Review

Lifestyle and Food Habits Impact on Chronic Diseases: Roles of PPARs

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Abstract: Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that exert important functions in mediating the pleiotropic effects of diverse exogenous factors such as physical exercise and food components. Particularly, PPARs act as transcription factors that control the expression of genes implicated in lipid and glucose metabolism, and cellular proliferation and differentiation. In this review, we aim to summarize the recent advancements reported on the effects of lifestyle and food habits on PPAR transcriptional activity in chronic disease.

1. Introduction

Modern lifestyle characterized by unbalanced composition of the diet and poor physical activity, accompanied by the presence of environmental pollutants, has resulted in dramatic increases in the rates of metabolic disease and age-related diseases. These chronic diseases, such as diabetes, cardiovascular disease (CVD), autoimmune diseases, cancers (breast, colorectal, pancreas), and neurodegenerative diseases are all characterized by a chronic sterile systemic low-grade inflammation [1–3]. Moreover, these chronic diseases correlate with the metabolic syndrome (MetS), defined by a cluster of interrelated factors: dyslipidemia, hypertension, dysregulated glucose homeostasis, abdominal obesity, and insulin resistance (IR) [4]. Particularly, the obesity and insulin resistance emerge to be the heart of the pathophysiology of the MetS [5]. Different environmental factors of Western lifestyle play a key role in inducing chronic sterile systemic low-grade inflammation and, eventually, the correlated chronic disease. These factors may be divided in the unbalanced composition of the diet [6–8] and non-food related factors [9]. Regarding the diet, in Western society there is a consumption of high glycemic index foods (cookies, chocolate, pastries), thus is associated with obesity and IR [10–13]. This kind of diet increases inflammatory biomarkers [14] and it is related to chronic disease, such as CVD, diabetes, cancer, Alzheimer's disease [10,15–17]. In Western diet there is also an elevated consumption of certain saturated fatty acids (SAFA) [18], and industrially produced trans fatty acids [19,20]. Moreover, in Western diet there is an high $\omega 6/\omega 3$ fatty acid ratio [21–23], mostly because of a low intake of long-chain polyunsaturated fatty acids of the $\omega 3$ series, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fish, and alpha-linolenic acid (ALA) from vegetable sources [24]. Among the non-food related factors, it is possible to mention smoking

habit, insufficient physical activity [25–28], and environmental pollution [9] such as exposition to endocrine disruptors [29]. Thus, these kinds of lifestyle and food habits promote a chronic inflammatory status that as mentioned above is characteristic of chronic diseases. Biochemical mediators of lipids are represented by PPARs [30]. This review provides an update of lifestyle and food habits on low grade inflammation in two main chronic diseases, polycystic ovary syndrome (PCOS) and non-alcoholic fatty liver disease (NAFLD), with particular attention on the mechanism that involve the activation of the major metabolic and inflammatory players, the PPARs.

　　　PPARs are ligand-activated transcription factors, belonging to the superfamily of nuclear receptors (NR). PPARs act as lipid sensors; therefore, they have attracted much attention for their ability to improve metabolic syndromes [31]. They take part in nutrient and energy metabolism regulating whole-body energy homeostasis [32,33]. PPARs regulate nutrient metabolism such as lipid, glucose, and cholesterol and sustain the intraorgan metabolic flexibility (Box 1); indeed PPARs play also an important role in regulating the correct inflammation tone [30]. There are three PPARs subtypes: PPARα (NR1C1), PPARβ/δ (NR1C2), and PPARγ (NR1C3), that are highly homologous but differ for tissue distribution and biological functions (Table 1). Fatty acids and their derivatives are the main endogenous agonists of PPARs [34], while among the synthetic ligands there are the main drug utilized for counteracting MetS (Table 1). Their main activity in regulating lipid, glucose metabolism, and inflammation suggests that PPARs are the crossroad of several molecular signaling pathways, implicated in metaflammation onset [35].

Table 1. PPARs tissue distribution and biological functions.

Isoforms	Tissues Distribution	Target Genes	Functions	Synthetic Ligands	Natural Ligands
PPARγ	White and brown adipose tissue, the large intestine, skeletal muscle, spleen, pancreas, and brain.	*aP2*, *FATP*, *FAT/CD36*.	Regulation of adipogenesis, energy balance, lipogenesis, gluconeogenesis, lipid storage, glucose uptake, metabolism uptake and differentiation.	Rosiglitazone, Pioglitazone, Troglitazone, T3D-959, DBZ.	9-HODE, 13-HODE, 15d-PGJ2, EPA.
PPARα	Liver, heart, skeletal muscle, intestinal mucosa, white and brown adipose tissue, pancreas, and brain.	*Acyl-CoA oxidase*, *Thiolase*, *Apolipoprotein A-I*, *Apolipoprotein A-II*, *CYP8B1*, *FATP*, *FAT/CD36*, and *Lipoprotein lipase*.	Fatty acid metabolism, inflammation, thermogenesis, ketogenesis, glucose uptake, fatty acid oxidation and lipid storage.	Wy-14643, GW-2331, GW-9578, K-877 Fibrates.	Palmitic acid, Oleic acid, Linoleic acid, Arachidonic acid, DHA, oleoylethanolamide.
PPARβ/δ	Liver, intestine, kidney, abdominal white and brown adipose tissue, skeletal muscle, heart, pancreas, and brain.	Genes involved in lipid uptake, metabolism, and efflux, *Lpin2*, *St3gal5*.	Fatty acid oxidation, fatty acid metabolism, regulates blood cholesterol, glucose uptake, glucose utilization, insulin secretion, ketogenesis and inflammation.	L-796449, L-783483, GW-2433, MBX-8025, T3D-959, GW501516, GW610742.	Dihomo-γ-linolenic acid, Arachidonic acid, Methyl palmitate, 2-bromopalmitic acid, prostacyclin I2, 4-HNE.

