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Review

Ferroptosis as a Therapeutic Target in Metabolic Syndrome, Mechanism Complications and Future Prospects

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Abstract

Metabolic syndrome (MetS) is a risk factor clustering multifactorial disorder, including obesity as experienced in the abdomen, resistance to insulin, dyslipidaemia, high blood pressure, and elevation in level of fasting glucose closely allied with the escalation of the threat of cardiovascular disease, type 2 diabetes, and different related health-related issues. Even though the rate of metabolic syndrome in the world is growing, the current treatment intervention measures have not been sufficient and new measures were desperately needed. The recent studies have emphasized ferroptosis, a regulated cell death process caused by the oxidative stress and lipid peroxidation, as a pathological process of metabolic syndrome. In this paper, the authors examine the processes of ferroptosis, its role in MetS, and its suitability as a therapeutic agent. The prevention of ferroptosis can be a new approach to reducing attacks on the oxidative system, inflammation, and metabolic regulation characteristic of MetS. Nevertheless, there are still difficulties in the interpretation of the exact process of ferroptosis and the creation of efficient and non-toxic inhibitors. Also, ferroptosis inhibition along with other interventions involving insulin resistance, inflammation, and dyslipidaemia could be a more holistic treatment strategy. Further studies are required to realize the therapeutic potential of ferroptosis in MetS and to implement them into clinical practice, which would provide new prospects in the treatment of this increasingly widespread health concern of the population.

Keywords

Ferroptosis, Insulin, Lipid peroxide, Metabolic syndrome, Obesity, Therapeutic target

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1. Introduction

Metabolic syndrome (MetS) is a complex of conditions disorders related to the high risk of cardiovascular diseases (CVD), Type 2 diabetes mellitus (T2DM) and other chronic disease [1]. It is characteristically typified by abdominal form of obesity, insulin resistance, dyslipidaemia and hypertension. MetS has also gained significant prevalence across the globe or the past several decades and its estimated that around 25-30% of adult population has been affected by it across the world today [2] . MetS is becoming increasingly high due to the aging population, unhealthy eating habits, and sedentary ways of living among others. The pathophysiology of MetS in the form of a complex of genetic, environmental, and lifestyle problems is difficult to understand in a simple manner. The insulin resistance and the low grade of chronic inflammation are the key findings in the pathogenesis of the MetS results in endothelial dysfunction, lipid metabolism and oxidative stress changes [3]. In particular, the insulin resistance has a significant effect on the glucose metabolism and facilitating dyslipidaemia, thereby putting at risk CVD and T2DM. This interventional pathophysiology has contributed to MetS becoming a significant public health issue with important long term economic and healthcare outcomes [4]. Ferroptosis, a regulated and iron-dependent type of cell death, has received particular interest in the pathogenesis and progression of MetS. Another cell death process, independent of apoptosis and necrosis, is ferroptosis which is marked by lipid peroxides accumulation and oxidative degradation of cellular membranes [5]. The iron accumulation and lipid peroxidation are the two main causes of ferroptosis that are closely interconnected with the oxidative stress, a characteristic of MetS [1]. Recent research indicates that ferroptosis could be implicated in a number of major characteristics of MetS [4]. As an example, overloading of iron, followed by lipid peroxidation, has been found to be the cause of the dysfunction of the pancreatic β-cells, worsening insulin resistance [6]. Likewise, ferroptosis of adipocytes leads to chronic inflammation and metabolic dysfunction, which further leads to obesity and insulin resistance [7]. Damage of vascular tissues in ferroptosis may also have a strong role in the endothelial dysfunction observed in MetS-related CVDs [8]. Owing to its contribution to the damage of cells, ferroptosis has become a potential therapeutic option to MetS [9]. By regulating ferroptosis pathways, there are new approaches to decreasing the cellular toxicity of metabolic dysfunction and enhancing insulin sensitivity [10]. Nevertheless, there are still difficulties in the selective treatment of ferroptosis in the MetS, such as the necessity of particular biomarkers, and the production of safe and efficient therapeutic agent [11]. Although increasing experimental evidence supports the involvement of ferroptosis in obesity, insulin resistance, cardiovascular disease, and MASLD/non-alcoholic fatty liver disease (NAFLD), its clinical application remains in the early stages. At present, no international clinical guideline recommends ferroptosis-targeted therapy for metabolic syndrome, and most available evidence originates from in vitro and animal studies. Nevertheless, ferroptosis has attracted considerable attention because it integrates iron metabolism, oxidative stress, lipid peroxidation, and chronic inflammation–key mechanisms underlying metabolic syndrome. Therefore, understanding ferroptosis may provide opportunities for the development of future therapeutic strategies while acknowledging the current translational limitations [12].

