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Review Article

Exploring the therapeutic potentials of peroxisome proliferated receptors family (PPAR)

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ABSTRACT

The nuclear hormone receptor family has three distinct subtypes: PPAR-α, PPAR-β/δ, and PPAR-γ.Peroxisome proliferator activated receptor (PPARs)are genes that are activated by compounds. Triglycerides levels are reduced and the balance of energy is maintained when PPAR-α is stimulated. Fibrates are compounds that act as agonists for the PPAR, and have been used to treat dyslipidemia because of their effects on reducing triglycerides and increasing HDL-C (high density lipoprotein cholesterol). Recent research has also demonstrated that PPAR- agonist have anti-inflammatory and anti- thrombotic properties in the arterial wall. The stimulation of PPAR-β/δ increases the efficiency of the metabolism of fatty acids, it also maintains physical stamina and is considered the primary option for dealing with metabolic disorders. The activation of PPAR-γ promotes glucose metabolism and increase the sensitivity of insulin. Today, it is commonly understood that the dysregulated IGF systems is associated with the developmental and progression of various human cancers. As a result, the balance of energy and metabolic processes is primarily determined by the nuclear receptors of the PPAR family. The current state of knowledge regarding the beneficial and detrimental effects of PPAR agonists on various diseases, including dyslipidemia, diabetes, adipocyte inflammation, cancer, and obesity is the subject of this review.

1. Introduction

A category of nuclear receptors called peroxisome proliferator-activated receptors is involved in several diseases. Subcellular structures called peroxisomes are common in the majority of cells in plants and animals. Numerous metabolic processes are conducted by them, including the metabolism of cholesterol, the β-oxidation of fatty acids (the FAs), and H O-based respiration. The nuclear hormone factors' protein family, which includes thePPAR proteins, is intrinsically linked to one another.[1] PPARs are part of a 48-member nuclear hormonal receptor family that was initially recognized in rats in 1990. However, these agents have no association with the transmission of humans. PPARs are initiated by small, lipophilic compounds that are triggered by the thyroid hormones and steroids. The rat liver has a significant increase in the total number of peroxisomes, this is due to several similar chemicals that are present in the liver.Other chemicals can cause hepatocarcinogenesis, the transcription of genes involved in the production of near enzymes, and increased liver size. Herbicides, commercial solvents, and hypolipidemic drugs are all examples of this type of substance. PPARs are categorized into three primary types: α, β/δ, and γ. The biological effects of numerous varieties of fatty acids and compounds derived from FAs are attributed to these subtypes. Additionally, activated PPARs may inhibit transcription through DNA-independent interactions with other transcription participants, such as STAT-1 and AP-1, as well as through interactions with

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the NFκB signal enhancer, these agents are said to be transcriptionally active.[2]

2. Peroxisome- proliferated activated receptor –α

High concentrations of PPAR-α are observed in hepatocytes, enterocytes, and vascular cells that are immune, including smooth muscle cells, microglia, and astroglia, as well as lymphocytes, monocytes, and epithelial cells. These cells are all associated with the brain.[3,4] It has a significant role in the conversion of FA to MHC in the liver, which is responsible for the peripheral tissues like the heart, kidneys, skeletal muscles, retina, and brown adipose tissues. Additionally, it may have a role in the oxidant/antioxidant pathway and increased rates of mitochondrial and peroxisomal fatty acid β-oxidation.[5,6] Both man-made and natural FAs can serve as ligands for PPAR-α, the latter of which are derived from molecules that are naturally occurring.[7] PPAR-α's physiological, pharmacological, and genetic activities have been studied extensively in recent decades. PPAR-α has a crucial role in lipid and lipoprotein metabolism, reducing dyslipidemia associated with metabolic syndrome.[8–10] Adipocyte-derived fatty acids stimulate PPAR-α during fasting, increasing the production of ketone bodies. The capacity of PPAR-α to bind chemicals that promote peroxisome proliferation led to its discovery as the first hereditary sensor for lipids in the early 1990s.[11] Although their development in animals has been associated with hepatomegaly as well as malignancy,[11] which have yet to be observed in humans, these organelles aid in the oxidative degradation of FAs.

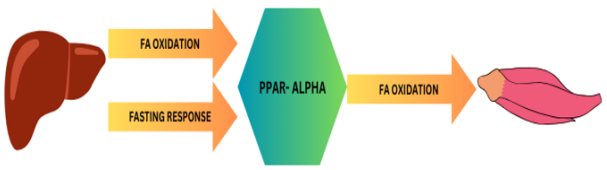

Figure 1: Metabolic integration by PPAR-α

2.1. PPAR-α: From fasting to elevated cholesterol levels (Hyperlipidaemia)

PPAR-α is primarily expressed in the hepatic system and, to a lesser degree, in the heart and muscle. It plays a vital function in modulating the oxidation of fatty acids.[12] Fasting releases fatty acids from the fat tissue and transports them through the liver, in which PPAR-α is strongly activated [13]. Fatty acids activate PPAR-α, leading to oxidation of fatty acids in liver and the production of ketone bodies, which provide energy to peripheral tissues. PPAR-α-null mice struggle to satisfy energy demands during fasting, resulting in low blood sugar, high cholesterol levels, hypoketonemia, and a fatty liver.[13] PPAR-α activation promotes fatty acid oxidation and enhances plasma lipid profiles. In animal models, PPAR-α agonists increase insulin sensitivity by lowering plasma triglycerides, obesity, and hepatic and muscular steatosis. Although PPAR-α-selective agonists like fibrates are commonly used to treat hypertriglyceridemia, their impact on insulin sensitivity in humans has not been thoroughly studied.

