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Review

The Metabolic Syndrome: An Overview and Proposed Mechanisms

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Abstract: Obesity has emerged as a major public health challenge in the 21st century, contributing to the rising prevalence of metabolic syndrome (MetS), a cluster of interrelated health risk factors. These factors include obesity or abdominal obesity, type 2 diabetes mellitus (T2DM), hypertension (HTN), and dyslipidaemia. In this review, we will explore important aspects of metabolic regulation and the dynamics of lipoprotein metabolism to see how they underlie each of these major health risks. Additionally, we will highlight the role of ferroptosis, an iron-dependent regulated cell death process, in relation to inflammatory responses and its critical contribution to the pathophysiology of MetS. These inflammatory responses include inflammasome activation, lipotoxicity, the influence of adipocytokines, and the role of adipose tissue macrophages. By exploring these interconnections, this review aims to provide insights into metabolic crosstalk, outline the pathological mechanisms occurring, and identify potential therapeutic targets for managing and preventing the progression of these health risk factors.

Keywords: obesity; metabolic syndrome; type 2 diabetes; hypertension

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1. Introduction

Over two-thirds of adults in Western countries are currently considered overweight or obese. In fact, obesity rates have significantly increased worldwide in the 21st century [1,2].

Metabolic syndrome refers to a cluster of comorbid conditions including central obesity, HTN, T2DM or impaired glucose metabolism, and dyslipidaemia. It also encompasses other health complications such as cardiovascular disease (CVD), chronic inflammation, chronic kidney disease, hyperuricaemia, and hepatic steatosis [3].

At the cellular level, MetS is the result of complex interactions among various metabolic processes including glycolysis, the tricarboxylic acid (TCA) cycle, and lipid metabolism [4]. These pathways are fundamental for energy production and are central to cellular homeostasis [5]. Disruption of these pathways may contribute to the initiation and/or worsening of the conditions associated with MetS [6].

Another component of MetS is the connection between lipid accumulation and HTN [7,8]. Hypertension, often associated with excess adiposity, highlights the role of adipose tissue as an energy store and as an active endocrine organ that contributes to systemic inflammation and vascular dysfunction [9]. Further, persistent low-grade chronic inflammation plays an important role in the aetiology and progression of MetS, mediated through inflammasome activation and the secretion of adipocytokines (also called adipokines) [10,11]. These inflammatory mediators play crucial roles in the development

of insulin resistance (IR), endoplasmic reticulum (ER) stress, and endothelial dysfunction, and other pathological processes [12].

Recent insights into iron-dependent lipid peroxidation, otherwise known as ferroptosis, have provided a new perspective on cell death mechanisms that may be linked to MetS pathologies, particularly impacting organs such as liver, kidneys, and adipose tissue [13,14].

This review will cover the underlying mechanisms associated with each of the major facets of MetS and will try to identify gaps in the understanding of these complex biological processes, as well as providing a comprehensive overview of the pathological mechanisms that drive the initiation and progression of MetS. By integrating diverse biochemical observations, it will encourage further research that could contribute to the development of more effective strategies for the management and treatment of MetS and its associated disorders.

2. Pathophysiology of the Metabolic Syndrome

Metabolic Syndrome, also referred to as Reaven syndrome, Syndrome X, IR syndrome, and 'the deadly quartet', is a set of metabolic dysfunctions [15]. It is characterised by abdominal obesity (waist circumference $\geq$102 cm for males and $\geq$88 cm for females) and at least two additional conditions, such as the following: hypertension, impaired glucose metabolism, or elevated non-high-density lipoprotein (HDL) cholesterol [3].

The Mechanisms of Metabolic Syndrome

The pathogenetic mechanisms of MetS are complex and not yet fully elucidated; however, chronic low-grade inflammation, also known as systemic inflammation, is widely recognised as a significant contributor to its associated diseases. Additionally, both genetic and environmental factors can contribute to the development of MetS [16]. Recently, there has been increasing attention on the dysregulation of insulin post-receptors. Increased systemic inflammation can lead to an increase in serine/threonine phosphorylation of insulin receptor substrate (IRS) 1. This phosphorylation is a crucial factor in the development of IR [17].

The World Health Organization has identified IR as central to MetS, with obesity also playing a significant role. The complexity of MetS arises from the interplays of multiple interconnected factors that contribute to its associated diseases [18]. See (Figure 1) for the proposed mechanisms of the MetS.