2. Overview of Metabolic Syndrome

The MetS is a condition arise in individual when three or more of the below five elements are established by the American heart association, as well as the national heart, lung and blood institute [13]. Abdominal obesity is a disease that is said to exist where the waist of the individual measures 40 inches among men and 35 inches among women [14]. This accumulation of fat particularly around the abdomen corresponds well with insulin resistance and other metabolic risks [15]. Insulin Resistance is the loss of normal ability to normalize the levels of glucose because of the inability of cells to respond to the insulin which causes the rise in level of blood glucose and consequential hyperinsulinemia as a secondary effect [16]. The issue is this disease that is the major factor in the pathogenesis of type-2 atherosclerosis. The state of dyslipidaemia is observed by a raised level of triglycerides (>150 mg/dl) and low one of high density lipoprotein (HDL) cholesterol (<40 mg/dl in men, 50 mg/dl in women) that server as a strong risk factor to CVS [17] . Hypertension ,the blood pressure of 130/80 mmHg,is major issue in the CVS and a major determinant of MetS [18]. Last but not the least, Elevated Fasting Blood Glucose is the condition when the quantity of fasting glucose is 100 mg/dL or more, and is the indication of poor tolerance of glucose and insulin resistance which often precedes T2DM [19]. A cumulative sum of these factors is MetS and are the causes of high rates of CVD, diabetes, and other health problems. Table 1 summarizes these components and diagnostic criteria [20]. Table 1 shows the diagnostic components of metabolic syndrome and their mechanistic association with ferroptosis.

Table 1. Pathophysiological features associated with metabolic syndrome and their relationship with ferroptosis.

S. No	Component	Diagnostic Criteria	Relevance	Ref.
1	Central obesity	BMI ≥30 or high adiposity	Enhancement of lipid peroxidation and iron burden − enhances the risk of ferroptosis.	[21]
2	Waist circumference	>102 cm (men), >88 cm (women)	Visceral fat produces ROS, which triggers ferroptosis.	[22]
3	High fasting blood glucose	≥100 mg/dL	Hyperglycaemia increases oxidative stress level → ferroptosis injury.	[23]
4	Insulin resistance	HOMA-IR ↑ or fasting insulin ↑	Stresses and overloads mitochondria, exposing cells to ferroptosis.	[24]
5	High triglycerides	≥150 mg/dL	The lipids rich in polyunsaturated fatty acids (PUFAs) are made targets of lipid peroxidation during ferroptosis.	[25]
6	Low HDL	<40 mg/dL (men), <50 mg/dL (women)	A low level of antioxidant defense permits additional lipid peroxidation → supports ferroptosis.	[26]
7	Hypertension	≥130/85 mmHg	The vascular oxidative stress enhances the ROS damage through iron.	[27]
8	Elevated LDL	≥130 mg/dL	LDL oxidation stimulates ferroptosis induction by lipid peroxidation.	[28]
9	NAFLD/MAFLD	True to Elevated ALT/AST or ultrasound.	Develops secondary to obesity and insulin resistance; hepatic iron overload and lipid peroxidation promote ferroptosis-mediated liver injury.	[29]
10	Chronic inflammation	↑CRP, ↑TNF-α	Cytokines disrupt iron homeostasis - raises the risk of ferroptosis.	[30]
11	Oxidative stress	↑MDA, ↓antioxidants	Examples of essential mediators of lipid peroxidation and ferroptosis.	[31]
12	Mitochondrial dysfunction	Abnormal ATP/ROS markers	Excess of ROS is a stimulus of ferroptosis pathways.	[32]
13	Iron overload	↑Saturation of Ferritin, ↑ transferrin saturation.	Surplus free iron becomes the cause of Fenton reaction → in order to cause ferroptosis.	[33]
14	Dysregulated lipid metabolism	Abnormal lipid profile	Accumulation of PUFA-phospholipids enhances ferroptosis.	[34]
15	Reduced antioxidant defense	↓Glutathione, ↓GPX4	Direct targeting of ferroptosis -protective system - therapeutic target.	[35]

3. Ferroptosis and Its Relevance in Metabolic Syndrome

Ferroptosis is a recently discovered mode of regulated cell death which is not similar to apoptosis, necrosis, and autophagy [36]. It is defined by the formation of lipid peroxides up to fatal amounts that cause the destruction of cells and death [37]. This is a distinctive form of cell death that is triggered by iron overload and oxidative stress and, therefore, is of great relevance in the context of many metabolic diseases, such as MetS pathophysiology includes chronic low-grade inflammation, oxidative stress, and metabolic dysfunction, which are all involved in causing ferroptosis [38]. Figure 1 represents the ferroptosis and its relevance in metabolic syndrome.