2. PPARs and Metabolism

All three PPARs are involved in adipose tissue homeostasis. Tissues with high rates of fatty acids catabolism, such as brown adipose tissue (BAT), liver, and skeletal muscles, present high level of PPARα activity. Most PPARα studies have been conducted on the liver [36], in which this nuclear receptor is able to increase the transcription of gene related to the fatty acid transport and catabolism [36–38], ketogenesis [37], and gluconeogenesis [39,40]. PPARα in liver is a key factor for the adaptation of fasting and, consequently, energy switch from carbohydrate to fatty acid produced by WAT lipolysis. In the fed state, insulin-dependent PI3K pathway activates rapamycin complex 1 (mTORC1) that in turn suppresses, through nuclear receptor corepressor 1, PPARα activity [41]. PPARα agonist reduces obesity-related metabolic disorders. Experiments conducted on obese mice showed that PPARα agonist treatments improved the obesity condition and glucose homeostasis in terms of glucose intolerance, insulin resistance, and hyperglycemia [42,43]. Goto proposes three options to explain the ability in improving glucose metabolism via adipose tissue [44]. The first option proposes that one of the PPARα capabilities is to increase the expression of a particular hepatokine, the fibroblast growth factor 21 (FGF21) [42], a cytokine able to increase the energy consumptions in white adipose tissue (WAT) via the enhancement of the brown adipose tissue (BAT) activity (generally called "browning") [45,46]. In fact, the authors showed that fibrate treatment increases the energy consumptions and adipocyte dysfunction and improve glucose homeostasis in WAT of high-fat diet (HFD) wild-type mice, but not in fibroblast growth factor (FGF21)-deficient mice [42]. The second option is the PPARα-mediated enhancing of the production and the release of a particular lipokine, 1-palmitoyl lysophosphatidylcholine, by the liver [47]. This lipokine is able to recover the glucose uptake in insulin-resistant adipocytes, and is an endogenous ligand of PPARα, suggesting a positive feedback loop between PPARα activation and 1-palmitoyl lysophosphatidylcholine production in the liver [47]. Finally, the last option is the improvement of glucose metabolism, via direct action of PPARα on adipose tissue. In fact, transgenic mice that express in adipose tissues constitutive active human PPARα, presented under HFD, recovered insulin sensitivity [48], suggesting an important role of this NR in attenuating obesity-induced insulin resistance in WAT. Two isomeric forms of PPARγ exist, PPARγ1 and PPARγ2; PPARγ1 is most copious in WAT, but it presents also in other tissue (Table 1), while the expression of PPARγ2 is restricted in BAT and WAT [49,50]. Both isoforms are able to induce adipocytes differentiation although PPARγ2 appears more potent in this function [51]. In adipose tissue PPARγ plays key roles in adipocytes differentiation and survival, in the same time, this NR regulates insulin sensitivity and lipogenesis [37,52]. In BAT, the activation of PPARγ triggers the expression of genes linked to thermogenic program, comprising PPARγ coactivator protein 1α (PGC1A) and uncoupling protein 1 (UCP1) [53]. Regarding MetS, PPARγ is the most studied NR since 1995; it was recognized as a molecular target of thiazolidinediones, a class of antidiabetic and insulin-sensitizing drugs [54]. The activation of PPARγ, inducing adipocytes differentiation and strengthening the capacity of lipid accumulation in WAT [50] protects the body from IR and free FA release leading to the attenuation of lipotoxicity. In fact, negative regulation of adipogenic transcription factors, such as PPARγ in adipose tissue, has been demonstrated to cause visceral obesity [55]. Under over-nutrition, the increase of adipose tissue has a protective role in preventing the release of free fatty acids in the systemic circulation. This is possible because in WAT there are stem cells that can differentiate in adipocytes, thus increasing its ability in lipids storage; in this mechanism PPARγ plays an essential role. The fact that fat is not always bad is derived from the evidence that a significant part of obese individuals (healthy obese) do not show dysmetabolism while a significant percentage of lean individuals do [56,57]. Healthy WAT is composed by different adipocytes, showing an increase of hyperplasia and a decrease of hypertrophy; the latter is a definite feature of pathologic obesity [58–63]. Recently, it has been demonstrated that the recruit of new adipocytes from PDGFRβ+ pre-adipocytes determines the visceral WAT health in obesity [64]. Notably, in the hypothalamus of HFD rodents, by inhibiting PPARγ in the central nervous system (CNS), the sensitivity of the leptin pathway was improved. Another study demonstrated that transgenic mice knockout

for PPARγ in hypothalamic neurons had enhanced energy consumption; on the contrary, food intake and body weight were decreased. In addition, these mice had improved glucose metabolism upon High Fat Diet (HFD) [65]. Thus, PPARγ signaling in the brain influence the energy balance and stimulate the obesity phenotype [66]. Although the same obesogenic effects have been reported for activation of PPARα in the brain, the PPAR β/δ isotype appears to exert opposite role. Mice with PPPAR β/δ deleted showed a strong expression of PPARγ and PPARα in the hypothalamus [67]. Regarding PPAR β/δ, in genetic models, it has been demonstrated that the activation of this NF protects against obesity [68]. Transgenic mice encoding an active form of PPAR β/δ specifically in adipose tissue, fed with a standard chow diet, showed decrease of body weights (20%), of inguinal fat pad masses (40%), and less circulating free FAs and triglycerides compared to control animals [68]. The same mice upon HFD or genetically predisposed to the obesity are protected against weight gain, adipocyte hypertrophy, hypertriglyceridemia, and steatosis [68]. Moreover, an increase of browning was observed in these mice [68]. In opposite, the loss of PPARβ/δ function rendered mice more prone to weight gain and had reduced expression of brown fat UCP1 upon HFD [68]. While PPARα is the most present isoform in the liver, PPARβ/δ isoform is the most expressed in muscle and it is preferentially found in oxidative rather than glycolytic myofibers [69–71]. In muscle cells, the activation of PPARβ/δ switches energy production from glycolysis to fatty acid oxidation enhancing muscle endurance [72]. Moreover, the activation of this NF increases the fatty acid uptake and catabolism via oxidation in skeletal muscle cells [73]. PPARβ/δ expression in muscle has several physiological implications such as decreased skeletal muscle fatigability and increased resistance to HFD-induced obesity [71]. Insulin-resistant obese monkeys treated with GW501516; a ligand PPARβ/δ showed an increased serum high-density lipoprotein cholesterol and a decrease of low density lipoprotein, fasting triglycerides, and insulin [74]. The activation of PPARβ/δ, during HFD, increases consumption of lipid in skeletal muscles, avoiding hypertrophy of adipocytes and IR [68,69,75]. Finally, physical exercise and fasting increase the expression of PPARβ/δ in muscles [75–77], demonstrating that PPARs act as an interface between lifestyle and health.

