Salahaddin University-Erbil

The relationship between T2DM and a high level of hepcidin

Prepared By:

Rayan Star Aziz

Fatima Raqib Hassan

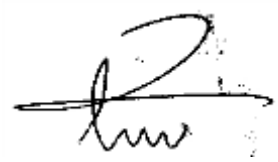
Supervised by:

Lecturer*:* Hemn J. Majeed

April, 2024

CERTIFICATE

The project has been written under my supervision and has been submitted for the award of the degree of B.Sc. in **chemistry** with my approval as supervisor.

Signature  Name: supervisor: Hemn J. Majeed

Date: 5 / 4 / 2024

I coniform that all requirements have been fulfilled.

Research project lecturer

Signature:

Name: **Asst. prof. Dr. Dler D. Kurda**

Date: / / 2024

Dedication

To all my family and friends

To all my teachers, especially my supervisor

To all who helped me to learn

Acknowledgment

Before all things thanks to Allah to giving us, a good health and an ability for doing this research. And then thanks a lot for the Salahaddin university college of education and department of chemistry to let me a chance for doing this project that helped me it increases my knowledge and skills I would also like to thank my supervisor and I am seriously to my kindest and scientific supervisors, Mr. Hemn j. Majeed for. For their supervision and precious scientific guidance and to prepare the research. And helped me for complete this project. I thank go to the everyone who support and helped me to finished this project.

Abstract

Type 2 diabetes mellitus is a chronic metabolic disorder characterized by high blood sugar levels, insulin resistance, and relative insulin deficiency. It typically develops in adulthood and is associated with lifestyle factors such as obesity, physical inactivity, and genetic predisposition. Hepcidin is a peptide hormone primarily produced by the liver that plays a key role in regulating iron metabolism in the body. It helps control the absorption of iron from the intestine and its release from iron-storing cells, thereby maintaining iron balance in the bloodstream.

In general, in this review we will discuss types and causes of diabetes disease, hepcidin horman and their role in disease as well as insulin hormone, and also deliberate the relationship between T2DM and a high level of hepcidin, Overall, the relationship between T2DM and high levels of hepcidin involves complex interactions among insulin resistance, inflammation, oxidative stress, and hepatic dysfunction, contributing to dysregulated iron metabolism and potentially worsening outcomes in diabetic individuals.

Keyword: Diabetes, Types of diabetes, Insulin & Hepcidin hormone.

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Abbreviation	Full name
T2DM	Type two diabetes mellitus.
T1DM	Type one diabetes mellitus.
T2D	Type two diabetes.
T1D	Type one diabetes.
ROS	Reactive oxygen species.
DM	Diabetes mellitus.
IDF	International diabetes federation.
GDM	Gestational diabetes mellitus.
HAMP	Human hepcidin gene.
FPN	Ferro protine.
HJV	Hemojuvelin.
BMP6	Bone morphogenic protiens.
BMP	Receptors.
HFE	Human hemostatic protien.
TF	Transferrin.
TRF1	Transferrin receptor 1.
TRF2	Transferrin receptor 2.
MT-2	Matriptase-2.
NEO	Neoginin.
SMAD	Sons of mother against decapentaplegic.
STAT3	Signal transducer and activator of transcription-3.
JAK2	Janus kinase 2.

1- Introduction:

Recently, attention has been shifting towards the iron regulatory hormone hepcidin and its possible role in the aetiopathogenesis of type 2 diabetes (T2D) (Aregbesola, Voutilainen et al. 2015). Diabetes mellitus is a group of metabolic diseases characterized by hyper glycaemia resulting from defects in insulin secretion or insulin action, or both. Diabetes and its complications have become a major public health problem in the world and its prevention has become a public health priority. Increasing evidence now suggests a potential role of iron in the pathogenesis of Type 2 DM. Iron is a strong pro-oxidant that catalyses several cellular reactions leading to the formation of reactive oxygen species (ROS) and resulting in elevated oxidative stress, interfering with insulin secretion which is proposed to contribute to an increased risk of Type 2 DM (Jiang, Sun et al. 2011).