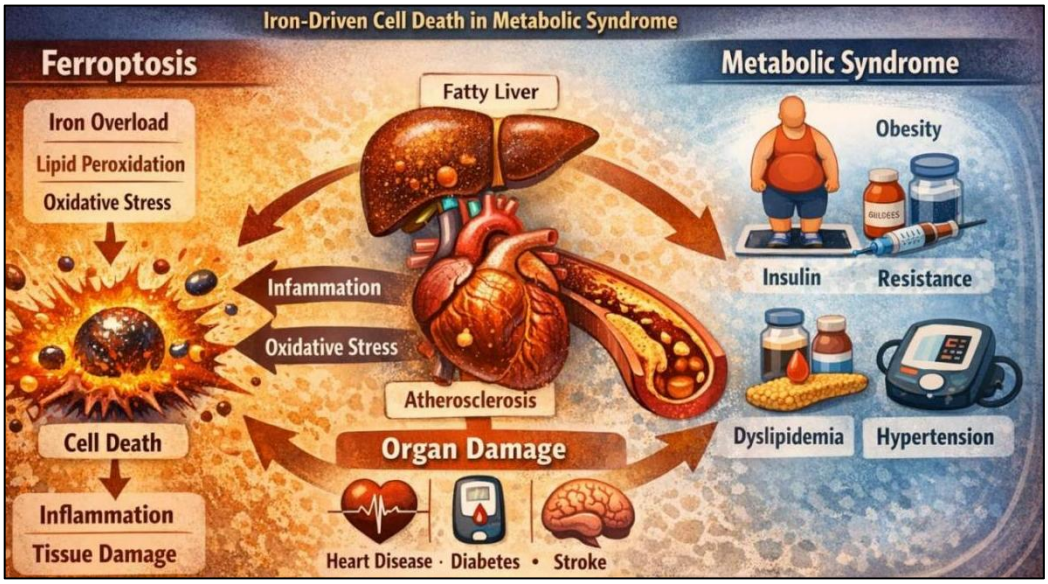

Figure 1. Mechanisms of ferroptosis and their relevance in metabolic syndrome.

4. Ferroptosis Mechanism

Ferroptosis occurs through breaking of cellular antioxidant defence systems with depletion of glutathione (GSH), an important antioxidant in cells [39]. GSH is important in the lowering of lipid hydroperoxides and deterring their concentration. In cases of low levels of GSH, lipid peroxidation takes place resulting in the production of the extremely reactive and toxic lipid peroxides [40]. These lipid peroxides mainly are produced by the means of the iron-dependent enzyme arachidonic acid lipoxygenase (ALOX) or the action of other enzyme lipoxygenase [41]. Iron is the key Fenton reaction catalytically controlled in ferroptosis which produces the hydroxyl radicals to start the lipid peroxidation [42]. Homeostatic regulation between antioxidant defence and iron metabolism is important in cell integrity [43]. As a component of the MetS, iron homeostasis regulation and escalated levels of oxidative stress are also contributors to ferroptosis predisposition of the cells [44]. Indicatively, surplus of the iron contents in the liver and adipose tissue has been indicated to worsen the oxidative stress further, complementing pathogenesis of MetS [45].

5. Ferroptosis as a Therapeutic Target in Metabolic Syndrome

The association between ferroptosis and a number of treatments and characteristics of MetS has been observed, i.e. insulin resistance, obesity, and NAFLD [12]. In the cases of obesity and the fat that is in the form of the visceral fat, the deposition of iron is increased and oxidative stress may increase [46]. These causes are known to induce ferroptosis, which causes tissue damage and inflammation which aggravates further the metabolic impairment [47].

Besides this, ferroptosis has been also linked to insulin resistance which is a characteristic of the MetS. Insulin resistance is a condition which happens when cells especially the muscle and liver cells become unresponsive to insulin leading to the rise in blood glucose levels and subsequent heightened insulin requirement. The oxidative stress and lipid peroxidation process of the insulin sensitive tissues might favour the occurrence of an insulin resistant state and ferroptosis is believed to be a principal facilitator of the process. Additionally, the ferroptosis has been indicated to aggravate endothelial dysfunction which in turn is a contributing factor of CVD that are usually associated with the metabolic syndrome [48]. Ferroptosis also affects NAFLD that is common among people with metabolic syndrome. Liver is very vulnerable to oxidative damages because of the various metabolic activities it engages in including the lipid metabolism. The excess lipids are deposited in NAFLD. Liver cells, which causes oxidative stress and iron overload and ultimate ferroptosis. This chain reaction leads to liver inflammation and fibrosis which are both major contributors to other serious liver diseases such as cirrhosis and hepatocellular carcinoma [49].

