Nature and Science of Sleep

Elevate Series

Open Access Full Text Article

REVIEW

Ferroptosis as a Potential Mechanism in the Pathophysiology of Obstructive Sleep Apnea Syndrome

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Abstract: Obstructive Sleep Apnea Syndrome (OSAS) is a prevalent sleep disorder characterized by recurrent upper airway obstruction, resulting in intermittent hypoxia, oxidative stress, and systemic inflammation. Ferroptosis, an iron-dependent form of regulated cell death triggered by lipid peroxidation, has recently been proposed as a potential contributor to the tissue injury observed in OSAS. OSAS appears to aggravate disturbances in iron homeostasis and oxidative imbalance, both of which may converge to exacerbate disease pathophysiology. However, the precise mechanisms linking ferroptosis to OSAS remain largely speculative. Emerging evidence from experimental studies indicates that ferroptosis-related genes and pathways might be involved in the cardiovascular, neurological, and renal complications associated with OSAS. This review summarizes current knowledge regarding oxidative stress and iron metabolism under intermittent hypoxia, explores the potential regulatory mechanisms of ferroptosis, and discusses its hypothesized contribution to OSAS-related organ injury. While targeting ferroptosis may represent a promising research direction, the current evidence remains preliminary and predominantly experimental. Further mechanistic and clinical investigations are essential to clarify whether ferroptosis plays a causal role in OSAS pathogenesis and to evaluate its translational relevance.

Keywords: obstructive sleep apnea syndrome, ferroptosis, oxidative stress, iron metabolism, inflammation, cardiovascular disease, neurodegeneration

Introduction

Obstructive Sleep Apnea Syndrome (OSAS) is a well-known multifactorial condition characterized by intermittent obstruction of the upper airway during sleep, leading to repeated episodes of hypoxemia, hypercapnia, and disrupted sleep patterns. Although OSAS is a significant concern due to its disruptive impact on sleep quality, an increasing number of studies emphasize its systemic effects, which contribute to the development of various comorbidities, including cardiovascular diseases, metabolic disorders, and neurocognitive impairments, among others.[1–3] While substantial progress has been made in understanding the epidemiological relationships between OSAS and these associated conditions, the underlying pathobiological mechanisms remain poorly understood. Recent studies have highlighted ferroptosis, an iron-dependent form of regulated cell death driven by lipid peroxidation, as potentially playing a significant role in the pathophysiology of OSAS.

Ferroptosis, first described in 2012, has recently emerged as a crucial form of regulated cell death implicated in multiple pathological processes, including cancer, neurodegenerative diseases, and cardiovascular disorders.[4] It is characterized by the accumulation of reactive oxygen species (ROS) and lipid peroxides, leading to oxidative injury and cell death in tissues exposed to elevated oxidative stress. Increasing evidence suggests that ferroptosis may contribute to the pathogenesis of obstructive sleep apnea syndrome (OSAS), particularly in organs subjected to intermittent hypoxia, such as the brain, heart, and kidneys.[5–7] However, despite growing interest, current understanding of the role of ferroptosis in OSAS remains limited. Only a few studies have investigated the mechanisms through which ferroptosis influences disease progression or affects clinical outcomes. Although alterations in oxidative stress and iron metabolism, as well as ferroptosis-related biomarkers, have

Received: 30 June 2025
Accepted: 18 October 2025
Published: 22 November 2025

been identified in OSAS patients,[8–10] existing research remains fragmented and inconclusive. The exact mechanisms by which hypoxia in OSAS induces ferroptotic cell death are still unclear. Some studies propose that hypoxia directly triggers ferroptosis, whereas others suggest that ferroptosis arises secondary to chronic inflammation, metabolic imbalance, or cellular dysfunction. Moreover, the interactions among these mechanisms are poorly understood, and whether ferroptosis serves as a primary driver or a secondary consequence in the pathophysiology of OSAS remains an open question under active investigation.

Herein, this review aims to critically examine ferroptosis as a potential pathophysiological mechanism contributing to the development of obstructive sleep apnea syndrome (OSAS), an area that remains largely unexplored compared with its well-documented involvement in other diseases. By highlighting the intersection between ferroptosis and OSAS, we seek to provide new insights into potential therapeutic targets that may attenuate disease progression and improve patient outcomes. Our objective is to enrich the existing body of knowledge and establish a coherent framework to guide future investigations into the role of ferroptosis in the pathogenesis of OSAS, ultimately facilitating the development of novel treatment strategies. Through this review, we also aim to offer practical perspectives on how clinical interventions can be designed and optimized to advance the field and contribute to more effective management of this debilitating and prevalent disorder.

Literature Search Strategy

Our literature search systematically covered PubMed, Web of Science, and Embase from January 2012, when the concept of ferroptosis was first introduced, to March 2025. Search terms included ferroptosis, iron-dependent cell death, and lipid peroxidation in combination with obstructive sleep apnea, OSA, or intermittent hypoxia, restricted to peer-reviewed English-language publications. Both experimental and clinical studies investigating the role of ferroptosis in obstructive sleep apnea or its related comorbidities were eligible for inclusion. Two reviewers independently screened titles, abstracts, and full texts to determine eligibility, with discrepancies resolved through discussion and, when necessary, consultation with a third reviewer. Methodological quality and risk of bias were assessed using established criteria adapted from the PRISMA framework and the Newcastle–Ottawa Scale, ensuring consistency, reproducibility, and transparency across the synthesis.

Mechanisms of Ferroptosis

Ferroptosis is a programmed form of cell death, which utilizes the synthesis of lipid peroxides with accumulation level leading to lethality varying on the existence of iron. It has also been determined that this cell death is distinct to other cell death responses which include apoptosis, necrosis and autophagy, both with respect to the molecular facet of the triggering mechanism and execution. Recent research resulted into a clearer picture on the molecular mechanisms underlying ferroptosis that are primed by central roles of the iron metabolism, lipid peroxidation and antioxidants defenses systems.[11–13] However, in the light of major progressions, the full mechanistic approach towards ferroptosis will not scale the challenge and numerous fronts of its regulation, interaction with other cascades associated with cell death, in addition to its role in various pathologies, will remain open. Cellular iron homeostasis disequilibrium is the earliest documented ferroptosis. Being a transition metal, iron takes a leading position in all of the numerous biological processes in addition to being very reactive that also facilitates the generation of reactive oxygen species (ROS) through the Fenton reaction. In ferroptosis, the accumulation of iron causes lipid peroxidation to become high, where a process in which unsaturated fatty acids in cellular membranes are oxidized thus obtaining toxic lipid peroxides becomes a possibility. These lipid peroxides result in cell death and membrane rupture, indicating that ferroptosis is executed. Iron plays the vital role of catalyzing the process of formation of these peroxides, and iron homeostasis is important as a regulatory junction in ferroptosis (Figure 1).

Iron Metabolism and Ferroptosis Regulation

Glutathione peroxidase 4 (GPX4) is widely recognized as a crucial regulator of ferroptosis, as it utilizes glutathione (GSH) as a cofactor to convert lipid hydroperoxides into non-toxic lipid alcohols. Experimental inhibition or depletion of GPX4 has been shown to promote ferroptotic-like cell death in various cell types, supporting its role in modulating lipid peroxidation and cellular susceptibility to oxidative injury.[14–17] Recent studies have also identified other enzymes involved in lipid peroxidation processes—such as acyl-CoA synthetase long-chain family member 4 (ACSL4) and

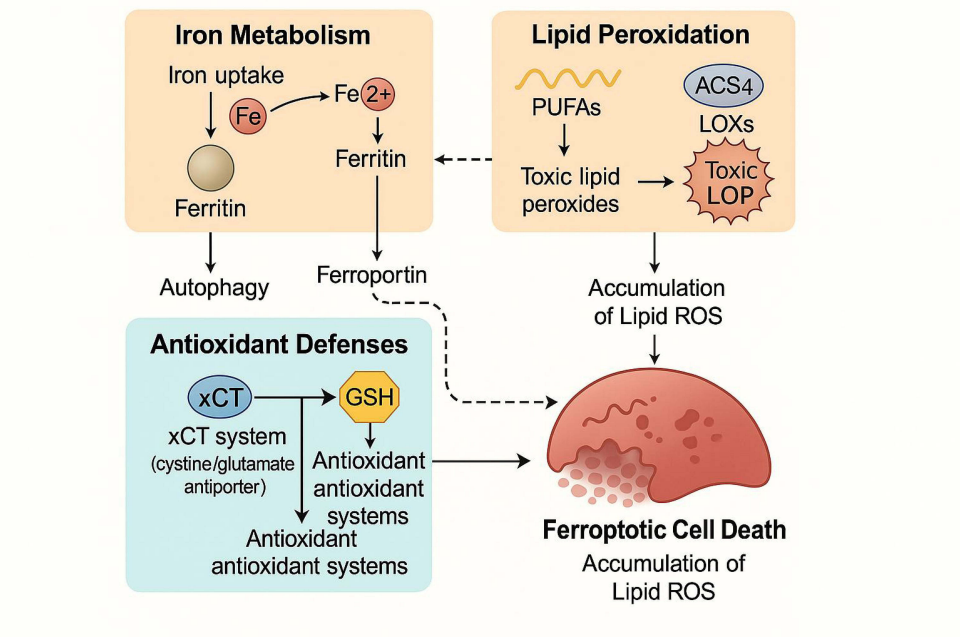

Figure 1 Schematic representation of the mechanisms of ferroptosis. Ferroptosis is an iron-dependent form of regulated cell death driven by lipid peroxidation of cellular membranes. Iron is imported as Fe^{3+} via the transferrin receptor and reduced to Fe^{2+} in endosomes by the divalent metal transporter 1 (DMT1). Fe^{2+} can participate in the Fenton reaction, converting into Fe^{3+} and generating reactive oxygen species (ROS), which initiate lipid peroxidation. Lipoxygenases (LOXs) and ACSL4 further promote lipid peroxidation by incorporating polyunsaturated fatty acids (PUFAs) into phospholipids (PL), generating lipid hydroperoxides (LOOH). Glutathione peroxidase 4 (GPX4) is the primary cellular defense mechanism against lipid peroxidation, reducing lipid hydroperoxides to their non-toxic alcohol forms. In the presence of high extracellular glutamate, system xCT is inhibited, reducing cystine import and thereby glutathione (GSH) synthesis. This depletion of GSH impairs GPX4 function, exacerbating lipid peroxidation. Inhibitors such as erastin, sorafenib, and glutamate inhibit system xCT, while RSL3, ML162, and FIN56 inhibit GPX4, leading to the induction of ferroptosis.

lipoxygenases (LOXs)—which participate in generating lipid peroxides associated with ferroptotic mechanisms.[18–20] In particular, ACSL4 facilitates the incorporation of polyunsaturated fatty acids (PUFAs) into phospholipids, including arachidonic and adrenic acids, making cellular membranes more prone to oxidative damage and ferroptosis-associated lipid peroxidation.[21–23]

Although the roles of iron and lipid peroxidation in ferroptosis have been extensively studied, recent evidence suggests that the regulation of ferroptosis may be more complex and closely associated with iron metabolism rather than being solely dependent on it. Ferroportin, the only known iron exporter, plays a central role in maintaining intracellular iron balance, and its activity has been reported to alleviate ferroptosis by limiting iron accumulation.[24–26] Furthermore, the involvement of ferritin, an intracellular iron storage protein, has been linked to ferroptosis regulation through a process known as ferritinophagy—selective autophagy of ferritin that releases stored iron into the cytoplasm, thereby promoting the Fenton reaction and lipid peroxidation. Liu et al demonstrated that ferroptosis-like responses could be induced in epithelial (BEAS-2B) and macrophage (RAW264.7) cells through NCOA4-mediated ferritinophagy and ferroportin (FPN) inhibition, emphasizing the contribution of ferritin degradation and iron release to ferroptotic signaling.[27] Moreover, a newly identified ferroptosis inhibitor, compound 9a, was shown to act on NCOA4 by disrupting the NCOA4–FTH1 interaction, thereby reducing ferroptosis (Fang et al). Collectively, these findings indicate that the regulation of ferroptotic cell death is closely associated with iron homeostasis and oxidative balance, although the specificity of common oxidative stress markers such as GPX4 and ferritin as definitive ferroptosis indicators remains limited and should be interpreted with caution.

