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Renal manifestations of hemochromatosis; an update to recent findings

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Abstract
Hemochromatosis is a genetic disorder that results in excessive iron absorption, followed by iron overload in various organs including the kidneys. IgA nephropathy, on the other hand, is the immunoglobulin A (IgA) deposition in the glomeruli mesangium. Hemochromatosis-associated IgA nephropathy is a condition described as both hemochromatosis and IgA nephropathy in an individual. Recently, there has been growing evidence suggesting a potential association between IgA nephropathy and hemochromatosis. Previous studies have indicated that individuals with hemochromatosis may have an increased risk of developing IgA nephropathy. Some studies suggest a higher prevalence of hemochromatosis-associated gene mutations particularly HFE gene mutations, in IgA nephropathy patients. These gene mutations may affect iron metabolism and contribute to the development of both conditions. Excessive iron in the kidney may also be associated with increasing inflammatory response and IgA deposition in the glomeruli. Treatment options for hemochromatosis-associated IgA include corticosteroids, RAS blockade, immunosuppressive agents, and supportive care for chronic kidney disease.
Keywords: IgA nephropathy, Hemochromatosis, Immunosuppressive agents, Chronic kidney disease, End-stage renal disease, Serum ferritin
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Introduction

Hemochromatosis is a genetic disorder characterized by an abnormal increase in iron absorption from the diet, leading to iron overload in various organs including the liver, heart, pancreas, and kidneys (1). Renal involvement in hemochromatosis refers to kidney damage and dysfunction due to excessive iron accumulation. In hemochromatosis, excess iron is deposited in the kidney glomeruli and distal tubules, resulting in progressive damage and kidney dysfunction (2). Several mechanisms contribute to kidney injury, including inflammation, oxidative stress, and fibrosis (3). The accumulation of iron in the kidney tubules can also impair their function, resulting in inadequate reabsorption and secretion processes, leading to electrolyte imbalances such as hypokalemia, hypomagnesemia, and hyperphosphatemia. It may also cause impaired acid-base balance, which leads to metabolic acidosis (4). Excessive iron deposition in the renal parenchyma may cause nephrocalcinosis. Consequently, kidney function may be impaired, resulting in kidney stones (2-5). Chronic iron overload in the kidneys triggers fibrotic changes, leading to progressive kidney damage and eventually end-stage renal disease (2,6). Hemochromatosis renal manifestations can vary from mild abnormalities in kidney function to more severe conditions such as end-stage renal disease (6,7). Proteinuria, hematuria, decreased urine output, hypertension, and fatigue are common manifestations. The diagnosis of renal involvement in hemochromatosis is generally conducted by a combination of clinical evaluations, laboratory tests (such as serum ferritin level), imaging studies (including ultrasound or magnetic resonance imaging [MRI]), and kidney biopsy if necessary (8,9). Hemochromatosis-associated immunoglobulin A (IgA) nephropathy is characterized by the deposition of iron and IgA immune complexes in the kidneys' glomeruli, leading to inflammation and damage (10,11).

This mini-review will focus on hemochromatosis-associated IgA nephropathy pathogenesis, clinical presentation, diagnosis, and management, in addition to the role of iron overload and immune dysregulation in the development of this renal disorder.

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Implication for health policy/practice/research/ medical education

Hemochromatosis is a genetic disorder characterized by excessive iron absorption followed by iron accumulation in different tissues. IgA nephropathy is one of the most common causes of chronic kidney disease, manifested by IgA depositions in the kidney's glomeruli. Shreds of evidence suggest an association between these two conditions, resulting in hemochromatosis-associated IgA nephropathy. The pathogenesis of this condition is not fully understood but may involve multiple factors. For instance, iron overload leads to oxidative stress and tissue damage in the kidneys, promoting inflammation and immune dysregulation. This inflammatory environment may trigger IgA deposition in the glomeruli mesangium. Genetic factors such as HFE gene mutations are another potential reason for this association. This paper gathers the latest information that was published about hemochromatosis-associated IgA nephropathy.