ferroptosis contributes to metabolic syndrome by affecting

5.1 Vasculature (Cardiovascular Disease)

Another cause of CVD problem of MetS is ferroptosis. The overriding causes, which lead to development of atherosclerosis, are persistent oxidative stress and inflammatory condition whereby the arteries are narrowed due to the fatty plaque deposits in the arteries. The arteries endothelial cells including the smooth muscle and the macrophages were discovered to experience ferroptosis that facilitate the instability and burst of the plaque and this can lead to heart attacks and strokes. Moreover, ferroptosis inflammation of the vascular system also leads to the worsening of the endothelial dysfunction that is seen in the metabolic syndrome, thus the CVD becomes prone to damage [50]. A cause of morbidity and mortality among people with MetS is CVD. Oxidative stress and inflammation are causative factors of endothelial dysfunction, atherosclerosis and plaque instability, all these being referable to ferroptosis. By this is because the ferroptosis in the cardiovascular system can be targeted, and the extent of oxidative damage could be decreased enhance endothelial activity, and avert the advancement of atherosclerosis. Recent researches have proposed that oxidative stress in the vascular cells can be reduced by ferroptosis inhibition, reduce inflammatory reactions, and stabilize atherosclerotic plaques. Such results show that ferroptosis can become an option of prevention and alleviation of cardiovascular events in people with MetS. In addition, treatments aimed at ferroptosis can be used as an addition to current cardiovascular treatment and enhance general cardiovascular health [51].

5.2 Pancreas (Insulin Resistance)

Oxidative stress and lipid peroxidation have a great impact on insulin resistance, which is a characteristic of MetS. Prevention of ferroptosis can provide a new way of reducing insulin resistance by lessening oxidative injury in the insulin sensitive tissue e.g. liver, muscle and adipose tissue. A number of researches have indicated the importance of ferroptosis in further worsening of insulin resistance. As one example, the prevention of ferroptosis in obese animal models has been observed to enhance the insulin sensitivity and glucose homeostasis [52].

Ferro statin-1 and Lepro statin-1, as ferroptosis inhibitors, have been reported to prevent the injury of insulin sensitive tissues by oxidative stress, which strengthens the metabolic impairments observed in MetS [53]. These inhibitors act as they inhibit lipid peroxidation and inhibit the formation of toxic lipid species, which cause ferroptosis cell death. Consequently, ferroptosis inhibition should be used to normalise insulin sensitivity and lower the chances of T2D which is often linked to the MetS [54].

5.3 Adipose Tissue (Obesity)

Obesity has been associated with the involvement of ferroptosis, in which oxidative stress, iron overload and lipid peroxidation play a role in adipose tissue dysfunction and inflammation. Addressing ferroptosis in adipose tissue may be able to decrease the inflammation and enhance the functioning of adipocytes thus preventing or lessening the impact of obesity [55]. Researchers have found that the inhibition of ferroptosis in obese mice results in the reduction of adipose tissue inflammation and metabolic outcomes, including the decrease of fat deposits and glucose metabolism, which is better. This implies that the use of ferroptosis inhibitors can be a useful approach to fight metabolic imbalances in obesity and stop the advancement to MetS [56].

5.4 Liver (NAFLD)

NAFLD is considered the hepatic manifestation of metabolic syndrome and is strongly associated with central obesity, insulin resistance, and T2DM. Excess adiposity and impaired insulin signalling promote hepatic lipid accumulation, oxidative stress, and chronic inflammation, creating conditions that favour ferroptosis-mediated hepatocyte injury. One of such comorbidities in MetS happens to be the NAFLD and it is marked with the retention of fats in liver cells leading to inflammation oxidative stress and liver damage. It has been proved that the extent of NAFLD relies crucially on the presence of ptosis, as the oxidative stress, and iron overload play a significant role in the pathogenesis of the liver damage [57]. Inhibition of ferroptosis has been suggested to be an effective therapeutic approach to preventing or treating NAFLD. Ferroptosis inhibitors e.g., Ferrostatin-1 have also been found to provide protective effect in liver cells inhibiting lipid peroxidation and iron-initiated oxidative stress. The inhibition of, in preclinical model systems ferroptosis has been reported to alleviate liver inflammation, steatosis and fibrosis which are characteristic features of NAFLD. It can perhaps be possible to stop or reduce the rate of ferroptosis once identified NAFLD and enhance liver function in patients with MetS [51].