Antioxidant Defense Mechanisms in Ferroptosis

Another important aspect of ferroptosis regulation involves the cellular antioxidant defense systems. Among these, the glutathione (GSH)-dependent pathway, particularly involving glutathione peroxidase 4 (GPX4), has been extensively

studied for its association with ferroptotic processes. GSH, a tripeptide composed of glutamate, cysteine, and glycine, functions as a major cellular antioxidant. Imbalance within this system—such as GSH depletion accompanied by insufficient GPX4 activity—has been correlated with increased lipid peroxidation and ferroptosis-related oxidative injury. The transport of cystine into cells via the cystine/glutamate antiporter system (xCT) is essential for GSH synthesis; inhibition of this system can reduce intracellular GSH levels and sensitize cells to ferroptotic damage. Conversely, pharmacological agents that promote xCT activity or enhance GSH biosynthesis have been shown to modulate ferroptosis sensitivity and may represent potential therapeutic strategies in diseases where ferroptosis contributes to pathology, including cancer. For instance, Zhang et al reported that targeting xCT and GSH biosynthesis pathways could influence ferroptosis and help overcome drug resistance in liver cancer treatment.[28]

Nevertheless, ongoing discussion continues regarding the relative importance of GSH depletion compared with the oxidation of other antioxidants, such as thioredoxin and vitamin E, in influencing ferroptosis susceptibility. Evidence suggests that GSH depletion alone may not be sufficient to induce ferroptosis, and additional antioxidant systems may also play complementary roles. The thioredoxin reductase (TrxR)–thioredoxin system has been implicated as a potential regulator of ferroptosis, with its inhibition shown to aggravate lipid peroxidation in specific cell models.[29–31] Similarly, vitamin E has been observed to attenuate lipid peroxidation and ferroptosis-like responses, whereas its inhibition enhances oxidative injury.[32–34] Collectively, these findings suggest that ferroptosis regulation depends on the interplay among multiple antioxidant systems, and therapeutic strategies targeting more than one antioxidant pathway may prove more effective in modulating ferroptosis-related cellular damage.

Ferroptosis and Other Cell Death Pathways

Ferroptosis is not a solo process as it is not independent of the mechanisms of controlled cell death that include their interaction with apoptosis, necroptosis and autophagy. The interaction between the two pathways is a complicated and situation-specific circumstance. This is because in other situations ferroptosis can also serve as a form of reserve process during the impairment of apoptosis as observed in certain cancerous cells that have developed resistance to the apoptotic signals.[35–37] Conversely, the necroptosis pathway that is mediated by the receptor-interacting protein kinase (RIPK) family has been indicated to be engaged with ferroptosis under specific conditions, specifically during ischemia-reperfusion injury.[38] Interestingly, it has been proposed in the literature that the prevention of necroptosis can increase ferroptosis, and this could be a viable therapeutic approach in diseases where one or the other of these has been appreciated.[39] Nonetheless, the mechanisms participating in this crosstalk are yet to be very well comprehended and need exploration. Ferroptosis/autophagy interaction is also another valuable area of study. Also, the recent research indicated that autophagy might facilitate ferroptosis by breaking down ferritin via ferritinophagy hence releasing iron and promoting the accumulation of lipid peroxides.[40,41] Nevertheless, alternative publications suggest that autophagy can be used as a protective mechanism against ferroptosis by removing cellular damage by removing organelles and avoiding the accumulation of iron in a toxic form.[42] Such a two-ching role of autophagy in ferroptosis is a paradox that should be overcome in subsequent research.

Although there has been great progress in the realization of ferroptosis, there are still some missing links. To begin with, there are not yet any specific and reliable biomarkers of ferroptosis due to human diseases. Although animal models have given relevant results, there have been challenges when applying the results to the clinical practices. Second, the molecular pathways controlling the exact time and spatial localization of ferroptosis in the tissues and organs are not fully comprehended. A tissue specificity to ferroptosis sensitivity partiality in research would enable further therapeutic approaches. Third, a promising but insufficiently analyzed future venue is the possibly unlimited combination of ferroptosis modulation with an already known therapy into chemotherapy/immunotherapy. Ferroptotic inhibition has the benefit of activating tumor cells to chemotherapy, but ferroptosis in normal tissues will need a dedicated focus to prevent off-target cell toxicity. To sum up, the processes of ferroptosis are associated with a complex interaction of the metabolism of iron, lipid peroxidation, and the antioxidant defense. Although great advances have been achieved in determining the most relevant players and molecular pathways discussed, lots to be learned remains, including how it crosstalk with other types of cell death and its impact in the context of disease. The control of ferroptosis, at molecular and tissue scales, and establishment of reliable biomarkers and interventions to combat the disease is vital to convert all the capabilities of ferroptosis into a useable tool to treat diseases.

Ferroptosis and OSAS

The concept of ferroptosis, where the absence of ions such as iron regulates cell death, was increasingly created by overindulgence of lipids peroxidation, and non-apoptotic cell death has become an important entity in an array of pathological settings. The recent literature has proposed an interesting connection between ferroptosis and Obstructive Sleep Apnea Syndrome (OSAS), the disease that includes episodes of intermittent hypoxia attacks, oxidative stress, and resultant cell dysfunction.[7,8,43] Though a promising relationship, it remains unexplained with a number of unanswered questions, controversies and gaps in knowledge which are threatening to the establishment of specific, curative interventions. The objectives of this section include synthesised major advances in the field of research, comparision of the correlation among various findings and critical assessment on the possibility of ferroptosis serving as a therapeutic mode of action in OSAS.

Mechanisms Linking Intermittent Hypoxia and Ferroptosis

The connection between OSAS and ferroptosis appears to be closely associated with the pathophysiological consequences of intermittent hypoxia (IH), particularly its effects on oxidative stress, sympathetic activation, inflammation, and metabolic dysregulation (Figure 2). IH-induced cycles of hypoxia and reoxygenation are known to trigger excessive production of reactive oxygen species (ROS), sympathetic overactivation, and systemic inflammatory responses, which together create a cellular environment favorable to ferroptotic injury. Elevated ROS levels disrupt antioxidant defenses, including glutathione peroxidase 4 (GPX4) activity and the cystine/glutamate antiporter system (xCT), thereby disturbing redox homeostasis and promoting lipid peroxidation and ferroptosis-related cellular damage.[44] For instance, Cai et al demonstrated that IH exposure in HepG2 and LO2 cells led to significant accumulation of lipid peroxides,[10] while rodent models of IH displayed increased lipid peroxidation, reflected by higher levels of malondialdehyde (MDA)—a marker of oxidative stress and lipid damage—under these conditions.[7–9,45,46] These results collectively suggest that ferroptosis may act as a downstream amplifier of IH-driven oxidative injury, linking OSAS-related oxidative stress to broader pathophysiological processes such as vascular dysfunction, sympathetic excitation, and metabolic impairment.

However, the precise mechanisms underlying this interaction remain debated. Other studies have proposed that intermittent hypoxia–related cellular injury may also involve mitochondrial dysfunction, apoptosis, and glutathione (GSH) depletion rather than direct iron overload.[47–56] For example, Wang et al hypothesized that ferroptosis-like cell death in OSAS could primarily result from GSH depletion rather than iron accumulation.[56] These insights underscore the

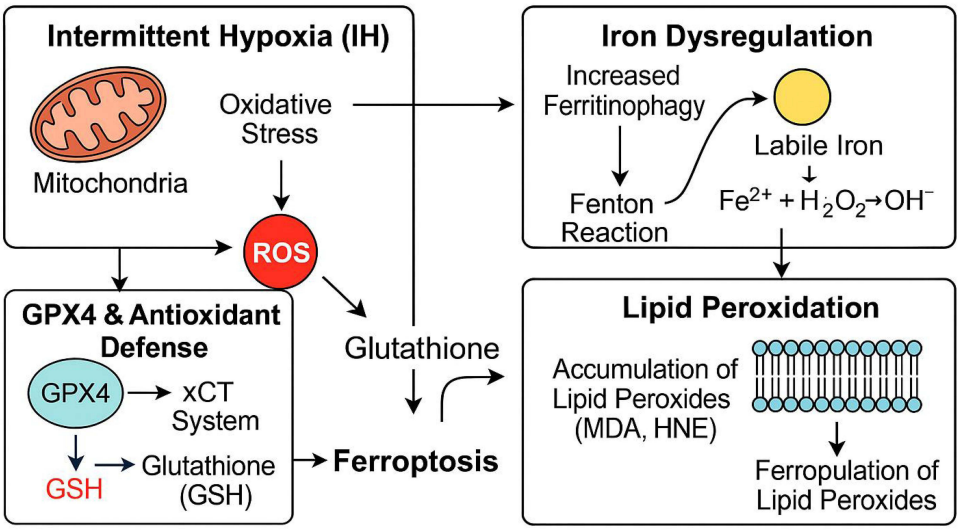

Figure 2 Mechanism of Ferroptosis in OSAS. Intermittent hypoxia (IH) induces oxidative stress, generating reactive oxygen species (ROS) that overwhelm cellular defenses. Iron dysregulation, through increased ferritinophagy and labile iron, triggers the Fenton reaction, producing hydroxyl radicals. These ROS, coupled with reduced GPX4 activity and compromised antioxidant defense (eg, depleted glutathione), lead to lipid peroxidation. The accumulation of lipid peroxides, such as MDA and HNE, drives ferroptosis, contributing to cellular dysfunction in OSAS.

https://doi.org/10.2147/NSS.S549883

multifactorial nature of OSAS pathophysiology and indicate that ferroptosis may intersect with established pathways—oxidative stress, inflammation, and metabolic dysregulation—to exacerbate tissue damage. Further studies are needed to delineate the precise molecular interplay and to clarify the conditions under which iron-dependent lipid peroxidation contributes to ferroptotic signaling within the broader OSAS framework.

Iron Homeostasis and Its Role in Ferroptosis in OSAS

The redistribution of iron has a central role in ferroptosis because iron serves as a catalyst in the Fenton reaction so as to produce highly reactive hydroxyl radicals. A number of trials have been conducted uncovering the influence of barrel iron mal-regulation in OSAS on how intermittent hypoxia (IH) might impact iron menu, transfer, and usage.[57–60] Eg, it was found that the ferritinophagy, a pathway leading to mobilization of iron in the ferritin storage sites has increased in the cells exposed to intermittent hypox and has been described.[61–63] This will lead to increased labile iron pool and may induce ferroptosis. Studies conducted by Christopher et al and Cheng et al showed that the OSAS patients had a higher ferritin levels, and it may be adapted that the accumulation of iron and the effect of OSAS against the cells may be connected.[64,65]

Nevertheless, it should be mentioned that although ferritin and other indicators of oxidative stress such as MDA are usually high in OSAS, they are not to be used fully across the board. High ferritin and MDA traces are not a specific predictors of ferroptosis, even their presence cannot be definitely taken as an indicator of ferroptosis. Indeed, the research studies have indicated discrepant findings on the relationship between ferritin concentrations and ferroptosis in OSAS. To illustrate, Thorarinsdottir et al discovered that there is no significant relationship between the level of ferritin and severity of OSAS.[66] This leaves the possibility that other causes, including the redox changes or the initiation of other cell death mechanisms as a result of hypoxia may also have a major role. Therefore, iron dysregulation is probably a contributor in OSAS, but more studies are required to understand why these biomarkers reflect ferroptotic mitosis and not the oxidative stress directly.