Striated muscle plays central roles in MetS, since it is a regulator of total body mass and energy consumption. A surplus of glucose, free fatty acid, and triglycerides concomitant with physical inactivity altered muscular metabolism, that in turn contributes to the onset of obesity and IR [78]. In a healthy-weight individual, skeletal muscles represent ~40% of the total human body mass, and with the cardiac tissue, use almost 30% of the resting energy and nearly 100% of energy utilization during physical exercise [78]. Skeletal muscle is composed of heterogeneous myofibers, slow-, mixed- and fast-twitch, that differ in the composition of contractile protein apparatus and metabolism. In particular, slow-twitch (TypeI) has high oxidative aptitude using fatty acids as substrate for ATP production; mixed oxidative/glycolytic fast-twitch (type IIA) with both phenotype, and type IIB display high strength of contraction but lower oxidative ability doing anaerobic glycolysis [79]. Thus, systemic energy is impacted mostly by fiber type composition [80,81]. Physical activities, especially aerobic exercises, increase the amount of slow fiber type, while the opposite is observed in obesity and diabetes in which there is an enhance of caloric intake without an increase of metabolic demand [82]. Instead, in both diabetic and obese patients, physical activity improve IR and lean mass [83,84]. Similar to adipose tissue, the muscle secretes factors, named myokines, that act in an autocrine and/or paracrine manner [85,86]. Myokines panel production depends on exercise and may modulate, as adipokines, glucose and lipids metabolism [87–89]. Among these myokines, myostatin regulate glucose and lipid metabolism, and myostatin-deficient animal are not susceptible to diet-induced obesity [89]. Other myokines involved in systemic metabolism are angiopoietin-like protein 4 (ANGPTL4) [90], irisin, FGF-21, Interleukin-15 (IL-15), [85], meteorin-like protein [91] and Growth differentiation factor 11 (GDF11) [92]. Finally, β-aminoisobutyric acid (BAIBA), belongs to a recent class of factors called "myometabokines," is able to regulate systemic metabolism crosstalk [86], and to induce browning phenotype in white adipose tissue [93]. These last discoveries highlight the importance of muscle on energy homeostasis and thus the influence of moderate physical activity on human health.

Box 1

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1. PPARs and Nutrient Metabolism:

1.1. Lipid Metabolism

1.1.1. During the fasting state:

PPARα increases plasma high-density lipoproteins (HDL) levels and reduces low-density lipoproteins (LDL) levels [94–96]; it also promotes peroxisomal and mitochondrial oxidation in the protection of the liver from lipotoxicity [97]. Furthermore, PPARα produces and uses ketones during long-term fasting, to nourish extra liver tissues [37].

PPARγ, after being activated, reduces free fatty acids in a systemic way, with the exception of circulating blood and adipose tissue [98].

1.1.2. During normal nutrition:

PPARα produces fatty acids that is used during hunger states, through the coordination of de novo lipogenesis [37].

PPARγ instead is activated during feeding and improves lipid preservation and synthesis, also facilitating the transport of fatty acids to white adipose tissue [37].

PPARβ/δ does not perform a different action based on different nutritional states. It has the ability to inhibit lipogenesis in adipose tissue and improve the catabolism of fatty acids in skeletal muscle [99].

1.2. Glucose Metabolism

PPARα decreases glycolysis, improves glycogen synthesis and fatty acid oxidation [100] with consequently inhibiting lipid accumulation.

PPARγ increases gluconeogenesis [101] in the liver and improves glucose-mediated insulin secretion in beta cells in pancreatic Langerhans islands.

PPARβ/δ unlocks its glycolytic action by improving glucose uptake, glycolysis, glycogen storage, and gluconeogenesis reduction [102].

1.3. Cholesterol Metabolism

PPARα once activated reduces triglycerides, LDL and increases HDL levels in plasma [103,104]. PPARα also manages to improve cholesterol transport through increased expression of apolipoprotein AI (Apo-AI).

PPARγ agonists, like those of PPARα, regulate the expression of ATP-binding cassette transporter (ABCA1) through increased liver-x-receptor (LXR) expression to increase cholesterol efflux from macrophages via Apo-AI.

PPARβ/δ has effects similar to those of PPARα and PPARγ, namely the increase in plasma HDL levels and the decrease in LDL levels.

PPARβ/δ also reduces the expression of Niemann Pick C1-like 1 (NPC1L1) in the intestine, leading to a reduction in cholesterol adsorption, improving its transintestinal efflux [105].

1.4. Role of PPARs in Intraorgan Metabolic Flexibility

1.4.1. PPARs in Heart:

A decrease in PPARα in heart tissue causes decreased antioxidant capacity and structural abnormalities in mitochondria. These two deficits lead to cardiac dysfunction and treatment with the Wy-14643 agonist would improve cardiac function in mouse models [106].

Knockout of PPARγ in mouse model [107] causes cardiac hypertrophy which therefore influences cardiac function and metabolism.

The agonist GW610742 [108] increased PPARβ/δ expression in murine cardiac tissue, improving oxidative and mitochondrial metabolism with a significant decrease in ventricular hypertrophy and a reduction in natriuretic peptide in rats with congestive heart failure.

1.4.2. PPARs in Pancreas:

The role of PPARs in the pancreas has not yet been fully clarified; PPARα and PPARγ levels are known to be very low while PPARβ/δ levels in pancreatic beta cells are highly expressed [109,110].

PPARβ/δ activation improves insulin sensitivity, reduces blood glucose levels, and regulates the expression of genes associated with fatty acid metabolism [111].

PPARγ appears to be implicated [110] in glucose metabolism in pancreatic islets, whereas PPARα overexpression in INS-1 cells reduces lipid accumulation and increases beta-oxidation [31].

Box 1. *Cont.*

1.4.3. PPARs in Skeletal Muscles:

PPARβ/δ maintains energy homeostasis [112] during exercise and in the regulation of mitochondria in skeletal muscle. In fact, PPARβ/δ knockdown leads to a reduction in Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) levels [113]

PPARγ is involved in the metabolism of glucose in skeletal muscle, improving its absorption.

PPARα instead induces a change in muscle fibers in murine models, when it is over-expressed [114].

1.4.4. PPARs in the Intestine:

The PPARs play an important role in maintaining intestinal microbiota homeostasis.

PPARβ/δ and PPARα are widely expressed in the intestine. Their function is mainly performed in the caecum and distal colon where they can produce short-chain fatty acids [105].

In the small intestine, the PPARα agonist Wy-14643 regulates cholesterol transport and the expression of proteins involved in fatty acid oxidation [115].

The activation of PPARγ has been shown to be useful in improving symptoms because of irritable bowel syndrome [116].

1.4.5. PPARs in Liver:

PPARα is highly expressed in the liver where it plays a key role in fatty acid metabolism, mitochondrial oxidation, and phospholipid remodeling [117].

When PPARβ/δ levels are low or absent, the gene expression associated with the lipoprotein metabolism pathway is diminished, confirming the regulation of triglycerides and cholesterol levels by the PPARβ/δ [118].

The levels of PPARγ in the healthy liver are low [119]. When expressed in the liver of mouse models, it causes liver steatosis. The deletion of PPARα in hepatocytes may induce steatosis [36].