5.5 Potential Therapeutic Agents

ferroptosis, an iron-dependent lipid peroxidation, alternatively referred to as a form of regulated cell death recently has been given much attention because of its duality in various pathophysiological processes such as metabolic disorders. MetS is a multi-factorial pathology of disorders which consists of central obesity, insulin resistance, dyslipidaemia, high blood pressure, and chronic low-grade inflammation as risk factors at the predisposition of CVD, NAFLD, and T2DM. This is in spite of the fact that the idea of ferroptosis targeting has emerged as an effective treatment strategy to dampen oxidative tissue injury and metabolic dysfunction which has been hampered by several mechanistic and translational challenges that have impeded the successful implementation of the strategy to the treatment of MetS [58]. The complication of pathophysiology of MetS is the key challenge the systemic metabolic deviance and the organ-specific oxidative stress. Interaction between Iron metabolism and maintenance of GSH homeostasis and lipid peroxidation pathways ferroptosis is regulated by a complex interplay between the body states and the processes of thiol maintenance and lipid peroxidation. Each of the three causes chronic hyperglycaemia, dyslipidaemia and mitochondrial dysfunction, combined together, is what contributes to the overproduction of reactive oxygen species (ROS) and an imbalance of iron homeostasis and predisposes the cells to ferroptosis death, in the environment of Metabolic syndrome. Nevertheless, ferroptosis in different tissues differs in its extent and direction. As an example, in hepatic cells, ferroptosis death can be a contributor of steatohepatitis, but in pancreatic b-cells or adipocytes, excess ferroptosis can cause insulin release or adipokine stimulation. Thus, ferroptosis therapeutic modulation should be extremely tissue-selective because a generalized inhibition or activation may cause unintended metabolic dysfunction or organ toxicity [59].

The other big shortcoming is that there are no definite biomarkers to help identify ferroptosis among other cell death modalities like apoptosis, necroptosis, and pyro ptosis, which also take place in oxidative stress conditions characteristic of metabolic syndrome. Majority of the indicators presently used such as lipid ROS accumulation, malondialdehyde (MDA) levels and depletion of GPX4 are not fully ferroptosis. This diagnostic vagueness complicates experimental interpretation as well as clinical translation since treatment interventions against ferroptosis can be overlapping and other pathways that are sensitive to redox. In addition, the dynamics of ferroptosis over time in the development of MetS not well known. There is a degree of uncertainty as to whether ferroptosis is an initiating trigger in tissue dysfunction, or a secondary reaction to already developed metabolic stress. In the absence of a clear conception of its chronological input, treatment targeting will have the potential to interfere with critical cellular adaptation pathways that sustain redox balance [33]. ferroptosis is also a multicellular process making pharmacological modulation therefore difficult to achieve because of the metabolic complexity of MetS. The Ferrostatin-1, Liproxstatin-1, and Deferoxamine are the examples of Ferro statin inhibitors which have proven their cytoprotective properties in preclinical models by inhibiting lipid peroxidation and recovering the antioxidant potential. Yet, the systemic therapeutic potential of them is limited by their pharmacokinetic weaknesses such as low solubility, high metabolic rate, and low bioavailability. Moreover, chronic inflammatory conditions of the MetS also modify the drug metabolism by modifying the hepatic enzymes in addition to imparting lipid carrier adjustments, which further complicates dosage adjustment. The long-term suppressing effect of ferroptosis also causes oncogenic risk concerns because ferroptosis is used by nature as tumour suppressive [60].

Another similar problem is the contribution of iron metabolism to the pathogenesis of MetS and its effect on ferroptosis regulation. Subclinical iron overload is often manifested by individuals with MetS who have high levels of saturation of serum ferritin and transferrin. This accumulation of iron as a metabolite increases oxidative stress by Fenton reactions, which increase lipid peroxidation and cellular damage in the liver, pancreas, and endothelium in the vascularity [61]. However, iron activity cannot be fully suppressed to be used as a treatment strategy, as iron is required in the mitochondrial respiration, erythropoiesis, and enzymatic activities. Chelation therapy with drugs such as Deferoxamine or Defer prone can help to reduce the effects of ferroptosis injury and has the risk of causing anaemia, mitochondrial dysfunction, and immune impairment. In this way, there is a need to balance iron sequestration with physiological availability, which also remains one of the flake-and-needle issues in the design of ferroptosis-targeted therapies of metabolic syndrome [62].