2.2. PPAR- α andlipidmetabolism

PPAR has effects on lipids and lipoproteins, which are listed below. PPAR activation leads to increased expression of genes associated with β-oxidation of fatty acids absorption in certain tissues. It includes carnitine palmitoyltransferase type 1 (CPT-1), a key enzyme associated with fatty acid breakdown inside the mitochondria in active metabolic tissue which include adipose tissue, cardiac and skeletal muscles with a PPRE in its promoter region, and acyl-Coenzyme A synthetase is an enzyme that plays an important function in the esterification of fatty acids, blocking their efflux from cells in the liver and kidney.[14] As a result, fewer free fatty acids are available for the formation and release of VLDL (very-low-density lipoprotein).[15]

2.3. Effect on triglyceride & LDL metabolism

Through mechanisms include enhanced free fatty acid oxidation, liver lipoprotein lipase production, and apo-V and apo-CIII expression, respectively, PPAR activation reduces TG levels. The mechanism by which PPAR stimulation impacts apo CIII transcription is currently unknown. Research conducted in vitro suggests that apo-CIII production is inhibited by interacting with the PPRE within the Reverb-promoter, since persons deficient in this protein had higher plasma levels of triglycerides and apo-CIII.[16] It is also unclear if apo-CIII affects TG conversion in vivo. In contrast to prior research, which found that apo-CIII only affected TG metabolism when coupled to lipoproteins in levels that were not present in vivo, other studies[17] found an impact in normolipidemic patients. VLDL particles have a detrimental impact on the amount and apo-CIII concentrations of other lipoprotein subtypes, resulting in an increase in small, dense LDL particles. PPAR activation facilitates an evolution in the particle distribution profile of LDL molecules, resulting in a reduction in atherogenic dense LDL cholesterol levels with a weak affinity for the LDL receptor and an increase of massive buoyant LDL particles with an elevated affinity for this particular receptor.[18]

2.4. Effect on HDL metabolism, and reverse cholesterol transport

By increasing the liver's synthesis of apo(A-I) and apo(A-II), PPAR controls HDL metabolism.[19] In order to enhance

HDL-mediated cholesterol efflux through macrophages, BI[20] & A1 (ABCA1)[21] expression levels should be raised. Reduce the synthesis of cellular cholesterol ester in vascular macrophages to reduce the formation and accumulation of foam cells.[22] As a result, more extra cholesterol is released to external receptors. Moreover, PPAR activation increases the amount of cholesterol available for efflux in the plasma membrane by controlling the stages involved in cholesterol mobilisation prior to cholesterol efflux.[23] This promotes reverse cholesterol transport in conjunction with expression regulation of SR-BI and ABCA1.

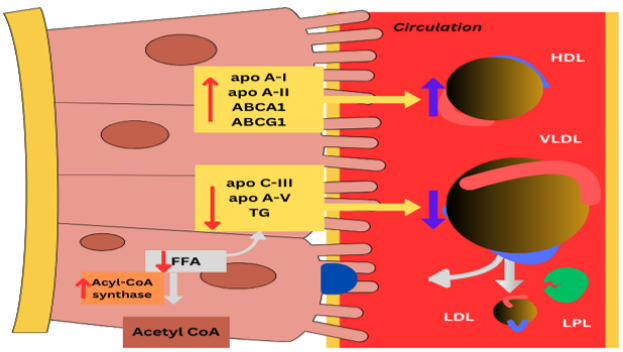

Figure 2: Fibrates influence lipid metabolism via modulating the expression of PPAR genes. Apolipoprotein CIII (apo-CIII) is expressed less when PPAR is activated, and genes implicated in fatty acid absorption and oxidation, hepatic lipoprotein lipase, and apolipoprotein V (apo-V) are expressed more when PPAR is activated. These actions have a net effect of increasing HDL (high-density lipoprotein) production, VLDL (very-low-density lipoprotein) elimination, and LDL (low-density lipoprotein) particle size, while decreasing VLDL formation & LDL particle concentration.

3. Peroxisome-Proliferated Activated Receptor -β/*δ*

The bulk of lipid metabolic pathways are regulated by PPARs. In the liver as well as muscles, and other organs, PPARα and PPARβ control the oxidative degradation of fatty acids, whereas PPAR-γ controls the accumulation of triglycerides in adipose tissue. Moreover, it has been demonstrated that PPARs function in the three main areas of intermediate metabolism-lipid, protein, and carbohydrate metabolism.[24] The function of PPARβ in fatty acid oxidation has been the subject of challenging research with many unanswered concerns. These first impediments resulted from PPARβ's ubiquitous activity, as this variation was found in every tissue studieddeveloping and mature. The second challenge is the lack of a truly selective ligand, either artificial or naturally occurring. The use of a minimum three synthetic substances in tests helps to overcome the latter difficulty to some extent. Strongly binding to PPARβ, all-trans-retinoic acid, sometimes referred to as antioxidant vitamin A, is a naturally found agonist[25]. However, the physiological importance of this discovery is still unknown. Last but not least, the null-allele mutation results in substantial premature embryonic mortality that also substantially penetrates,[26] which makes it very challenging to generate a PPARβ mutant mouse line.