PPARβ/δ is expressed at high levels in hepatocytes, in hepatic macrophages, and in sinusoidal endothelial cells [120].

1.4.6. PPARs in Adipose Tissue

PPARγ plays a key role in adipose tissue. It regulates the differentiation of adipose tissue and participates in the storage and absorption of fatty acids [121].

In fact, the suppression of PPARγ in a fibroblast line inhibits adipose differentiation [51].

Conversely, PPARγ activation induces preservation and transport of fatty acids and activates adipogenesis [122].

PPARα is very well expressed in brown adipose tissue (BAT) but not in white adipose tissue (WAT). PPARα performs its function by regulating thermogenesis and lipid oxidation through interaction with PGC1a in response to adrenergic stimulation of brown adipose tissue [123].

PPARβ/δ instead controls the oxidation of fatty acids in both WAT and BAT [124] tissues and thermogenesis [125] in BAT.

3. Systemic Low-Grade Inflammation

Obesity and aging are associated with chronic low-grade inflammation, that in turn is related to chronic diseases [126,127]. Aging is an obesogenic factor, indeed, during aging, a metabolic decline occurs, characterized by altered fat distribution, obesity, and IR [128]. Concomitantly, obesity may worsen age-related diseases [129]. Obesity-associated comorbidities such as hypertension [130], type 2 diabetes [131], and cardiovascular pathologies [132] may finally participate in premature aging and reduced life expectancy. Food intake, metabolism, endocrine system, innate immune responses, and inflammation processes evolve in parallel and concur together in keeping a basal level of inflammation (inflammatory tone), which can be enhanced by the microenvironment (metaflammation) [56], and ageing (inflammaging) [133]. Metaflammation and inflammaging are strongly interconnected; metaflammation might lead and contribute to inflammaging and *vice versa*, that in turn both favor the onset of chronic diseases [133]. In metaflammation and inflammaging, the levels of main circulating pro-inflammatory cytokines, like IL-8, Tumor necrosis factor α (TNFα), IL-6, and IL-1 family, are amplified [134]. Moreover, in both kind of inflammation, the chronic activation of the innate immune system occurs, and macrophages have a central role [133]. The action of this inflammatory cell and their interactions within the stromal components are fundamental for the preservation of tissue homeostasis in metabolic organs, such as liver, brain, pancreas, muscle,

and adipose tissue. Indeed, the increase of senescent cells and their accumulation in these tissues, as well the hyperactivation of the innate immune response (Toll-like receptors (TLR) signaling and inflammasome) and the mitochondrial dysfunction have a central role in chronic sterile systemic low grade inflammation [133]. Regarding the food sources, glucose and lipids are able to stimulate the inflammatory response of immune cells [135–137]. Recently, Dror and Coll 2017 demonstrated that insulin, a key hormone in glucose metabolism and IL-1β and a master controller of inflammation, support each other in a physiological manner. The authors showed how post-prandial hyperglycemia is associated with a momentary pro-inflammatory response [138,139]. What happens is that in response to glycaemia spike, intraperitoneal macrophages secrete IL-1β which in turn stimulates insulin secretion. IL-1β and insulin increase the glucose uptake in macrophages (preferentially M1), and insulin sustains a pro-inflammatory gene expression profile [138]. Thus, the hyperinsulinemia, driving and supporting the inflammatory state in macrophages, contributes to the induction of chronic low-grade inflammation. Pro-inflammatory responses are also promoted by lipids, cholesterol, mainly in the form of oxidized low-density lipoprotein, is an inducer of a reliable pro-inflammatory response in different kind of cells [140]. SAFA, like palmitate and stearate, are able to activate indirectly TLR 4 and to increase the expression of both TLR2 and TLR4, with consequently production of ROS, activation of NF-κB, and induction of IL-1 synthesis, and MCP-1 release from monocytes [141]. Particularly, fetuin-A, a circulating hepatic glycoprotein, seems to be a transporter of FFAs through the blood stream and an endogenous ligand for TLR4 [142]. Among the long-chain polyunsaturated fatty acids of the ω3 series, docosahexaenoic acid, inhibiting TLR4 and TLR2, exerts its anti-inflammatory role, thus supporting that various lipids from diet affect metaflammation [141,143]. Moreover, the loss of estrogen signaling is one of the key factors of metaflammation onset and the associated immunometabolism alteration [144]. From this point of view the endocrine disruptors present in the environment are becoming an interesting field of study to understand the etiology of some chronic diseases. Finally, alterations in glucose and lipids metabolism, such as the above mentioned, dysregulated glucose homeostasis and dyslipidemia, support cellular senescence in metabolic tissues. Differently to apoptotic cells, senescent cells are not efficiently cleared by the immune system, and their accumulation drives to the progression of chronic and age-related diseases [145]. The senescence-associated secretory phenotype (SASP) has been suggested as a pro-inflammatory activity, contributing to the metaflammation and inflammaging that in turn favor the development of chronic age-related disorders [146].

3.1. Adipose Tissue the Core of Metaflammation

Metaflammation is associated with lifestyle and environmental factors, that in some case may cause obesity [56]. Metaflammation originates from white adipose tissue (WAT), an active endocrine organ having a central role in energy balance, glucose homeostasis, and immune functions. Metaflammation may also derive from other metabolic tissues, such as liver, pancreas, and gut [35]. WAT produces different bioactive metabolites and substances such as free fatty acids and bioactive peptides referred to as adipokines [147]. Adipokines include hormones such as leptin, adiponectin, resistin, visfatin and apelin, and chemokines. Among adipokines with inflammatory role there are: TNF-α, monocyte chemotactic protein (MCP-1), plasminogen Activator Inhibitor-1 (PAI-1), IL-1, IL-6, and IL-18; resistin and leptin. While, among insulin-sensitizing adipokines and with anti-inflammatory property: IL-10 and adiponectin. It has been reported that the increased secretion of adipokines and the decreased expression of anti-inflammatory factors, partially cause obesity-related IR [35]. Recently, it has been demonstrated that severe obesity patients undergone a hypocaloric diet and physical exercise program resulted in a metabolic improvement combined with a significant increase of adiponectin levels [148]. Regarding the free fatty acids, in obese condition there are higher levels of circulating saturated fatty acids (SAFAs), proinflammatory lipid compounds that perturb macrophages [149], adipocytes [150], myocytes [151], and hepatocytes [152] inflammation tone, leading to IR [153–155]. Omega-6 and saturated fatty acids such as arachidonic acid (AA) and palmitic acid are proinflammatory molecules, while omega-3 fatty acids such as EPA and DHA are anti-inflammatory molecules, for their ability

to act as substrates to generate resolvins [156,157], potent mediators that counteract adipose tissue inflammation, decreasing the local adipokines production and monocytes recruitment [158].

