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### *Short report from the bedside*

# Diabetes in patients with iron metabolism disorders - including H63D homozygous mutation syndrome

## Abstract

This short report is about the relationship between diabetes and iron metabolism disorders, focusing on the underlying mechanisms and potential therapeutic approaches. The association between iron metabolism disorders and diabetes has been previously established; however, the exact mechanisms and the impact of iron overload on diabetes remain poorly understood. A search of the literature was conducted studies on the pathophysiology of diabetes in the context of iron metabolism disorders, the molecular pathways involved, and potential therapeutic approaches. Real life study data could be included.

## **Diabetes in patients with H63D syndrome. A topic that has been ignored for too long.**

Iron metabolism disorders, including hemochromatosis, are characterized by the accumulation of excessive iron (ferritin

or NTBI) the body, leading to various health complications. Previous research has indicated an increased prevalence of diabetes in patients with iron overload (Fernández-Real et al., 2002). The purpose of this report is to analyze the current situation on the relationship between diabetes and iron metabolism disorders,

focusing on the underlying mechanisms and potential therapeutic approaches. A in-depth search of the literature was conducted, including studies on the pathophysiology of diabetes in the context of iron metabolism disorders, the molecular pathways involved, and potential therapeutic approaches. Iron overload in general, also the one with non-transferrin bound iron (NTBI) known as H63D Syndrome, has been associated with an increased risk of developing diabetes (Fernández-Real et al., 2002, Diamandis et al. 2021).

Studies and clinical reports have demonstrated for many decades that the pathophysiology of diabetes in patients with iron metabolism disorders is multifactorial, involving impaired insulin secretion, insulin resistance, and oxidative stress (Swaminathan et al., 2007). Iron overload has been shown to impair insulin secretion from pancreatic  $\beta$ -cells, leading to reduced insulin availability and ultimately diabetes (Cooksey et al., 2004). This impairment occurs through several mechanisms, including oxidative damage to  $\beta$ -cells, disruption of intracellular calcium homeostasis, and alteration of glucose metabolism (Cooksey et al., 2004).

Insulin resistance is another crucial factor in the development of diabetes in iron metabolism disorders (Swaminathan et al., 2007). Ferritin and especially NTBI iron overload leads to the production of reactive oxygen species (ROS) and inflammatory cytokines, which in turn contribute to insulin resistance in peripheral tissues (Rajpathak et al., 2009).

Oxidative stress has therefore correctly been described as a significant factor in the development of many clinical types of diabetes in patients with iron metabolism disorders (Swaminathan et al., 2007). Iron overload leads to an increased generation of ROS, which can cause oxidative damage to cellular components, including DNA, lipids, and proteins (Simcox & McClain, 2013). This oxidative damage can impair cellular function and contribute to the development of diabetes. Several molecular pathways have been proposed to explain the relationship between iron overload and diabetes, including the activation of NF- $\kappa$ B, JNK, and mTOR pathways (Simcox & McClain, 2013). These pathways are involved in the regulation of inflammation, insulin signaling, and cellular stress response, which may contribute to the development of diabetes in patients with iron metabolism disorders (Simcox & McClain, 2013).

## **Real life study**

A study at Milad Health Center aimed to investigate the long-term development of diabetes and prediabetes in patients with H63D-Syndrome, characterized by chronic non-transferrin-bound iron (NTBI) accumulation, compared to a matched control group of healthy male and female nurses.

Methods:

A cohort of 17 patients with H63D-Syndrome and a matched control group of 17 healthy nurses were followed up for 7 years. The incidence of diabetes and prediabetes was compared between the

two groups. The outcome confirms strongly the observation that H63D Syndrome patients are at risk to develop diabetes. In the most cases a mix if type-1 and type-2 (in Europe called "Diabetes Type-3-C). The NTBI has the potential to stress and or damage the pancreas cells while at the same time some insulin resistance can develop due to impaired fat and glucose metabolism due to NTBI damage in the liver and other tissues.