3.1. PPAR-β particular features and patterns of expression

PPARβ, in contrast to PPARα and PPARγ, possesses a short N-terminal region that lacks a known ligand-independent activation domain. Studies indicate that cAMP-dependent phosphorylation in this region controls PPARβ activity.[27] The simplest of the three isotypes of PPARβ is attached to the flexible hydrocarbon tail of unsaturated fatty acids.[28] Notably, PPARβ has low molar affinities for three polyunsaturated fatty acids: arachidonic acid (AA), eicosapentaenoic acid, and dihomo-γ-linolenic acid. PPARβ is known to be activated by the eicosanoids PGA1, PGE2, PGD2.[29,30] Thus far, the only endogenous preferred eicosanoid for PPARβ that has been found is prostacyclin (PGI), a product of COX-2 arachidonate.Carbaprostacyclin (cPGI), a stable analogue of PGI, has been proven in transient transfection studies to increase PPARβ-mediated transcription activity. PGI production is strongly linked to PPARβ activation.[31] In its unliganded state, PPARβ is associated with co-repressors like the nuclear receptor co-repressor silencing modulator for retinoid and thyroid stimulating hormone receptors (SMRT). PPARβ inhibits the expression of PPAR-α and PPAR-γ targeted genes by interfering with PPRE binding. Co-repressors are released during PPARβ activation and can be utilised to repress non-PPRE genes. To completely understand the physiological significance of this method of action, more in-vivo research is required. There might be many major trans-repression mechanisms involved, such fighting for limited pools of co-activators or particular protein-protein interactions with different transcription factors like PPARα and NF-κB.

3.2. Potential role of PPARβ in metabolic diseases

Metabolic syndrome, often known as syndrome X, is a group of conditions characterised by hypertension, insulin resistance, overweight and obesity, low level of lipids, & high blood pressure. Elevated blood levels of saturated fats seem to be a major factor in insulin resistance development, which in turn propels the slow progression of TDM2, including cardiovascular problems. Usually, obesity and a rise in the depot of abdominal fat, which is particularly sensitive to the antilipolytic effects of insulin, set off a series of events that culminate in syndrome X. Although there are a number of contributing variables, the main cause of obesity is the disparity between energy intake and usage. To restore this balance, then, the main focus should be on dietary and lifestyle choices. However, in order to reestablish the

disturbed regulatory mechanisms brought on by significant fat depot accumulations, therapeutic interventions are frequently necessary. Because of its functions in lipoprotein control, skeletal muscle biological functioning, and obesity, PPARβ is a viable treatment target for metabolic syndrome. Research both in vivo and in vitro has connected PPARβ stimulation to transcriptional regulation, which leads to the uncoupling of energy expenditure and the enhancement of lipid oxidation in the muscles and brown adipose tissue. Moreover, it is noteworthy that in conditions of obesity and diabetes, muscle fibres undergo a change in metabolism towards a more type 2 fibre phenotype. Concomitantly, PGC1α expression is downregulated in TDM2 patients. Furthermore, compared to lean controls, the skeletal muscles of highly obese individuals have a decreased ability to oxidise fat. It follows that PPARβ's stimulation of the β-oxidation pathway would be advantageous. In fact, PPARβ agonists protect mice against diet-induced osteoporosis & genetically defined obesity by improving their blood sugar tolerance and sensitivity to insulin. Consistent with our findings, transgenic mice expressing PPARβ-VP16 in their skeletal muscle demonstrate a resistance to food-induced obesity.[32] Finally, individuals who have type II diabetes can more effectively control the amount of sugar in their blood thanks to the PPAR-β ligand GW 0742, which speeds up the process of muscle uptake of glucose.[33] One possible explanation for the beneficial benefits of PPARβ ligands in the therapy of metabolic syndrome is their influence on circulating lipoproteins. PPARβ ligands can increase HDL concentrations in animal studies of obesity, but PPAR-γ agonist cannot. This action is distinct from the other metabolic roles of PPARβ and may be highly beneficial in lowering the risk of cardiovascular disease, especially in those with high blood sugar.

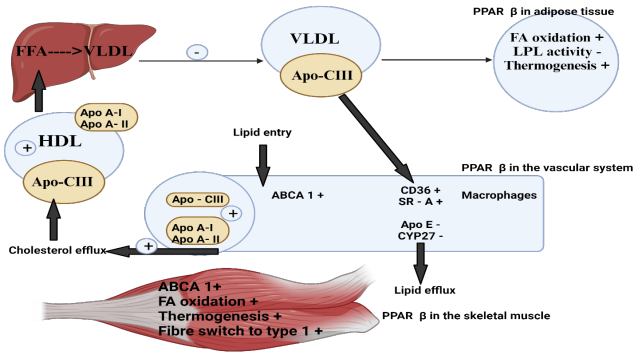

Figure 3: Particular PPAR tissue actions that raise the atherogenic lipoprotein profile. Hepatic VLDL discharges into the

bloodstream are decreased and fat accumulation is inhibited when PPARβ is activated in the liver. By increasing genes engaged in the β-oxidation pathway and respiratory chain separating in muscle and adipose tissue, PPARβ acts as a fat burner.The cumulative effect of these actions lowers blood triglyceride levels. Additionally, PPARβ stimulates the manufacture of the transporter gene ABCA1 within muscle cells, macrophages, as well as endothelial cells—all of which are a component of the vascular tissue. This leads to increased cellular cholesterol efflux and thus enhanced levels of circulating HDL, consistent with the elevated levels of Apo AI, Apo AII, and Apo CIII seen in plasma after PPAR ligand delivery. Marked + and - signs denote the triggering or repression of certain genes, complexes, and or pathways following PPARβ activation, respectively.