GPX4 and Antioxidant Defense in OSAS

Glutathione peroxidase 4 (GPX4) is an important antioxidant enzyme that plays a critical role in neutralizing lipid peroxides and maintaining redox homeostasis. Its activity helps regulate oxidative stress and has been linked to ferroptosis, an iron-dependent form of regulated cell death. In OSAS, where oxidative stress is markedly elevated, a reduction in GPX4 activity may increase cellular vulnerability to oxidative injury and ferroptosis-related processes. Intermittent hypoxia and subsequent reoxygenation cycles are the primary drivers of oxidative stress in OSAS, promoting excessive generation of reactive oxygen species (ROS). Several studies have suggested that under hypoxic conditions, the expression of GPX4 in different tissues may be downregulated, accompanied by elevated lipid peroxidation, thereby contributing to cellular oxidative damage potentially associated with ferroptosis.[67–71] Liu et al further reported that plasma GPX4 levels in patients with OSAS were significantly lower than those in healthy controls, which correlated with increased markers of oxidative injury.[72] Although these findings imply that dysregulation of GPX4 could play a role in OSAS-related oxidative damage, it should be emphasized that GPX4 activity—similar to ferritin and malondialdehyde (MDA)—serves as a general indicator of oxidative stress rather than a specific biomarker of ferroptosis.

Other antioxidant defense systems, including superoxide dismutase (SOD), catalase (CAT), and thioredoxins, also contribute to cellular protection against oxidative damage in OSAS alongside GPX4. Impairment of these systems may further enhance susceptibility to ferroptosis-associated oxidative injury, though their relative contributions require clarification through future studies. Furthermore, while lipid peroxidation repair is dependent on GPX4, the overall redox balance also involves interactions among intracellular glutathione (GSH) levels and the cystine/glutamate antiporter system (xCT). Elevated glutamate levels-a characteristic finding in OSAS-may inhibit xCT function, reducing GSH synthesis and, consequently, diminishing GPX4 activity. This cascade may increase oxidative stress and promote ferroptosis-related damage; however, more comprehensive research is needed to delineate the precise molecular links between these processes.

In conclusion, while GPX4, ferritin, and MDA are valuable biomarkers for assessing oxidative stress, they should not be interpreted as specific or definitive indicators of ferroptosis in OSAS. Further targeted investigations are warranted to

clarify the relationship between oxidative stress–related biomarkers and ferroptosis mechanisms and to identify more specific molecular indicators capable of distinguishing ferroptosis from other forms of cell death and oxidative injury in OSAS.

Lipid Peroxidation: A Critical Link Between Ferroptosis and OSAS

Lipid peroxidation is another crucial process in ferroptosis that has been involved in an ever-growing number of studies on OSAS pathophysiology. Polyunsaturated fatty acids (PUFAs) are prone to exporting oxidative damages to cell membranes in the case of chronic IH due to their high concentration. This is based on the fact that the elevated levels of MDA and 4-hydroxy-2-nonenal (HNE) that are identified as the biomarkers of lipid peroxidation are reported in OSAS models.[73–76] During oxidative stress, specific PUFAs are peroxidated, such as arachidonic acid (AA) and docosahexaenoic acid (DHA), and are involved in ferroptosis,[77,78] although other lipids could also be involved, including eicosapentaenoic acid (EPA) and linoleic acid.[79,80] Disturbed phospholipids also destroy membrane integrity, which is also a feature of ferroptotic death.[81,82]

Notably, according to OSAS, lipid peroxidation does not work alone. Mitochondrial dysfunction and autophagy can enhance ferroptosis through increases in iron uptake, perpetuation of oxidative distress and mitochondrial peroxidated lipid and damage turnover.[83,84] Based on this interaction, we put forward that it is a multifactorial process, in which the presence of lipid peroxidation is a major and not the sole event. Future studies should involve high-resolution lipidomics to identify the species of lipids driving ferroptosis in OSAS and establish the relationship between these processes and mitochondrial and autophagic processes. These may provide indications of a therapeutic measure to reduce the disorders induced by OSAS such as cardiovascular and neuro degenerative diseases.

Diagnostic and Therapeutic Implications

The previous years saw the diagnostic and therapeutic settings of the obstructive sleep apnea syndrome (OSAS) transformed in numerous ways considering the new trends in molecular biology, diagnostic imageries as well as the treatment process itself. Its fundamental problems, particularly, the integration of new instruments of observation during the clinical procedure and the development of personalized methods of dealing with diseases with which considerable long-term and credible effects are achieved, exist. The new dimension of the disease management also arrives through the disease pathophysiological findings recently, Ferroptosis as a type of regulated cell death that is associated with oxidative stress and iron imbalances is a recent addition to the newly developed reality of the OSAS treatment. The paper gives a review of the recent and most impactful research on ferroptosis in OSAS that have its research results that remain unanswered and those that have potential to give a stepping stone. Although the discovery of using biomarkers including lipid peroxidation products and iron-related signals has potential on this issue in early diagnosis, clinical usefulness should be supported by additional investigations. Moreover, in spite of successfully building up evidence on ferroptosis inhibitors and modulators in preclinical trials, their clinical implementation is still unclear. The major gaps and controversies including the most effective targets of therapeutic activities, safety issues, oxidative stress modulation deserve additional investigation to optimize the therapeutic applications and improve the patient outcomes.

Diagnostic Advances

Obstructive sleep apnea syndrome (OSAS) is a common sleeping illness which is typified by repeated blockage of the upper airways at the time of sleeping, consequently causing random hypoxemia and hypercapnia conditions. Even though the field of diagnostics has developed issues with major progress over the years, OSAS is still underdiagnosed, particularly when the patients have light symptoms. Classic medical instruments, including an overnight polysomnography (PSG), have become the gold standard but they are both expensive and time-intensive and in some health care environments are unavailable. It has promoted other diagnostic techniques like home sleep apnea testing (HSAT) examined, and portable monitoring gadgets. Such approaches provide more convenient effective but cheaper solution which is often not as diagnostic as PSG, or more diagnostic but general in multiple comorbidities or similarly demanding cases. Even though they are convenient and practical, HSATs and handheld devices might fail to support finding subtle changes in the sleeping behavior and the findings cannot be entirely trusted to identify the entire band of OSAS severity.

To address these problems, the search of non-invasive OSAS biomarkers has become more heated. Of growing importance are those biomarkers which are responsible of reflecting the underlying pathophysiology of OSAS, especially the ones concerned with oxidative stress, systemic inflammation and tissue destruction. As a potential biomarker development candidate, Ferroptosis has become an impressive promising alternative of cellular death pathway. Clinicians can be in a position to identify the biomarkers of ferroptosis in body fluids like blood, saliva, exhaled breath condensate, in order to be able to detect OSAS at an earlier stage even in its mild stage and detect the advancement of the disease more accurately.

The lipid peroxidation products, reactive oxygen species (ROS), and proteins pertinent to the iron metabolism are the characteristic biomarkers of ferroptosis, including ferritin, transportrin, and iron regulatory proteins (Table 1). Table 1 lists biomarkers that are associated with ferroptosis in OSAS but some are speculative or experimental. The reviewer notes that this might overstate the clinical utility of these biomarkers. To address this, we should add a comment in the text that highlights the current limitations of these biomarkers and their status in clinical practice. The IH revealed elevated levels of lipid peroxides

Table 1 Ferroptosis-Related Diagnostic Biomarkers in OSAS

Biomarker	Description	Measurement Method	Clinical Relevance
Lipid Peroxidation Products (eg, 4-Hydroxynonenal, 4-HNE)	Products of lipid peroxidation, particularly 4-HNE, are indicators of oxidative stress and have been linked to OSAS severity. Elevated levels are observed in OSAS patients.	Can be measured in blood, urine, or exhaled breath condensate. Commonly detected through mass spectrometry, ELISA, or NGS.	Lipid peroxidation products, especially 4-HNE, are correlated with the severity of OSAS. Elevated levels can indicate higher oxidative stress and tissue damage.
Reactive Oxygen Species (ROS)	Reactive molecules formed when oxygen interacts with tissues, contributing to oxidative damage in OSAS. ROS levels may correlate with disease progression and severity.	Typically measured in blood or serum using advanced techniques like chemiluminescence assays or fluorescence-based assays.	ROS production is a hallmark of oxidative stress and is directly linked to cellular damage in OSAS. It serves as a general marker for oxidative stress.
Ferritin	An iron storage protein that increases in response to oxidative stress. Higher ferritin levels may indicate increased oxidative stress in OSAS patients.	Measured in blood or serum using ELISA or immunoturbidimetric assays.	Elevated ferritin levels are often seen in OSAS patients due to systemic inflammation and oxidative stress. It can be a reliable marker for disease severity and comorbidities.
Transferrin	A protein involved in iron transport. Elevated transferrin levels can indicate systemic oxidative stress and iron dysregulation in OSAS.	Measured in blood or serum using ELISA or immunoturbidimetric assays.	Transferrin levels, linked to iron metabolism and oxidative stress, may serve as an indicator of OSAS-related organ damage, especially in the cardiovascular and neurological systems.
Iron Regulatory Proteins (eg, Ferroportin, Hephaestin)	Proteins regulating iron homeostasis, including Ferroportin and Hephaestin, are involved in iron uptake and export. Dysregulation of these proteins is linked to oxidative damage in OSAS.	Quantified in blood or tissue samples through immunoassays, including Western blot and ELISA.	Dysregulated iron homeostasis, reflected by changes in iron regulatory proteins, may indicate ongoing ferroptosis and contribute to organ dysfunction in OSAS.
Exhaled Nitric Oxide (NO)	Exhaled NO is a marker of oxidative stress in the lungs and may be used for real-time, non-invasive monitoring of OSAS-related oxidative damage.	Detected in exhaled breath using nitric oxide sensors, providing a real-time, non-invasive diagnostic tool.	Exhaled NO can be used to monitor lung-specific oxidative stress in OSAS, providing a quick and non-invasive method to assess disease progression.
Glutathione Peroxidase 4 (GPX4)	An antioxidant enzyme that plays a central role in preventing ferroptosis by reducing lipid peroxides. Decreased GPX4 activity may indicate ferroptosis and OSAS-related organ damage.	Measured in blood or tissue samples, primarily through ELISA or Western blot assays.	GPX4 is a key antioxidant enzyme that protects against ferroptosis. Reduced GPX4 activity in OSAS can indicate organ damage, particularly in the brain and heart.

(*Continued*)

Table 1 (Continued).