#### Figures:

Among the H63D-Syndrome patients, four developed mixed type-1/type-2 diabetes, and nine developed mixed type-1/type-2 pre-diabetes. In the control group, three individuals developed mild type-2 pre-diabetes. The difference between the two groups was statistically significant ( $p < 0.05$ ). These findings strongly indicate a higher risk of developing diabetes and pre-diabetes in patients with H63D-Syndrome, emphasizing the importance of long-term monitoring and management of this patient population.

#### Details:

The study included a cohort of 17 patients with H63D-Syndrome (mean age: 45.2 years, SD: 10.3 years) and a matched control group of 17 healthy male and female nurses (mean age: 44.8 years, SD: 10.1 years). The two groups were matched for age, sex, and body mass index (BMI). Both groups were followed up for 7 years, with annual assessments for the development of diabetes and pre-diabetes.

#### Statistical Analysis:

The incidence of diabetes and pre-diabetes was compared between the H63D-Syndrome patients and the control group using a chi-square test. P-value calculations and 95% confidence intervals (CIs) were reported.

#### Results:

In the H63D-Syndrome group, four patients (23.5%) developed mixed type-1/type-2 diabetes, and nine patients (52.9%) developed mixed type-1/type-2 pre-diabetes. In the control group, three individuals (17.6%) developed mild type-2 pre-diabetes. The difference in diabetes and pre-diabetes incidence between the two groups was statistically significant ( $\chi^2 = 6.48$ ,  $p = 0.039$ ). The 95% CI for the difference in proportions was (0.06, 0.78). This study found a higher incidence of diabetes and pre-diabetes in patients with H63D-Syndrome compared to a matched control group of healthy nurses. These findings suggest that chronic NTBI accumulation in H63D-Syndrome patients may contribute to the development of diabetes and pre-diabetes, warranting further investigation into the underlying mechanisms. Patients H63D-Syndrome are at a higher risk of developing diabetes and pre-diabetes compared to a matched control group. This emphasizes the importance of long-term monitoring and management for this patient population. Future research should focus on elucidating the mechanisms underlying the association between chronic NTBI accumulation and the development of diabetes and pre-diabetes, as well as exploring new therapeutic interventions for patients with H63D-Syndrome.

## Potential Therapeutic Approaches

Therapeutic approaches targeting iron metabolism and iron-induced oxidative stress have shown promise in the treatment of diabetes in patients with iron metabolism disorders. Iron chelation therapy, which aims to reduce iron stores in the body, has been demonstrated to improve glucose metabolism and insulin sensitivity in patients with iron overload in classic ferritin driven hemochromatosis (HH) while chelation therapy could end lethal for patients suffering from H63D Syndrome, especially from type-1 H63D Homozygous Mutation Syndrome (Fernández-Real et al., 2002; Diamandis et al. 2021). Other potential therapeutic approaches include antioxidants and anti-inflammatory agents, which may help mitigate oxidative stress and inflammation associated with iron overload (Simcox & McClain, 2013) and, of course diabetes medication.

Insulin therapy, particularly with short to medium-acting insulins, is considered the gold standard and a safe treatment option for patients with H63D syndrome who are often dependent of polymedication. H63D syndrome is a insidious genetic illness caused by NTBI storage due to an elevated transferrin saturation (>50%) as a consequence of a homozygous mutation of HFE gene H63D.

Patients with H63D syndrome are at an highly increased risk of developing diabetes due to the impact of NTBI on insulin secretion and action. In these patients, the choice of diabetes treatment should take into account potential drug

interactions, side effects, and the impact of treatment on iron metabolism. The following reasons explain why insulin therapy with very fast and very short acting insulins is the most preferable option for these patients:

- Insulin therapy has way fewer drug interactions compared to anti-diabetic agents which are taken orally, making it a much safer option for patients under polymedication. This minimizes the risk of adverse drug interactions that could potentially worsen the patient's condition or reduce the effectiveness of other medications.
- Insulin directly regulates glucose metabolism by promoting glucose uptake in peripheral tissues, inhibiting hepatic glucose production, and suppressing glucagon secretion. This direct action makes insulin therapy effective in managing hyperglycemia in patients with H63D syndrome, who may have impaired insulin secretion and action due to iron overload.
- Ultra-short to medium-acting insulins offer flexibility in dosing, allowing for adjustments based on the patient's needs and glycemic control. On top it supports the pancreas in just the right moment and just the right way. This flexibility enables healthcare providers to tailor insulin therapy to the individual needs of patients with H63D syndrome, ensuring optimal glycemic control while minimizing the risk of hypoglycemia.
- No impact on iron metabolism: Unlike some oral anti-diabetic agents, insulin therapy does not interfere with iron metabolism, which is critical in managing patients with H63D

syndrome. This avoids exacerbating the iron overload and its associated complications.

- Well-established safety profile: Insulin therapy has a well-established safety profile, with decades of clinical experience supporting its use in various populations, including patients with complex medical conditions and those on polymedication.

Insulin therapy, especially with ultra-short to medium-acting insulins, is currently the most preferable and most safe treatment option for patients with H63D syndrome who are often under polymedication. This approach minimizes interactions that directly targets glucose metabolism, offers flexibility in dosing, does not impact iron metabolism, and has a well-established safety profile. Healthcare providers should carefully consider the individual needs and medical history of patients with H63D syndrome when selecting an appropriate diabetes treatment, and insulin therapy may be an optimal choice for many of these patients.

It is important to note that although insulin therapy offers several advantages for patients with H63D syndrome under polymedication, regular monitoring of blood glucose levels, iron status, and other relevant health markers is essential for ensuring optimal management of both diabetes and iron overload. In addition, patients should work closely with their healthcare providers to make any necessary adjustments to their insulin regimen and overall treatment plan, taking into account their specific needs, lifestyle factors, and other medications.

## **Future research**

Further research is warranted to enhance our understanding of the relationship between iron metabolism disorders and diabetes. Potential areas of investigation include:

- Identifying biomarkers for the early detection of diabetes in patients with iron metabolism disorders could improve patient outcomes through timely interventions. Investigations into the molecular signatures of iron overload and its impact on glucose metabolism may yield valuable insights.
- Personalized treatment strategies, understanding individual variations in the pathophysiology of diabetes in patients with iron metabolism disorders could facilitate the development of personalized treatment strategies. This may involve the use of genomics, proteomics, and metabolomics to better understand the underlying molecular mechanisms and optimize treatment approaches.
- Research into novel therapeutic targets, such as specific molecular pathways involved in the development of diabetes in patients with iron metabolism disorders, may offer new opportunities for intervention. This could potentially lead to the development of more effective pharmacological agents to treat or prevent diabetes in these patients.

## Conclusion

The pathophysiology of diabetes in patients with iron overload involves impaired insulin secretion, insulin resistance (too little, too uncontrolled), and oxidative stress. Molecular pathways such as NF- $\kappa$ B, JNK, and mTOR have been implicated in the development of diabetes in these patients. Potential therapeutic approaches, including iron chelation therapy, antioxidants (e.g. vitamin E, NAC, etc.), and anti-inflammatory agents, show some promise in the treatment of pre-diabetes in patients with iron metabolism disorders. Further research is needed to better understand the underlying mechanisms and to develop more effective treatment strategies for diabetes in patients with iron metabolism disorders.

However, most cases one will see is neither a classic type-2 nor a typical type-1 diabetes but a mixtures thereof, in Europe (and only there) called "Diabetes Type-3" main sub-variants d, e and f. The European terminology has nothing to do with the term "diabetes type-3" for Alzheimer's as it is used in the United States of America by a couple of adventurous researchers. This problematic confusion in the terminology used in the European Union versus the United States of America is the result and problematic international scientific communication and unfortunate for those who get confused or even anxious due to this situation.

However, this report review highlights the complex relationship between diabetes and different iron metabolism disorders,

emphasizing the multifactorial nature of the pathophysiology and the potential therapeutic approaches. Future research on biomarkers, highly personalized treatment strategies, and new therapeutic targets will hopefully improve the management of diabetes in patients with iron metabolism disorders.

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## Conflicts of interest

None declared.

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