Evidence suggests that iron plays a role in the pathogenesis of Type 2 diabetes mellitus. Iron influences glucose metabolism, even in the absence of significant iron overload. Mildly elevated body iron stores are associated with increased fasting serum insulin and blood glucose. Lowering iron stores by venesection increases peripheral insulin sensitivity in patients with high-ferritin Type 2 diabetes. Hepcidin is the key hormone regulating iron homeostasis. It is a 25-amino-acid peptide predominantly synthesized in the liver. Hepatic secretion of hepcidin in response to iron overload negatively regulates iron homeostasis. Hepcidin prevents iron efflux from enterocytes, macrophages and hepatocytes into the plasma by inducing internalization and degradation of the iron exporter ferroportin in these cells (Ganz and Nemeth 2012).

Diabetes is defined as a state of hyperglycemia in either fasting or postprandial states. The chronic hyperglycemia of diabetes mellitus (DM) is associated with end organ damage, dysfunction, and failure in organs and tissues including the retina, kidney, nerves, heart, and blood vessels. The International Diabetes Federation (IDF) estimates an overall prevalence of diabetes mellitus to be 366 million in 2011, and this is expected to rise to 552 million by 2030 (Nasri, Shirzad et al. 2015) (Alam, Asghar et al. 2014).

Type 2 diabetes mellitus (T2DM) is an expanding global health problem, closely linked to the epidemic of obesity. Individuals with T2DM are at high risk for both microvascular

complications (including retinopathy, nephropathy and neuropathy) and macrovascular complications (such as cardiovascular comorbidities), owing to hyperglycaemia and individual components of the insulin resistance (metabolic) syndrome. Environmental factors (for example, obesity, an unhealthy diet and physical inactivity) and genetic factors contribute to the multiple pathophysiological disturbances that are responsible for impaired glucose homeostasis in T2DM. Insulin resistance and impaired insulin secretion remain the core defects in T2DM, but at least six other pathophysiological abnormalities contribute to the dysregulation of glucose metabolism (DeFronzo, Ferrannini et al. 2015).

2. Insulin

Insulin and Insulin Signaling Insulin is a 51 amino acid dipeptide containing an A chain and a B chain linked by 2 disulfide bonds derived from cysteine residues. The A chain has 21 amino acids and the B chain 30 amino acids. Insulin is encoded by the short arm of chromosome 11 in pancreatic β-cells as 100 amino acids (referred to as pre-proinsulin) which comprises a signal peptide, the B chain, a connecting (C) peptide and the A chain (Rachdaoui 2020).

Insulin is a polypeptide hormone mainly secreted by β cells in the islets of Langerhans of the pancreas. The hormone potentially coordinates with glucagon to modulate blood glucose levels; insulin acts via an anabolic pathway, while glucagon performs catabolic functions. Insulin regulates glucose levels in the bloodstream and induces glucose storage in the liver, muscles, and adipose tissue, resulting in overall weight gain. The modulation of a wide range of physiological processes by insulin makes its synthesis and levels critical in the onset and progression of several chronic diseases (Rahman, Hossain et al. 2021).

Insulin plays an indispensable role in the management of hyperglycaemia that arises in a variety of settings, including Type I and II diabetes, gestational diabetes, as well as is in hyperglycaemia following a severe inflammatory insult. However, insulin receptors are also expressed on a range of cells that are not canonically implicated in glucose homeostasis. This includes immune cells, where the anti-inflammatory effects of insulin have been repeatedly reported. However, recent findings have also implicated a more

involved role for insulin in shaping the immune response during an infection (Van Niekerk, Christowitz et al. 2020).

is used alone or in combination with oral hypoglycemic agents. Augmentation therapy with basal insulin is useful if some beta cell function remains. Replacement of basal-bolus insulin is necessary if beta cell exhaustion occurs. Rescue therapy using replacement is necessary in cases of glucose toxicity which should mimic the normal release of insulin by the beta cells of the pancreas. Insulin comes in injectable forms - rapid acting, short acting, intermediate acting and long acting. The long-acting forms are less likely to cause hypoglycemia compared to the short acting forms (Mayfield and White 2004).