ABCA1: Transporter ATP-binding cassette A1; Apo A-I: Apolipoprotein AI; Apo A-II: Apolipoprotein AII; Apo C-III: Alipoprotein CIII; Apo E: Apolipoprotein E; CD36: Clusters of differentiation; CYP27: Cholesterol 27-hydroxylase; FFA: Free fatty acids; HDL: High-density lipoprotein; LPL: Lipoprotein lipase; PPAR: Peroxisome proliferator-activated receptor; SR-A: Macrophage-scavenger receptor Class A; VLDL: Very low-density lipoprotein.

4. Peroxisome Proliferator-Activated Receptor–γ

Thiazolidinediones (TZDs) are the PPAR-γ ligands that have been studied the most. The first drug approved for this use was troglitazone, which was followed by pioglitazone and rosiglitazone. The mechanism of action of TZDs was unknown prior to Lehmann's 1995 publication, which showed that TZDs were highly selective agonists for PPAR-γ, a ligand-dependent gene transcription factor and member of the nuclear receptor superfamily. Nuclear receptors serve as sensors of vitamins, hormones, endogenous metabolites, and external chemicals, which in turn controls the expression of several genes. It has long been known that PPAR-γ regulates the formation of adipocytes, FA buildup, and glucose metabolism. This protein is the target of anti-diabetic drugs. The effects of TNF-α on adipocytes are countered by PPAR-γ agonist, which increases insulin resistance. When PPAR-γ is present, the expression of numerous genes that generate proteins associated with hyperglycemia and metabolism of lipids increases. Nuclear receptor proteins called peroxisome proliferator-activated receptors (PPARs) play a role in a number of regulatory processes,[34] which makes them useful targets in the management of metabolic disorders. Potential biological targets, PPARs are connected to a variety of disease processes. Atherosclerosis, obesity, TDM2, and other illnesses have been linked to PPAR gamma (PPAR-γ) dysregulation.[35] Most agonists have been used with the intention of making them more active. Abnormalities in PPAR-γ are linked to dysregulated metabolism and, in turn, to obesity and a number of medical conditions, such as cardiovascular diseases and type 2 diabetes mellitus. PPAR-γ overexpression has been proposed to improve metabolic parameters in TDM2 along with other chronic conditions,

despite the fact that downregulation of the protein has been shown to have anti-obesity benefits.[36] In one investigation, electroporation was used to examine whether compelled expression of PPAR-γ could cause satellite cells to undergo a transformation into adipocytes in vivo. For this reason, the rat tibialis dorsal muscle was injected with the PPAR-γ gene, and histological examination was carried out.

Several PPAR-γ gene deletion investigations in mice have demonstrated communication between adipose tissue, skeletal muscle, and hepatic glucose and lipid metabolism, suggesting that PPAR-γ is essential for preserving appropriate insulin tolerance & whole-body glucose and cholesterol homeostasis.[37,38] Furthermore, it has been proposed by genome-wide correlation and association studies that the PPAR-γ gene contributes genetically to the onset of type 2 diabetes.[39] The study investigated the potential effects of the PPAR-γ gene on the metabolic traits and psychotic behavioural characteristics of Taiwanese patients with schizophrenia.[40]

Cow ghee, as opposed to soybean oil, offers protection against the DMBA-induced breast carcinogenesis; this defence is mediated by both increased and decreased COX-2 expression.[41] One of these genes seems to be the human homologue to a different gene that modulates adipogenesis in C. elegans, and the goal is to determine the novel PPAR-γ sensitive PPAR-γ genes and their significance in controlling human adipocyte proliferation and differentiation.[42] Affymetrix gene expression analysis in human adipocytes after differentiation was triggered showed approximately 1000 genes that were significantly enhanced. Using a novel chemically modified antisense oligonucleotide, PPAR-γ expression was reduced prior to initiating differentiation.

4.1. PPAR-γ, adipocyte function, & TDM2

With the rise in obesity rates, it is crucial to comprehend the mechanisms underlying the formation of adipose tissue in the body and its seemingly boundless capacity to store fat. PPAR-γ is an expert regulator in the growth of lipid cells and their ability to function properly in adulthood, as numerous studies have shown.[43] PPAR-γ is produced as adipocytes develop, and non-adipogenic cells can express it to become mature adipocytes.[44] Moreover, PPAR-γ-deficient animals do not develop adipose tissue.[45–47] These results are consistent with human cases of significant lipodystrophy & insulin resistance caused by dominant-negative variants in a single genotype of PPARG (the gene expressing PPAR-γ). According to studies conducted in vitro, PPAR-γ is the final transcriptional cascade mediator of adipogenesis that comprises the C/EBP gene transcription factor family.[48,49]

Adipose tissue is crucial in maintaining overall glucose homeostasis, even though it only contributes 10% of insulin-stimulated glucose clearance. The discovery that TZDs that are sensitive to insulin are potent agonists of PPAR-γ led to the theory that PPAR-γ, a fatty acid sensor, would play a critical role in controlling glucose metabolism.[50,51] TZDs improve insulin action, which promotes muscle glucose outflow and suppresses hepatic glucose synthesis, to improve insulin resistance in a variety of experimental animal models and human populations.