The other understudied problem is the lipid metabolism cross-talks with ferroptosis. MetS is also defined by impaired lipid production and build-up of PUFAs which are lipid peroxidation substrates. The acyl-CoA synthesise long-chain family member 4 (ACSL4) facilitates the uptake of PUFAs into phospholipids making them highly vulnerable to ferroptosis oxidation. Even though ACSL4 inhibition has been suggested as a possible therapeutic option, this enzyme is also important in the maintenance of lipid homeostasis and insulin sensitivity. Consequently, to achieve lipid peroxidation therapy in MetS, the balance between the intervention needs to be delicate so as not to interfere with physiological lipid turnover and energy metabolism. There is an additional complexity due to the effect of microbiota in the gut on ferroptosis. Recent studies propose that dysbiosis in metabolic syndrome modulates the bioavailability of iron and antioxidant micronutrients like selenium and vitamin E which are key ferroptosis regulators. Besides, microbial metabolites like lipopolysaccharides and short-chain fatty acids have the ability to regulate host redox response and inflammation, indirect modulation of ferroptosis sensitivity. Therefore, individual differences in gut microbial makeup can be an important predictor of therapeutic response to ferroptosis agents suggesting individualized or micro biota focused therapy in the treatment of metabolic illnesses by ferroptosis regulation. Also, the difference between sex and genetic factors complicates ferroptosis-targeted interventions in MetS. Research has also found that oestrogen has protective antioxidant activity, improving the expression of GPX4 and inhibiting lipid peroxidation, which makes premenopausal females less prone to ferroptosis damage than males. Cellular vulnerability to iron-induced oxidative damage can also be modified by genetic polymorphisms in main ferroptosis regulators, including SLC7A11, GPX4 and FTH1. Individual genetic profiling can be required to maximize treatment efficacy and reduce unfavourable consequences in the implementation of ferroptosis modulation in metabolic disorders [63].

Another significant problem in the therapeutic context of the translation with respect to ferroptosis is that of contextual dependence. Although unregulated ferroptosis leads to tissue degeneration in metabolic syndrome, regulated ferroptosis can be useful in diseases such as cancer or fibrosis associated with obesity, where abnormal cell removal is a good idea. Such a duality makes it more difficult to design general ferroptosis-targeted agents and emphasizes the need to have accuracy medicine tools that have the capacity to spatially and temporally regulate ferroptosis activity. More complex delivery systems like Nano carriers, liposomes and prodrug preparations are under investigation in order to obtain loco specific modulation [64].

6. Current Challenges and Limitations

Despite the potential of ferroptosis as a therapeutic target of MetS, there are a number of obstacles to its clinical use. ferroptosis is a type of programmed cell death that is based on iron-dependent lipid peroxidation and its regulation is highly linked to metabolic processes that regulate glucose, lipid and energy levels. The major problem is that ferroptosis is very complex and tissue specific. Oxidative stress and iron overload react differently in various organs of the metabolic syndrome, i.e. liver, pancreas, heart, and adipose tissue. Indicatively, ferroptosis inhibition can preserve the β-cells of the pancreas against oxidative stress yet also increase lipid retention in the hepatocyte. Thus, the regulated ferroptosis without the interference of the normal metabolic activities is a significant challenge. The second shortcoming is that there are no biomarkers of ferroptosis that are specific to clinical environments. Even though, such indicators as GPX4 depletion, ACSL4 expression, and lipid ROS accumulation are employed in experimental models, they have not been demonstrated to be validated in human diagnosis yet. ferroptosis can be confused with other types of cell death-inducing mechanisms, including apoptosis and necroptosis, which makes it even more difficult to accurately estimate ferroptosis. In the absence of standardized biomarkers, the efficacy of ferroptosis-targeting drugs in MetS is hard to assess, and the treatment outcome is hard to measure in patient [65]. Figure 2 represents the challenges and limitations of targeting ferroptosis in metabolic syndrome.