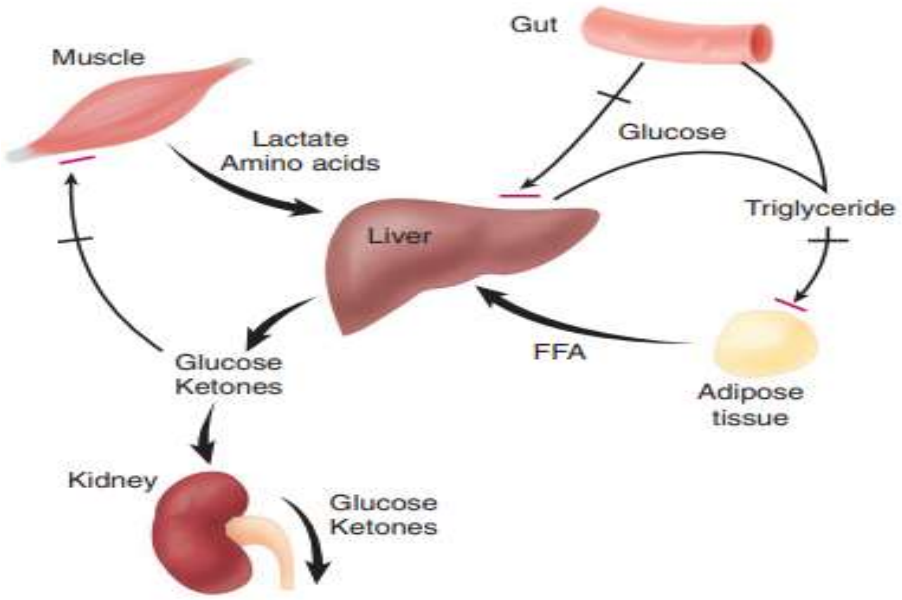

FIGURE 1. Effects of severe insulin deficiency on body fuel metabolism. Lack of insulin leads to mobilization of substrates for gluconeogenesis and ketogenesis from muscle and adipose tissue, accelerated production of glucose and ketones by the liver, and impaired removal of endogenous and exogenous fuels by insulin-responsive tissues. The net results are severe hyperglycemia and hyperketonemia that overwhelm renal removal mechanisms. FFA = free fatty acids.

3. Types of Diabetes Mellitus

3.1 Type 1 diabetes mellitus:

Type 1 diabetes mellitus (T1DM), also known as autoimmune diabetes, is a chronic disease characterized by insulin deficiency due to pancreatic β-cell loss and leads to hyperglycaemia (Eizirik, Pasquali et al. 2020).

Although the age of symptomatic onset is usually during childhood or adolescence, symptoms can sometimes develop much later. Although the aetiology of T1DM is not completely understood, the pathogenesis of the disease is thought to involve T cell-mediated destruction of β-cells (Quattrin, Mastrandrea et al. 2023).

Islet-targeting autoantibodies that target insulin, 65 kDa glutamic acid decarboxylase, insulinoma-associated protein 2 and zinc transporter 8 — all of which are proteins associated with secretory granules in β-cells — are biomarkers of T1DM-associated autoimmunity that are found months to years before symptom onset, and can be used to identify and study individuals who are at risk of developing T1DM. The type of autoantibody that appears first depends on the environmental trigger and on genetic factors (De Stefano, D'Onofrio et al. 2021).

The pathogenesis of T1DM can be divided into three stages depending on the absence or presence of hyperglycaemia and hyperglycaemia-associated symptoms (such as polyuria and thirst). A cure is not available, and patients depend on lifelong insulin injections; novel approaches to insulin treatment, such as insulin pumps, continuous glucose monitoring and hybrid closed-loop systems, are in development. Although intensive glycaemic control has reduced the incidence of microvascular and macrovascular complications, the majority of patients with T1DM are still developing these complications. Major research efforts are needed to achieve early diagnosis, prevent β-cell loss and develop better treatment options to improve the quality of life and prognosis of those affected (Katsarou, Gudbjörnsdottir et al. 2017).