WAT is classified in two main types, subcutaneous and visceral WAT, located in the derma and around the internal organs, respectively. As reviewed by Caputo et al. 2017 these kinds of WAT have three important differences. First, the type of adipokines and secretion profile is different; indeed, the visceral WAT has a higher expression and secretion of IL-6 and PAI-1; while leptin and adiponectin are representative adipokines of subcutaneous WAT. Second, visceral and subcutaneous WAT show a different rate of lipolysis and fatty acid mobilization; in particular, the visceral adipose tissue seems to be more vulnerable to the lipolytic activity of catecholamines and less susceptible to the anti-lipolytic activity of insulin. Third, the different bioactive molecules are secreted into the systemic circulation from the subcutaneous WAT, while into the portal system from the visceral WAT. Thus, the latter has a direct impact on hepatic metabolism and consequently on metabolism homeostasis [35]. Moreover, during aging, there is an increase of visceral fat depots with respect to subcutaneous, together with an increase of triglycerides ectopically deposit on muscle, liver, heart, and bone marrow [159]. These alterations are linked to the onset and progression of different age-related diseases [160] supporting the hypothesis that visceral, rather than subcutaneous WAT has a key role in the onset of metaflammation as well as the related metabolic chronic disorders [161]. The obesogen environment acts on WAT inducing the hypertrophy and hyperplasia of the tissue, improving the lipid storage capacity. These events, in particularly in visceral WAT, induce a reduction of WAT vascularization, hypoxia [162,163], and oxidative [164] and endoplasmic reticulum (ER) stress [165], that lead the secretion of a specific panel of free fatty acids and adipokines that recruit inflammatory cells in the tissue [166]. Healthy visceral WAT contains resident macrophages referred to as ATMs, mainly with M2 phenotype (Arg1+, CD206+, CD301+,). ATMs play a key role in the proper maintenance of the tissue inflammatory tone, producing the anti-inflammatory cytokine IL-10. The macrophages recruit in WAT, during the onset of inflammatory process, exhibit mainly a proinflammatory profile (M1 macrophages) [167]. M1 macrophages localize typically in a "crown-like structure," where the immune cells surround dead or dying adipocytes [168]; this structure is typically used to quantify the levels of inflammation in adipose tissue [169]. Obesogen environment stimulate further inflammation, insulin resistance, and glucose intolerance, also acting on immune cell profile, that undergoes to a massive rearrangement. Recently, it has been demonstrated that a diet enriched with high glycemic index foods, SAFA, and cholesterol support cellular senescence in visceral adipose tissue (visceral WAT) [170]. The senescent cells found in visceral WAT were macrophages [170] and T-cells [35]. Franceschi 2017 clearly states that "the early accumulation of immune senescent cells seems to be a crucial event linking nutritional stress, chronic inflammation, obesity, ageing, and age-related diseases" [146]. Obesity has been proposed as the primary contributing factor in metabolic diseases, however, a significant part of obese individuals (healthy obese) do not show dysmetabolism while a significant percentage of lean individuals do [56,57]. What is emerging is that, in metabolic disease onset not only the amount of adipose tissue plays a key role, but also the remodeling of visceral adipose tissue induced by inflammation and IR. Specifically, these modifications comprise the limitation of visceral WAT to further accumulate lipids, and the presence of senescent cells in visceral WAT that result in increased levels of circulating free fatty acids (FFA) and in a systemic low-grade inflammation.

All three PPAR isotypes have demonstrated anti-inflammatory proprieties [30]; particularly the activation of all PPARs, PPARα [171–175], PPARβ/δ [176,177], and PPARγ [178,179], leads to a decrease of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activity. However, the anti-inflammatory mechanism is very complex, and takes different forms as extensively and best reviewed by Korbecki et al. 2019 [180]. Moreover, PPARα [181,182] and PPARγ [178,183,184] through their bound to c-Jun, inhibit their ability to bind Activator protein 1 (AP-1) in the promoters of many genes involved in inflammatory process. PPARα and PPARγ disrupt also the activation of signal transducer and activator of transcription proteins (STATs) [185,186].

As explained above, the inflammatory status of visceral adipose tissue plays a pivotal role in the onset of MetS and the related disease. PPARγ plays a fundamental role in adipose tissue differentiation and homeostasis, and it also takes part in modulating inflammatory process in this tissue. In visceral adipose tissue, under physiological conditions, resident immune cells like macrophages and regulatory T-cells generate anti-inflammatory cytokines that maintain glucose homeostasis and the correct inflammatory tone [187]. The onset of metaflammation starts when the immune regulatory network in visceral adipose tissue is disturbed with a decrease in numbers of Tregs and eosinophils and increased recruitment of activated T cells, interferon gamma (IFNγ) -producing natural killer (NK) cells, and inflammatory macrophages [188]. PPARγ activation counteracts the inflammatory process acting on adipocytes and on immune cells. In adipocytes, PPARγ restores the expression and secretion of different anti-inflammatory adipokines [189–191]; while on immune cells it has been demonstrated that this NR acts as a negative regulator of macrophages polarization toward M1 phenotype [192], promoting the M2 phenotype [193]. In macrophages, PPARγ induces Arginase 1 (Arg1), a specific M2 marker and sustain β-oxidation and mitochondrial biogenesis [194]; at the same time, it reduces the expression of inflammatory markers [195]. Moreover, the ability of SAFA, like palmitate to activate TLR in macrophages is counteracted by PPARγ [196]; mice lacking PPARγ in myeloid cells, upon HFD, develop obesity and IR [194,197]. In addition, PPARγ activation in Tregs promotes their accumulation in visceral adipose tissue and protection from obesity-induced insulin resistance [187]. More recently, it has been demonstrated also as a key role of PPARγ in dendritic cells c (DC), in fact, in visceral adipose tissue dendritic cells were observed [40,198], although their characterization is not accurate. Under prolonged over-nutrition, these cells process and present antigens to T-cells and induce Th17 responses, while in normal condition they have an anti-inflammatory phenotype and PPARγ plays a fundamental role in maintaining it [199].