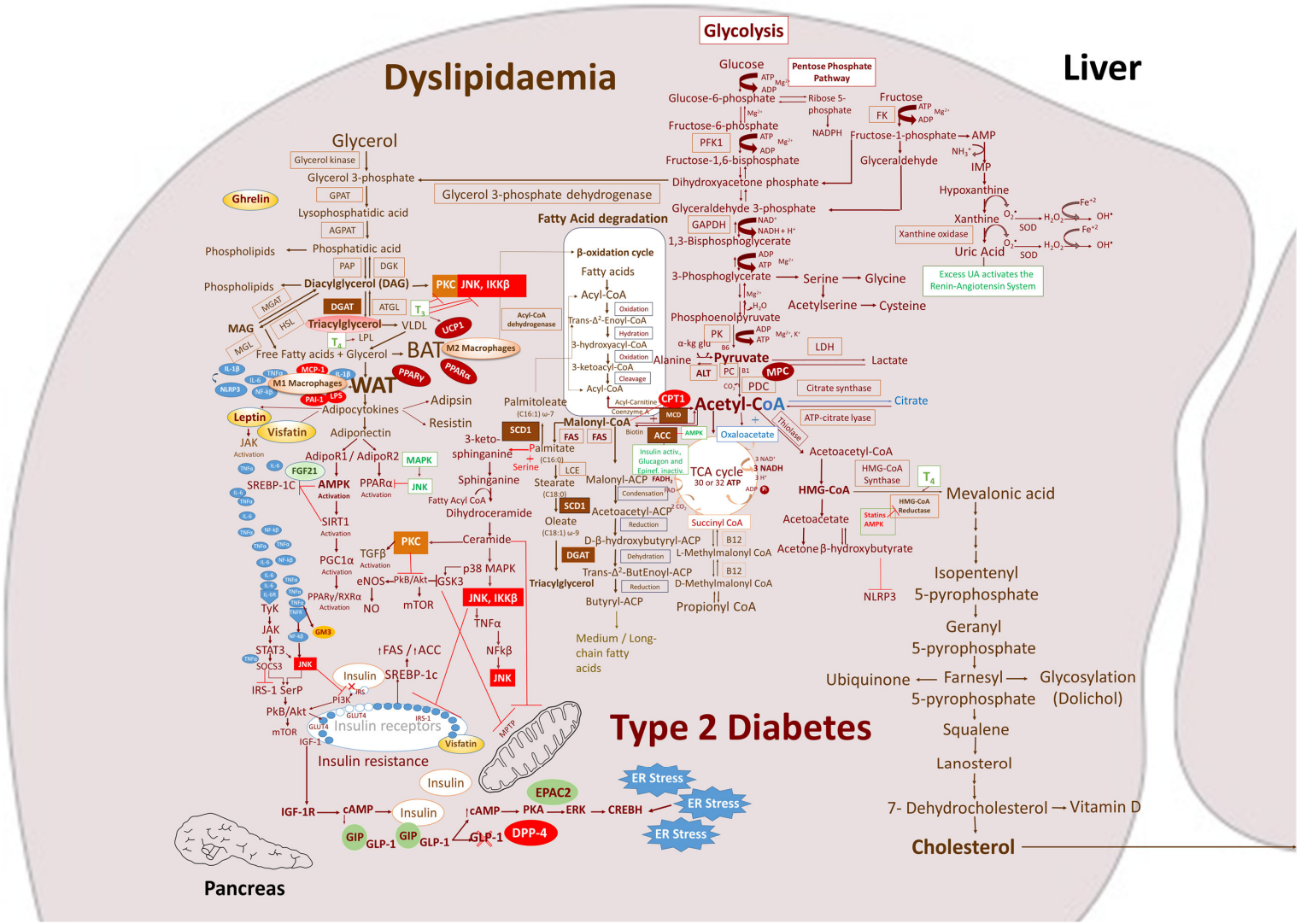

Figure 1. *Cont.*

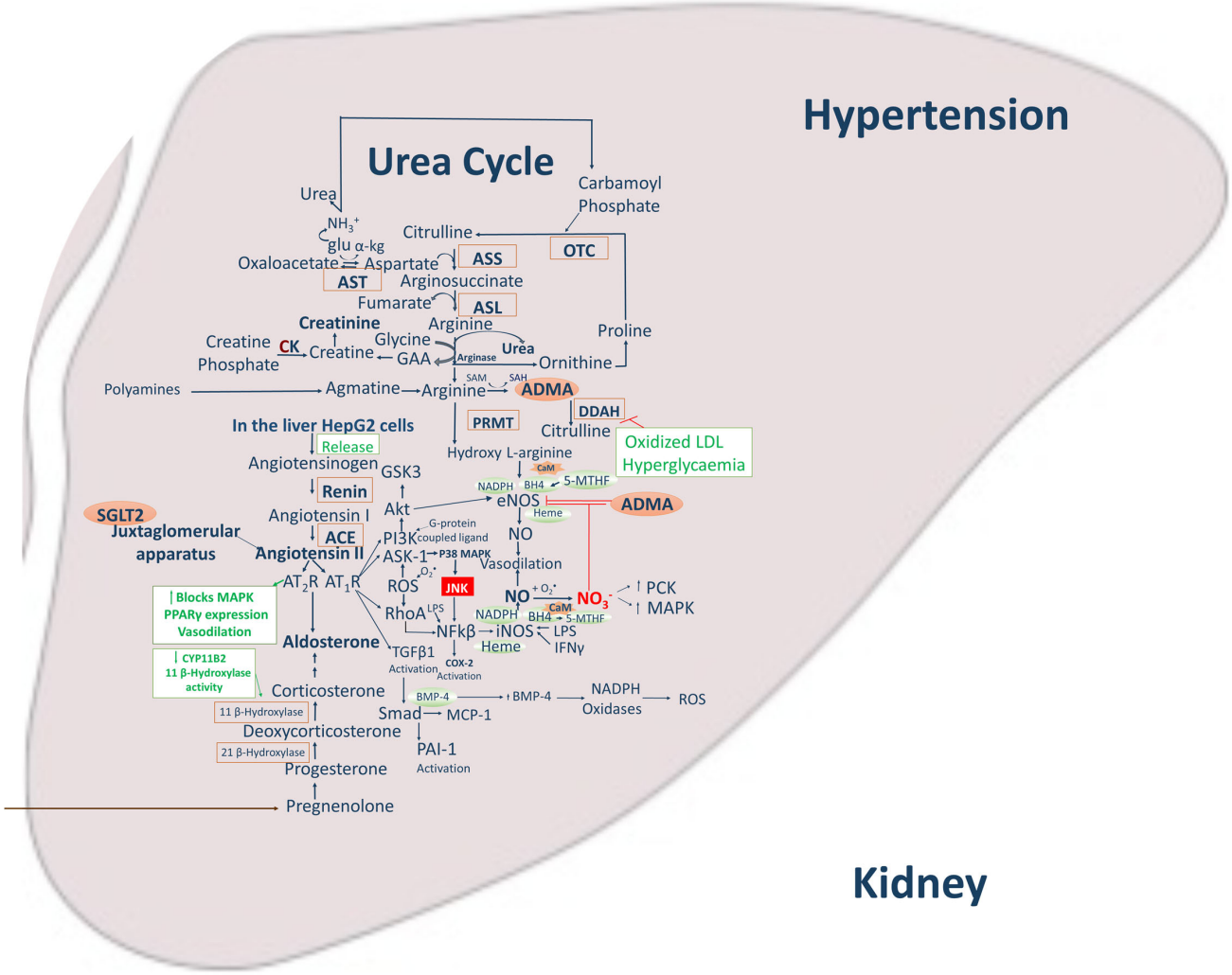

Figure 1. Schematic Representation of the metabolic syndrome. The diagram is a schematic representation of the proposed metabolic crosstalk between dyslipidaemia, type 2 diabetes mellitus, and hypertension. Blunt arrows (⊥) indicate inhibition or blockage while sharp arrows (→) indicate stimulation or correlation. ACC: Acetyl-CoA Carboxylase; ACE: Angiotensin-converting enzyme; ACTH: Adrenocorticotropic Hormone; ADMA: Asymmetric Dimethylarginine; ADP: Adenosine Diphosphate; AGPAT: 1-Acylglycerol-3-phosphate-O-acyltransferase; Akt: Protein Kinase B; AMP: Adenosine Monophosphate; AMPK: 5′AMP-Activated Protein

Kinase; ASL: Argininosuccinate Lyase; ASS: Argininosuccinate Synthase; AST: Aspartate Aminotransferase; AT1R: Angiotensin II Receptor Type 1; ATGL: Adipose Triglyceride Lipase; ATP: Adenosine Triphosphate; BAT: Brown Adipose Tissue; BH4: Tetrahydrobiopterin; cAMP: Cyclic Adenosine Monophosphate; CPT1: Carnitine Palmitoyltransferase I; DAG: Diacylglycerol; DDAH: Dimethylarginine Dimethylaminohydrolase; DGAT: Diacylglycerol O-acyltransferase; DGK: Diacylglycerol Kinase; DPP-4: Dipeptidyl Peptidase-4; eNOS: Endothelial Nitric Oxide Synthase; EPAC2: Exchange Protein Directly Activated by cAMP 2; ER: Endoplasmic Reticulum; ERK: Extracellular Signal-Regulated Kinase; FADH2: Flavin Adenine Dinucleotide (in its reduced form, as a hydrogen donor); FAS: Fatty Acid Synthase; Fe^{+2}: Ferrous Ion; FK: Fructokinase; GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase; GIP: Gastric Inhibitory Polypeptide; GLP-1: Glucagon-Like Peptide-1; GM3: Monosialodihexosylganglioside; GPAT: Glycerol-3-phosphate Acyltransferase; GSK3: Glycogen Synthase Kinase 3; H_2O_2: Hydrogen Peroxide; HMGR-CoA: 3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase; HSL: Hormone-Sensitive Lipase; IGF-1R: Insulin-like Growth Factor 1 Receptor; IL-1β: Interleukin 1 Beta; IL-6: Interleukin 6; IL-6R: Interleukin 6 Receptor; IKKβ: Inhibitory kappa B kinase beta; IMP: Inosine Monophosphate; IRS-1 SerP: Insulin Receptor Substrate 1 Serine Phosphorylation; JAK: Janus Kinase; JNK: c-Jun N-terminal Kinase; LPL: Lipoprotein Lipase; LDH: Lactate Dehydrogenase; LDL: Low-density Lipoprotein; MCD: Malonyl-CoA Decarboxylase; MAG: Monoacylglycerol; MAPK: Mitogen-Activated Protein Kinase; MGL: Monoacylglycerol Lipase; Mg^{2+}: Magnesium Ion; MPC: Mitochondrial Pyruvate Carrier; mTOR: Mammalian Target of Rapamycin; NFκB: Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells; NLRP3: NLR Family Pyrin Domain Containing 3; NO: Nitric Oxide; $OH\cdot$: Hydroxyl Radical; OTC: Ornithine Transcarbamylase; PAP: Phosphatidate Phosphatase; PAI-1: Plasminogen Activator Inhibitor-1; PC: Pyruvate Carboxylase; PCK: Phosphoenolpyruvate Carboxykinase; PDC: Pyruvate Dehydrogenase Complex; PFK1: Phosphofructokinase-1; PI3K: Phosphoinositide 3-Kinase; PK: Pyruvate Kinase; PKA: Protein Kinase A; PKB: Protein Kinase B; PPARα: Peroxisome Proliferator-Activated Receptor Alpha; PPARγ: Peroxisome Proliferator-Activated Receptor Gamma; PRMT: Protein Arginine Methyltransferase; PGC1α: Peroxisome Proliferator-activated Receptor Gamma Coactivator 1-alpha; ROS: Reactive Oxygen Species; SCD1: Stearoyl-CoA Desaturase 1; SGLT2: Sodium-glucose Co-transporter 2; SIRT1: Sirtuin 1; SOD: Superoxide Dismutase; SOCS3: Suppressor of Cytokine Signalling 3; STAT3: Signal Transducer and Activator of Transcription 3; T3: Triiodothyronine; T4: Thyroxine; TAG: Triacylglycerol; TCA Cycle: Tricarboxylic Acid Cycle; TGFβ: Transforming Growth Factor Beta; TNFα: Tumour Necrosis Factor Alpha; UCP1: Uncoupling Protein 1; VLDL: Very Low-Density Lipoprotein; WAT: White Adipose Tissue.

3. Obesity and Cellular Energy Metabolism

Diet is the fundamental source of nutrients. It plays an important role in growth and development; however, its composition can change people's nutritional status, affecting the metabolism and regulation of the whole body through glucose metabolism, hormones, and lipid metabolism changes [19]. The modern Western diet is rich in saturated and hydrogenated fats and carbohydrates, such as sucrose and fructose [20]. This excessive energy intake has been associated with numerous diet-induced chronic diseases, including obesity, HTN, non-alcoholic fatty liver disease (NAFLD), and MetS [21].

Obesity is characterised by long-term excess energy intake which leads to adipose tissue remodelling by inducing hypertrophy and/or hyperplasia [22].

Hypertrophic adipocytes in expanded visceral fat release inflammatory signals and decrease insulin's ability to suppress lipolysis, leading to elevated circulating free fatty acids (FFA). These FFAs accumulate in non-adipose tissues, causing lipotoxicity in pancreatic β cells and disrupting insulin signalling in the liver and muscles [18].

When the endocrine function of hypertrophic adipocytes is disrupted, it can affect cell function through paracrine and autocrine mechanisms, leading to increased circulating concentration of most adipocytokines [23].

Adipocytokines, including chemerin [23], adipsin, apelin, resistin, leptin, vaspin, visfatin, and adiponectin, are associated with several chronic conditions. These conditions include obesity, MetS, various inflammatory disorders, and IR [24,25].