Type 1 diabetes (T1D) is the commonest form of diabetes in children and adolescents, but type 2 diabetes, monogenic diabetes, and other forms also occur. Based studies on T1D incidence in children and adolescents aged up to 20 years. If more than one study was

available for a country, the following criteria were applied to select the most suitable: recent; population-based studies; high (90%) ascertainment level; covering a large part of the country; providing age- and sex-specific rates; and including the age ranges 0–14 and 15–19 years. For some countries where two or more studies met these criteria to an equal extent, results were combined by averaging age- and sex-specific rates. If a country did not have any information available, the incidence rate for ages under 15 years was estimated using data from a similar country, based on geographical proximity, income, and ethnicity. For ages 15–19 years, in the absence of specific country or area data the incidence rate was estimated using the average regional ratio of incidence in the 15–19 years and 0–14 years' age groups. Unless stated, data are presented for ages 0–14 years (Ogle, James et al. 2022).

3.2 Type 2 diabetes mellitus:

Type 2 diabetes mellitus (T2DM) is an expanding global health problem, closely linked to the epidemic of obesity. Individuals with T2DM are at high risk for both microvascular complications (including retinopathy, nephropathy and neuropathy) and macrovascular complications (such as cardiovascular comorbidities), owing to hyperglycaemia and individual components of the insulin resistance (metabolic) syndrome (Nithya, Sangavi et al. 2023).

Environmental factors (for example, obesity, an unhealthy diet and physical inactivity) and genetic factors contribute to the multiple pathophysiological disturbances that are responsible for impaired glucose homeostasis in T2DM. Insulin resistance and impaired insulin secretion remain the core defects in T2DM, but at least six other pathophysiological abnormalities contribute to the dysregulation of glucose metabolism. The multiple pathogenetic disturbances present in T2DM dictate that multiple antidiabetic agents, used in combination, will be required to maintain normoglycaemia. The treatment must not only be effective and safe but also improve the quality of life (Zhou, Xu et al. 2022).

Several novel medications are in development, but the greatest need is for agents that enhance insulin sensitivity, halt the progressive pancreatic β-cell failure that is

characteristic of T2DM and prevent or reverse the microvascular complications. For an illustrated summary of this Primer (DeFronzo, Ferrannini et al. 2015).

Diabetes mellitus is one of the most common metabolic diseases, affecting every tenth person on the planet. According to the latest edition of the IDF Diabetes Atlas, there are more than 537 million people who suffer from diabetes in the world. It has been recently predicted that 643 million people will have diabetes by 2030 (11.3% of the population). If trends continue, this number will jump to a staggering 783 million (12.2%) by 2045. A great majority of diabetics in the world suffer from type 2 diabetes mellitus, or non-insulin- dependent diabetes mellitus, a serious chronic disease that develops when the body does not produce enough insulin or is unable to use it effectively. Epidemiological studies of T2D conducted over the past decades indicate that T2D is a heterogeneous disease determined by genetic, epigenetic, and environmental risk fac- tors that closely interact with each other (Sheikhpour, Abolfathi et al. 2020).

A huge number of genetic studies have been conducted to elucidate the molecular mechanisms of T2D, including beta-cell dysfunction, insulin resistance, imbalance in redox homeostasis, and impairment of incretion signaling; from these studies, multiple disease-associated gene polymorphisms have been identified. Nonetheless, many aspects of the molecular mechanisms of disease pathogenesis remain poorly characterized. In particular, numerous studies have shown that oxidative stress (the imbalance caused by excess ROS or oxidants over the cell's ability to realize an effective antioxidant response) resulting from an imbalance between the production of free radicals and their neutralization by antioxidant enzymes is one of the major pathological disorders underlying the development and progression of type 2 diabetes (Azarova, Polonikov et al. 2023).