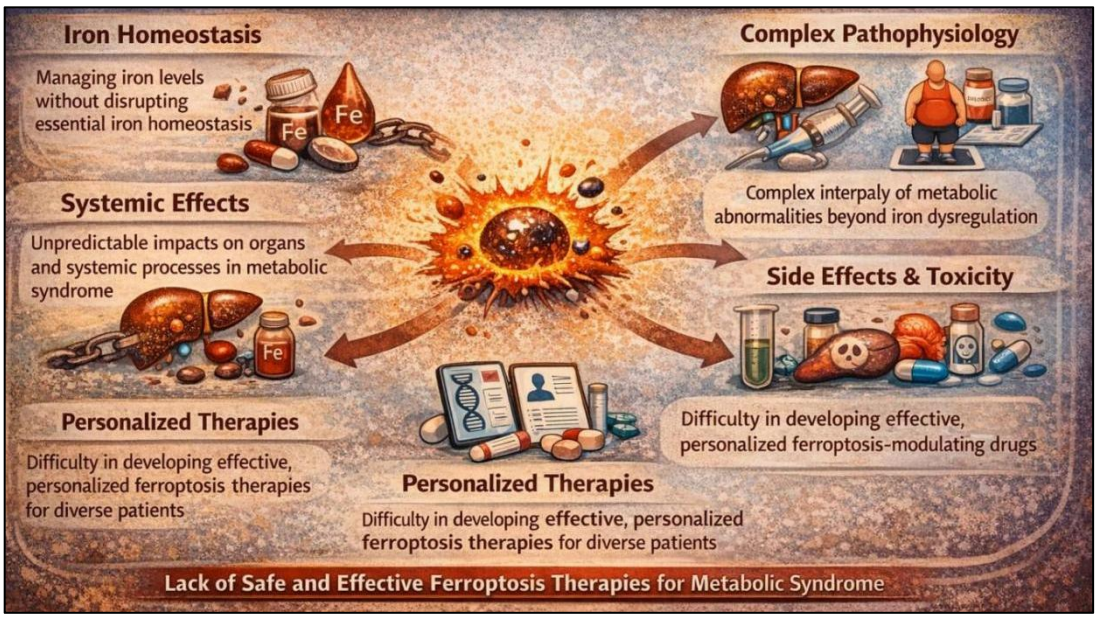

Figure 2. Therapeutic strategies targeting ferroptosis in metabolic syndrome and associated complications.

Another challenge is the dual role of ferroptosis in the metabolic regulation. Although ferroptosis inhibition can be used to reverse the lipid build-up and inflammation in obese or fatty liver tissues, over induction can lead to further oxidative stress and organ damage. On the other hand, inhibiting ferroptosis to save the cells against oxidative stress would increase insulin resistance and metabolic disproportion. Such a fine balance emphasizes that such a regulation is required, either in terms of time or space, since it may be detrimental in case of over-activation or over-inhibition. Pharmacologically, delivery of drugs and selectivity is a major challenge. A majority of known ferroptosis modulators, including liproxstatin-1, ferrostatin-1, and Deferoxamine, have poor solubility, a low bioavailability, and low tissue penetration. This is a technical challenge to reach effective concentrations in the target tissues, such as those in the liver and the pancreas, and avoid off-target toxicity. Furthermore, the manipulation of the systemic iron metabolism may have unwanted effects, which may be anaemia, neurotoxicity, or immune dysfunction. The mechanisms of the interactions between ferroptosis and metabolic pathways remain not fully comprehended mechanistically. It is not clear whether the ferroptosis is a cause or an effect of metabolic dysfunction. Different experimental findings on the same model system have diverse results and this restricts the application of findings in clinical care. In addition, it is also the case that recent research is predominantly preclinical, based upon animal or in vitro models that are not as complex as human MetS. Lastly, regulatory and safety are important obstacles. Since ferroptosis is an oxidative and iron-driven process, long-term regulation may interfere with redox systemic [66].

7. Future Perspectives

Even though ferroptosis is a promising therapeutic target to MetS, there are a number of obstacles to its use in clinical practice. Ferroptosis is a regulated type of cell death which is caused by iron-dependent lipid peroxidation, and the regulation of ferroptosis is closely linked to glucose, lipid, and energy metabolism. The major problem is the complexity and tissue specificity of ferroptosis. Oxidative stress and iron overload have a specific response in the various organs of the MetS, including liver, pancreas, heart, and adipose tissue. As an example, inhibition of ferroptosis may spare pancreatic 5-cells to oxidative damage but may also trigger lipid build-up in hepatocytes. Accordingly, the regulation of ferroptosis without interfering with the normal metabolic functioning is still a significant challenge. The other weakness is that specific biomarkers that could be used to detect ferroptosis in clinical practice are not available. Even though experimental models use markers of GPX4 depletion, ACSL4 expression, and lipid ROS accumulation, the markers are not yet validated to be used in human diagnosis. The similarity of ferroptosis with the other types of cell death, including apoptosis and necropsies, also makes proper evaluation even more difficult. In the absence of standardized biomarkers, the efficacy of ferroptosis-targeting drugs in MetS/pivot ate the outcome of treatments in patients is hard to assess. ferroptosis has a dual role on metabolic regulation, which is an added challenge. Although ferroptosis should be encouraged to limit lipid build-up and inflammation in fatty or obese liver tissues, when over induced, ferroptosis will worsen oxidative stress and damage organs. On the other hand, inhibition of ferroptosis to prevent cell oxides may aggravate insulin resistance and metabolic perturbation. This fine balancing gives prominence to the fact that there should be a strict control of time and space since either too much activation or inhibition may be detrimental [67]. On the pharmacological side, there are major challenges of drug delivery and selectivity. The majority of the known ferroptosis modulators, including liproxstatin-1, ferrostatin-1, and Deferoxamine, have poor solubility, low bioavailability, and low tissue penetration. Effective concentrations of the drug in target tissues such as the liver and pancreas and the prevention of off-target toxicity are a technical challenge. In addition, the systemic intervention in the metabolism of iron may have the side effects, including the development of anemia, neurotoxicity, or immune