Leptin and adiponectin play critical roles in the regulation of chronic diseases. Leptin can act as an immunomodulator by promoting the production of pro-inflammatory cytokines [26,27]. In contrast, adiponectin generally serves an anti-inflammatory function, reducing inflammation, activating 5′ AMP-activated protein kinase (AMPK), and enhancing insulin sensitivity by inhibiting pro-inflammatory cytokines and promoting anti-inflammatory responses [28].

Adipocytokines have been shown to stimulate tyrosine kinase (Tyk) phosphorylation, thereby activating the Janus kinase/Signal transducer and activator of transcription 3 (JAK/STAT-3) signalling pathway (Figure 1) [29]. Chronic activation of the JAK/STAT pathway may contribute to the development of several chronic diseases, including cancer and obesity [29,30].

The JAK family comprises four identified members as follows: JAK1, JAK2, JAK3, and Tyk2. The STAT protein family includes seven members as follows: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6. Additionally, there are eight members in the suppressors of cytokine signalling (SOCS) family, ranging from SOCS1 to SOCS7, along with the cytokine-inducible SH2-containing protein [31]. Each STAT protein has a different role in the regulation of adipose tissue function and development [32]. The SOCS proteins play a crucial role in the regulation of the JAK/STAT signalling pathway. They function as a negative feedback mechanism that inhibits the activation and phosphorylation of JAK/STAT, effectively controlling the pathway's activity [31].

The STAT3 protein can activate SOCS3 directly [31,33]. Elevated concentrations of SOCS3 are associated with the inhibition, phosphorylation, and proteasomal degradation of IRS-1 and IRS-2, contributing to cell death and consequently to IR [33]. Additionally, tumour necrosis factor alpha (TNF-α) can activate and upregulate SOCS1, SOCS3, the ganglioside monosialodihexosylganglioside 3, nuclear factor-kappa B (NF-κB), and cJNK, which further promotes the degradation or regulation of IRS-1 and IRS-2 [33–35].

The phosphorylation of IRS-1 activates phosphoinositide 3-kinase (PI3K). Subsequently, this activation increases protein kinase B (Akt) phosphorylation, which facilitates the translocation of glucose transporter protein type 4 (GLUT4) to the plasma membrane and enhances glucose uptake [35–37].

The PI3K/Akt pathway is a critical regulator of various cellular functions, including cell survival, migration, and glucose metabolism [38,39]. It is activated by the phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3), which then recruits and activates Akt [38]. The Akt signalling path-

way modulates several downstream effectors that influence processes such as protein synthesis, cell cycle progression, and apoptosis [39,40]. This pathway also plays a role in immune regulation by influencing the production of type I interferons and modulating the expression of inflammatory cytokines like TNF-α and interleukin (IL)-12 [41]. Abnormal activity of the PI3K/Akt pathway has been implicated in various chronic diseases, including metabolic-associated fatty liver disease, liver fibrosis, and cancer [42].

3.1. Immunometabolic Influence of Adipose Tissue

The changes in adipocytes, including differentiation of the stromal vascular fraction (SVF) cells, occur during adipose tissue remodelling [43]. These cells play an important role in the development of obesity-related diseases [43,44]. The SVF cells in adipose tissue are infiltrated with type 1 and type 2 macrophages [45]. These large phagocytic cells are responsible for the clearenceof apoptotic cells [46]. Then, the recruitment and modulation of monocytes, lymphocytes, and neutrophils to inflamed sites is mediated by the activation of type 1 adipose tissue macrophages via lipopolysaccharide, through the expression of NF-κB [47,48]. Consequently, several pro-inflammatory cytokines are generated, such as TNF-α, IL-6, and IL-1β, as well as PAI-1, iNOS, and monocyte chemoattractant protein 1 [49–51]. Interferon gamma is also produced by the activation of natural killer cells (Figure 1) [52]. However, when type 2 adipose tissue macrophages are activated (predominately expressed in lean adipose tissue), anti-inflammatory signalling is initiated [48].

Innate immune cells, like macrophages, use pattern-recognition receptors to detect pathogen- or danger-associated molecular patterns, leading to the triggering of various immune responses, including the activation of inflammasomes [53].

Inflammasomes are multiprotein complexes residing in the cytosol, comprising various types such as certain NOD-like receptors (NLRs), including NLRP1, NLRP3, NLRP6, NLRP7, NLRP9, NLRP12, and NLRC4 [54]. The NLRP3 inflammasome, a well-characterised component of the innate immune system is primarily composed of the sensor protein NLRP3, the adaptor protein ASC (Apoptosis-associated Speck-like protein containing a CARD), and pro-caspase-1 [55]. ASC bridges pattern-recognition receptors to caspase-1 through interactions between their CARD domains [56].

Inflammasome activation is mediated by various molecular signals produced in response to infections, tissue injury, or metabolic disturbances [57–59]. These signals induce the assembly of NLRP3 inflammasome, leading to the activation of caspase-1. Subsequently, caspase-1 facilitates the cleavage and secretion of pro-inflammatory cytokines such as IL-1β and IL-18 and mediates a form of programmed cell death known as pyroptosis [60].

Several inflammasomes play key roles in sensing inflammatory signals and triggering the innate immune response [61]. Among them, the NLRP3 inflammasome has been extensively researched and identified as a major contributor to various neurodegenerative and metabolic diseases [12]. These diseases include T2DM, IR, obesity, kidney damage, cancer, Alzheimer's disease, multiple sclerosis, and Parkinson's disease [62–64]. In addition, the activation of the NLRP3 inflammasome has been linked to atherogenic dyslipidaemia through its response to FAs and cholesterol crystals [65].

While the NLRP3 inflammasome has been relatively well characterised, the complex interactions involved in its initiation and pathways are still not fully understood [61,66].

3.2. Metabolic Pathway of Cellular Energy Metabolism

Additionally, excessive nutrient consumption can impair mitochondrial function. Mitochondria primarily produce adenosine triphosphate (ATP), essential for energy metabolism. However, their role extends beyond energy production, as they are also the primary source of reactive oxygen species (ROS) during ATP synthesis. When the mitochondria are compromised, it leads to multiple dysfunctions including reduced capacity to produce sufficient ATP, metabolic substrate disorders, calcium buffering dysregulation, mitochondrial deoxyribonucleic acid (DNA) mutations, changes in size and morphology, and increased ROS production [67].

The main generation of adenosine triphosphate ATP occurs in the cytosol, where glucose is converted to pyruvate via glycolysis; and in the mitochondria, where the oxidation of pyruvate occurs via the TCA cycle [68].

The mitochondria play a crucial role in the metabolism of the MetS. The major functions include the TCA cycle, oxidative phosphorylation, ketogenesis, and β-oxidation [4]. The TCA cycle can efficiently provide large quantities of ATP, although it requires oxygen. Under anaerobic conditions, pyruvate undergoes conversion to lactate rather than entering the TCA cycle [5]. However, in the presence of oxygen, pyruvate is transported into mitochondria by the mitochondrial pyruvate carrier [5], a key transporter in the regulation of cellular growth, metabolism, and survival [69–71].

In the cytosol, the glycolysis process also produces other substrates for serine/glycine, cysteine biosynthesis, glycerol 3-phosphate, and glucose-6-phosphate for the pentose phosphate pathway (PPP), which forms ribose 5-phosphate and nicotinamide adenine dinucleotide phosphate (NADPH) [72–74]. Pyruvate plays a crucial role in cellular homeostasis, mainly because it functions as a bridging point between an oxidative pathway involving the mitochondria and a fermentative pathway occurring in the cytosol [75]. Perturbation of its metabolism can potentially lead to the development of many chronic diseases including T2DM, obesity, aging, Alzheimer's disease, and Parkinson's disease [76,77]. Both pyruvate carboxylase and pyruvate dehydrogenase complex have been associated with lessening oxidative stress [78,79]. However, more studies are needed to fully elucidate its mechanisms [79,80].

Processes involving glycolysis, the TCA cycle, and the PPP have been shown to regulate key ferroptosis biomarkers such as NADPH, glutathione (GSH), and ROS, impacting ferroptosis regulation [81].

Ferroptosis is a form of regulated cell death characterized by iron-dependent lipid peroxidation [82]. It contributes to cellular and tissue damage in various human diseases, including cancer, neurodegenerative disorders, and ischemia-reperfusion injury [83]. In ferroptosis, lipid peroxidation occurs due to the accumulation of ROS, leading to cell membrane damage and cell death. Cell death by ferroptosis is distinct from other cell death mechanisms such as apoptosis, unregulated necrosis, and necroptosis [82].

Recent research has elucidated the role of ceramides in ferroptosis. During ferroptosis, ceramide levels increase, contributing to the process of lipid peroxidation [84,85]. This form of cell death is characterised by the accumulation of ROS, which damages cell membranes and is further exacerbated by the accumulation of ceramide that enhances lipid peroxidation. Lipid peroxidation involves the oxidation of polyunsaturated fatty acids (PUFA) in cell membranes, which leads to the generation of lipid ROS. It has been shown recently that ceramide is accumulated during ferroptosis when induced by various ferroptotic compounds [86].

