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REVIEW

Research Progress on Relationship Between Iron Overload and Lower Limb Arterial Disease in Type 2 Diabetes Mellitus

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Abstract: Iron is one of the most important trace elements in life activities. It participates in a variety of important physiological processes in the body through oxidation-reduction reaction. A large number of studies show that iron overload (IO) is closely related to the progression of diabetes and its various chronic complications. However, the mechanism of iron overload in the pathogenesis of diabetes and the mechanism of iron overload in atherosclerosis (AS) are still controversial, and the relationship between iron overload and diabetic lower extremity arterial disease (LEAD) remains still unclear. Some recent reviews and original research articles suggest further studies to explain the complex relationship between iron metabolism and atherosclerosis. This article reviews the relationship between iron overload and diabetes and its relationship with LEAD, and discusses its mechanisms from various aspects, such as lipid peroxidation induced by iron overload, so as to provide clinical diagnosis and treatment ideas for diabetic lower extremity arterial disease. It is hoped that early evaluation, diagnosis and treatment of LEAD will be inspired.

Keywords: iron overload, lower extremity arterial disease, atherosclerosis, serum ferritin, type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is a class of chronic metabolic disease with multiple complications that can affect multiple organs. According to the latest epidemiological survey, in the national sample of 2015 to 2017, the prevalence of adult diabetes in China was as high as 11.2%,[1] And the global diabetes prevalence in 2019 is estimated to be 9.3% (463 million people).[2] Lower extremity-arterial disease (LEAD), one of the life-threatening complications of diabetes, mainly presents atherosclerotic stenosis or occlusion of the lower limbs (Lower extremity atherosclerosis). Compared with non-diabetic patients, diabetic patients have a higher incidence and prevalence of LEAD.[3] In serious cases, it can lead to artery blockage,[4] tissue ischemia and hypoxia,[3] diabetic foot ulcer (DFU),[5] gangrene, and so on, which can seriously affect the quality of life of patients and increase the economic burden.[6] Therefore, it is of great significance for the clinical medical community to research and develop accurate and effective early evaluation, diagnosis and treatment methods for diabetes LEAD.

Iron is one of the most abundant essential microelements in the human body. Iron is required in a variety of important biological processes including oxygen transport (as heme in hemoglobin), DNA biosynthesis (as a cofactor of ribonucleotide reductase), and ATP generation (as a cofactor for many proteins in the citric acid cycle and electron transport chain); therefore, cells must maintain a sufficient amount of iron.[7] Iron overload refers to the imbalance of iron metabolism due to the excessive iron supply that exceeds its demand. Iron is redox-active and iron overload can generate reactive oxygen species (ROS), leading to oxidative stress and initiation of signaling pathways crucial for cell survival and cell death.[7]

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A large number of studies have shown that elevated iron levels in the body can lead to many diseases, such as diabetes.[8] Iron overload is closely related to the occurrence and progression of diabetes mellitus and LEAD. Serum ferritin (SF) consists of ferritin heavy chain (FTH) and ferritin light chain (FTL), and that binds to iron in vivo and directly participates in iron metabolism.[9] The expression of SF can reflect the storage of iron in the human body. Transferrin saturation (TS) is the ratio of serum iron and total iron-binding capacity.[10] TS, an index that takes into account both plasma iron and its main transport protein, is considered an important biochemical marker of body iron status.[11] Therefore, SF and TS can be used as an effective and simple index to clinically judge iron deficiency and iron overload in vivo. Clinically, iron overload can be determined when the internal SF level exceeds 300 ug/L or when the TS is greater than 45%.

Numerous clinical reports and mechanistic research have shown that iron overload is closely related to chronic diseases, such as diabetes and arterial lesions.[12,13] However, there is still debate about whether iron overload can be used as a unique biomarker for the diagnosis of diabetes, arterial lesions and other diseases,[8] and the relationship between iron overload and diabetic LEAD is still not well understood. This paper reviews the relationship between iron overload and diabetes, possible pathological mechanisms, and the correlation between SF and arterial lesions, in order to provide new ideas and insights into the early evaluation, diagnostics and treatment of diabetic LEAD.

Research Progress in Iron Overload and Diabetes

Iron Overload is Closely Related to Diabetes Mellitus

Iron overload as a risk factor for diabetes was first found in studies of hereditary hemochromatosis and thalassemia.[14] Epidemiological observations in humans and experimental studies in animal models have established a clear association between tissue iron reserve and diabetes risk.[15,16] Studies showed that tissue iron overload and excessive SF were positively associated with insulin resistance and type 2 diabetes.[17–19] Guo et al found that serum ferritin levels in diabetic patients were significantly higher than controls.[20] Some studies have found that SF is significantly increased in the early stage of glucose and lipid metabolism disorder, indicating that iron metabolism is abnormal in prediabetes.[21,22] In addition, when the body SF increases, the probability of diabetes also increases.[23] The conclusions of various studies fully indicate the causal relationship between iron overload and diabetes, that is, the body iron overload completely leads to the occurrence of diabetes.