3.3 Gestational diabetes mellitus:

Gestational diabetes mellitus (GDM) is the most common medical complication of pregnancy. It is associated with maternal and neonatal adverse outcomes. Maintaining adequate blood glucose levels in GDM reduces morbidity for both mother and baby. There is a lack of uniform strategies for screening and diagnosing GDM globally. The initial treatment of GDM consists of diet and exercise. If these measures fail to achieve glycemic

goals, insulin should be initiated. Insulin analogs are more physiological than human insulin, and are associated with less risk of hypoglycemia, and may provide better glycemic control. Insulin lispro, aspart, and detemir are approved to be used in pregnancy. Insulin glargine is not approved in pregnancy, but the existing studies did not show any contraindications. The use of oral hypoglycemic agents; glyburide and metformin seem to be safe and effective in pregnancy (Alfadhli 2015).

Gestational diabetes mellitus (GDM) is a state of hyperglycemia (fasting plasma glucose ≥ 5.1 mmol/L, 1 h ≥ 10 mmol/L, 2 h ≥ 8.5 mmol/L during a 75 g oral glucose tolerance test according to IADPSG/WHO criteria) that is first diagnosed during pregnancy. GDM is one of the most common medical complications of pregnancy, and its inadequate treatment can lead to serious adverse health effects for the mother and child. According to the latest estimates of the International Diabetes Federation (IDF), GDM affects approximately 14.0% (95% confidence interval: 13.97–14.04%) of pregnancies worldwide, representing approximately 20 million births annually. Mothers with GDM are at risk of developing gestational hypertension, pre-eclampsia and termination of pregnancy via Caesarean section (Unnikrishnan, Singh et al. 2020).

In addition, GDM increases the risk of complications, including cardiovascular disease, obesity, and impaired carbohydrate metabolism, leading to the development of type 2 diabetes (T2DM) in both mother and infant. Despite numerous studies, the pathogenesis of GDM remains unclear, and the results obtained so far indicate a complex mechanism of interaction of many genetic, metabolic and environmental factors. The basic methods of treating GDM include an appropriate diet and increased physical activity, and when these are inadequate, pharmacotherapy, usually insulin therapy, is used. In developing countries, such as Brazil, oral hypoglycemic agents are also used, mainly metformin and glibenclamide (glyburide). The prevention and appropriate treatment of GDM are needed to reduce the morbidity, complications and economic effects of GDM that affect society, households and individuals (Modzelewski, Stefanowicz-Rutkowska et al. 2022).

Gestational diabetes mellitus (GDM) is a condition in which glucose intolerance is first recognized during pregnancy. After delivery, these affected women are advised to perform glucose tolerance test as to screen for type 2 diabetes mellitus (T2DM). However, the low

rate of postpartum screening for T2DM implies that we should make more efforts to improve their compliance. Postpartum follow-up screening is often a responsibility for obstetricians who often pay more attention to pregnancy-related diseases but might ignore the conversion of GDM to T2DM (Potzel 2021).

Although meta-analysis has shown that women with GDM have at least a seven-fold increased risk of developing T2DM, compared with those who have had a normal glycaemic pregnancy, there is no available meta-analysis on the incidence of T2DM after GDM. In addition, the reported incidence of T2DM after GDM varied widely from 1.3% to 70%. Consequently, demonstrating the incidence of T2DM among women with a history of GDM may help obstetricians attach more importance to this conversion and thus encourage more affected women to screen for T2DM (Li, Cheng et al. 2020).

4. Hepcidin

Hepcidin is primarily a hepatic peptide synthesized as a pre pro hepcidin, which is an 84-amino acid peptide. It undergoes enzymatic cleavage into a 60- to 64-residue prohepcidin peptide and finally into a biologically active 25-amino acid peptide hormone, hepcidin. Tissues of the kidney, pancreatic beta cell, macrophages and adipocytes have also been reported to produce hepcidin, but the role of this extra hepatic contribution to serum hepcidin is still unclear (Piperno, Mariani et al. 2009).

Hepcidin's role is to maintain iron homeostasis. It performs this action by regulating the expression and function of cell membrane-embedded ferroportin (FPN), the cellular iron exporter in iron-transporting cells. In response to the level of body iron stores, hepcidin regulates dietary iron absorption from the intestine and iron release from macrophages, by decreasing the cell surface expression of FPN (Aregbesola, Voutilainen et al. 2015).