Additionally, ceramide has an impact on mitochondrial function, which is crucial for ferroptosis. The mechanisms by which ceramide causes mitochondrial dysregulation include the disruption of outer membrane permeability, inhibition of mitochondrial respiratory chain complexes, induction of oxidative stress, alteration of mitochondrial dynamics, promotion of lethal mitophagy, and interference with mitochondrial biogenesis [87].

Dysfunctional mitochondria release iron ions into the cytoplasm, contributing to the iron-dependent lipid peroxidation characteristic of ferroptosis [88]. Additionally, elevated concentrations of cytosolic iron contribute to mitochondrial damage, further exacerbating this cycle through a feedback loop once initiated [89].

Glutathione peroxidase 4 (GPX4) is an enzyme that protects cells from lipid peroxidation by reducing lipid hydroperoxides. Ceramide has been shown to inhibit GPX4 activity [90], leading to decreased GSH-dependent lipid peroxide detoxification. Reduced GPX4 activity allows lipid ROS to accumulate, promoting ferroptosis [82,90].

Ceramide accumulation disrupts redox homeostasis, enhances lipid peroxidation, and impairs cellular antioxidant defences. These effects collectively contribute to ferroptosis, a regulated form of cell death [91].

Recent studies have shown an association between obesity and iron deficiency [92]. Inadequate iron intake in children and adolescents has been correlated with increased risks of being overweight or obese [14,93]. Ferroptosis plays a pivotal role in various biological functions, including amino acid metabolism, iron metabolism, and lipid metabolism [94].

Research has also shown that high uric acid (HUA) concentrations suppress the nuclear factor erythroid 2-related factor 2 (NRF2)/solute carrier family 7 member 11 (SLC7A11)/GPX4 signalling pathway in macrophages within atherosclerotic plaques, a key mechanism against ferroptosis [95]. These findings suggest that elevated uric acid levels facilitate NRF2-mediated ferroptosis, contributing to the progression of hyperuricemia-associated atherosclerotic vascular disease [96]. The study further revealed that HUA enhances cell death induced by oxidized low-density lipoprotein (LDL) in THP-1 cell line and RAW264.7 macrophage cells. This increase in cell death is associated with several ferroptotic processes, including the accumulation of iron, production of malondialdehyde, depletion of GSH, and increased generation of lipid ROS [96]. Additionally, studies suggest that HUA triggers mitochondrial dysfunction and promotes ferroptosis in macrophage-derived foam cells, which play a crucial role in the formation of atherosclerotic lesions [96,97].

Lipid droplets are enveloped by a protective factor known as FA-associated factor 1, shielding them from direct exposure to Fe^{2+} [98]. In the cytoplasm, FFAs can initiate the Fenton reaction when there is an excess of Fe^{2+}. This leads to the easy formation of peroxidized polyunsaturated fatty acids (PUFA-OOH). In the presence of Fe^{2+}, PUFA-OOH can further oxidize into PUFA-O•, initiating a cascade of lipid oxidation reactions [94].

Furthermore, the GTP cyclohydrolase-1 (GCH1)-tetrahydrobiopterin (BH4)-phospholipid pathway plays a role in preventing ferroptosis by exhibiting an antioxidant effect, which is mediated by Coenzyme Q10 (CoQ10). Tetrahydrobiopterin acts as a redox-active cofactor for crucial enzymes involved in the synthesis of nitric oxide (NO), neurotransmitters, and aromatic amino acids. The BH4 cofactor facilitates the production of CoQ10 by converting phenylalanine into tyrosine, which serves as a building block for CoQ10. Additionally, BH4 helps safeguard PUFA phosphatidylcholines against damage, thereby contributing to the prevention of ferroptosis [99].

Hence, the underlying process of ferroptosis in obesity involves several key factors such as iron overload, excessive accumulation of lipid peroxides, inhibition of GPX4 activity, systemic reduction of HUA [97], and suppression of the Xc-system [99]. Additionally, increasing vitamin D intake can enhance calcium absorption and further aid in mitigating the effects of ferroptosis [99,100].

The activation of inflammation, including various inflammation-related signalling pathways, can induce ferroptosis [13,101,102]. In T2DM, hyperglycaemia induces iron overload, lipid peroxidation, oxidative stress, inflammation, and renal fibrosis [13]. The two primary features of ferroptosis are intracellular iron accumulation and perturbation of the oxidation–reduction system [103,104].

4. Type 2 Diabetes Mellitus

The aetiology of T2DM is multifactorial. Several studies have associated the dysregulation of the liver, pancreas, gut microbiome, muscles, and adipose tissue with the development of T2DM [105,106]. Moreover, many other factors including hormones, inflammation, oxidative stress, mitochondrial dysfunction, genetics, and lifestyle factors are major contributors to T2DM [107,108].

Pancreatic β-cell dysfunction plays a crucial role in ER stress associated with dysregulation in insulin biosynthesis and secretion [109,110]. The insulin precursor, pre-proinsulin, is produced in the cytoplasm and translocated into the lumen of ER to be catabolised into proinsulin. In the lumen of the ER, proinsulin is transported to the Golgi apparatus, packaged into secretory granules, and converted into mature insulin, which is then released through exocytosis [110].

Excessive amounts of glucose precipitate a large demand for insulin. An increase in the production of insulin by the ER of the β cells can lead to stress in the ER system [111].

Continuous stress in the ER can be provoked by multiple factors, such as environmental toxins, infections, chronic inflammation, and abnormal protein folding [112]. As a consequence, there is an increase in the accumulation of unfolded proteins within the ER lumen, prompting the activation of various response mechanisms [112,113]. This orchestrated adaptive response modulates the balance between the availability and degradation of unfolded proteins to reinstate ER homeostasis [114]. However, when the stress is unresolved and prolonged in the ER lumen and membranes, chronic activation of the unfolded protein response is induced, initiating cell death [115].

Insulin Resistance

Glucose homeostasis is regulated by insulin production from beta cells in response to increased blood glucose concentrations [109]. This insulin release triggers a cascade that controls several metabolic processes, including reducing liver glucose production, increasing glucose uptake in adipose tissue and muscle, and inhibiting FFA release from adipocytes [17].

Insulin resistance occurs when target cells do not properly respond to normal insulin concentrations due to disruptions in metabolic processes. This condition is influenced by both intrinsic and extrinsic signalling pathways [17]. The intrinsic pathway regulates mitochondrial function and ER stress [110], while the extrinsic pathways involve adipocytokines, FFA, and inflammation [53]. It is widely accepted that obesity and the accumulation of metabolic by-products and FFAs are the primary contributors to IR [17]. However, recent research suggests that other factors also contribute, such as inflammatory responses, intracellular stress pathways, impacts of lipid accumulation, metabolic overload in muscles, and mitochondrial dysfunction [17,106].

Glucose and insulin activate the mechanistic target of rapamycin (mTOR) [116]. The mTOR is a cytoplasmic kinase involved in cellular growth, survival, and metabolism of several compounds, including vascular endothelial growth factor, amino acids, FA, glucose, insulin, and cytokines. Moreover, many studies have shown that overactivated mTOR is associated with impaired insulin signalling (blocking postprandial glucose uptake), IR, and cerebral IR-induced mitochondrial damage [117].

The mTOR signalling pathway also plays a central role in glucose, protein, and lipid metabolism [116,118]. There are two functionally distinct complexes, mTOR complex1 (mTORC1) and mTOR complex 2 (mTORC2) [119]. Proper functioning of the mTORC1 and mTORC2 complexes is crucial for preventing disease and supporting cellular homeostasis and longevity [120]. These complexes are regulated by mechanical stimuli, growth factors, energy, and protein consumption. The mTOR complexes activate and phosphorylate many signalling cascades, including the PI3K/serine/threonine-specific protein kinase Akt/mTOR pathway [121]. They are also involved in the regulation of several critical proteins like insulin growth factor receptors, and sterol-responsive element-binding proteins (SREBPs) [116]. The dysfunction of either mTOR and its complexes have been associated with various diseases including T2DM, obesity, atherosclerosis, infection, cancer, renal, liver, and neurodegenerative diseases [116,118,122].

Insulin-like growth factor-1 (IGF-1) is a hormone that modulates insulin sensitivity, lipid oxidation in the liver, FFA, and glucose uptake by the muscle [123–125]. The IGF-1 receptor can activate mTORC1 and insulin receptors through Tyk activity on IRS, stimulating serine phosphorylation and modulating insulin signalling [123]. Furthermore, IGF-1 can inhibit insulin secretion in response to elevated glucose or glucagon-like peptide-1 (GLP-1) stimulation. It decreases cyclic adenosine monophosphate (cAMP) concentration and consequently decreases insulin secretion (Figure 1) [126,127]. However, activating GLP-1 receptors can stimulate insulin secretion by increasing cAMP concentrations in pancreatic β cells and activating second messenger pathways like protein kinase A and exchange protein [127–129]. The IGF-1 and glucose-dependent insulinotropic peptide (GIP) are the two main incretin hormones secreted from the intestinal cells after glucose or nutrient

intake to stimulate insulin production in pancreatic β cells [130,131]. These two intestinal hormones play a major role in glucose homeostasis [132].