Biomarker	Description	Measurement Method	Clinical Relevance
Malondialdehyde (MDA)	MDA is a reactive product of lipid peroxidation and a widely used marker of oxidative stress. Increased MDA levels correlate with the severity of OSAS and related complications.	Measured in blood or urine using thiobarbituric acid-reactive substance (TBARS) assays, or by mass spectrometry.	MDA is a well-established marker for oxidative stress and can be used to track disease severity and progression in OSAS patients.
Iron (Fe2+ and Fe3+)	Iron in its reduced (Fe2+) and oxidized (Fe3+) states plays a critical role in ferroptosis. Abnormal iron accumulation has been associated with oxidative stress and OSAS progression.	Measured through blood tests, including serum iron tests and total iron-binding capacity (TIBC), or tissue biopsies.	Abnormal iron levels in OSAS are associated with tissue damage and ferroptosis. Iron dysregulation can be linked to oxidative damage in various organs.
Apolipoprotein E (ApoE)	A protein involved in lipid metabolism and inflammation, ApoE has been shown to modulate ferroptosis by influencing oxidative stress responses in neurological tissues.	Quantified in serum or tissue samples using immunoassays or Western blot analysis.	Apolipoprotein E (ApoE) has been linked to lipid metabolism and ferroptosis. Its role in the pathogenesis of OSAS, particularly in neurodegeneration, is under investigation.
Lipid Hydroperoxides	Lipid hydroperoxides are products of lipid peroxidation and are key intermediates in the ferroptosis pathway. Elevated levels are found in OSAS-related oxidative damage.	Measuring lipid hydroperoxides through mass spectrometry or specific ELISA tests.	Lipid hydroperoxides are intermediates in lipid peroxidation that directly contribute to ferroptosis. Elevated levels indicate cellular damage in OSAS.
Tissue Iron Distribution (Ferritin, Hemosiderin)	Tissue iron distribution, indicated by ferritin and hemosiderin, reveals iron accumulation in tissues. Increased tissue iron is associated with oxidative stress and ferroptosis in OSAS.	Tissue samples can be examined for iron deposition using histological staining (eg, Perl's Prussian blue stain) or serum tests for ferritin.	Tissue iron distribution provides insights into iron overload and its association with oxidative stress in OSAS-related organ damage.
Cysteine and Cystine	Cysteine and cystine are involved in the regulation of oxidative stress and ferroptosis. Imbalances in their levels can reflect cellular redox state and indicate OSAS-related stress.	Cysteine and cystine levels can be assessed in plasma or serum using HPLC or mass spectrometry.	Changes in cysteine and cystine levels may indicate a disruption in redox balance, suggesting increased oxidative stress in OSAS patients.
p53 Protein	p53, a tumor suppressor protein, is involved in the regulation of ferroptosis. Its role in OSAS-related oxidative stress and cellular damage has been under investigation.	p53 levels can be measured using ELISA, Western blot, or immunohistochemistry.	p53 is involved in regulating oxidative stress and ferroptosis. Elevated p53 activity in OSAS may indicate severe cellular damage and disease progression.
Prostaglandin Endoperoxide Synthase 2 (COX-2)	COX-2 is an enzyme involved in inflammation and oxidative stress. Elevated levels of COX-2 in OSAS tissues indicate the role of inflammation in ferroptosis.	COX-2 expression can be quantified using immunohistochemistry, ELISA, or Western blot.	COX-2 is a key player in inflammation and oxidative stress. Its elevated levels in OSAS suggest a strong link between inflammation and ferroptosis.

especially 4-hydroxynonenal (4-HNE) which are associated with severity of OSAS. Also, the indicators of iron metabolism, such as ferritin and transferrin, can indicate the presence of systemic oxidative stress and ferroptosis in OSAS.[60,64,66,85] These biomarkers may be quantified in blood, urine, or even exhaled breath condensate, and are more accurate and real time and non-invasive form of diagnosing OSAS and measuring disease progress.

The high-throughput technologies can be useful to detect the biomarkers of ferroptosis in OSAS. The techniques by which they can determine and measure the signs of oxidative stress and iron transporting proteins are mass spectrometry, elevation of linked immunosorbent assessment (ELISA), and next-generation-sequencing (NGS).[86–89] The technologies are a sound

foundation in the detection of the biomarkers of ferroptosis process in clinical conditions. Also, the new opportunities to analyse OSAS through the means of portable diagnostic features that could evaluate oxidative stress, as well as revise this evaluation in real-time, generate exciting opportunities.[90–92] Suggestively, computer-aided and prompt diagnosis of OSAS can be conducted by making use of such sensors that establish exhaled nitric oxide (NO), level: a biomarker of oxidative stress.[93] With the assistance of such gadgets, the patients will be able to monitor their health at home as it would be convenient and determine to intervene in a timely manner. Another potentially promising direction is the implementation of the use of artificial intelligence (AI) and machine learning (ML) to process sophisticated diagnostic data.[94–97] The application of AI algorithms could provide a higher level of predicting the OSAS risk and severity when combining clinical and molecular data and ferroptosis-related biomarkers. Use of such technologies could assist in diagnosing OSAS at a more gestative level, and also assist in detecting those who are those who are at risk of developing comorbid conditions (eg cardiovascular disease or stroke).

Ferroptosis biomarkers could be considered as potentially valuable in terms of their application in the future as a part of the OSAS diagnostic algorithm such that the likelihood of early disease detection and management would be enhanced. It is therefore recommended that future research be carried out on validating these biomarkers using large cohort studies in order to determine the diagnostic accuracy and clinical relevance of these biomarkers. Moreover, the role of ferroptosis in organ damage under OSAS and, especially in the cardiovascular and neurological systems, will be necessary to understand the outcome in the long-term and inform treatment procedures. A combination of diagnostic technologies with the use of ferroptosis-related biomarkers may potentially reduce the difference in individualization of the process of diagnosing and treating OSAS. With the help of the integration of molecular markers and conventional methodologies such as PSG and HSAT, clinicians will be able to design interventions depending on the more relevant idea of the patient state. Such a case-based practice may elevate treatment stabilizations and save patient revenue expenses besides increasing the life expectancy of patients having OSAS.

Therapeutic Developments

Iron chelators are among the principal therapeutic strategies currently under investigation for mitigating ferroptosis in OSAS. Ferroptosis is initiated by intracellular iron overload, which stimulates the production of reactive oxygen species (ROS) and lipid peroxides. Free iron may be bound by chelating agents such as deferoxamine and ciclopirox, thereby preventing oxidative damage by inhibiting ferroptosis. Iron chelators can theoretically be useful in preventing ferroptotic injury under OSAS conditions, where recurrent hypoxia–reoxygenation cycles promote iron accumulation. However, there is limited clinical evidence to support this approach; current preclinical findings suggest that such agents may attenuate iron-induced oxidative injury in neuronal and cardiovascular tissues commonly affected by chronic hypoxia.[45] Nonetheless, issues of bioavailability, dosing, and targeted delivery remain major translational challenges in clinical contexts.

In parallel, antioxidants targeting lipid peroxidation have emerged as another promising but largely preclinical approach. Since lipid peroxidation is a key step in ferroptosis, the use of ferrostatin-1 and liproxstatin-1 has demonstrated protective effects in experimental models. These compounds stabilize cellular membranes and decrease lipid peroxide accumulation, and may theoretically reduce intermittent hypoxia–induced oxidative stress in the brain, heart, and kidneys.[48,98–101] Nevertheless, these observations are confined to preclinical studies, and their clinical feasibility and safety in OSAS remain unproven. Glutathione peroxidase 4 (GPX4), a critical enzyme that inhibits lipid peroxidation, represents another potential therapeutic target. Small-molecule modulators such as RSL3 have shown efficacy in controlling GPX4 activity and ferroptotic cell death in neuronal and cardiovascular models.[102–107] While modulation of GPX4 activity could, in theory, mitigate OSAS-related oxidative injury, the therapeutic translation of GPX4 modulators remains at an early, exploratory stage.

Beyond direct ferroptosis inhibition, modulation of inflammatory cascades that exacerbate oxidative stress may represent an adjunctive strategy. Recurrent hypoxia in OSAS activates cytokines such as TNF-α, IL-6, and IL-1β,[108–110] which are known to facilitate ferroptotic processes. Pharmacological blockade of these cytokines using monoclonal antibodies has proven effective in other inflammatory diseases,[111,112] though no data currently support similar use in OSAS. Activation of the Nrf2 pathway has also been proposed as a potential intervention, given its role in upregulating antioxidant enzymes such as GPX4 and catalase; experimental data indicate that Nrf2 activation may attenuate ferroptosis

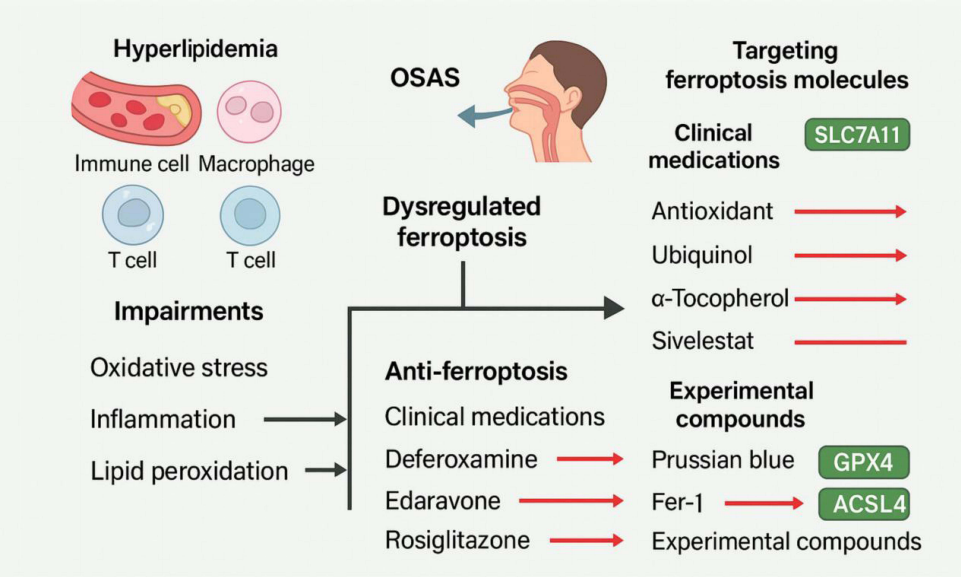

Figure 3 Strategies for targeting ferroptosis in treating obstructive sleep apnea syndrome (OSAS). It highlights the role of dysregulated ferroptosis in OSAS pathophysiology, including oxidative stress, inflammation, and lipid peroxidation. The diagram distinguishes between clinical medications for anti-ferroptosis, such as Deferoxamine, Edaravone, and Rosiglitazone, which target key molecular pathways, and experimental compounds like Prussian blue and Fer-1 that affect ferroptosis markers GPX4 and ACSL4. Additionally, clinical medications like antioxidants and ubiquinol aim to counteract the pathological processes by modulating ferroptosis. The right side focuses on key molecular targets, including SLC7A11 and GPX4, central to therapeutic strategies in OSAS management.

under hypoxic stress.[113–119] Yet, clinical evidence for Nrf2 activators in OSAS is currently lacking. Emerging technologies—including gene editing and nanomedicine—may eventually broaden the therapeutic landscape. Theoretically, ferroptosis-related genes (eg, GPX4[120–122]) could be modified via gene therapy (eg, CRISPR/Cas9), while nanocarriers might improve targeted delivery of ferroptosis inhibitors to vulnerable organs.[123,124] However, these approaches remain highly experimental, and their applicability to OSAS has yet to be established.

Overall, the therapeutic landscape of OSAS is evolving with growing interest in ferroptosis as a potential mechanism of tissue injury (Figure 3). Figure 3 outlines therapeutic strategies targeting ferroptosis in OSAS, distinguishing between agents with established clinical relevance (eg, deferoxamine, edaravone) and those in preclinical development (eg, Prussian blue, Fer-1). Importantly, the experimental status and evidentiary limitations of these approaches are now explicitly acknowledged. Correspondingly, Table 2 has been revised to more accurately represent the type and strength of evidence supporting each intervention, classifying iron chelators, antioxidants, GPX4 modulators, anti-inflammatory agents, and Nrf2 activators as preclinical or exploratory. Rigorous clinical research remains essential to determine the safety, efficacy, and translational value of these therapeutic strategies, which at present should be regarded as preliminary and hypothesis-generating avenues for future investigation.