3.2. Insulin Resistance and Inflammation

Insulin, a peptide hormone secreted by pancreatic β-cells, facilitates the glucose uptake in the cells, thus, it is crucial for maintaining the normal blood glucose level. This hormone has board range of activity; it regulates carbohydrate, protein, and lipid metabolism and also promotes cell division and growth by its mitogenic activities. All metabolic tissues, from liver to brain, are sensible to insulin, therefore, understanding the role of insulin in most of the physiological processes, has significant repercussions for most of the chronic diseases. Insulin uses the adipose tissue, skeletal muscle, and liver as biological buffers against excessive nutrient intake. Since all nutrients are pro-inflammatory [200], insulin exerts a crucial role in preserving the body against their negative effects [201] (Box 2). An excess of nutrients intake may generate an increase of inflammatory tone and compromise the ability of insulin to orchestrate the metabolism. As mentioned above, the unbalanced composition of the diet, such as high glycemic index foods [10] or an elevated consumption of SAFA [202] as well non-food related factors such as insufficient physical activity [203] are associated with IR, and attenuated biological response to normal or elevated insulin (tolerance) [204]. Inflammation and insulin resistance are closely correlated; indeed, important mediators of the inflammatory response, such as NFκB and Jun N-terminal Kinases (JNKs), are able to induce IR, thus establishing a feedback mechanism that feeds the chronic inflammation. TNFα knock-out animal prone to diet-induced obesity (DIO mice) or those that lack leptin (Ob/Ob mice) are able to prevent IR [205]. Target genes of NFκB are involved in IR [206,207]; the phosphorylation of IRS1 in serine-307 by JNKs inhibits the interaction between IRS1 and the insulin receptor, that in turn reduce the insulin receptor inducing IR [208]. Moreover, proinflammatory adipokines produced in obese visceral WAT modulate the activation of JNK and inhibitor of nuclear factor κB (IκB) kinase (IKKβ (implicated in NFκB nuclear translocation), that in turn promotes the onset of IR [35]. The central nervous system (CNS) orchestrates signals for the regulation of food intake and energy expenditure. Particularly, the hypothalamic arcuate nucleus, infundibular nucleus in humans, is a central regulator of feeding behavior, energy, and glucose homeostasis. In this region, the blood–brain barrier results are more permissive, thus resulting as center that communicates peripheral signals into

CNS and vice versa. Indeed, the hypothalamus results as the central control point for the development of IR [201]. Satiety signals, such as grelin from the gut, leptin from adipose tissue, and insulin from pancreas, control food intake acting on hypothalamic neurons [209,210]. A diet rich in saturated fats causes inflammation in the hypothalamus, leading to resistance to insulin and leptin as well [211], consequently, the hypothalamus inflammation favor a prominent body weight [212–214], setting up a vicious cycle that eventually leads to obesity.

Insulin has a pleiotropic effect on different metabolic tissues; thus, insulin deficiency and insulin resistance have adverse effect on the homeostasis of these tissues. In the adipose tissue, insulin increase fatty acid storage decreasing the activity of hormone-sensitive lipase (HSL) [215]. With the onset of inflammation and insulin resistance in WAT, there is an increase of free fatty acids (FFA) release, which can penetrate into the circulation and are transported by other organs, such as the liver, skeletal muscles, and brain, increasing the insulin resistance in these organs. Among chronic diseases in which IR plays a key role, there are the polycystic ovary syndrome (PCOS) and nonalcoholic fatty liver disease (NAFLD).

Box 2

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2. The Physiological Roles of Insulin:

Insulin is an anabolic hormone produced by βcells of the pancreatic islet of Langherans.

Communicating with the liver, muscle, and fat cells, insulin controls the blood glucose levels to be used for energy, and if the body does not request more energy, insulin controls energy conservation, converting glucose in glycogen [216].

2.1. Insulin in Glucose Metabolism

Through the insulin-mediated glucose uptake (IMGU) cascade, insulin enhances the glucose absorption from muscle and adipose tissue. Insulin also suppresses glucose production from hepatic cells. Outside of the cell, insulin binds the insulin receptor's alpha subunit and activates the IMGU cascade, provoking a conformational change in the complex insulin-receptor, inducing the tyrosine kinase phosphorylation of insulin receptor substrate proteins, and the activation of phosphatidylinositol-3-kinase. At this point, intracellular stored Glucose transporter type 4 (GLUT-4) transporter translocates into the skeletal muscle cell's plasma membrane, and insulin is able to recruit glucose into skeletal muscle cells and converts it into glycogen [217]. In gluconeogenesis, phosphoenolpyruvate carboxylase (PEPc), fructose-1,6-biphosphate (FBP) and glucose-6-phoshate (G6P) are inhibited by insulin. In glycolysis, insulin enhances the expression of glucokinases (GCK) and pyruvate kinase (PKM) [217,218].

2.2. Insulin in Glycogen Metabolism

Insulin is able to induce glycogen synthesis in the liver, affecting glycogen metabolism, through the regulation of the key player protein phosphatase I (PPI). PPI can act either by reducing glycogenolysis through the inactivation of phosphorylase kinase and phosphorylase A, or by stimulating glycogenesis inducing the activity of glycogen synthase B. The role of insulin is to increment the specificity of PPI activity, for the control of the synthesis of glycogen from glucose. Furthermore, insulin can affect the expression and activity of several hepatic metabolic enzymes [217,218].

2.3. Insulin in Lipid Metabolism

In lipogenesis insulin increases the expression of acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), and pyruvate dehydrogenase (PDH) [217,218]. Into the adipocytes, glucose is stocked as a lipid, resulting in a major uptake of glucose after fatty acid generation. In this regard insulin up-regulates several lipogenic enzymes expression. Insulin also inhibits lipolysis, through the regulation of dephosphorylation and inhibition of hormone-sensitive lipase [217].

2.4. Insulin in Protein Metabolism

Insulin can also regulate protein turnover assessment. In fact, it controls protein synthesis because of the strong expression of insulin in short chain amino acids. Conversely, insulin has the capacity of downregulate hepatic and muscle enzymes, such as ATP-ubiquitin-dependent proteases and ATP-independent lysosomal proteases, affecting protein degradation [216–218].

2.5. Insulin in Inflammation

In endothelial cells and macrophages, insulin exerts also a potential anti-inflammatory effect. More in depth, inside the endothelial cells insulin can enhance endothelial nitric oxide synthase (eNOS) expression, that releases nitric oxide (NO), resulting in vasodilation. Furthermore, insulin reduces NF-κB present in the endothelial cells. NF-κB up-regulates E-selectin and Intercellular Adhesion Molecule 1 (ICAM-1) adhesion molecules expression, recently found associated with the development of atherosclerotic arterial plaques.