Dipeptidyl peptidase 4 (DPP-4) has been well-studied for its cleavage function [106]. It mainly cleaves the two NH2-terminal amino acids of GLP-1 and GIP, which inactivates their insulinotropic activities [131]. DDP-4 degrades IGF-1 and GIP. The deficiency or inhibition of DPP-4 has been reported to enhance insulin secretion in diabetic patients [133].

Additionally, GLP1 and GIP bind to their respective receptors, which triggers the activation of guanine nucleotide-binding proteins [126]. This process increases intracellular cAMP and the activation of protein kinase alpha and cAMP-regulated guanine nucleotide exchange factor II [129]. These activations stimulate extracellular signal-regulated kinase, activating the cAMP response element-binding protein (CREB) [134–136]. The cAMP pathway activates an essential intracellular signalling molecule involved in several biological pathways including differentiation, proliferation, migration, and cell survival [137,138].

The CREB, a cellular transcription factor, exerts its regulatory function by selectively binding to specific DNA sequences, thereby regulating the transcriptional activity of target genes [139,140]. The CREB, hepatocyte specific (CREBH), is identified as a liver-specific transcription factor situated on the ER membrane [139,141]. Many studies have investigated the influence ER stress or inflammation on CREBH, suggesting that ER stress activates the CREBH pathway to stimulate an acute inflammatory response [141,142].

The SREBPs and CREBH are both membrane-bound transcription factors that regulate the synthesis and uptake of lipids [143–145]. They are located in the ER and have a similar post-translational activation system [144,146]. Once transported to the Golgi, they are cleaved by site-1 and site-2 proteases [143,145]. The CREBH is activated in response to energy deficits, whereas SREBPs are activated in conditions of energy surplus. Collectively, CREBH and SREBPs coordinate to maintain homeostasis of lipid metabolism through transcriptional regulation [143].

5. Basics of Lipid Metabolism

The Western diet is marked by high dietary FA, refined sugar, low dietary fibre, and a significant amount of processed foods. In the United States, 72.1% of the total daily energy intake is attributed to consumption of dairy products, cereals, refined sugars, refined vegetable oils, and alcohol. Processed foods such as cookies, cakes, bakery items, breakfast cereals, and snacks are particularly prevalent in contemporary diets [147].

Following the ingestion of dietary FA, there are several steps for FA metabolism, which include transportation, degradation, and storage. These processes rely on the following two primary triacylglycerol (TAG)-rich lipoproteins: chylomicrons secreted by the intestine, and very low-density lipoprotein (VLDL) synthesized in the liver. In the upper small intestine, absorption by enterocytes is facilitated by Niemann–Pick C1-like 1 transporter [148]. Simultaneously, the liver acquires Fas via either plasma lipoprotein uptake or de novo lipogenesis (DNL) pathways [149]. These chylomicrons are involved in the transportation of endogenous and exogenous Fas in the body [148].

The remodelling and catabolism of HDL depends on various enzymes, cell receptors, and proteins to generate or degrade HDL in the plasma [150]. HDL cholesterol interacts with the cholesteryl ester transfer protein, which mediates the transfer of cholesteryl esters from atheroprotective HDLs to proatherogenic lipoproteins, such as nascent VLDLs, intermediate-density lipoproteins, and LDLs [129]. Elevated HDLs and reduced LDLs concentrations have been well recognised as promoters of cardiovascular (CV) health [151].

Nascent HDLs collect cholesterol from various tissues in the body to form mature HDLs, subsequently taken up by scavenger receptor class B member 1 (SRB1) in the liver, enhancing systemic clearance of Fas and cholesterol [152].

An LDL comprises a single apolipoprotein, apoB100, which binds with apolipoprotein(a) produced by hepatocytes to generate lipoprotein(a). This complex consists of an LDL particle bonded with apolipoprotein(a) [153]. Lipoprotein(a) particles are significant

CV risk factors that have been highly associated with atherogenesis and the formation of thrombi (Figure 2) [154].

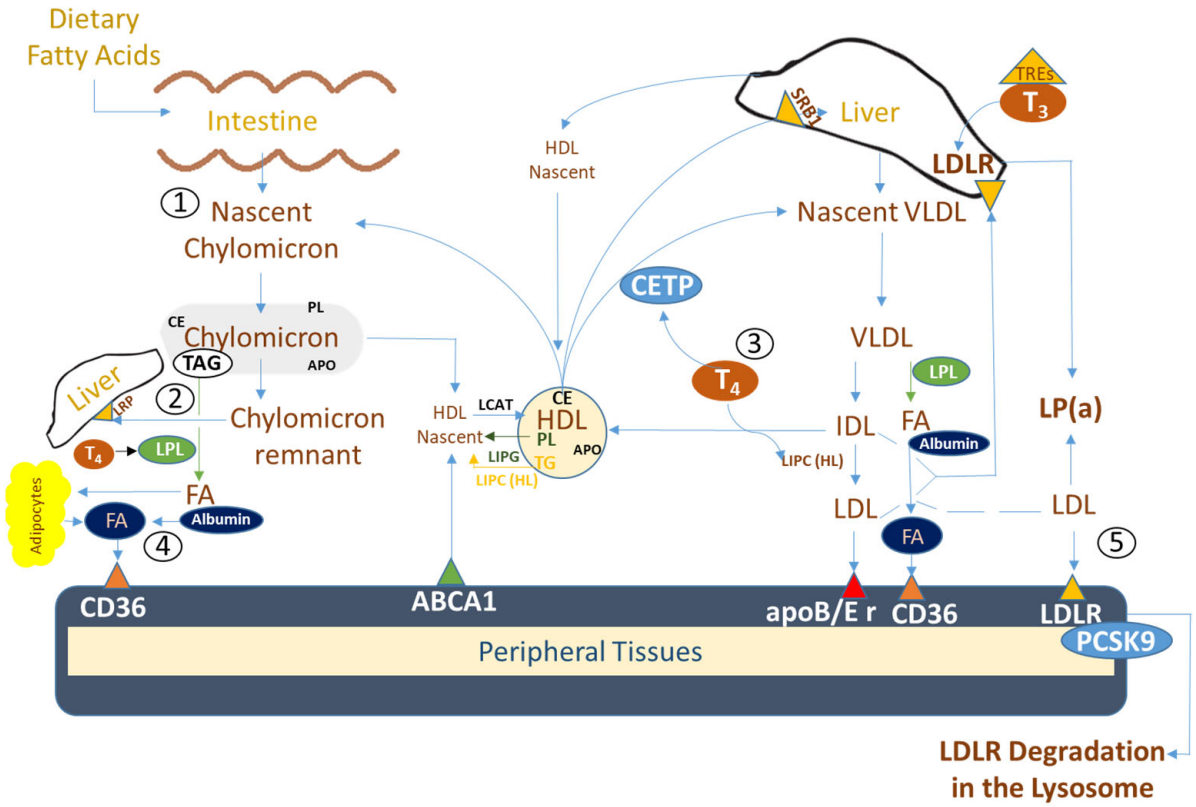

Figure 2. A schematic representation of the metabolism of lipoproteins and lipoprotein particle: the exogenous or endogenous pathway. (**1**) Chylomicrons carry exogenous dietary fatty acids (FA) as triacylglycerol (TAG), cholesteryl ester (CE), apolipoproteins (APO), and phospholipids (PL) and are secreted into the lymph; (**2**) TAG is hydrolysed by lipoprotein lipase (LPL) into FA, which are absorbed by adipose tissue; (**3**) thyroxine (T4) stimulates LPL and hepatic lipase C (LIPC or HL) activity; (**4**) other Fas bind to albumin and are taken up by peripheral tissues via cellular surface receptors like CD36; (**5**) LDL receptors (LDLR) are bound to proprotein convertase subtilisin/kexin type 9 (PCSK9), which activates a short-circuit recycling of LDLRs, leading to LDLR lysosomal degradation in cells.

In the glycolytic pathway, dihydroxyacetone phosphate is partly converted to glycerol 3 phosphate by glyceraldehyde 3-phosphate dehydrogenase [155]. Glycerol 3 phosphate then undergoes a series of reactions to be converted into phospholipids, and subsequently into diacylglycerol (DAG) and TAG [155,156].

In DNL, DAG is a key substrate in the biosynthesis of phospholipids including phosphatidylserine, phosphatidylcholine, and phosphatidylethanolamine, as well as TAG. It is also involved in the activation of stress-sensitive and serine/threonine protein kinases such as protein kinase C (PKC), c-Jun N-terminal kinase (cJNK), and inhibitor of nuclear factor kappa-B kinase. These kinases play pivotal roles in various cellular signalling pathways, generating inflammation and leading to several metabolic and CV complications, including NAFLD and coronary artery disease [157–159].

Diacylglycerol is involved in the hydrolysis and turnover of TAG lipid droplets [160,161]. Excessive energy intake is stored in adipose tissues as TAG via the lipogenic pathway. The accumulation of excess TAG can result in the enlargement of lipid droplets, leading to adipocyte expansion and contributing to obesity [162]. However, during periods of food deprivation, TAG stored within adipocytes is hydrolysed into FFAs and glycerol through the lipolytic pathway [163]. Once glycerol and FFAs are separated, glycerol contributes

to both lipogenesis and gluconeogenesis pathways, while FFAs can be stored in adipose tissue or converted into fatty acyl-CoA (Figure 1) [164].