Table 2 Treatment Strategy of Ferroptosis in OSAS

Treatment Strategy	Mechanism of Action	Effectiveness	References	Clinical Application Potential
Iron Chelators	Iron chelation prevents iron from catalyzing lipid peroxidation, reduces oxidative damage.	Effective in reducing ferroptosis-induced damage in preclinical models of OSAS.	Zhong et al (2024)[45]	Strong potential for reducing iron overload in OSAS patients.
Lipid Peroxidation Inhibitors	Inhibition of lipid peroxidation to prevent membrane damage.	Shown to reduce cellular damage in both in vitro and animal models of OSAS.	Shi et al (2024)[99]	Could be used in combination with other therapies to reduce tissue damage in OSAS.

(*Continued*)

https://doi.org/10.2147/NSS.S549883

Table 2 (Continued).

Treatment Strategy	Mechanism of Action	Effectiveness	References	Clinical Application Potential
GPX4 Activation	Enhancing GPX4 activity to neutralize reactive oxygen species (ROS), counteracting ferroptosis.	Strong protective effects observed in models of neurodegeneration, cardiovascular damage in OSAS.	Sui et al (2018)[102]	Could be used to limit ferroptosis-induced damage in OSAS-related tissues.
Ferrous Sulfate Supplementation	Increase iron levels to balance iron homeostasis and prevent overload.	Controversial; risk of exacerbating ferroptosis if not carefully controlled.	Zhao et al (2022)[125]	Risk of iron overload in OSAS; requires careful monitoring.
Atractyloside	Inhibition of mitochondrial permeability transition pore (mPTP) prevents mitochondrial dysfunction and ferroptosis.	Protects against ferroptosis in various cell types, reducing oxidative stress.	Sergey et al (2023)[126]	Potential for treatment in OSAS, but requires more clinical evidence for safety.
N-acetylcysteine (NAC)	Antioxidant effects by replenishing glutathione, a key ROS scavenger.	Shown to mitigate ferroptotic damage in multiple organs, including lung and brain in OSAS models.	Huang et al (2022)[49]	Already used in clinical practice for oxidative stress management, potential as adjunct therapy in OSAS.
Ferrostatin-1 (FST-1)	Specific inhibitor of ferroptosis that blocks lipid peroxidation and ferroptosis-associated cell death.	Demonstrated strong effects in preclinical models of cancer and neurodegeneration, as well as in OSAS-related oxidative damage.	Chen et al (2024)[48]	Not yet clinically approved for OSAS; needs further exploration.
Vitamin E and Other Antioxidants	Scavenging of ROS to reduce oxidative damage.	Protective effects shown in OSAS-related cardiovascular and neuronal damage, reducing inflammation.	Hu et al (2021)[32]	Potential as adjunct therapy in OSAS treatment.
Targeting p53 Pathway	Modulating the p53 pathway to regulate ferroptosis.	Inhibited ferroptosis in several models of disease; promising but early-stage for OSAS.	Jiang et al (2015)[127]	Potential for targeted therapy in OSAS, particularly in comorbid conditions like cardiovascular disease.
Mitochondrial Modulators	Stabilizing mitochondrial integrity to prevent ROS generation and mitochondrial dysfunction.	Preclinical studies suggest reduction in ferroptosis-related cell death in OSAS models.	Alejandro et al (2023)[128]	Potential adjunct therapy to prevent oxidative damage in OSAS, particularly in lung and brain tissues.
Pharmacological Inhibition of ACSL4	Blocking ACSL4 reduces lipid peroxidation and ferroptosis.	Showed protective effects in models of acute lung injury and cancer.	Huang et al (2024)[129]	Could offer a new avenue for treatment in OSAS-related tissue damage.
Novel Small Molecule Inhibitors (eg, RSL3)	Inhibition of GPX4 or other ferroptosis-associated proteins.	Proven effective in cancer therapy models, showing promise in neurodegenerative diseases and OSAS-related tissue injury.	Hou et al (2024)[106]	High potential in targeting ferroptosis in OSAS; ongoing clinical trials.
Ferritin Overexpression	Boosting ferritin levels to sequester excess iron and reduce ROS generation.	Strong evidence in neurodegenerative diseases; emerging data in OSAS models showing protective effects against vascular and neuronal damage.	Chen et al (2021)[130]	Could be a potential therapeutic approach to manage iron overload in OSAS.
Liposomal Delivery of Antioxidants	Targeted delivery of antioxidants to affected tissues to reduce ROS.	Effective in preclinical studies, improving targeted tissue protection without systemic side effects.	Zhen et al (2023)[131]	Potential for localized therapy in OSAS, improving efficacy while reducing toxicity.
Ketone Bodies (eg, β-Hydroxybutyrate)	Modulating metabolism and reducing oxidative stress.	Shown to reduce oxidative stress and ferroptosis in neurological and metabolic models.	Tian et al (2024)[132]	Potential for metabolic modulation in OSAS-related oxidative stress, especially in obesity-associated OSAS.

Challenges and Future Directions

Ferroptosis remains a new point of therapeutic intervention against Obstructive Sleep Apnea Syndrome (OSAS). However, its therapeutic intervention must be executed fully with several serious scientific and clinical questions to notice. The inadequate understanding of the complicated molecular mechanisms of ferroptosis-induced OSAS is among the most pressing ones to mention. Even though a body of literature has already established a connection between the intermittent hypoxia (IH), the oxidative stress and the iron homeostasis dysregulation, the manifestation of ferroptosis has minimal knowledge on detailing the involved disrupted molecular processes in connecting the pathophysiology of the OSAS with the ensuing pathway systemic complications. It should be mentioned that the effects through which ferroptotic depends on the inflammatory responses, cellular metabolic disorders and neurodegeneration homeostatic with the help of OSAS are not well studied. This lack of such knowledge handicaps the production of effective and target therapy and predictable biomarkers that may monitor or prevent the consequences of ferroptosis-living cell injury. One of the major challenges is a selective modulation of ferroptosis in concerned tissues. Even though growing evidence continues to implicate ferroptosis in the pathology of OSAS-induced cell death, the biggest complication is the challenge of localizing induction of ferroptosis in pathological tissue (say-hypoxic stress) but sparing normal cells. The current strategies often fail to take into account the tissue-specificity of ferroptosis, or even the possibility of other similar comorbidities, eg cardiovascular dysfunction, neurodegeneration and even fibrosis in OSAS after such drugs. Controlling the level of ferroptosis precisely at the cellular and tissue factors without any form of adverse effects is going to be the most vital pillar towards translating ferroptosis-related therapies currently at the experimental stages to clinical applications. Additionally, a successful linkage and confirmation of potent and delicate biomarkers of ferroptosis in OSAS is an even better gap in science. The lack of consistent biomarkers can almost be considered the biggest obstacle in the study of the ferroptosis progress, the success of therapeutic measures, and the interpretation as to the most efficient therapeutic intervals. New and dynamic biomarkers that outright denote the occurrence and the course thereof in ferroptosis, and the contributions displayed vis a vis other cell death mechanisms (apoptosis and necrosis) will also be critical not only in the diagnostics and treatment of OSAS. Multi-modal approach that encompasses the progressive imaging modalities or liquid biopsy-based analyses can offer new possibilities of real-time monitoring of ferro-ptosis of the patients of OSAS.

It demands the paradigm shift of directions of research. First, the introduction of the most recent and high throughput multi-omics research, such as single-cells RNA sequencing, spatial transcriptomics, and even proteomics ones, is to facilitate the realization of cellular and tissue-level of ferroptosis in OSAS. Such plans will enable the discovery of tissue specific-molecular signatures and the perception of the location of ferroptosis in the pathophysiology of the OSAS in general. With systems biology available and artificial intelligence (AI)-based data analysis, potential new pathways and predictive biomarkers associated with ferroptosis can be found, which will help get treatments and diagnostics developed faster. In addition, invasion of gene-editing tools, such as CRISPR/Cas9, as well as delivery strategies, eg targeted nanoparticles or viral vectors, might enable the specific regulation of the expression of ferroptosis-associated genes in individual tissues. This would make it possible to engage or suppress ferroptosis in the organs affected by OSAS selectively to develop very precise and effective therapeutic solutions. Moreover, screening nanomedicine through targeted delivery of ferroptosis modulators has the potential to make treatment more specific to a disease, reduce side effects in the entire body, and improve the healing effect. Simultaneously, there is a promising prospect in the area of artificial intelligence and machine learning-driven drug discovery platforms to reduce the time it requires to discover ferroptosis modulators. Brother AI-controlled screening systems, considered over large drug collections, could be used to repurpose drugs which currently have FDA approval, screening compounds that can carry out ferroptosis pathways in OSAS. With the enhancement of the ML algorithms with the personal patient data, one can potentially predict the best therapies given the particular genetic and environmental factors put in place and thus lead to a new personalized approach to the treatment of OSAS. Last but not the least is convergence of interdisciplinary research, eg bioinformatics, nanomedicine, and pharmacogenomics, where this is an untapped potential that can overcome the current constraints in ferroptosis field. The three disciplines will be combined to create new tools and solutions to high throughput screening, direct delivery of drugs, and non-invasive monitoring of ferroptosis activity and may be used to make large-scale lung changes in realizing ferroptosis-targeted therapies to OSAS.

Even though much was done in explaining the efficacy of ferroptosis in OSAS, it is still vibrating. Some improvements will be required in the field by working on the problem of tissue-specific targeting of ferroptosis, enhancement of biomarker development, and the development of new technologies such as AI, CRISPR and nanomedicine. Otherwise referred to as capping, this method has served to propose new approaches using cleaner scales of the Saagonin with the potential to make substantial advances to the clinical treatment of the OSAS that would interface with precision medicine solutions that would aid in stabilizing the on-progress course of the disease and to achieve improved results in medical outcome of the patient. The two factors residenced to give the solution to the work are; technological innovation and interdisciplinary collaboration in the case of the ferroptosis in the context of the OSAS treatment work.

Critical Appraisal of Included Studies

While this review synthesizes the potential role of ferroptosis in the pathophysiology of obstructive sleep apnea syndrome (OSAS), it is important to critically appraise the available evidence. The majority of studies included in this review rely on preclinical models, particularly in vitro cell experiments and animal models of intermittent hypoxia, which provide valuable mechanistic insights into oxidative stress, iron dysregulation, and lipid peroxidation. However, these studies are limited by small sample sizes, short observation periods, and methodological heterogeneity, which hinder the direct extrapolation of findings to human OSAS. Furthermore, while animal models are essential for understanding pathophysiological mechanisms, their ability to replicate the complexity of human OSAS—characterized by multi-factorial comorbidities and long-term disease progression—remains uncertain. Clinical studies investigating the direct relationship between ferroptosis and OSAS pathophysiology are scarce, and most of the available literature relies on indirect biomarkers, rather than validated diagnostic markers of ferroptosis. Thus, while the evidence suggests a potential role for ferroptosis in OSAS-related cardiovascular, neurological, and renal complications, the current body of work remains preliminary and largely hypothetical. Given these limitations, further research, including large-scale clinical trials and longitudinal studies, is essential to better define the role of ferroptosis in OSAS and to explore its clinical applications with rigorously validated biomarkers and therapeutic strategies.