Iron Overload Damages Pancreatic Islet Cells, Causing Insulin Resistance

The experimental study of iron overload rats observed that iron overload promoted apoptosis of pancreatic islet cells, leading to a decrease in insulin secretion function, followed by abnormal glucose tolerance, and eventually inducing diabetes.[24] Experiments by Varghese et al showed that iron overload can activate the Akt/AMPK pathway and inhibit the phosphorylation process, thus reducing the sensitivity of the insulin receptor in hepatocyte.[25] In addition, reactive oxygen species (ROS) accumulated by iron overload can reduce adiponectin secretion,[26] promote adiponectin resistance,[27] and eventually lead to insulin resistance.

Relationship Between Iron Overload and Diabetes Complications

In terms of large vascular complications, the study by Mokhtari et al showed that SF is closely linked with the possibility of occurrence and severity of coronary disease.[28] Although the relationship between iron overload and AS has been controversial,[29] the latest study maintains that iron overload is an important risk factor for AS.[30]

In terms of microvascular complications, relevant animal model studies found a significant increase in retinal iron accumulation in diabetic mice compared with non-diabetic mice, and that iron overload accelerated the progression of retinopathy in mice.[31] A possible mechanism is that iron overload destroys the function and integrity of the blood-retinal barrier through the oxygen free radicals and inflammatory reactions generated by oxidative stress.[31] Relevant studies of diabetic nephropathy have found an increase in the iron concentration in the kidney. This means that iron overload can aggravate kidney damage through ROS produced by oxidative stress.[32]

Neuropathy occurs slowly in animal models of diabetes, so few studies have been conducted. The mechanisms of iron overload and neuropathy remain unclear.

Iron Overload and Possible Pathogenesis of Atherosclerosis

Lipid Peroxidation

Iron in the human body exists mainly in the form of $Fe2^{+}$, while $Fe2^{+}$ has a strong oxidability. It is believed that iron can aggravate ROS accumulation through Haber-Weiss reaction and Fenton reaction, and promote lipid peroxidation of endothelial cells, which can lead to iron death of endothelial cells, damage endothelial blood vessels, and affect its dilation function. ROS induces lipid peroxidation (LP) by affecting the biological activity of superoxide dismutase (SOD).[33] The occurrence of LP causes the rupture and remodeling of lipids, destroys the physiological function of the cell membrane, and damages cells, tissues and even organs.[34] LP also promotes the generation of low-density lipoprotein-C (LDL-C)[35] and engulfment it into foam cells, which slowly deform and disassemble, producing a chyac-like substance and eventually leading to the formation of vascular atherosclerotic plaques. Among them, the highly active free radicals generated by oxidized LDL-C can enhance ferritin cleavage to release active Fe2+ and Fe2+ can stimulate oxygen radicals into more oxidized hydroxyl radicals,[36] thus opening a series of chain effects, participating in and promoting the occurrence and development of AS, and even leading to vascular lumen stenosis and occlusion.

Inflammatory Response and Endothelial Dysfunction

Iron overload can lead to altered lipid profiles, sustained endothelial activation, elevated inflammatory mediators, altered vascular permeability, and reduced nitric oxide availability, resulting in vasodilatory dysfunction and AS. Hu et al demonstrated in mice that high-iron diet induced the expression of inflammatory factors in vivo and also promotes macrophage polarization, that is, iron overload accelerates AS by induction of inflammatory response and increasing glycolysis of macrophages.[37] Iron deposition in the middle artery was associated with plaque formation and arterial diastolic and systolic dysfunctions as demonstrated by Vinchi et al.[38] In addition, iron ion accumulation in the body can induce the activation of related proinflammatory genes, release a large number of inflammatory cytokines during AS, produce various inflammatory mediators, increase the permeability of endothelial cells, slow blood flow, and damage tissue necrosis. The arterial wall inflammatory response generated by iron overload promotes AS formation, damage to vascular endothelial cells, and altered permeability of the cell membrane.[39] A large number of monocytes enter the vascular wall and the enlarged cellular space, and are swallowed to form foam cells, producing atherosclerotic plaque (Atherosclerotic plaque).[40] Mao Mao et al proposed that serum ferritin, as an acute phase protein, enhanced the inflammatory response in cells and tissues through the oxidation process, affected the function of various important cells, promoted the apoptosis of macrophages, and the development of AS.[41]