Pharmacologic activation of PPAR-γ reduces lipids toxicity in the liver as well as muscles by increasing adipose tissue's fat storage capacity. This model activates genes that encode molecules such as lipoprotein lipase (lipoprotein hydrolysis), aP2 (fatty acid binding protein), CD36 (lipoprotein receptor), FATP-1, glycerol kinase, & SREBP-1 and SCD-1 (sterol and fatty acid synthesis regulators, respectively). This metabolic route promotes insulin sensitivity and enables body-wide lipid partitioning by increasing adipose tissue triglyceride content while decreasing free fatty acids and triglycerides in the circulation, liver, and muscle.[52,52]

Second, drugs that block PPAR-γ alter the way fat releases signalling molecules like resistin, adiponectin, leptin, and tumour necrosis factor-α (TNF-α), which, because of serum transfer, affects many other tissues' metabolisms. For example, PPAR-γ agonists suppress the synthesis of resistin and TNF-α, both of which promote insulin resistance. On the other hand, PPAR-γ agonists promote adiponectin production, which raises insulin sensitivity and muscle and liver fatty acid oxidation. Hepatic glucose production falls when muscle glucose consumption rises.[53–57]

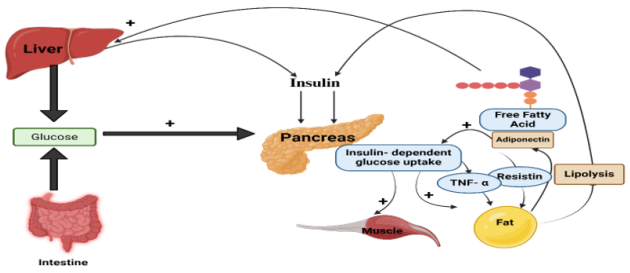

Figure 4: Tissue-tissue cross-talk in glucose and lipid homeostasis. Glucose derived from diet or endogenous sources stimulates insulin secretion. Insulin promotes glucose uptake by skeletal muscle and fat, opposes hepatic glycogenolysis and gluconeogenesis, and inhibits fat lipolysis. Free fatty acids liberated from adipose tissue contribute to insulin resistance in the skeletal muscle and liver. Additional fat-derived signals, including TNF-α, resistin, and adiponectin, modulate insulin sensitivity and fatty acid metabolism in the muscle and liver

4.2. PPARg and Atherosclerosis

PPARα activation is an important anti-inflammatory strategy during inflammation.[58] Initially, PPARα was

discovered to be a transcription factor that regulated the metabolism of lipids and carbohydrates and belonged to the superfamily of hormone receptors located in the nuclear membrane.[59] Consequently, PPAR can be dissociated from its significant function in the pathogenesis of diabetes, obesity, and arteriosclerosis.[60] Synthetic TZDs that are antidiabetic and selectively activate PPAR.[61,62] These drugs enhance the therapeutic effects of insulin and lower blood glucose levels.[63] The most current study by Kaul et al. gathers information from recent trials to investigate the long-term effects of TZD use. These results indicate that higher incidences of heart failure are associated with pioglitazone and rosiglitazone, and rosiglitazone is associated withhigher risk of cardiovascular events.[64]

Regardless of how they impact glycemic management, TZDs' activation of PPAR-γ has a variety of effects on standard and unconventional risk factors for cardiovascular disease. Several examples of these include halting the progression of intermedia thickness,[65] reducing platelet activity circulation,[66] reducing PAI-1 expression,[67] preventing glycation,[68] increasing plasma adiponectin,[69] and lowering CRP,[70] IL-6,[71] and MMP-9.[72] More research is required to ascertain the relative contributions of the various elements to TZD-dependent cardiovascular alterations. PPAR is expressed by monocytes and macrophages that are activated during atherogenesis. Activated endothelial cells attract monocytes to the arterial wall of big arteries first. Monocytes penetrate the subendothelial region after attaching to integrins and selectins. Mostly, they follow a chemokine gradient that starts at the infection site, such as IL-8. They differentiate into macrophages there.[73] This process is altered when PPARα activation occurs. Therefore, by decreasing macrophage accumulation in the intima, troglitazone inhibited the formation of early plaque lesions in LDL receptor knockout (LDL-R–/–) mice. This result is consistent with the in vitro observation that rosiglitazone and troglitazone inhibited the MCP-1-directed trans-endothelial migration of monocytes.[74]

TZDs can reduce the progression of atherosclerosis but are unable to reverse it, according to research elucidating the role of PPARα in progressive plaque formation in LDL-R–/– mice.[75,76] They may potentially hasten atherosclerosis in some circumstances by encouraging macrophage demise and plaque necrosis. Gene therapy was able to preserve atherosclerotic plaques and reduce plaque formation in Apo E–/– mice that had previously developed atherosclerosis by using a recombinant adenovirus carrying mouse PPARg cDNA.