Conclusion

Ferroptosis has recently emerged as a potential mechanism of interest in the context of obstructive sleep apnea syndrome (OSAS). Although disturbances in iron metabolism have long been linked to cardiovascular, neurological, and metabolic comorbidities, the specific molecular interplay between ferroptosis and OSAS remains largely speculative. Current evidence, derived primarily from preclinical and experimental models, suggests that excessive reactive iron and lipid peroxidation may contribute to the oxidative and inflammatory burden observed in OSAS. However, the precise regulatory pathways and causal relationships are not yet clearly defined. While therapeutic strategies such as iron chelation and ferroptosis inhibition appear promising in alleviating iron overload–associated tissue injury in experimental settings, there is insufficient clinical evidence to support their use in OSAS patients at present. Future investigations should focus on mechanistic studies to delineate how ferroptosis contributes to OSAS pathophysiology, alongside well-designed clinical research to assess its translational potential. In conclusion, ferroptosis represents a hypothetical but intriguing link between disrupted iron metabolism and the multisystem complications of OSAS. Clarifying this relationship will require comprehensive molecular, translational, and clinical research to determine whether targeting ferroptosis could ultimately provide a viable therapeutic avenue.

Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analysed in this study.

Author Contributions

XZ and FZ–Conceptualization, methodology, writing-original draft, and writing-review and editing. All authors agreed to submitting the paper to Nature and Science of Sleep; approved the final version for publishing and agreed to be accountable for the content of the paper.

Funding

This work was partly funded by Open Project of State Key Laboratory of Respiratory Disease (SKLRD-OP-202510).

Disclosure

The authors declare that they have no competing interests related to the content of this paper. The figures in this paper are original and have not been adapted or reproduced from any other sources.

References

1. Redline S, Azarbarzin A, Peker Y. Obstructive sleep apnoea heterogeneity and cardiovascular disease. *Nat Rev Cardiol*. 2023;20(8):560–573. doi:10.1038/s41569-023-00846-6
2. Kono M, Tatsumi K, Saibara T, et al. Obstructive sleep apnea syndrome is associated with some components of metabolic syndrome. *Chest*. 2007;131(5):1387–1392. doi:10.1378/chest.06-1807
3. Lal C, Strange C, Bachman D. Neurocognitive impairment in obstructive sleep apnea. *Chest*. 2012;141(6):1601–1610. doi:10.1378/chest.11-2214
4. Dixon SJ, Lemberg KM, Lamprecht MR, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell*. 2012;149(5):1060–1072. doi:10.1016/j.cell.2012.03.042
5. Wu Z, Huang X, Lu X, et al. The interplay of sleep deprivation, ferroptosis, and BACH1 in cardiovascular disease pathogenesis. *Tissue Cell*. 2025;95:102848. doi:10.1016/j.tice.2025.102848
6. Chen B, Dong L, Chi W, et al. Machine learning identifies potential diagnostic biomarkers associated with ferroptosis in obstructive sleep apnea. *Exp Ther Med*. 2025;29(5):95. doi:10.3892/etm.2025.12845
7. Chen L-D, Wu R-H, Huang Y-Z, et al. The role of ferroptosis in chronic intermittent hypoxia-induced liver injury in rats. *Sleep Breathing*. 2020;24(4):1767–1773. doi:10.1007/s11325-020-02091-4
8. Liu Z, Huang Y, Wang X, et al. The role of ferroptosis in chronic intermittent hypoxia-induced cognitive impairment. *Sleep Breathing*. 2023;27(5):1725–1732. doi:10.1007/s11325-022-02760-6
9. Chen J, Zhu H, Chen Q, et al. The role of ferroptosis in chronic intermittent hypoxia-induced lung injury. *BMC Pulm Med*. 2022;22(1):488. doi:10.1186/s12890-022-02262-x
10. Cai W, Wu S, Ming X, et al. IL6 derived from macrophages under intermittent hypoxia exacerbates NAFLD by promoting ferroptosis via MARCH3-led ubiquitylation of GPX4. *Adv Sci*. 2024;11(41):2402241. doi:10.1002/advs.202402241
11. Bayır H, Dixon SJ, Tyurina YY, et al. Ferroptotic mechanisms and therapeutic targeting of iron metabolism and lipid peroxidation in the kidney. *Nat Rev Nephrol*. 2023;19(5):315–336. doi:10.1038/s41581-023-00689-x
12. Wang B, Wang Y, Zhang J, et al. ROS-induced lipid peroxidation modulates cell death outcome: mechanisms behind apoptosis, autophagy, and ferroptosis. *Arch Toxicol*. 2023;97(6):1439–1451. doi:10.1007/s00204-023-03476-6
13. Dodson M, Castro-Portuguez R, Zhang DD. NRF2 plays a critical role in mitigating lipid peroxidation and ferroptosis. *Redox Biol*. 2019;23:101107. doi:10.1016/j.redox.2019.101107
14. Imai H, Matsuoka M, Kumagai T, et al. Lipid peroxidation-dependent cell death regulated by GPx4 and ferroptosis. *Apoptotic and Non-Apoptotic Cell Death*. 2017;2017:143–170.
15. Ma T, Du J, Zhang Y, et al. GPX4-independent ferroptosis—a new strategy in disease's therapy. *Cell Death Discovery*. 2022;8(1):434. doi:10.1038/s41420-022-01212-0
16. Seibt TM, Proneth B, Conrad M. Role of GPX4 in ferroptosis and its pharmacological implication. *Free Radic Biol Med*. 2019;133:144–152. doi:10.1016/j.freeradbiomed.2018.09.014
17. Gaschler MM, Andia AA, Liu H, et al. FINO2 initiates ferroptosis through GPX4 inactivation and iron oxidation. *Nat Chem Biol*. 2018;14(5):507–515. doi:10.1038/s41589-018-0031-6
18. Ding K, Liu C, Li L, et al. Acyl-CoA synthase ACSL4: an essential target in ferroptosis and fatty acid metabolism. *Chin Med J*. 2023;136(21):2521–2537. doi:10.1097/CM9.0000000000002533
19. Zhang HL, Hu BX, Li ZL, et al. PKCβII phosphorylates ACSL4 to amplify lipid peroxidation to induce ferroptosis. *Nat Cell Biol*. 2022;24(1):88–98. doi:10.1038/s41556-021-00818-3
20. Gan B. ACSL4, PUFA, and ferroptosis: new arsenal in anti-tumor immunity. *Signal Transduct Target Ther*. 2022;7(1):128. doi:10.1038/s41392-022-01004-z
21. Doll S, Proneth B, Tyurina YY, et al. ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. *Nat Chem Biol*. 2017;13(1):91–98. doi:10.1038/nchembio.2239
22. Lin J, Lai Y, Lu F, et al. Targeting ACSLs to modulate ferroptosis and cancer immunity. *Trends Endocrinol Metab*. 2024;36(7):677–690.
23. Bouchaoui H, Mahoney-Sanchez L, Garçon G, et al. ACSL4 and the lipoxygenases 15/15B are pivotal for ferroptosis induced by iron and PUFA dyshomeostasis in dopaminergic neurons. *Free Radic Biol Med*. 2023;195:145–157. doi:10.1016/j.freeradbiomed.2022.12.086
24. Li L, Wang K, Jia R, et al. Ferroportin-dependent ferroptosis induced by ellagic acid retards liver fibrosis by impairing the SNARE complexes formation. *Redox Biol*. 2022;56:102435. doi:10.1016/j.redox.2022.102435
25. Namgaladze D, Fuhrmann DC, Brüne B. Interplay of Nrf2 and BACH1 in inducing ferroportin expression and enhancing resistance of human macrophages towards ferroptosis. *Cell Death Discovery*. 2022;8(1):327. doi:10.1038/s41420-022-01117-y
26. Fang J, Kong B, Shuai W, et al. Ferroportin-mediated ferroptosis involved in new-onset atrial fibrillation with LPS-induced endotoxemia. *Eur J Pharmacol*. 2021;913:174622. doi:10.1016/j.ejphar.2021.174622
27. Liu B, Jiang W, Ye Y, et al. 2D MoS2 nanosheets induce ferroptosis by promoting NCOA4-dependent ferritinophagy and inhibiting ferroportin. *Small*. 2023;19(24):2208063. doi:10.1002/smll.202208063