Search strategy

For this mini-review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ), and Embase, using different keywords including IgA nephropathy, hemochromatosis, immunosuppressive agents, chronic kidney disease, end-stage renal disease, serum ferritin, phlebotomy, iron chelation therapy, kidney biopsy and IgA deposition.

Discussion

IgA nephropathy is detected by the IgA antibody accumulation in the kidneys, leading to inflammation and damage (12). Hemochromatosis, on the other hand, is a genetic condition that may cause kidney damage by iron accumulation causing excess iron to accumulate in the body's organs and tissues (13). Recently, there has been growing evidence suggesting a potential association between IgA nephropathy and hemochromatosis. Previous studies have indicated that individuals with hemochromatosis may have an increased risk of developing IgA nephropathy (11,14). It is believed that iron overload caused by hemochromatosis may contribute to the extension and progression of IgA nephropathy since iron overload can promote oxidative stress and inflammation, which are known to play a role in the pathogenesis of IgA nephropathy (15,16). Previous studies also showed that iron metabolism is connected with chronic inflammation in IgA nephropathy, and both promote each other (15). Additionally, iron has been found to enhance the production of IgA antibodies, potentially increasing their deposition in kidneys (15,17,18). The High Fe2+ gene (HFE gene) encodes a transmembrane protein named human homeostatic iron regulator protein (HFE protein) that regulates iron uptake. Homozygous mutation in the HFE gene is the most common mutation in hemochromatosis patients. IgA nephropathy patients are often affected by hemochromatosis-associated gene mutations, notably the HFE gene mutation. These gene mutations may affect iron metabolism and contribute to the development of both conditions (14,19). Even in patients with chronic renal hemosiderosis, hemochromatosis alone does not usually result in kidney dysfunction. It seems that IgA nephropathy is responsible for the progressive kidney function deterioration. Hemochromatosis-associated IgA nephropathy diagnosis requires a combination of clinical evaluation, laboratory parameters, imaging studies, and kidney biopsy (10). Laboratory tests may reveal elevated serum ferritin levels and abnormal kidney function markers. Imaging studies such as MRI or computed tomography (CT) scans can assess iron deposition in various organs including kidneys (20,21). A kidney biopsy is often necessary to confirm the presence of IgA deposition and assess the severity of kidney damage (22). Management of hemochromatosis-associated IgA nephropathy involves addressing both iron overload and kidney disease. In a case report of a patient suffering from IgA nephropathy secondary to hemochromatosis, a steroid pulse followed by 30 mg/day oral prednisolone resulted in a 2.6 mg/dL decline in serum creatinine in less than a week (6,10). Treatment options may include supportive care, renin-angiotensin system (RAS) blockade, and immunosuppressive therapy. Regular monitoring of iron levels, kidney function, and proteinuria is essential to assess treatment response and adjust management accordingly. Supportive care treatment includes but is not limited to blood pressure control, fluid, sodium, and protein intake management, and lifestyle modification. High-dose corticosteroids regain kidney function fast, the adverse effects limit their usage though. Infection is common in patients who receive corticosteroids, especially in obese patients. Corticosteroids are still a wise choice when IgA nephropathy propagates with rapid progressive glomerulopathy. RAS blockade by angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may improve kidney function and proteinuria. Adding mycophenolate mofetil to RAS blockade is associated with a more favorable outcome (23).

Conclusion

Hemochromatosis-associated IgA nephropathy is an uncommon hemochromatosis complication that affects the kidneys. Iron accumulation in renal tubules may interfere with kidney function and electrolyte imbalance as well as inflammation and fibrosis. An inflammatory response and oxidative stress may lead to IgA deposition in the glomeruli. Hemochromatosis-associated gene mutations, particularly those in the HFE gene, are prevalent in patients suffering from IgA nephropathy. Despite chronic renal hemosiderosis, hemochromatosis alone is rarely associated with kidney dysfunction. It seems that IgA nephropathy is responsible for progressive kidney function deterioration. Treatment options may include supportive care, RAS blockade, and immunosuppressive therapy. Further investigations may reveal the exact mechanisms that are involved in the pathogenesis of the disease and the proper treatment for patients.

Authors' contribution

Conceptualization: Shahrzad Alimohammadi.
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Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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