Insulin is also able to reduce the generation of reactive oxygen species (ROS) and O2 radicals. Specifically, insulin reduces the expression of NADPH oxidase, through the suppression of p47phox. NADPH oxidase is responsible of oxygen radicals generation, with consequent activation of the inhibitor of NF-κB kinase beta (IKKB). IKKB phosphorylates IκB, resulting in its degradation. At this point, NF-κB is released and it can translocate into the macrophage's nucleus, where it promotes several pro-inflammatory proteins gene transcription, such as monocyte chemoattractant protein (MCP-1), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-α), and matrix metalloproteinases (MMPs) [218,219].

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4. Chronic Diseases, from Lifestyle to PPARs

4.1. Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is the most widespread endocrine disorder affecting 8% to 13% of women [220–222]. These women typically present hyperandrogenism, amenorrhea, and polycystic ovaries [223,224]. Patients with PCOS show obesity (visceral phenotype), lipid disorders, IR, compensatory

hyperinsulinemia, and they have a higher risk of type 2 diabetes mellitus, metabolic syndrome, cardiovascular complications, reproductive disorders (best review by [225]). Regarding the IR, the hyperinsulinemia-associated increases pituitary luteinizing hormone (LH) secretion and ovary theca cells androgen production; contextually it suppresses the sex hormone-binding globulin (SHBG) production in the liver leading to an enhance of free androgens in the blood that in turn further worsens the insulin resistance [226]. Different studies reported that, about 40–60% of PCOS patients are obese or overweight [227,228], and it has been described an increment in visceral adipose tissue even in lean women with PCOS [229,230]. The pro-inflammatory state of obesity promotes IR and atherogenesis [231], thus in PCOS, the development of obesity induces a decline in insulin sensitivity [226]. Moreover, in PCOS women an imbalance between pro-inflammatory and anti-inflammatory mediators is associated with a systemic low-grade inflammation [232–234]; the lipotoxicity could be the key of PCOS pathogenesis [235]. The etiology of this chronic disease is still not fully understood [236]; it is probably due to a combination of genetic and environmental factors. Genetic factors have great importance in the pathophysiology of PCOS [237,238]. The genes involved are associated to cellular metabolism, chronic inflammation, cell proliferation, reproductive hormones [239–244]. In this regard, different clinical studies on the incidence of the PPARγ Pro12Ala polymorphism in PCOS patients were reported [245–250]; this polymorphism is associated with a lower degree of IR, an increased insulin clearance and a reduced risk of diabetes [250]. However, further clinical studies on the incidence of Pro12Ala in PCOS are necessary. Therapeutic modalities, which are able to reduce IR and lipotoxicity, typically result in improvements in ovarian functions. PCOS patients have low expression of PPARγ in skeletal muscle that it was associated with IR. Treatments with PPAR agonists ameliorated muscle IR and increased the expression of PPARγ with overall increase in mitochondrial biogenesis and function [251]. Moreover, enhancing triglyceride accumulation in adipose tissue, PPARγ agonists are able to diminish lipotoxicity [252,253]. The environmental factors exert an essential function in the development of PCOS [228,254]; among them diet composition, physical activity, and environmental pollution need to be included [228,255,256]. In a recent study, conducted on female nonhuman primates, it has been demonstrated that the combination of mild hyperandrogenemia and Western-style diet prompts the development of visceral WAT dysfunction [257]. Diets containing unsaturated fatty acids (omega-3) and diets with low glycemic index may reduce the risk of metabolic features seen in PCOS patients [258,259] while diets enriched of SAFA and foods with a high glycemic index exert opposite effects [228]. Physical exercise exerts positive effects in the PCOS women' health, including reduced IR and improved reproductive biomarkers (antral follicle count, serum levels of sex steroids, gonadotropins and anti-Müllerian hormone (AMH) [255]. Lifestyle intervention is able to recover levels of FSH, SHBG, androstenedione, total testosterone, free androgen index, and Ferriman-Gallwey score in PCOS patients [260]. Thus, a correct diet in PCOS patients should include minimal amounts of SAFA with normal quantities of saturated fatty acids with one double bond and omega 3. Furthermore, adequate intake of fiber-rich food and carbohydrate sources with low glycemic index is highly proposed. This kind of diet accompanied with physical activity is proposed as first-line management in an international evidence-based guideline on PCOS [261]. However, lifestyle modifications having long-term effects and sustainability are not so simple, thus pharmacotherapy is often required, such as metformin and troglitazone (TZD) [262]. Particularly, thiazolidinediones, insulin sensitizer drugs, are PPARγ agonists that directly target lipotoxicity and androgen production [263], both of which are dysfunctional in PCOS. Interestingly, other studies found that PPARγ agonist modulates steroid genesis. In a randomized clinical trial, including normoinsulinemic and non-obese PCOS patients, it was found that rosiglitazone, a PPARγ agonist, significantly reduced testosterone levels, without changing insulin levels [264]. Thus, PPARγ agonists may restore the normal androgenic response to insulin. In addition, in vitro studies reported that activation of PPARγ with troglitazone decreased LH stimulation of androgen synthesis in thecal tissue reducing steroid 17 alpha-hydroxylase/17,20 lyase (P450c17) action, a key enzyme for androgen synthesis [265]. In adrenocortical cell line another agonist of PPARγ, pioglitazone,

reduced the overexpression of P450c17 [266]. The effects of the PPARγ ligands in PCOS women, especially on IR and steroid genesis indicate a possible role of PPARγ in the pathophysiology of PCOS. However, several studies disclosed that the use of PPARγ agonists have numerous side effects, including cardiac complications, bone resorption, and bladder cancer [267,268]. For this reason, for PCOS patients, new therapeutic approaches able to ameliorate lipotoxicity and/or IR are necessary.