Adipose tissue is a highly active multicellular organ [165,166]. Adipose tissue is composed of nerve tissue, connective tissue matrix, and various cell types. These cells include adipocytes, SVF cells such as preadipocytes, immune cells like macrophages and lymphocytes, as well as stem cells, pericytes, fibroblasts, endothelial cells, smooth muscle cells, and mature adipocytes. These are found in both brown adipose tissue (BAT) and white adipose tissue (WAT) [167,168].

The BAT is widely known for its thermogenic functions through both in vitro and animal studies [166,169,170]. Recent advances in research have also highlighted its role as a metabolic regulator, influencing systemic metabolism, energy balance, and glucose homeostasis [170–172]. Peroxisome proliferator-activated receptor (PPAR) α is highly expressed in BAT, leading to the activation of the mitochondrial β-oxidation and elevation of the uncoupling protein 1 (UCP-1) expression, produced by BAT and beige adipocytes (Figure 1) [173–175]. The activation and regulation of UCP-1 occurs following the release of excessive FFAs or the stimulation of β3-adrenergic receptors by norepinephrine. This process is initiated by exposure to cold and is mediated through the sympathetic nervous system (SNS) [176–178]. Evidence of BAT activation by exercise has been investigated; however, the results have been inconsistent, and further studies are warranted [179–181]. Similarly, while the thyroid hormone triiodothyronine is known to play a crucial role in the activation of BAT and the expression of UCP-1, further studies are needed to fully elucidate this association [182,183].

Sex hormones also exert a significant impact on BAT functionality, albeit with variations depending on gender and life stage [184]. Research indicates that BAT mass remains stable and may even increase during childhood, in close correlation with the levels of sexual maturation. This trend is particularly noticeable in girls before puberty, who exhibit higher baseline and cold-induced BAT activity compared to boys [185]. This difference persists into young adulthood, where women generally have higher BAT activation than men [184,186]. However, as women enter the postmenopausal phase, the gender difference in BAT activity tends to diminish, indicating a strong connection between sex hormones and BAT functionality [187]. The decline in sex hormone levels as people age is believed to enhance the suppressive effects of glucocorticoids on BAT, resulting in decreased BAT activity and increased lipid accumulation [184].

Both BAT and WAT have been recognised as endocrine organs [188,189]. In addition to its endocrine activities, adipose tissue acts as the body's fuel reservoir, regulating heat and lipid synthesis or degradation [190]. The PPARγ is highly expressed in WAT [191]. The accumulation and distribution of the WAT have been associated with obesity and several other metabolic disorders such as T2DM, dyslipidaemia, HTN, CVD, MetS, inflammation, and lipotoxicity [192–194].

5.1. Dyslipidaemia

Dyslipidaemia is characterised by elevated cholesterol and TAG concentrations, increasing the risk of atherosclerotic cardiovascular disease. This risk is associated with increased LDL, total cholesterol, TAG, and lipoprotein(a), and decreased HDL cholesterol. Obesity and type 2 diabetes frequently contribute as secondary predisposing factors [149].

The alterations in complex lipid production associated to dyslipidaemia impact the size, morphology, and motility of mitochondria [195]. Lipid droplets, also known as adiposomes, are independent cellular organelles that play a central role in energy storage. Recent research has revealed crucial insights into the lipid droplet proteome [44,196]. Lipid droplets possess a distinct proteomic profile in which the functional roles, protein targeting mechanisms, and degradation pathways are still not fully understood [44]. The oxidation process of unsaturated fatty acids (UFA) shares similarities with the oxidative pathway of saturated fatty acids (SFA). However, due to the presence of double bonds, UFAs require two additional enzymatic steps (a reductase and an isomerase) to effectively metabolize a

wide range of UFAs [197]. The accumulation of Fas such as fatty acyl-CoA, propionyl-CoA, and odd-chain Fas can induce toxicity, contributing to metabolic disruptions [198].

The accumulation of TAG, FFA, fatty acyl CoA, and cholesterol can disrupt normal cellular functions [199]. Free fatty acids are transformed into acyl-CoA by acyl-CoA synthetase for use in catabolic or anabolic pathways [200–202]. Elevated concentrations of intracellular acyl-CoA have been linked to an increased production of free radicals and mitochondrial stress [203]. Carnitine, β-hydroxy-γ-N-trimethylaminobutyric acid plays a vital role in protecting cellular and mitochondrial integrity by converting acyl-CoA into acylcarnitine (Figure 1) [204].

Additionally, propionyl-CoA is a very small three carbon Fas that possesses the biochemical properties of other Fas [205,206]. It originates from propionate, odd-chain Fas, and amino acids such as a branched-chain amino acid [207]. However, its accumulation can cause several metabolic disorders including methylmalonic acidaemia, propionic aciduria, and implications in the development of MetS, IR and T2DM [205,208]. Therefore, the degradation of propionyl-CoA is important to maintain cellular health [205]. In humans, propionyl-CoA is carboxylated to methyl malonyl-CoA by vitamin B12-dependent enzymes and then to succinyl-CoA, which can be utilized in the TCA cycle [206,209].

Other cytotoxic Fas are stearoyl-CoA and palmitoyl-CoA [210]. Long exposure to palmitate or stearate can induce inflammation, IR, mitochondrial dysfunction, and even cellular death [211,212]. Palmitate is a bioproduct of palm oil a SFA that can be converted into palmitoleate (ω-7) or stearate and then oleate (ω-9) as a protective measure against palmitate [213–215].

The mitochondrial FA synthesis occurs when the malonyl group binds to an acyl carrier protein (ACP) arm of fatty acid synthase to synthesise Fas, from malonyl-ACP to butyryl-ACP [68,216,217]. Malonyl-CoA is recognised for its regulatory role in FA metabolism, specifically by inhibiting the oxidation of long-chain acyl-CoA molecules such as palmitate. It acts by inhibiting carnitine palmitoyltransferase I, the enzyme responsible for facilitating the entry of Fas into the mitochondria for β-oxidation [218]. It also facilitates DNL by catalysing key enzymatic steps, including condensation, reduction, dehydration, and further reduction (Figure 1) [68,219].

Additionally, palmitate can be also converted to ceramide after condensation with amino acid serine-producing 3-keto-sphinganine, which synthesises sphinganine that is condensed with fatty acyl-CoA to form dihydroceramide and then ceramide, generating lipotoxicity [220,221].

Ceramide, a lipid located within the bilayer of the cell membrane, and sphingosine-1-phosphate (S1P) are major regulators of several cellular functions. These include angiogenesis, embryonic development, cellular growth and death, differentiation, proliferation, and inflammation [222]. Disruption in the ceramide pathway has been associated with lipotoxic, activation ROS, and NLRP3 inflammasome, contributing to metabolic disorders [223]. Ceramide accumulation is linked to many diseases such as T2DM, IR, obesity, and CVD [222,224]. Elevated ceramide concentration also induces p38 mitogen-activated protein kinases (MAPK), cJNK, and inhibitor kappa-B kinase β (IKKβ) activation, increasing the concentration of IL-1β, which leads to inflammation, cell necrosis, and apoptosis (Figure 3) [225,226]. Additionally, ceramide increases mitochondrial membrane permeability and inhibits mitochondrial respiration, impairing cell survival regulation [227].

The inflammatory mediator PKC also plays a critical role in mitochondrial dysfunction via activation of a variety of cellular signalling, including ET-1 and NADPH oxidase [228]. Ceramide is a regulator and direct activator of PKC. Both S1P and PKC can activate NF-κB [222]. PKC is also involved in cellular regulation. It belongs to the AGC kinase family, such as Akt, also known as protein kinase B (PKB). This PKB/Akt protein kinase is a key element in the signalling pathways of insulin, inflammatory cytokines, and growth factors, having a substantial effect on the development of cancer, neurological disorders, HTN, and T2DM [229].