dysfunction. The mechanisms of interaction between ferroptosis and metabolic pathways are yet to be comprehensively understood. It is not clear to determine whether ferroptosis is a cause or effect of metabolic dysfunction. The results related to the experiments are also not applicable to clinical practice because the results vary with the model system utilized. Besides, the available studies are largely preclinical and they employ animal or in-vitro model that is not too representative of the human MetS. Lastly, safety and regulatory issues are also significant challenges. Ferroptosis is an oxidative process that is iron-based, hence long-term change can ignore the redox control of the organism. The absence of validated assays and safety data has been among the factors that no ferroptosis-targeting drug has hitherto been passed to late-stage clinical trials [68]. Table 2 represents the future research directions and therapeutic strategies targeting ferroptosis in metabolic syndrome.

Table 2. Future research directions and therapeutic strategies targeting ferroptosis in metabolic syndrome.

S. No	Future Directions	Rational/Scientific Need	Potential Strategies & Research focus	Ref.
1	Selective Ferroptosis Modulators Development.	The existing ferroptosis inhibitors are not tissue specific and could have an impact on normal cells.	Focused on GPX4 activators, ACSL4inghibitors, and lipid ROS suppressors of high metabolic tissue selectivity were designed.	[69]
2	Targeting of Organelle-Specific Ferroptosis.	Lipid peroxidation and iron release occur through mitochondria and lysosomes respectively.	Design mitochondrial iron, lipid peroxidation and Ferritinophagy (NCOA4 inhibitors) targeting agents.	[70]
3	Ferroptosis Biomarkers of Early Diagnosis.	There are no clinically approved ferroptosis markers of Metabolic syndrome.	Find circulating lipid peroxides, ACSL4 levels, GPX4 levels, labile iron, and oxidized PUFA panels to be used in clinical practice.	[71]
4	Delivery Systems based on Nanomedicine.	Off-target toxicity can be brought about by systemic ferroptosis inhibition.	Selectively target ferroptosis modulators to liver, adipose or vascular tissues with the help of nanoparticles, liposomes and polymeric carriers.	[72]
5	Attacking Ferroptosis-inflammation crosstalk.	Ferroptosis increases metabolic inflammation and the reverse.	Consider dual-action agents, which inhibit ferroptosis + cytokines (e.g., NF-κB pathway).	[65]
6	Translational Research and Clinical Trials.	The majority of the ferroptosis studies are preclinical.	Phase I/II pilot trials and safe antioxidants, iron modulators and GPX4 boosters in obesity, NAFLD and insulin resistance.	[73]

Note: Ferritinophagy is a selective form of autophagy in which the iron-storage protein ferritin is degraded to release intracellular iron.

8. Conclusion

MetS is a complicated and rising health issue of the population, and its escalation urgent need throughout the world. The diagnostic criteria, which evaluate such components as are as abdominal obesity, insulin resistance, dyslipidaemia, hypertension, and high fasting glucose crucial in determining the high-risk people. The overlapping of these components, however, is present outlines a necessity in further investigation and optimization of diagnostic procedures. Recent future in ferroptosis studies is holding therapeutic promise in MetS. Targeting ferroptosis, a type of cell death, which is caused by oxidative stress, might assist in mitigating the oxidative damage inflammation as a cause of metabolic syndrome. Nevertheless, there are still obstacles on the way to the comprehension of the exact mechanisms of ferroptosis and safety and efficacy of inhibitors in the clinical setting. In the future, personalized medicine techniques based on genetic and metabolic profiles will be the key to optimizing ferroptosis-based therapy. These interventions are used in combination with insulin interventions resistance and inflammation would make a more holistic approach to MetS management. Although ferroptosis represents a promising therapeutic target for metabolic syndrome, current evidence is predominantly preclinical, and no ferroptosis-targeted therapy has yet been incorporated into clinical guidelines. Future studies should focus on validating biomarkers, conducting well-designed clinical trials, and developing tissue-specific therapeutic approaches before ferroptosis can be translated into routine clinical practice.

Conflict of Interest

The authors declare no conflict of interest.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

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