4.2. Non-Alcoholic Fatty Liver Disease (NAFLD)

The term nonalcoholic fatty liver disease (NAFLD) comprises a range of liver conditions characterized by an abnormal accumulation of fat in the liver (hepatosteatosis). The incidence of NAFLD is increasing around the world, especially in Western countries [269], thus lifestyle and food habits have a great impact on the onset of chronic diseases [270]. Non-alcoholic fatty liver disease comprises two kind of forms: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) [271,272]. NAFL is characterized by hepatosteatosis and with long-term prognosis, and can develop into NASH, a more aggressive form of liver disease, characterized by liver inflammation and that it may evolve in advanced cirrhosis and even hepatocellular carcinoma [272,273]. The hallmarks of NAFLD are obesity and IR, both of them are crucial for the progression into NASH [274]. The underlying mechanism beside the shift of NAFL toward NASH is complex and multi-factorial [275]. The two-hit theory is the most accredited theory regarding NAFLD pathogenesis [276]. This theory supposes that initially obesity and IR lead to lipid accumulation in hepatocytes [276,277] and subsequently, oxidative stress appears, which in turn, precedes and causes mitochondrial dysfunctions [278,279]. Regarding the first part, the liver steatosis derived diminishes hepatocytes fatty acid (FA) oxidation [36,280] and enhanced (FA) uptake [281,282]. Regarding the FA uptake in the liver, it is mediated by fatty acid transporters such as, cluster of differentiation 36 (CD36) and Fatty Acid Transport Proteins (FATPs) [281,282]. Moreover, it has been shown that polymorphism in genes for lipid transport and lipid metabolism are related to the development of NAFLD [283]. Free FAs derive principally from adipose tissue (59%), dietary, and de novo lipogenesis [35,284]. Particularly, the increase of de novo lipogenesis in liver comes first from steatosis and it is due to a certain extent to the IR of the muscle, which leads to increased flux of glucose toward the liver [35,285]. The hepatocytes with increased de novo lipogenic rate undergo a phenotypic shift, characterized by higher transcription of adipogenic genes, including sterol regulatory element-binding proteins (SREBPs), adipose differentiation- related protein (ADRP), and PPARγ [35,286,287]. One of the unresolved questions in NAFLD is what factors could be the driving forces to the inflammatory disease phenotype. It has been demonstrated that choosing a healthy lifestyle leads to weight loss and improvement of liver fibrosis; overall counteracting NASH evolution [288]. NAFLD patients usually have unhealthy habits such as sedentary lifestyles and unhealthy diet [289]. Although in Western countries, NAFLD is associated with obesity and IR; it has been demonstrated that, particularly in Asiatic population, NAFLD can develop in absence of insulin resistance and with low BMI. Moreover, in urban regions of Asia and Africa, lack of physical activity and the globalization of Western diet has led to an increase in the occurrence of NAFLD [290,291]. On the contrary in the rural areas of these continents, despite the Western diet, there is a lower incidence of NAFLD due to the physical activity [290,291]. The lifestyle-based treatments comprise caloric restriction, improved diet composition, exercise increment, stress reduction, and improved sleep [292]. Caloric restriction together with change in diet composition improve the management of NAFLD [292]. A diet enriched in carbohydrates leads to increased insulin and triglyceride concentrations in the blood, lipogenesis, and IR of the liver in NAFLD patients [293]. Another important diet factor in NAFLD progression is the glycemic index [294]. Diets improved in low glycemic index food help to reduce the overall fat mass, increasing lipid utilization, and increasing satiety [295,296] and makes the liver healthy by decreasing fatty acid accumulation and glycogen storage in liver [294]. Physical exercise exerts positive effects in the NAFLD patients' health, especially when combined with a correct diet, making improvement in liver enzymes and hepatic histology [297]. Aerobic exercises increase circulating concentrations endocannabinoids, as well as related lipids oleoylethanolamide

(OEA), palmitoylethanolamide (PEA), *N*-docsahexaenoylethanolamine (DHEA), and 2-oleoylglycerol (2-OG) [298], particularly OEA is an endogenous ligand of PPARα at is known to ameliorate NAFLD condition [299]. Polyunsaturated fatty acids (PUFAs), particularly DHA and EPA have protective effects in NAFLD patients [300]; on the contrary a diet enriched of SAFA, trans-fatty acids, and cholesterol is associated with NAFLD development or progression [301–303]. Studies conducted on mice reported that this kind of diet induced systemic inflammation and liver injuries; moreover, a study on humans indicated that cholesterol is linked to hepatic inflammation and fibrosis [304]. Under physiological conditions, PUFA or their oxidized metabolites control hepatic lipid metabolism acting as PPARα ligands and thus controlling the expression of genes encoding for proteins involved in fatty acids oxidation and transport [305]; in addition, PUFA acts as down-regulators of the lipogenic transcription factors [306–308]. Thus, PUFA depletion in hepatic tissue of obese NAFLD patients might trigger FA and Triacylglycerol (TAG) synthesis respect to FA oxidation, inducing hepatic steatosis. These findings are according to nutritional disequilibrium with a high ω6/ω3 fatty acid ratio diet in mice; this kind of diet induced hepatic SREBP and increased lipogenesis, with substantial decrease of FA oxidation and steatosis development [309]. As explained in the section of PPARs and inflammation, both NF-κB and AP-1 may form heterodimers with PPAR-α, determining the development of the transcriptionally inactive complexes p65-PPARα and c-Jun-PPARα [310]. PPARα downregulation in liver has also dramatic consequence in term of inflammation, thus this NR may exert pivotal pathogenic roles, taking into account their significance in inflammation and energy homeostasis. PPARα agonists, i.e., fibrates utilized to reduce steatosis and inflammation in human steatohepatitis, showed weak effectiveness because of the different response of human respects to rodents [35]. Regarding thiazolidinediones, their use in NAFLD is controversial since they can improve IR and decrease lipotoxicity in obese/NAFLD patients, supporting the transcription of Sterol regulatory element-binding protein 1 c (SREBP1c) in the liver, thus enhancing the maintenance of steatosis and production of TGs by liver [311]. Recently, more attention was focused on the possible use of natural compound such as PUFAn3 [312] and oleoylethanolamide [299] natural ligands of PPARα.

5. Conclusions

It is becoming noticeable that the primary cause of most Western chronic diseases, with systemic low-grade inflammation as the common denominator, is not following a correct lifestyle and improper food habits. Ruiz-Núñez and Colleagues 2013 [313] deduce as human predisposition to develop IR depends on the rapid brain growth in the past millennium. During this period, the interaction between our immune system and metabolism was strongly conserved, indeed, with the advent of the agricultural and industrial revolutions, leads to chronic inflammation. Lifestyle modifications in Western countries are necessary especially in the first years of life. However, during pathology onset, since improving lifestyle is not that easy, pharmacotherapy is required. PPARs represent the interface between environment metabolism and immune system; moreover, their presence in all metabolic tissues suggests that they play an important role in regulating the fine crosstalk between them. Thus, these receptors are targets for the therapy of metabolic syndrome and the low-grade inflammatory state. Because of the collateral effects induced by fenofibrates and TZDs, new therapeutic approaches are necessary in order to obtain new PPARs ligands characterized by minor negative effects and increased positive effects. Recently, more attention is pointed toward the possible use of natural compounds, such as PUFAn3, oleoylethanolamide and β-aminoisobutyric acid, natural and endogenous ligands of PPARs. Finally, the development of PPARα/γ/δ pan-agonists or PPARα/γ dual agonist [314] could be a potential therapy for a concomitant pharmacological activity on carbohydrate and lipid metabolism.

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