This study suggests that PPARα could be a promising target for gene therapy, which could accelerate the onset of atherosclerosis. When taken into account collectively, PPARα mostly protects against atherosclerosis. Therefore, the primary objectives of therapeutic techniques may be PPAR downregulation or prolonged PPAR activation.

However, it is crucial to keep in mind that the formation of the dead centre in the intima is one of the main factors causing atherosclerosis to progress. This process may be started, at least in part, by desensitised macrophages that are not able to remove the debris from cells that is accumulating.[77,78] Activation of PPARα, which induces an anti-inflammatory macrophage phenotype, would be even more detrimental under these circumstances. Consequently, more research is needed to comprehend how PPARα's pro-versus anti-atherosclerotic action changes over time as atherosclerosis develops.

5. Effects of TZD Treatments and PPARg Gene Dosage on Experimental Animals of Inflammation

Table 1: Abbreviations: Ad, adenovirus; CI, ciglitazone;GW, GW7845;PI, pioglitazone; Ro, rosiglitazone; SB, SB219994;TR, troglitazone.

Disease	Effect	References
Obesity	Inflammation Adipose tissue inflammation	79
Arthritis	Incidence and severity Severity in PPAR g+/- mice	80–82
Psoriasis	Epidermal keratinocyte proliferation; Differentiation Paw edema, pleural exudate formation, mononuclear cell infiltration, histological injury	83
Airway inflammation	Symptoms of asthma Eosinphilic influx, mucus production, serum IgE Neutrophila Edema, lung injury	84,85
Experimental autoimmune encephalomyelitis	Severity in PPAR g+/- mice	86

6. PPARg and Cancer

PPAR-g role in carcinogenesis as an antineoplastic or pro-tumor agent has been a topic of intense discussion. PPAR-g has a complicated and tissue-specific role, according to earlier research. In colon cancer, it has been shown that PPAR promotes colon epithelial proliferation while suppressing the growth of implanted tumours or cultured cell carcinomas.

Tumor-restricted PPAR-g expression changes the course of the tumour, improving survival, lowering mortality, and eventually explaining a good prognosis, as reported in cases of bladder, breast, and colon cancer.

Indeed, mounting evidence indicates that PPAR activates many antineoplastic mechanisms. In particular, its antiproliferative actionswhich include triggering cell differentiation and death and reducing angiogenesisas well

as halting the cell cycle are investigated as possible PPAR-g antineoplastic mechanisms in this line.

By recognising genetically defective cells and either inducing apoptosis or halting the cell cycle so they can survive, the tumor-suppressor protein p53 lowers the likelihood of harmful mutations. Numerous p53 actions are achieved via activating target genes, like proapoptotic Bax, which promotes apoptosis, or p21(Cip1/WAF1), which pauses the cell cycle. In this case, the ability of PPAR to bind to the NF-B–responsive component present in the p53 promoter region and increase p53 production is especially noteworthy. Nevertheless, down-regulating PPAR results in MCF-7 breast carcinoma cells undergoing apoptosis and reduces cell proliferation, as demonstrated by Zaytseva et al. in 2008.[87]

According to certain studies, intact PPAR-α impairment promotes cancer. In a particular type of thyroid follicular carcinomas, a translocation of chromosomes (t (2;3) (q13; p25)) results in the creation of a linked box gene-8 (PAX8)-PPAR-g protein fusion.[88] When the PAX8/PPAR -gfusion protein was excessively expressed, primary human thyroid cells multiplied, suggesting that the PPAR-g moiety-dependent conversion of this fusion protein is essential for its carcinogenic activity.[89,90] Mutations have been shown to inhibit the formation and function of PPAR in a variety of malignancies, including bladder cancer. Therefore, the capacity to produce antitumorigenic activity is diminished due to binding to the sensitive region on the DNA as well as heterodimerization with RXR being impeded.

Colon cancer cells exposed to PPAR had G1 cell cycle arrest and produced more carcinoembryonic antigen. Furthermore, when PPAR is activated, the tumor-suppressor protein cavedin-1 is increased. This effect was abolished by treatment with the PPAR-g antagonist GW9662, suggesting that the PPAR-g pathway is activated prior to tumour suppression resulting from PPAR-g agonists. This was confirmed using a mouse model of human bladder cancer, where treatment with PPAR-α agonist significantly inhibited tumour growth.[91]

The development of genetic mutations that eventually lead to a pronounced inflammatory phenotype that grows aggressively and is generally resistant to treatment is linked to the establishment of tumours. Even though acute inflammation is an essential defence mechanism the body uses to protect itself after an injury, untreated chronic inflammation can promote the formation of cancer by providing the perfect environment for tumour growth.[92–94] Although the mechanisms beneath this link have only been tangentially studied, epidemiological studies show an elevated association among inflammation and cancer.[95,96] Therefore, cytokines produced in response to inflammation, infection, and immunology can obstruct the development and spread of tumours.