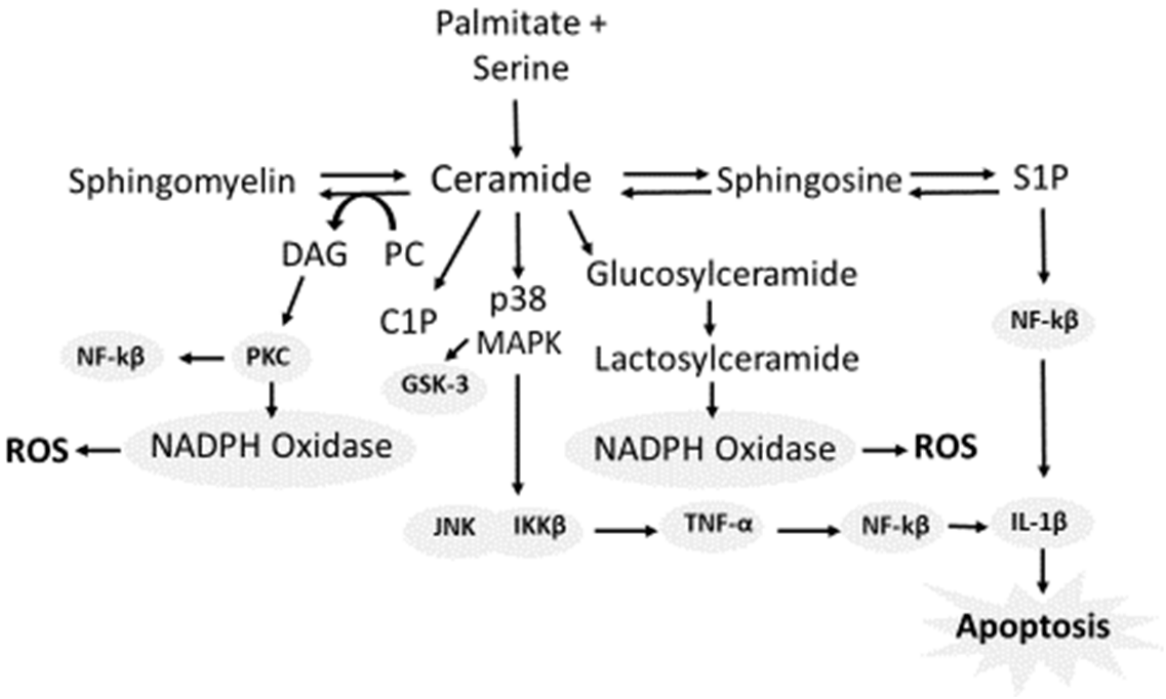

Figure 3. Metabolism of ceramides. De novo ceramide production from the catalyses of condensed palmitate and serine to 3-keto-shinganine, then sphinganine and dihydroceramide (post incorporation of fatty acyl-CoA) activates a series of inflammatory pathways. (1) Transformation of ceramide into sphingosine 1–phosphate (S1P) and then nuclear Factor κB (NF-κB). (2) Sphingomyelin to ceramide into ceramide 1-phosphate (C1P) or glucosylceramide. (3) Condensation of phosphatidylcholine (PC) and ceramide molecules to form one molecule of sphingomyelin and one molecule of diacylglycerol (DAG), which activates protein kinase C (PKC), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and then NF-κB, inducing apoptosis.

In the PKB/Akt signalling pathway, the activation of PKB/Akt leads to the phosphorylation and subsequent inactivation of GSK3β. This inactivation plays a role in various cellular processes, including the regulation of transcription factors such as NF-κB and CREB. Furthermore, PKB/Akt activation stimulates other key signalling proteins, including the mTOR and eNOS. The activation of mTOR and eNOS facilitates the production of NO, an important cellular signalling molecule [230,231]. The postprandial increase of insulin and glucose also activates mTOR (Figure 1) [119]. Further, mTOR upregulates PPARγ, facilitating lipid synthesis and deposition [232].

Peroxisome proliferator-activated receptors are ligand-activated transcription factors [191]. They play a critical role in the regulation of metabolic processes including glucose homeostasis, and insulin sensitivity, as well as diseases such as dyslipidaemia, NAFLD, and HTN [191,233]. The PPARs family comprises three distinct isoforms, namely PPARα, PPARγ, and PPARδ (also referred to as PPARβ), each of which contributes to the modulation of metabolic pathways in diverse cellular contexts [191]. Although PPARs perform overlapping functions across different tissues, their role as FA sensors helps maintain systemic energy homeostasis [233].

The transcriptional stimulation of PPARs occurs through the interaction of two identified adiponectin receptors, adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2) [234,235].

AdipoR1 and AdipoR2 are primarily expressed in the liver and skeletal muscle [236]. They activate AMPK, acting as a central metabolic sensor responsible for cellular metabolism, growth, and survival [237–239]. Additionally, dysregulation of the AMPK system has been associated with the pathogenesis of various diseases, such as T2DM, inflammatory and CV disorders, atherosclerosis, cancer, and neurodegenerative diseases. [238]. AMPK plays

a critical role in regulating various anabolic and catabolic pathways that are essential for glucose and lipid metabolism. It facilitates the translocation of GLUT4 and reduces gluconeogenesis and the activity of the enzyme acetyl-CoA carboxylase (ACC), key processes in maintaining metabolic balance [238,240,241]. Furthermore, AMPK significantly influences metabolic regulation by activating sirtuin 1 (SIRT1) and reducing the expression of SREBP-1C, ACC, and fatty acid synthase (Figure 1) [234]. It also plays an important role in enhancing mitochondrial function and biogenesis through SIRT1 activation [242]. This stimulates proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) to activate PPARγ and PPARα, key regulators of energy metabolism [243–245]. Additionally, AMPK's activity is influenced by fibroblast growth factor 21 (FGF21), a hormone that plays a critical role in managing glucose homeostasis, ketogenesis, β-oxidation, and insulin sensitivity [246,247].

The PPARγ and PPARα are involved in several metabolic pathways, influencing lipoprotein metabolism [248]. They facilitate an increase in HDL cholesterol and a decrease in both TAG and LDL cholesterol concentration [249]. Moreover, these nuclear receptors are critical for the functional regulation of cardiac and skeletal muscle, as well as adipose tissue metabolism [250]. Research has suggested that both PPARγ and PPARα contribute to metabolic homeostasis by downregulating pro-inflammatory pathways and upregulating the mechanisms involved in β-oxidation, hormone-sensitive lipase activity, and the expression of uncoupling protein 1 (UCP1) [248,251]. Dysregulation of AMPK/SIRT1 has been associated with numerous conditions [252]. These include hyperinsulinemia, IR, T2DM, altered oxidative and lipid metabolism, ER stress, mitochondrial dysfunction, cancers, and neurodegenerative diseases [242,253].

Another key regulator in dyslipidaemia is SREBPs, which play a central role in maintaining lipid balance by regulating the transcription of genes involved in TAG, FA, and cholesterol synthesis [254,255]. The AMPK is known to inhibit SREBPs activity through direct phosphorylation, which affects both the cleavage and transcriptional activation of SREBPs and influences other transcriptional regulators like ChREBP [256,257]. Moreover, SIRT1 and AMPK are vital in processes such as DNL and in reducing hepatic steatosis in conditions like NAFLD [257]. Complementing this, insulin also facilitates DNL by activating SREBP1c through the mTOR pathway and indirectly through glucose-mediated ChREBP stimulation [17].

5.2. Adipogenesis: From Lipid Accumulation to Hypertension

In vascular smooth muscle cells, the AMPK signalling pathway plays an important role in maintaining ER function. Dysregulation of the AMPK pathway may also contribute to the development and progression of HTN and atherosclerosis [258]. Additionally, angiotensin II (Ang II) aggravates disease progression by inducing ER stress through multiple mechanisms. Inhibiting the renin–angiotensin system can mitigate this stress, potentially offering a protective effect [259].

Further, some studies suggest that AMPK activators like metformin protect against pulmonary hypertension (PH); however, other studies indicate that AMPK activation could worsen the condition by inducing hypoxic pulmonary vasoconstriction [260,261]. Conversely, AMPK deficiency in smooth muscle cells has been associated with persistent pulmonary hypertension of the newborn, highlighting its critical role in neonatal health [262]. These conflicting findings underscore the complex and not yet fully understood impact of AMPK on PH [263].

The ER plays a significant role in regulating lipid metabolism, particularly in macrophages and the liver [264]. In macrophages, ER stress can modulate the expression of transporters associated with cholesterol metabolism and homeostasis, by inhibiting the efflux and stimulating the uptake of cholesterol [265]. Furthermore, altered cholesterol metabolism can induce ER stress, creating a feedback loop that exacerbates metabolic dysfunction [7].

Cholesterol is a crucial substrate for aldosterone synthesis in the adrenal cortex, where it is converted through several steps into aldosterone [8]. This hormone significantly influ-

ences blood pressure regulation and is correlated with the amount of visceral adipose tissue, independently of plasma renin activity [8,266]. Aldosterone also exacerbates inflammation, oxidative stress, and fibrosis, contributing to metabolic abnormalities, coronary artery disease, and renal dysfunction [267,268]. Additionally, it promotes vascular and structural changes in the heart, increasing the risk of CVD and mortality [267–269].

6. Hypertension

One of the major contributors to HTN is the dysregulation of the renin–angiotensin–aldosterone system. The adrenal cortex secretes the mineralocorticoid hormone aldosterone. Its primary function is to control blood pressure and fluid balance by facilitating the excretion of potassium and hydrogen ions and reabsorbing water, salt, and chloride from renal tubules [9]. Angiotensin II is the main bioactive compound of the renin–angiotensin–aldosterone system. The activation of Ang II stimulates and regulates several biological functions, including SNS activity, vascular tone, and aldosterone regulation, contributing to the management of systemic blood pressure [270]. However, overactivation of Ang II has been associated with elevated NADPH oxidase and arginase activity, and endothelial dysfunction in CVD, such as heart failure, cardiomyopathy, congenital heart disease, and HTN. Arginase, an important enzyme in the urea cycle, has been identified as a major factor contributing to endothelial dysfunction. It plays a crucial role in promoting the development of microvascular endothelial dysfunction, particularly in individuals with obesity [271]. Overexpression of arginase competes with endothelial nitric oxide synthase (eNOS) for L-arginine, reducing the available substrate and subsequently impairing NO production. Moreover, decreased bioavailability of L-arginine due to increased arginase activity leads to a reduced NO production, which, combined with increased oxidative stress, contributes to the pathogenesis of obesity-associated HTN [272].