Although, the peptide hormone that inhibits iron entry into the plasma compartment from the three main sources of iron: dietary absorption in the duodenum, the release of recycled iron from macrophages and the release of stored iron from hepatocytes (Fig. 2). Hepatocytes have evolved as the predominant producers of the iron-regulatory hormone hepcidin, perhaps because of their location astride the portal venous system that delivers iron absorbed in the intestine, because of their involvement in iron storage, or because of

their proximity to Kupffer cells that sense pathogens and recycle erythrocytes. The production of hepcidin is regulated by iron, so that more hepcidin is produced by hepatocytes when iron is abundant, limiting further iron absorption and release from stores. When iron is deficient, hepatocytes produce less or no hepcidin, allowing more iron to enter plasma. Both diferric plasma transferrin and stored iron in hepatocytes can stimulate hepcidin synthesis, by distinct mechanisms (De Domenico, Ward et al. 2007).

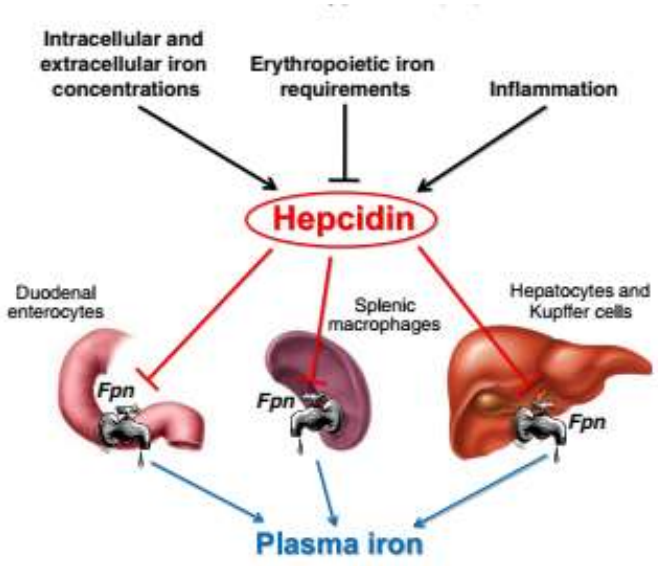

Fig. 2. Hepcidin has a central role in maintenance of iron homeostasis. Hepcidin synthesis is regulated at the transcriptional level by multiple stimuli. Intracellular and extracellular iron concentrations increase hepcidin transcription, as does inflammation, whereas increased erythropoietic activity suppresses hepcidin production. In turn, hepcidin regulates plasma iron concentrations by controlling ferroportin concentrations on iron-exporting cells including duodenal enterocytes, recycling macrophages of the spleen and liver, and hepatocytes.

4.1 Regulation of iron homeostasis

In all species, the concentration of iron in biological fluids is tightly regulated to provide iron as needed and to avoid toxicity, because iron excess can lead to the generation of reactive oxygen species. Iron homeostasis in mammals is regulated at the level of intestinal absorption, as there is no excretory pathway for iron. Hepcidin, a circulating peptide hormone, is the master regulator of systemic

iron homeostasis, coordinating the use and storage of iron with iron acquisition (Abbaspour, Hurrell et al. 2014).

This hormone is primarily produced by hepatocytes and is a negative regulator of iron entry into plasma (Figure 3). Hepcidin acts by binding to ferroportin, an iron transporter present on cells of the intestinal duodenum, macrophages, and cells of the placenta. Binding of hepcidin induces ferroportin internalization and degradation. The loss of ferroportin from the cell surface prevents iron entry into plasma (Figure 3A). Decreased iron entry into plasma results in low transferrin saturation, and less iron is delivered to the developing erythroblast. Conversely, decreased expression of hepcidin leads to increased cell surface ferroportin and increased iron absorption (Figure 3C) (De Domenico, Ward et al. 2007).