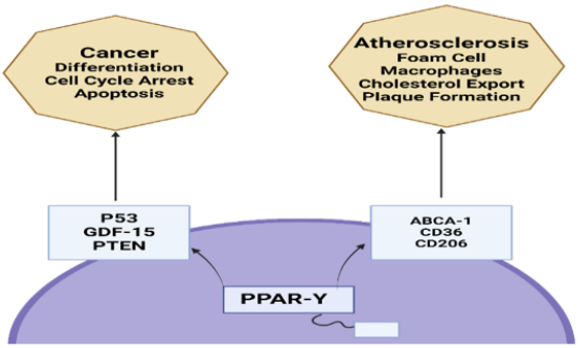

Figure 5: Summary of PPARg-dependent effects incancer, and atherosclerosis.

Enhancing our understanding of PPAR-α′s function in physiology & pathophysiology could lead to better understanding of cancer & its management. While the precise genes underlying the antiproliferative effects of PPAR-ggcells.[97]-g-g. Moreover, TZDs reduced the invasion capacity of pancreatic tumour cells derived from patient pancreatic adenocarcinomas via PPAR-gpathways.[98]PPAR-gtumour-signallingtumours. PPAR-α may have a role in regulating the distribution of energy, cellular metabolism, and cancer development. PPAR-tumour

(a) Cancer initiation and progression are inhibited by PPARg-mediated expression of the tumor suppressor p53, the antiproliferative operating phosphatase PTEN, and the cell cycle arresting GDF-15.

(b) PPARg activation is involved in atherosclerosis by inducing CD36 expression, increasing oxLDL uptake, consequently fostering foam cell formation and contributing to M2 macrophage polarization. This might be involved in plaque formation due to incomplete phagocytosis of apoptotic debris and concomitant generation of the necrotic core. However, PPARg-dependent induction of ATP binding cassette transporters, such as ABCA1, provokes enhanced cholesterol export, thus counteracting atherosclerosis progression.

6.1. Present scenario

To investigate its full therapeutic potential, upcoming PPAR research will focus on producing selective medicines with tissue& gene-specific effects, known as selective PPAR regulators (SPPARMs). This notion is backed by studies indicating that gemfibrozil and fenofibrate exhibit distinct PPAR-dependent impacts on hepatic apoA-I expression. Although gemfibrozil and fenofibrate both enhance apoA-I levels, fenofibrate also effectively raises HDL cholesterol levels, whilst gemfibrozil has little to no impact on human cholesterol levels. In vitro pharmacological profile shows that fenofibrate is a complete PPAR agonist, whereas gemfibrozil is a partial agonist, due to differential

Table 2: Drugs used for targeting of PPAR receptors

Generic Name (Brand Name)	Indications	Types of PPAR agonist	Adverse reaction and toxicity
Rosiglitazone maleate/metformin hydrochloride(Avandamet)	Diabetes	PPAR-γ agonist; AMPK activator	Lactic acidosis, cardiac failure, adverse cardiovascular events, edema, weight gain, hepatic effects, macular edema, fractures, hematologic effects, and ovulation
Glimepiride/rosiglitazone maleate (Avandaryl)	Diabetes	Sulfonylurea receptor modulator/ PPAR-γ agonist	Cardiac failure with rosiglitazone, major adverse cardiovascular events, hypoglycemia, edema, weight gain, hepatic effects, macular edema, fractures, hypersensitivity reactions, hematologic effects, hemolytic anemia, and increased risk of cardiovascular mortality for sulfonylurea drugs
Rosiglitazone maleate(Avandia)	Diabetes	PPAR-γ agonist	Headache, cough, cold symptoms, and back pain
Glimepiride/pioglitazone hydrochloride(Duetact)	Diabetes	Sulfonylurea receptor modulator/PPAR-γ agonist	Congestive heart failure, hypoglycemia, edema, fractures, and hemolytic anemia
Pioglitazone hydrochloride(Actos)	Diabetes	PPAR-γ agonist	Cold or flu-like symptoms, headache, gradual weight gain, muscle pain, back pain, tooth problems, and mouth pain
Pioglitazone hydrochloride/metformin hydrochloride(Actoplus Met)	Diabetes	PPAR-γ agonist/ adenosine monophosphate-activated protein kinase (AMPK) activator	Headache, nausea, vomiting, stomach upset, diarrhea, weakness, sore throat, muscle pain, weight gain, tooth problems, a metallic taste in the mouth, and sneezing, runny nose, cough, or other signs of a cold
Lobeglitazone sulfate(Duvie)	Diabetes	Dual PPARα/γ agonist	Edema and weight gain
Alogliptin benzoate/pioglitazone hydrochloride (Oseni)	Diabetes	Dipeptidyl peptidase IV inhibitor/PPAR-γ agonist	Upper respiratory tract infection, bone fracture, headache, nasopharyngitis, and pharyngitis
Fenofibrate/simvastatin (Cholib)	Mixed hyperlipidemia	PPARα agonist/HMGCR inhibitor	Raised blood creatinine levels, upper-respiratory-tract infection (colds), increased blood platelet counts, gastroenteritis (diarrhea and vomiting) and increased levels of alanine aminotransferase
Pravastatin sodium /fenofibrate (Pravafenix)	Mixed hyp rlipidemiaCoronary heart disease	3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) inhibitor/PPARα agonist	Abdominal distension (bloating), abdominal pain (stomach ache), constipation, diarrhea, dry mouth, dyspepsia (heartburn), eructation (belching), flatulence (gas), nausea (feeling sick), abdominal discomfort, vomiting, and raised blood levels of liver enzymes
Choline fenofibrate (Fenofibric Acid)	Hyperlipidemia	PPARα agonist	Diarrhea, dyspepsia, nasopharyngitis, sinusitis, upper respiratory tract infection, arthralgia, myalgia, pain in extremities, dizziness
Ciprofibrate (Lipanor)	Hyperlipidemia	PPARα agonist	Hair loss, balding, headache, balance problems, feeling dizzy, drowsiness or fatigue, feeling sick (nausea) or being sick (vomiting), diarrhea, indigestion or stomach pains, muscle pains
Fenofibrate (Antara)	Hypercholesterolemia Hypertriglyceridemia	PPARα agonist	Common: abnormal liver tests including aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and headacheRare: high blood pressure, dizziness, itching, nausea, upset stomach, constipation, diarrhea, urinary tract infections, muscle pain, kidney problems, and respiratory tract infections
Bezafibrate(Bezalip)	Hypertriglyceridemia hypercholesterolemia mixed hyperlipidemia	PPARα agonist	Stomach upset, stomach pain, gas, or nausea may occur in the first several days; itchy skin, redness, headache, and dizziness
Gemfibrozil(Lopid)	Hyperlip demiaI chemic heart disorder	PPARα agonist	Stomach upset, stomach/abdominal pain, nausea, vomiting, diarrhea, constipation, rash, dizziness, headache, changes in the way things taste, muscle pain

