after pellets. The day before scarification, all rats prevented from food and liquid for 12 hours. Gastric tissue will be removed and taken out, after cut open to the stomach the inner surface will be cleansed with saline 0.9% to clean any remains inside the stomach and hold it by bins to exposed its mucosa and stomach ulcer will examined under magnifying land lens to calculate ulcer index by the number and depth of the ulcers (gastric ulcer scoring), [30]. Part of the stomach (fundus) fixed in formalin and exposed to histopathological study to compare it with diclofenac [27].

5.7 Drug-drug Interaction

Aleglitazar used in combination with warfarin which used as an anticoagulant drug, it affects

the efficacy and safety by affecting the viscosity of the blood through angiotensin-2 receptor blocker so the blood vessels dilated that lead to decrease the velocity of the blood stream and increase the susceptibility of thrombosis [31].

In patients with normal to borderline impaired renal function and impaired glomerular filtration rate using aleglitazar in supratherapeutic dose will increase serum creatinine and decrease glomerular filtration rate that leads to progressive nephropathy and bilateral oedema so it interacts with diuretics [31].

6 BIOCHEMICAL TESTS

6.1 Fasting Blood Glucose

A daily dose of aleglitazar150 µg observed to modulate the fasting plasma glucose (FBG) [5].

6.2 Insulin

Aleglitazar treatment helped to increase body's sensitivity to insulin significantly compared to placebo.

6.3 HbA1c

Clinical trials of aleglitazar in patients with type 2 diabetes were conducted for 26 weeks (150 µg/day). The primary endpoint was significant reduction in glycated hemoglobin (HbA1c) concentration from baseline to week 26 [32] (Fig. 8).

6.4 Serum Creatinine

Serum creatinine (SC) is a routine test for kidney function assessment [33]. Serum creatinine showed to increase and show to be reversible after cessation of aleglitazar within a follow-up period from 4 to 8 weeks [29].

6.5 Immuno-inflammatory Reactions in Obesity-Related Disorders

C-reactive protein (CRP) is a crucial inflammatory biomarker [34]. High sensitivity to aleglitazar shows a significant reduction in CRP [35].

6.6 Free Fatty Acids (FFA) and Triglycerides and – HDL

PPARα and PPARδ enhance the movement of lipid out of circulation by increase uptake of free fatty acid and oxidation in tissue, while PPAR γwill stimulate the process of lipid storage in adipose tissue. [36].

It has the most effective improvement in high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL), and triglycerides. The result of lowering lipid profile reduce the risk of cardiovascular disease and particularly atherosclerosis [5].

6.7 Detection and Estimation of Serum Level of Tumor Necrosis Factor Alpha (TNF-α)

In the patient with diabetes the inflammatory mediators levels of gingival crevicular fluid (GCF), interleukin 1 beta (IL-1beta) and monocytic secretion of prostaglandin E2 (PGE2) are increased more than the non-diabetic patient [37]. Tumor necrosis factor-alpha (TNF-α) synthesis in adipose tissue, the degree of adipose tissue related to the level of synthetase

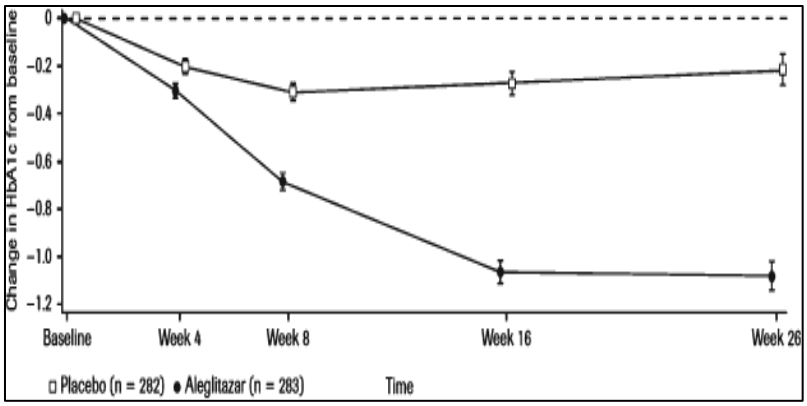

Fig. 8. Gradually reduction inHbA1c. Significant reduction in HbA1c by aleglitazar was apparent by week [32]

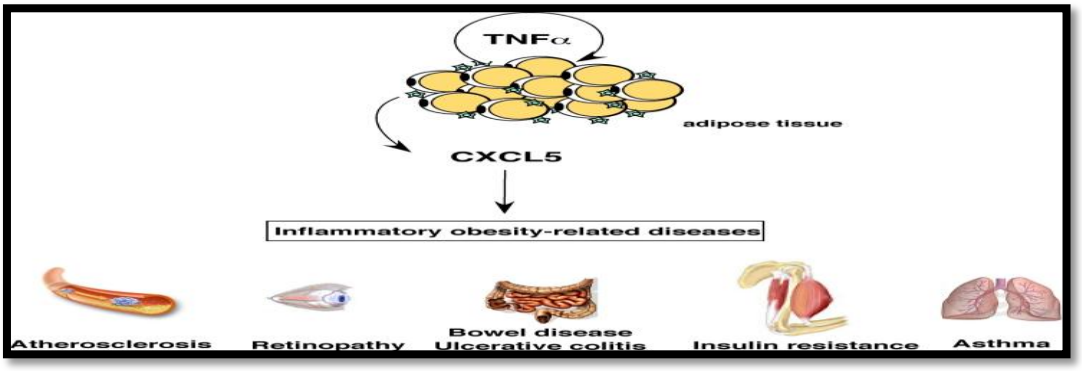

Fig. 9. TNF-α concentration in T2DM. (4.4+/-0.2 pg/ml) [41]

of TNF-α, this is the bond between obesity and T2DM [38]. Serum level of TNF- α in obese patients with T2DM increased than normal or non-obese patient with T2DM, serum level of TNF- α show positive correlation to degree of adipose tissue and negative correlation with glucose-insulin rate (GIR),increase TNF- α highly associated with increased insulin resistance (Fig. 9) [39].

6.8 Nitric Oxide (NO) Concentrations in Serum

Obese rats were assigned to treatment by aleglitazar, the treatment was administered for nine weeks. Nitric oxide (NO) was measured. Aleglitazar increased NO release by 25% as the nitric oxide/peroxynitrite ratio (NO/ONOO-) which is an indicator of NO synthase uncoupling increased by 33% with aleglitazar treatment [40].

7. CONCLUSION

Aleglitazar is a new promising drug, used as an anti-inflammatory, anti-diabetic, and anti-hyperlipidemic drug. In comparison with diclofenac the standard anti-inflammatory drug. Inthe field of pharmacokinetics the AUC of aleglitazar. Increased with dose with values of (8.66 - 402) ng.h/ml while in diclofenac the AUC is between (72.6 - 177.5) ng.h/ml. Aleglitazar has more potent and has less side effect than diclofenac. But in some cases aleglitazar must be monitored under the supervision of a physician because it affects the safety and efficacy of warfarin and diuretics.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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