Plasma hepcidin levels are regulated by different stimuli, including cytokines, plasma iron, anemia, and hypoxia. Dysregulation of hepcidin expression results in iron disorders. Overexpression of hepcidin leads to the anemia of chronic disease, while low hepcidin production results in hereditary hemochromatosis with consequent iron accumulation in vital organs Most hereditary iron disorders result from inadequate hepcidin production relative to the degree of tissue iron accumulation (Patil, Thorat et al. 2018).

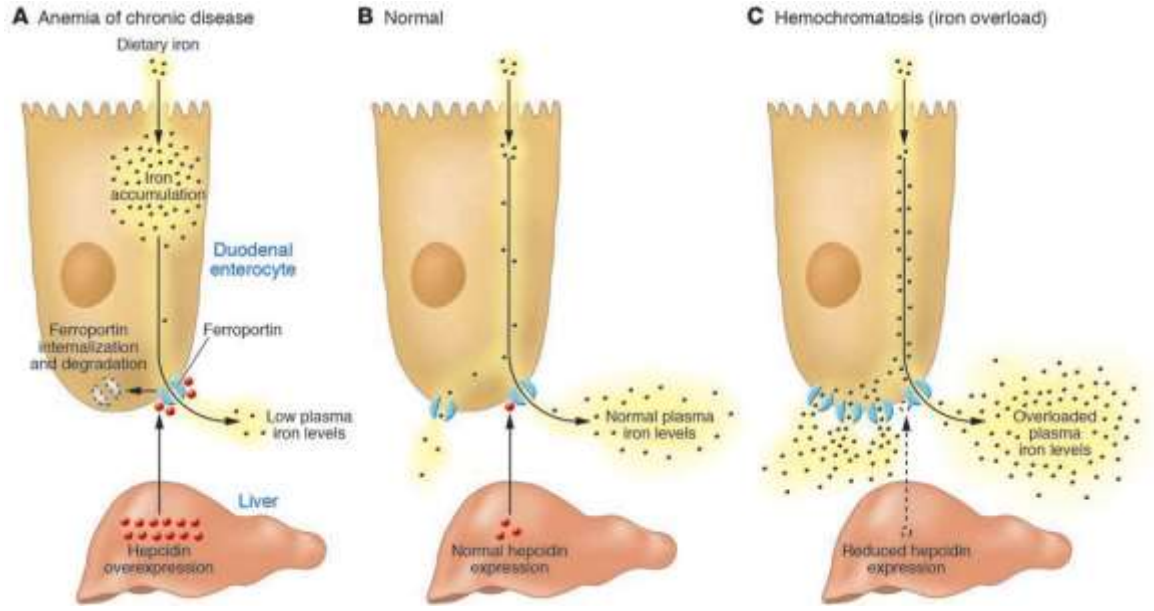

Figure 3: Hepcidin-mediated regulation of iron homeostasis. (**A**) Increased hepcidin expression by the liver results from inflammatory stimuli. High levels of hepcidin in the bloodstream result in the internalization and degradation of the iron exporter ferroportin. Loss of cell surface fer- roportin results in macrophage iron loading, low plasma iron levels, and decreased erythropoiesis due to decreased transferrin-bound iron. The decreased erythropoiesis gives rise to the anemia of chronic disease. (**B**) Normal hepcidin levels, in response to iron demand, regulate the level of iron import into plasma, normal transferrin saturation, and normal levels of erythropoiesis. (**C**) Hemochromatosis, or iron overload, results from insufficient hepcidin levels, causing increased iron import into plasma, high transferrin saturation, and excess iron deposition in the liver.

4.2 Structural configuration and functionality

Hepcidin is a long peptide hormone consisting of 25 amino acids with two different isoforms including 20 & 25 (Fig 4 and 5). It also exists in the form of preprohormone and prohormone containing 84 and 60 amino acids (aa), respectively. Furin and alpha-1 antitrypsin convertase enzyme is responsible for the conversion of prohepcidin to hepcidin. Structurally, hepcidin comprises of β-sheet (32%) and a β-hairpin loop like structure stabilized through disulfide linkages. NMR technique has been employed for determination of tertiary structure of hepcidin at 325K & 253K. In human, HAMP (Human hepcidin gene) is positioned on Chromosome (Rauf, Shariati et al. 2020).