28. Zhang P, Zhou C, Ren X, et al. Inhibiting the compensatory elevation of xCT collaborates with disulfiram/copper-induced GSH consumption for cascade ferroptosis and cuproptosis. *Redox Biol*. 2024;69:103007. doi:10.1016/j.redox.2023.103007
29. Muri J, Kopf M. The thioredoxin system: balancing redox responses in immune cells and tumors. *Eur J Immunol*. 2023;53(1):2249948. doi:10.1002/eji.202249948
30. Jia J, Xu G, Zhu D, et al. Advances in the functions of thioredoxin system in central nervous system diseases. *Antioxid Redox Sig*. 2023;38 (4):425–441.
31. Benhar M. Roles of mammalian glutathione peroxidase and thioredoxin reductase enzymes in the cellular response to nitrosative stress. *Free Radic Biol Med*. 2018;127:160–164. doi:10.1016/j.freeradbiomed.2018.01.028
32. Qian H, Zhang Y, Lou H, et al. GPX4 and vitamin E cooperatively protect hematopoietic stem and progenitor cells from lipid peroxidation and ferroptosis. *Cell Death Dis*. 2021;12(7). doi:10.1038/s41419-021-04008-9.
33. Luo S, Zeng Y, Chen B, et al. Vitamin E and GPX4 cooperatively protect treg cells from ferroptosis and alleviate intestinal inflammatory damage in necrotizing enterocolitis. *Redox Biol*. 2024;75:103303. doi:10.1016/j.redox.2024.103303
34. Gupta PS, Karmakar S, Biswas I, et al. Vitamin E alleviates chlorpyrifos induced glutathione depletion, lipid peroxidation and iron accumulation to inhibit ferroptosis in hepatocytes and mitigate toxicity in Zebrafish. *Chemosphere*. 2024;359:142252. doi:10.1016/j.chemosphere.2024.142252
35. Chen X, Kang R, Kroemer G, et al. Broadening horizons: the role of ferroptosis in cancer. *Nat Rev Clin Oncol*. 2021;18(5):280–296. doi:10.1038/s41571-020-00462-0
36. Liu Z, Liu S, Liu B, et al. Fe (III)-naphthazarin metal–phenolic networks for glutathione-depleting enhanced ferroptosis–apoptosis combined cancer therapy. *Small*. 2023;19(19):2207825. doi:10.1002/smll.202207825
37. Vinik Y, Maimon A, Dubey V, et al. Programming a ferroptosis-to-apoptosis transition landscape revealed ferroptosis biomarkers and repressors for cancer therapy. *Adv Sci*. 2024;11(17):2307263. doi:10.1002/advs.202307263
38. Du B, Deng Z, Chen K, et al. Iron promotes both ferroptosis and necroptosis in the early stage of reperfusion in ischemic stroke. *Genes Dis*. 2024;11(6):101262. doi:10.1016/j.gendis.2024.101262
39. Du B, Fu Q, Yang Q, et al. Different types of cell death and their interactions in myocardial ischemia–reperfusion injury. *Cell Death Discovery*. 2025;11(1):87. doi:10.1038/s41420-025-02372-5
40. Hou W, Xie Y, Song X, et al. Autophagy promotes ferroptosis by degradation of ferritin. *Autophagy*. 2016;12(8):1425–1428. doi:10.1080/15548627.2016.1187366
41. Park E, Chung SW. ROS-mediated autophagy increases intracellular iron levels and ferroptosis by ferritin and transferrin receptor regulation. *Cell Death Dis*. 2019;10(11):822. doi:10.1038/s41419-019-2064-5
42. Zhao Y, Lu J, Mao A, et al. Autophagy inhibition plays a protective role in ferroptosis induced by alcohol via the p62–Keap1–Nrf2 pathway. *J Agric Food Chem*. 2021;69(33):9671–9683. doi:10.1021/acs.jafc.1c03751
43. Liu P, Zhao D, Pan Z, et al. Identification and validation of ferroptosis-related hub genes in obstructive sleep apnea syndrome. *Front Neurol*. 2023;14:1130378. doi:10.3389/fneur.2023.1130378
44. Park MW, Cha HW, Kim J, et al. NOX4 promotes ferroptosis of astrocytes by oxidative stress-induced lipid peroxidation via the impairment of mitochondrial metabolism in Alzheimer's diseases. *Redox Biol*. 2021;41:101947. doi:10.1016/j.redox.2021.101947
45. Zhong ZP, Li L, Feng X, et al. Neuronal ferroptosis and ferroptosis-mediated endoplasmic reticulum stress: implications in cognitive dysfunction induced by chronic intermittent hypoxia in mice. *Int Immunopharmacol*. 2024;138:112579. doi:10.1016/j.intimp.2024.112579
46. Wang R, Lv Y, Ni ZY, et al. Intermittent hypoxia exacerbates metabolic dysfunction-associated fatty liver disease by aggravating hepatic copper deficiency-induced ferroptosis. *FASEB J*. 2024;38(13):e23788. doi:10.1096/fj.202400840R
47. Barrera G. Oxidative stress and lipid peroxidation products in cancer progression and therapy. *Int Scholarly Res Notices*. 2012;2012(1):137289.
48. Chen J, Deng X, Lin T, et al. Ferrostatin-1 reversed chronic intermittent hypoxia-induced ferroptosis in aortic endothelial cells via reprogramming mitochondrial function. *Nat Sci Sleep*. 2024;Volume 16:401–411. doi:10.2147/NSS.S442186
49. Huang J, Xie H, Yang Y, et al. The role of ferroptosis and endoplasmic reticulum stress in intermittent hypoxia-induced myocardial injury. *Sleep Breath*. 2023;27(3):1005–1011. doi:10.1007/s11325-022-02692-1
50. Zheng X, Liang Y, Zhang C. Ferroptosis regulated by hypoxia in cells. *Cells*. 2023;12(7):1050. doi:10.3390/cells12071050
51. Song J, Chen Q, Xu S, et al. Hydrogen attenuates chronic intermittent hypoxia-induced cardiac hypertrophy by regulating iron metabolism. *Curr Issues Mol Biol*. 2023;45(12):10193–10210. doi:10.3390/cimb45120636
52. Lee S-D, Kuo -W-W, Lin JA, et al. Effects of long-term intermittent hypoxia on mitochondrial and Fas death receptor dependent apoptotic pathways in rat hearts. *Int J Cardiol*. 2007;116(3):348–356. doi:10.1016/j.ijcard.2006.03.064
53. Chen J, Liao W, Gao W, et al. Intermittent hypoxia protects cerebral mitochondrial function from calcium overload. *Acta Neurol Belg*. 2013;113 (4):507–513. doi:10.1007/s13760-013-0220-8
54. Mankovska IM, Serebrovska TV. Mitochondria as a target of intermittent hypoxia. *Int J Physiol Pathophysiol*. 2015;6(4):347–362. doi:10.1615/IntJPhysPathophys.v6.i4.90
55. Su Y, Ke C, Li C, et al. Intermittent hypoxia promotes the recovery of motor function in rats with cerebral ischemia by regulating mitochondrial function. *Exp Biol Med*. 2022;247(15):1364–1378. doi:10.1177/15353702221098962
56. Wang Y, Zhang PP, Han X, et al. Effects of glutathione on oxidative stress, leptin and adiponectin in patients with obstructive sleep apnea complicated with metabolic syndrome. *Linchuang Er Bi yanhou Toujing Waike Zazhi*. 2019;33(8):726–729.
57. O'Brie n LM, Koo J, Fan L, et al. Iron stores, periodic leg movements, and sleepiness in obstructive sleep apnea. *J Clin Sleep Med*. 2009;5 (6):525–531. doi:10.5664/jcsm.27652
58. Roy B, Vacas S, Kang DW, et al. Regional brain iron mapping in obstructive sleep apnea adults. *Sleep Med*. 2025;126:211–217. doi:10.1016/j.sleep.2024.12.022
59. Yumrukuz Şenel M, Şahin R, Çolak M, et al. Are the serum iron parameters related to the severity of obstructive sleep apnea syndrome? *Sleep Breath*. 2025;29(2):132. doi:10.1007/s11325-025-03301-7
60. Ming X, Li Z, Yang X, et al. Serum transferrin level is associated with the severity of obstructive sleep apnea independently of obesity: a propensity score-match observational study. *Obesity Facts*. 2022;15(4):487–497. doi:10.1159/000524542

61. Cui F, Haichao M, Wang R, et al. The effect of chronic intermittent hypobaric hypoxia improving liver damage in metabolic syndrome rats through ferritinophagy. *Res Square*. 2023;2023:5.
62. Fuhrmann DC, Mondorf A, Beifuß J, Jung M, Brüne B. Hypoxia inhibits ferritinophagy, increases mitochondrial ferritin, and protects from ferroptosis. *Redox Biol*. 2020;36:101670. doi:10.1016/j.redox.2020.101670
63. Ni S, Yuan Y, Qian Z, et al. Hypoxia inhibits RANKL-induced ferritinophagy and protects osteoclasts from ferroptosis. *Free Radic Biol Med*. 2021;169:271–282. doi:10.1016/j.freeradbiomed.2021.04.027
64. Seifen C, Pordzik J, Huppertz T, et al. Serum ferritin levels in severe obstructive sleep apnea. *Diagnostics*. 2023;13(6):1154. doi:10.3390/diagnostics13061154
65. Cheng ETW, Au CT, C RNC, et al. Ferritin is a potential marker of cardiometabolic risk in adolescents and young adults with sleep-disordered breathing. *Sleep Adv*. 2024;5(1):zpae048. doi:10.1093/sleepadvances/zpae048
66. Thorarinsdottir EH, Arnardottir ES, Benediktsdottir B, et al. Serum ferritin and obstructive sleep apnea—epidemiological study. *Sleep Breath*. 2018;22(3):663–672. doi:10.1007/s11325-017-1598-y
67. Zou Y, Palte MJ, Deik AA, et al. A GPX4-dependent cancer cell state underlies the clear-cell morphology and confers sensitivity to ferroptosis. *Nat Commun*. 2019;10(1):1617. doi:10.1038/s41467-019-09277-9
68. Song X, Chen J, Xu H, et al. Regulation of fatty acid oxidation involved in high altitude hypoxia induced cardiomyocyte ferroptosis via the SIRT1-PPARα-GPX4 signaling pathway. *bioRxiv*. 2025;2025:1.
69. Liu Q, Song T, Chen B, et al. Ferroptosis of brain microvascular endothelial cells contributes to hypoxia-induced blood–brain barrier injury. *FASEB J*. 2023;37(5). doi:10.1096/fj.202201765R.
70. Zhu K, Zhu X, Sun S, et al. Inhibition of TLR4 prevents hippocampal hypoxic-ischemic injury by regulating ferroptosis in neonatal rats. *Exp Neurol*. 2021;345:113828. doi:10.1016/j.expneurol.2021.113828
71. Lai Y, Dong J, Wu Y, et al. Lipid peroxides mediated ferroptosis in electromagnetic pulse-induced hippocampal neuronal damage via inhibition of GSH/GPX4 axis. *Int J Mol Sci*. 2022;23(16):9277. doi:10.3390/ijms23169277
72. Liu H, Yan L, Niu H, et al. Effects of glutathione tablets on ferroptosis pathway and oxidative stress-related indexes in serum of patients undergoing sevoflurane inhalation general anesthesia and its clinical significance. *Altern Ther Health Med*. 2024;30(5):249–255.
73. Chai C-Z, Mo W-L, Zhuang X-F, et al. Protective effects of sheng-mai-san on right ventricular dysfunction during chronic intermittent hypoxia in mice. *Evid Based Complement Alternat Med*. 2016;2016(1):1–9. doi:10.1155/2016/4682786
74. Lin X, Jagadapillai R, Cai J, et al. Metallothionein induction attenuates the progression of lung injury in mice exposed to long-term intermittent hypoxia. *Inflammation Res*. 2020;69(1):15–26. doi:10.1007/s00011-019-01287-z
75. Shortt CM, Fredsted A, Chow HB, et al. Reactive oxygen species mediated diaphragm fatigue in a rat model of chronic intermittent hypoxia. *Exp Physiol*. 2014;99(4):688–700. doi:10.1113/expphysiol.2013.076828
76. Zhou S, Wang Y, Tan Y, et al. Deletion of metallothionein exacerbates intermittent hypoxia-induced oxidative and inflammatory injury in aorta. *Oxid Med Cell Longev*. 2014;2014:1–11.
77. Panaroni C, Fulzele K, Soucy R, et al. Arachidonic acid induces ferroptosis-mediated cell-death in multiple myeloma. *Blood*. 2018;132 (Supplement 1):4498. doi:10.1182/blood-2018-99-118482
78. Shan K, Feng N, Zhu D, et al. Free docosahexaenoic acid promotes ferroptotic cell death via lipoxygenase dependent and independent pathways in cancer cells. *Eur J Nutr*. 2022;61(8):4059–4075. doi:10.1007/s00394-022-02940-w
79. Chen L, Yang Y, Zhang N, et al. DHA and EPA alleviate depressive-like behaviors in chronic sleep-deprived mice: involvement of iron metabolism, oligodendrocyte-lipids peroxidation and the LCN2-NLRP3 signaling axis. *Free Radic Biol Med*. 2024;225:654–664. doi:10.1016/j.freeradbiomed.2024.10.298
80. Beatty A, Singh T, Tyurina YY, et al. Ferroptotic cell death triggered by conjugated linolenic acids is mediated by ACSL1. *Nat Commun*. 2021;12(1). doi:10.1038/s41467-021-22471-y.
81. Li Z, Hu Y, Zheng H, et al. LPCAT1-mediated membrane phospholipid remodelling promotes ferroptosis evasion and tumour growth. *Nat Cell Biol*. 2024;26(5):811–824. doi:10.1038/s41556-024-01405-y
82. Qiu B, Zandkarimi F, Bezjian CT, et al. Phospholipids with two polyunsaturated fatty acyl tails promote ferroptosis. *Cell*. 2024;187(5):1177–1190.e18. doi:10.1016/j.cell.2024.01.030
83. Cui F, Hu HF, Guo J, et al. The effect of autophagy on chronic intermittent hypobaric hypoxia ameliorating liver damage in metabolic syndrome rats. *Front Physiol*. 2020;11. doi:10.3389/fphys.2020.00013
84. Song J-X, Zhao Y-S, Zhen Y-Q, et al. Banxia-Houpu decoction diminishes iron toxicity damage in heart induced by chronic intermittent hypoxia. *Pharm Biol*. 2022;60(1):609–620. doi:10.1080/13880209.2022.2043392
85. Le Tallec-Estève N, Chloé Rousseau C, Desrues B, et al. Transferrin saturation is independently associated with the severity of obstructive sleep apnea syndrome and hypoxia among obese subjects. *Clin Nutr*. 2021;40(2):608–614. doi:10.1016/j.clnu.2020.06.007
86. Gorman BL, Taylor MJ, Tesfay L, et al. Applying multimodal mass spectrometry to image tumors undergoing ferroptosis following in vivo treatment with a ferroptosis inducer. *J Am Soc Mass Spectrom*. 2024;35(1):5–12. doi:10.1021/jasms.3c00193
87. Nguyen CTN, Kim SM, Kang YP. Mass spectrometry-based approaches to explore metabolism regulating ferroptosis. *J Biochem Mol Biol*. 2022;55(9):413–416.
88. Toyokuni S, Ito F, Yamashita K, et al. Iron and thiol redox signaling in cancer: an exquisite balance to escape ferroptosis. *Free Radic Biol Med*. 2017;108:610–626. doi:10.1016/j.freeradbiomed.2017.04.024
89. Li Y, Feng D, Wang Z, et al. Ischemia-induced ACSL4 activation contributes to ferroptosis-mediated tissue injury in intestinal ischemia/reperfusion. *Cell Death Differ*. 2019;26(11):2284–2299. doi:10.1038/s41418-019-0299-4
90. Lux LJ, Boehlecke B, Lohr KN. Effectiveness of portable monitoring devices for diagnosing obstructive sleep apnea: update of a systematic review. *Null*. 2004;2004:1.
91. Cooksey JA, Balachandran JS. Portable monitoring for the diagnosis of OSA. *Chest*. 2016;149(4):1074–1081. doi:10.1378/chest.15-1076
92. Krishnaswamy UM, Aneja A, Kumar RM, et al. Utility of portable monitoring in the diagnosis of obstructive sleep apnea. *J Postgraduate Med*. 2015;61(4):223. doi:10.4103/0022-3859.166509
93. Wu Z-H, Tang Y, Niu X, et al. The role of nitric oxide (NO) levels in patients with obstructive sleep apnea-hypopnea syndrome: a meta-analysis. *Sleep Breath*. 2021;25(1):9–16. doi:10.1007/s11325-020-02095-0