Nitric oxide is a cellular signalling molecule that has an extremely short half-life (0.1–2 s) [273]. Dysfunction in NO production has been associated with many chronic diseases, including neurodegenerative disorders, arthritis, MetS, and CVD. When NO signalling is impaired, it can affect endothelial function and vascular tone, promote inflammation, and increase the risk of thrombosis. Additionally, the decreased availability of NO has also been linked to impaired insulin activity. This impairment contributes to dysfunction in insulin signalling pathways, which is a key factor in the development of metabolic disorders [270].

In mammals, NO biosynthesis is facilitated by nitric oxide synthase (NOS), an enzyme with the following four distinct isoforms that vary based on tissue type and expression pattern: eNOS, inducible NOS (iNOS), neuronal NOS, and mitochondrial NOS [274]. The biosynthesis of NO involves a two-step process of mono-oxidation reactions of L-arginine. These reactions use molecular oxygen and NADPH as electron donors. First, N-ω-hydroxy-L-arginine is produced, and then it is converted into citrulline and NO [275].

Dimerization is essential for NO catalysis in a two-step monooxygenation reaction. This reaction is known as a coupling reaction (Figure 4a) [276,277].

Tetrahydrobiopterin is a very important component of the coupling reaction in NO production. Its production requires the active metabolites of 5-methyltetrahydrofolate [277]. These metabolites serve as methyl and formyl donors for methylation reactions and purine synthesis [278]. In addition, NOS concentration and activity in a tissue is regulated by the amount and availability of co-factors and metabolites [274].

When the NOS enzyme lacks sufficient amounts of L-arginine, oxygen, and BH4, it is unable to synthesise NO. This is because electrons cannot transfer smoothly through the two parts, as they can in a coupling reaction, leading to inadequate NO production [277]. Instead, a small amount of NO is generated, and oxygen free radicals are produced, which causes the production of NO and free O_2^- radicals, forming peroxynitrite (Figure 4b) [277,279]. Peroxynitrite is a highly reactive molecule associated with endothelial dysfunction, uncoupling of NOS, constriction of blood vessels, destruction of NO, DNA damage, and protein damage in the body. This occurs through the 'cross-linking'

of molecules, leading to reduced function or destruction [279–281]. The main reasons for uncoupling are as follows: (1) insufficient or large amounts of L-arginine; (2) insufficient amounts of oxygen or (heme); (3) inadequate amounts of BH4; (4¬) stress, leading to (i) increased oxidative stress (ii) chronic pathogenesis, mediating increased production of iNOS and consequently, HTN; (5) atherosclerosis; (6) hypercholesterolemia; (7) stroke due to blood vessels constriction and improper amount of NO; (8) T2DM; and (9) cancer [281,282]. Endothelial dysfunction and NO regulate endothelial NADPH oxidase, leading to the activation of superoxide dismutase (SOD) and the development of CVD, including atherosclerosis [271]. Superoxide and NADPH oxidase increase ROS production [283]. However, in vitro studies have suggested that bilirubin can inhibit the SOD formation, acting as a CV protective agent [284].

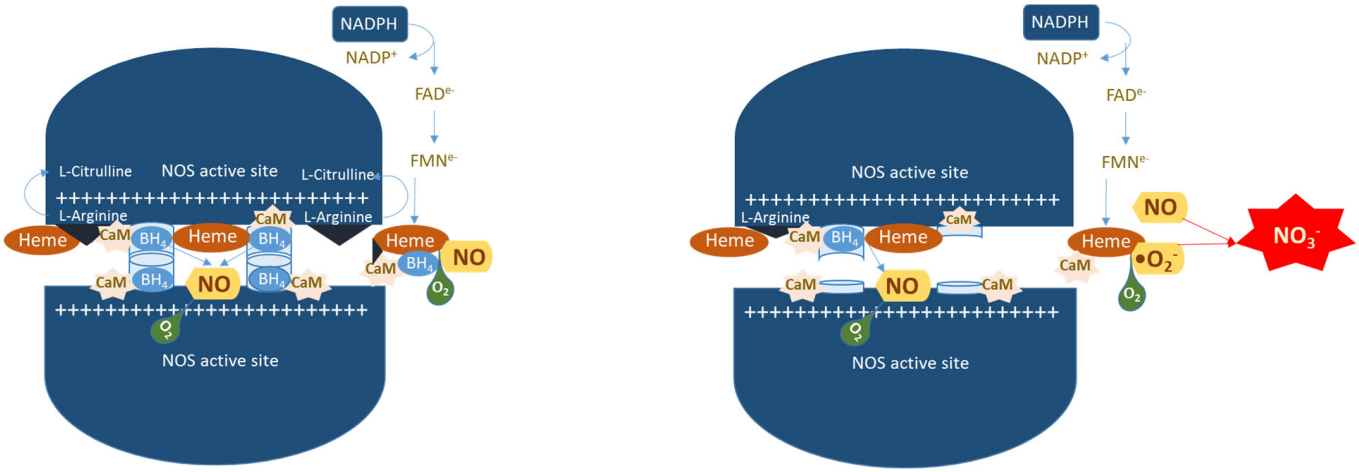

Figure 4. (**a**) Nitric oxide synthase coupling reaction. Coupling of the NOS enzyme occurs when NOS enzyme, a homodimer, consists of two large subunits that engage in the coupling process when the components L-arginine, tetrahydrobiopterin (BH4), calmodulin (CaM), heme, and nicotinamide adenine dinucleotide phosphate (NADPH) come together at the active site, initiating electrostatic interactions. This alignment facilitates the transfer of electrons between the two subunits, energising the enzyme and enabling the optimal production of NO. Key steps in this process include the insertion of heme into each subunit, reconfiguration of the enzyme to align its reductase and oxygenase domains for efficient electron flow, stabilization of the dimer structure by BH4, and interaction between BH4 and heme propionate side chains. L-arginine is bound within the oxygenase domain, positioned for oxidation, and electrons are transferred from NADPH via flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) to the heme, activating bound molecular oxygen. Crucial prosthetic groups such as FMN, iron porphyrin (heme), FAD, CaM, and BH4 are incorporated, vital for the structural integrity and functional capability of the enzyme. This complex assembly and sequence of events ensure the efficient production of nitric oxide (NO) and L-citrulline; (**b**) Nitric oxide synthase uncoupling reaction. Uncoupling in NOS primarily occurs at the heme component of the oxygenase domain, particularly in the absence of the cofactor BH4 or the substrate L-arginine. This condition does not lead to the production of nitric oxide (NO); instead, it results in the formation of superoxide radicals (O_2^-). These superoxide radicals can react with any available NO, produced under suboptimal conditions, to form peroxynitrite ($NO3^-$), a potent oxidant that can cause cellular damage. This uncoupling mechanism highlights the critical role of BH4 in maintaining the enzyme's coupling efficiency and preventing the harmful production of reactive oxygen species (ROS).

Furthermore, NOS uncoupling reactions often occur when the body is under oxidative stress, which elevates inflammatory markers, such as C reactive protein, plasminogen activator inhibitor-1 (PAI-1), and endothelin-1 (ET-1) [285]. This process leads to the activation of two major molecules involved in arterial remodelling, the vascular cell adhesion molecule and the intercellular cell adhesion molecule [286].

Endothelin-1 is a key contributing factor in the development of HTN [287]. It functions as a potent vasoconstrictor and pro-inflammatory peptide, leading to the upregulation of iNOS, fibrogenesis, and increased CV-related risks [274,288]. In a study using obese Zucker rats that were fed commercial food pellets and glucose drinking water (10% w/v) for 3 weeks, the results showed a significant increase in the expression of ET-1 compared with the lean control group. This observation indicated a significant association between elevated glucose levels and the enhancement of the ET-1 pathway, potentially linking T2DM to cardiac dysfunction [289].

7. Conclusions and Future Directions

The metabolic signalling networks that govern cellular communication are intricate and critical for determining cell survival. The onset and prolonged effects of inflammation and metabolic dysfunction, arising from complex interplays among obesity, dyslipidaemia, T2DM, and HTN, are central to the development of MetS. This review has outlined the main pathways involved, with the aim of providing a clearer understanding of MetS targets and demonstrating the complexity along with its downstream effects.

Future research should focus on expanding our understanding through proteomic screens, ribonucleic acid interference, and broad-based genetic approaches to uncover novel interactions within cellular functions and metabolic pathways. Moreover, prospective approaches should target the treatment of multiple pathways and disturbances. These include mitochondrial dysfunction, dysregulation of enzymes and protein factors involved in glycolysis, and the PI3K/AKT/mTOR signalling pathway. Additionally, attention should be given to PPARs and AMPK dysregulation, cytotoxicity, lipotoxicity, ER stress, NO and endothelial dysfunction, and inflammatory processes. The regulation of this metabolic crosstalk presents new opportunities for managing disease progression. Gaining a thorough understanding of the different metabolic effectors and their roles is a critical step toward identifying effective interventions targeting MetS and its associated complications.

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