coactivator binding to the promoter region of the receptor [79]. With the use of pharmacological profiling examinations, gene profiling, microarray analysis, and in vivo investigations, the SPPARM concept has been applied to the identification and creation of novel PPAR activators in order to evaluate potential side effects and implications on lipid and glucose metabolism. This approach produced a potential SPPARM in the form of GFT505, a powerful partial PPAR agonist with SPPARM characteristics. Enhanced lipid-modifying activity of GFT505 as a PPAR-selective SPPARM modulator is superior to that of fenofibrate; it reduces total cholesterol and TG while boosting HDL cholesterol and apoA-I to a greater extent than equal fenofibrate dosages. Its lipid-modifying effect reduced atherosclerotic plaque by 50% in an in vivo animal study. Clinical trials investigating the effectiveness of GFT505 in treating dyslipidemia associated with abdominal obesity are now underway. This study highlights the potential applications of these novel PPAR agonists in the regulation of cardiometabolic risk.[84] The modulation of energy homeostasis has been better understood as a consequence of recent findings about the physiological relevance, mechanisms of action, and regulation of PPARβ expression. Although the prospects seem promising, it is evident that additional investigation into PPARβ's functions is necessary to more accurately define its characteristics as a target for therapy. The effects of PPARβ on cellular processes that are frequently not considered to be necessary for metabolism are also significant in terms of potential negative outcomes.In the end, it appears that the development of SPPARMs possessing both single or dual agonist characteristics is the appropriate approach. With the aid of numerous intervention techniques, complex and varied metabolic disorders will be able to be treated because these substances exhibit a wide range of partially or fully selective agonistic effects. PPARs are important therapeutic targets. Many good tactics are currently under consideration. The utilisation of humanised mice bearing the human PPAR gene or PPARg knockout mice specific to specific cell types or tissues may facilitate a better understanding of the numerous roles of PPARg in various illnesses.Moreover, an alternative approach is the creation of SPPARMs as opposed to PPARg full agonists, which maintain most of the benefits of PPARg activation while reducing its drawbacks. Moreover, irritating PPAR may have therapeutic benefits. For instance, by lessening T-cell depletion and minimising immune paralysis, this may improve sepsis outcomes. Depending on the type of tumour, PPARα activation or antagonization could halt the growth and advancement of the tumour.[83,85]

Finally, the situation with atherosclerosis is identical. The initial phase of PPAR activation can avoid inflammatory circumstances in the intima and/or vessel, considerably postponing or delaying plaque formation. To prevent inadequate clearance of apoptotic debris, it may become more attractive to activate PPAR. A variety of illnesses, particularly sepsis, inflammatory conditions, carcinoma, and atherosclerosis, can benefit from PPAR-targeted treatments.

Approved Drug Status based on PPAR Family TargetsTable 2

7. Conclusion

PPAR is engaged in a variety of different autonomous and DNA-dependent metabolic and enzymatic processes in the muscles of the skeleton, the liver, and adipose tissue. Illness has an influence on these pathways, causing a metabolic energy imbalance. As a result, targeting PPAR through intervention can provide therapeutic targets for a variety of diseases, including diabetes, obesity, cancer, inflammation, and dyslipidemia. Finally, evidence supporting the idea that PPARs might be helpful therapeutic targets for controlling inflammation caused by diabetes, obesity, hyperlipidemia, atherosclerosis, and possibly even anti-cancer capabilities is reviewed. Since its start a few decades ago, the PPAR study has developed into a lively arena for showcasing global work in a rapidly increasing field of inquiry. Following that, several no. of reviews discuss how PPAR agonists can help treat a variety of ailments. Examining the subjects of these particular concerns reveals a considerable interest in discovering unexpected physiological functions for PPARs and producing new and improved PPAR agonist therapies.

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None.

9. Conflict of Interest

None.

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