94. Hannah LB, Kirby SD. The role of artificial intelligence in the treatment of obstructive sleep apnea. *J Otolaryngol Head Neck Surg*. 2023;52 (1):1.
95. Bazoukis G, Bollepalli SC, Chung CT, et al. Application of artificial intelligence in the diagnosis of sleep apnea. *J Clin Sleep Med*. 2023;19 (7):1337–1363. doi:10.5664/jcsm.10532
96. Mencar C, Gallo C, Mantero M, et al. Application of machine learning to predict obstructive sleep apnea syndrome severity. *Health Inform J*. 2020;26(1):298–317. doi:10.1177/1460458218824725
97. Kim YJ, Jeon JS, Cho S-E, et al. Prediction models for obstructive sleep apnea in Korean adults using machine learning techniques. *Diagnostics*. 2021;11(4):612. doi:10.3390/diagnostics11040612
98. Zhang M, Liu Z, Zhou W, et al. Ferrostatin-1 attenuates hypoxic-ischemic brain damage in neonatal rats by inhibiting ferroptosis. *Transl Pediatr*. 2023;12(11):1944–1970. doi:10.21037/tp-23-189
99. Shi Z, Du Y, Zheng J. Liproxstatin-1 alleviated ischemia/reperfusion-induced acute kidney injury via inhibiting ferroptosis. *Antioxidants*. 2024;13(2):182. doi:10.3390/antiox13020182
100. Feng Y, Madungwe NB, Aliagan AD, et al. Liproxstatin-1 protects the mouse myocardium against ischemia/reperfusion injury by decreasing VDAC1 levels and restoring GPX4 levels. *Biochem Biophys Res Commun*. 2019;520(3):606–611. doi:10.1016/j.bbrc.2019.10.006
101. Feng YC, Aliagan AC, Tombo NC, et al. Inhibition of ferroptosis by liproxstatin-1 compound protects the myocardium against ischemia/ reperfusion injury by decreasing VDAC1 levels and increasing in GPX4 activity. *FASEB J*. 2020;34(S1):1. doi:10.1096/fasebj.2020.34.s1.08892
102. Sui X, Zhang R, Liu S, et al. RSL3 drives ferroptosis through GPX4 inactivation and ROS production in colorectal cancer. *Front Pharmacol*. 2018;9. doi:10.3389/fphar.2018.01371
103. Shintoku R, Takigawa Y, Yamada K, et al. Lipoxygenase-mediated generation of lipid peroxides enhances ferroptosis induced by erastin and RSL3. *Cancer Sci*. 2017;108(11):2187–2194. doi:10.1111/cas.13380
104. Dächert J, Schoeneberger H, Rohde K, et al. RSL3 and erastin differentially regulate redox signaling to promote Smac mimetic-induced cell death. *Oncotarget*. 2016;7(39):63779–63792. doi:10.18632/oncotarget.11687
105. Yangyun W, Guowei S, Shufen S-F, et al. Everolimus accelerates Erastin and RSL3-induced ferroptosis in renal cell carcinoma. *Gene*. 2022;809:145992. doi:10.1016/j.gene.2021.145992
106. Hou M, Huang X, Zhu BT. Mechanism of RSL3-induced ferroptotic cell death in HT22 cells: contributing role of protein disulfide isomerase. *Null*. 2024;2024:1.
107. Popko K, Górska E, Potapińska O, et al. Frequency of distribution of inflammatory cytokines IL-1, IL-6 and TNF-alpha gene polymorphism in patients with obstructive sleep apnea. *J Physiol Pharmacol*. 2008;59 Suppl 6:607–614.
108. Téllez Corral MA, Daza EH, Jimenez NA. Biomarkers for the severity of periodontal disease in patients with obstructive sleep apnea:IL-1 β, IL-6, IL-17A, and IL-33. *Heliyon*. 2023;9(3):e14340. doi:10.1016/j.heliyon.2023.e14340
109. Fei Q, Tan Y, Yi M, et al. Associations between cardiometabolic phenotypes and levels of TNF-α, CRP, and interleukins in obstructive sleep apnea. *Sleep Breath*. 2023;27(3):1033–1042. doi:10.1007/s11325-022-02697-w
110. Jae-Tak O, Chung J-W. Inflammatory cytokine level in patients with obstructive sleep apnea and treatment outcome of oral appliance therapy. *J Oral Med Pain*. 2016;41:3):126–132.
111. Bin S, Xin L, Lin Z, Jinhua Z, Rui G, Xiang Z. Targeting miR-10a-5p/IL-6R axis for reducing IL-6-induced cartilage cell ferroptosis. *Exp Mol Pathol*. 2021;118:104570. doi:10.1016/j.yexmp.2020.104570
112. Wang M, Zheng C, Zhou F, Ying X. Iron and inflammatory cytokines synergistically induce colonic epithelial cell ferroptosis in colitis. *J Gastroenterol Hepatol*. 2025;40(3):666–676. doi:10.1111/jgh.16826
113. Zhou L, Ouyang R, Luo H, et al. Dysfunction of Nrf2-ARE signaling pathway: potential pathogenesis in the development of neurocognitive impairment in patients with moderate to severe obstructive sleep apnea-hypopnea syndrome. *Oxid Med Cell Longev*. 2018;2018(1):3529709. doi:10.1155/2018/3529709
114. Wang Y, Chai Y, He X, et al. Intermittent hypoxia simulating obstructive sleep apnea causes pulmonary inflammation and activates the Nrf2/ HO-1 pathway. *Exp Ther Med*. 2017;14(4):3463–3470. doi:10.3892/etm.2017.4971
115. Davinelli S, Medoro A, Savino R, Scapagnini G. Sleep and oxidative stress: current perspectives on the role of NRF2. *Cell Mol Neurobiol*. 2024;44(1):52. doi:10.1007/s10571-024-01487-0
116. Wang X, Chen X, Zhou W. Ferroptosis is essential for diabetic cardiomyopathy and is prevented by sulforaphane via AMPK/NRF2 pathways. *Acta Pharm Sin B*. 2022;12(2):708–722. doi:10.1016/j.apsb.2021.10.005
117. Zhang Y-Q, Shi C-X, Zhang D-M, Zhang L-Y, Wang L-W, Gong Z-J. Sulforaphane, an NRF2 agonist, alleviates ferroptosis in acute liver failure by regulating HDAC6 activity. *J Integr Med*. 2023;21(5):464–473. doi:10.1016/j.joim.2023.08.002
118. Greco G, Schnekenburger M, Catanzaro E, et al. Discovery of sulforaphane as an inducer of ferroptosis in U-937 leukemia cells: expanding its anticancer potential. *Cancers*. 2021;14(1):76. doi:10.3390/cancers14010076
119. Zheng Z, Xu J, Mao Y, et al. Sulforaphane improves post-resuscitation myocardial dysfunction by inhibiting cardiomyocytes ferroptosis via the Nrf2/IRF1/GPX4 pathway. *Biomed Pharmacother*. 2024;179:117408. doi:10.1016/j.biopha.2024.117408
120. Chen Y, Li L, Lan J, et al. CRISPR screens uncover protective effect of PSTK as a regulator of chemotherapy-induced ferroptosis in hepatocellular carcinoma. *Mol Cancer*. 2022;21(1):11. doi:10.1186/s12943-021-01466-9
121. Cheng Y, Wang X, Huang S, et al. A CRISPR-Cas9 library screening identifies CARM1 as a critical inhibitor of ferroptosis in hepatocellular carcinoma cells. *Mol Ther Nucleic Acids*. 2023;34:102063. doi:10.1016/j.omtn.2023.102063
122. Zheng H, Jiang J, Xu S, et al. Nanoparticle-induced ferroptosis: detection methods, mechanisms and applications. *Nanoscale*. 2021;13 (4):2266–2285. doi:10.1039/D0NR08478F
123. Kim SE, Zhang L, Ma K, et al. Ultrasmall nanoparticles induce ferroptosis in nutrient-deprived cancer cells and suppress tumour growth. *Nat Nanotechnol*. 2016;11(11):977–985. doi:10.1038/nnano.2016.164
124. Shen Z, Liu T, Li Y, et al. Fenton-reaction-acceleratable magnetic nanoparticles for ferroptosis therapy of orthotopic brain tumors. *ACS Nano*. 2018;12(11):11355–11365. doi:10.1021/acsnano.8b06201
125. Zhao X, Zhang X, Xu T, et al. Comparative effects between oral lactoferrin and ferrous sulfate supplementation on iron-deficiency anemia: a comprehensive review and meta-analysis of clinical trials. *Nutrients*. 2022;14(3):543. doi:10.3390/nu14030543

126. Sergey Popov SV, Maslov LN, Mukhomedzyanov AV, et al. Apelin is a prototype of novel drugs for the treatment of acute myocardial infarction and adverse myocardial remodeling. *Pharmaceutics*. 2023;15(3):1029. doi:10.3390/pharmaceutics15031029
127. Jiang L, Kon N, Li T, et al. Ferroptosis as a p53-mediated activity during tumour suppression. *Nature*. 2015;520(7545):57–62. doi:10.1038/nature14344
128. Marmolejo-Garza A, Krabbendam IE, Luu MDA, et al. Negative modulation of mitochondrial calcium uniporter complex protects neurons against ferroptosis. *Cell Death Dis*. 2023;14(11). doi:10.1038/s41419-023-06290-1.
129. Huang Q, Ru Y, Luo Y, et al. Identification of a targeted ACSL4 inhibitor to treat ferroptosis-related diseases. *Sci Adv*. 2024;10(13). doi:10.1126/sciadv.adk1200.
130. Chen W, Jiang L, Hu Y, et al. Ferritin reduction is essential for cerebral ischemia-induced hippocampal neuronal death through p53/SLC7A11-mediated ferroptosis. *Brain Res*. 2021;1752:147216. doi:10.1016/j.brainres.2020.147216
131. Yuan Y, Tian C, Wang Q, et al. Synergistic amplification of ferroptosis with liposomal oxidation catalyst and Gpx4 inhibitor for enhanced cancer therapy. *Adv Healthcare Mater*. 2023;12(28). doi:10.1002/adhm.202301292.
132. Tian R, Tang S, Zhao J, et al. β-hydroxybutyrate protects against cisplatin-induced renal damage via regulating ferroptosis. *Renal Failure*. 2024;46(1). doi:10.1080/0886022X.2024.2354918.