Other Possible Mechanisms

Zhang et al found that iron can be deposited on atherosclerotic plaques through multiple paths to bind iron to transferrin receptors and transport within the body,[42] further suggesting the possibility that iron overload is spatially associated with the occurrence of AS. A review shows that increased SF changes the ultrastructure of platelets and erythroid cells, promoting the activation and aggregation of platelets, and accelerating the progression of AS.[43] Elevated iron concentration in the body can increase hemoglobin concentration, red blood cell hematocrit, enhance blood viscosity, produce greater resistance to blood flow, slow down the blood flow speed and form thrombosis, and then fiber tissue hyperplasia, leading to arterial wall hardening, lumen stenosis, and eventually resulting in artery block or even occlusion.[44] Xu et al showed that iron overload can lead to calcification, phenotypic conversion, proliferation, and apoptosis in vascular smooth muscle cells, which in turn can affect the smooth muscle contraction and diastolic function.[30] In addition, iron overload can induce the formation of AS and plaque instability and rupture by affecting the expression of transferrin receptor 1 in the atherosclerotic plaque.[45]

In conclusion, iron overload can lead to iron accumulation in the artery through a variety of possible mechanisms, damage cells, affect vascular endothelial function, and eventually form atherosclerotic plaques, and even plaque rupture, which provides a physiological basis into the correlation between iron overload and diabetic LEAD.

Related Study of Iron Overload and Diabetic Lower Extremity-Arterial Disease

Correlation Between Iron Overload and Diabetic Lower Extremity-Arterial Disease

Type 2 diabetes already has peripheral vascular lesions early on, which is the formation of atherosclerotic plaques. Diabetes and atherosclerosis are linked through multiple pathological pathways. Studies have shown that patients with diabetes have a higher risk of atherosclerosis, and that diabetes accelerates the development of atherosclerosis.[46,47] Various causes lead to vascular endothelial damage, lipid and compound sugar deposition, macrophages transferred to foam cells, and then fibrotic tissue hyperplasia, calcium and salt calm, causing fiber necrosis of vascular intima, the formation of atherosclerotic substances,[6] vascular transformation and calcification.

Studies have long suggested that changes in SF play a role in endovascular lining lesions in diabetes patients with arterial lesions.[48,49] SF is involved in the occurrence and development of type 2 diabetes mellitus and its vascular lesions. Zhan et al analyzed the association between SF and glucose, hemoglobin A1c (HbA1c), insulin, inflammatory markers, and lipid markers in 8235 participants through multivariate logic and linear regression model and found that elevated serum ferritin levels were associated with higher risk of diabetes and higher levels of HbA1c.[50] Recent proteomic and molecular biology studies have shown that diseased tissue arteries contain higher levels of ferritin, further supporting the inference that ferritin is associated with atherosclerosis.[51] Many studies have speculated that SF can be used as one of the predictors of early arterial lesions in type 2 diabetes patients, and also as one of the observed indicators for the development of arterial lesions in type 2 diabetes.[17,52]

Research Progress of Iron Overload and Diabetic Lower Extremity-Arterial Disease

Although the role of SF and IO in atherosclerosis remains debated,[51] deep research into the biological regulation of SF and iron content reveals the remarkable significance of developing new diagnostic or therapeutic approaches for diabetes and atherosclerotic diseases.[53] In addition, according to the guidelines, LEAD can be divided into the following 5 Fontaine stages: stage I-asymptomatic, stage IIa-mild intermittent claudication, stage IIb-moderate to severe intermittent claudication, stage III–ischemic static pain, stage IV–ischemic ulcer or gangrene. Relevant studies of LEAD stages and iron overload have rarely been reported, and the more refined pathological relationship between iron overload and LEAD needs further investigation.

Questions and Outlook

Iron overload in the body is not only a pathogenic factor for diabetes but also a risk factor for diabetic lower extremity-arterial disease. A large number of studies have confirmed that the positive correlation between SF expression and the incidence of diabetes, but there are the following problems: ①The interrelationship between SF and LEAD. Is elevated SF the cause of LEAD or a byproduct in the pathogenesis? The specific relationship and the principle of interaction need further research. ②Whether SF is an independent risk factor for LEAD needs to be confirmed. ③The sites of iron and LDL-C interaction with each other and its significance for treatment have not been clarified.

Iron metabolism-related indicators, such as SF, are a simple, economical, and non-invasive laboratory indicator. In clinical practice, the iron metabolic status of diabetic patients can be evaluated and monitored early by measuring the iron metabolic indicators, so as to early evaluate the control of their metabolism and the risk of chronic complications.

Conclusion

Iron overload is closely related to lower limb artery disease in type 2 diabetes mellitus. Iron overload participates in the occurrence of diabetes and its complications, induces atherosclerosis and promotes lower limb arteriopathy in type 2 diabetes through a variety of mechanisms, such as lipid peroxidation, inflammation and affecting vascular endothelial function. However, more studies are needed to verify the relationship between iron overload and lower extremity arterial disease in type 2 diabetes.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

An ethics statement was not required for this study type, no human or animal subjects or materials were used.

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Disclosure

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