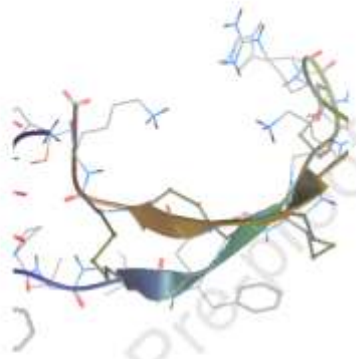

Fig4 Schematic of Hepcidin 20 isoform (modified by ICM software)

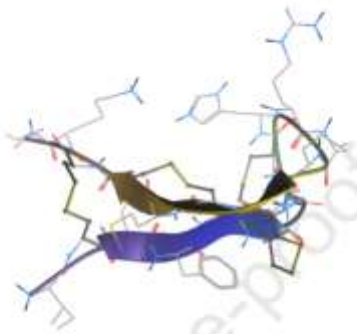

Fig5 Schematic of Hepcidin 25 isoform

4.3 Synthesis and regulation of hepcidin

Homeostatically, regulation of hepcidin is a multifaceted mechanism regularized by various inhibitory (erythropoiesis, anemia, and hypoxia) and stimulatory (increased iron content & inflammation) regulators. Production of hepcidin is stimulated due to excess concentration of plasma iron which eventually inhibits the uptake of dietary iron therefore prevents from further iron absorption. Similarly, synthesis of hepcidin is also elevated by interleukin-6 (IL-6), an inflammatory cytokine secreted during inflammatory conditions (Rauf, Shariati et al. 2020).

On the contrary, during iron deficiency conditions and elevated erythropoietic activities the production of hepcidin is suppressed. Regulation of hepcidin through iron is achieved by a feedback mechanism involving intracellular and extracellular iron sensors together with various signal transduction pathways. Regulation of hepcidin expression by plasma iron is a multifactorial process requiring coordination of several proteins like HJV (hemojuvelin), BMP6 (bone morphogenic proteins), BMPreceptors, HFE (human hemostatic protein), Tf (transferrin), TfR1 (transferrin receptor 1), TfR2 (transferrin receptor 2), MT-2 (matriptase-2), NEO (neoginin), SMAD (sons of mothers against decapentaplegic), and STAT3 (signal transducer and activator of transcription 3) (Sangkhae and Nemeth 2017).

Synthesis of hepcidin is regulated by expression of HAMP gene through bone morphogenetic proteinsons of mothers against decapentaplegic (BMP-SMAD) and signal transducer and activator of transcription 3 (STAT3) pathways. Hepcidin transcription in hepatocytes is controlled by iron-transferrin (Fe2-Tf) complex. In iron deficient conditions, synthesis of hepcidin is not achieved due to binding of Fe2- Tf complex to transferrin receptor-1 (TfR1) as this binding doesn’t activates the BMP-SMAD pathway. On the and production of hepcidin [28]. Inflammation is known to be another stimulator of hepcidin synthesis via Act-B (activin-B) and interleukin-6 (IL-6)-an inflammatory cytokinethrough BMP and JAK2-STAT3 (Janus kinase2-signal transducer and activator of transcription-3) pathways (Saad, Abd Rahman et al. 2022).

5. Discussion

Increases in hepcidin concentration reflect the degree of renal impairment. Obesity is also associated with elevated levels of serum hepcidin. The participants of hepcidin levels in patients with Type 2 diabetes had significantly higher serum creatinine and higher BMI than control subjects, suggesting that the higher hepcidin levels in patients with Type 2 diabetes were secondary to differences in renal function or BMI (Sam, Busbridge et al. 2013).

However, control subjects were matched for serum creatinine and BMI, excluding the confounding effects of renal impairment and body weight on serum hepcidin. In addition, measured the serum hepcidin: ferritin ratio in the two groups to allow an assessment of the appropriateness of hepcidin concentrations in response to the participants' iron burden (Bek, Üstüner et al. 2020). The gene encoding hepcidin has also been reported to be up-regulated by inflammation. High-sensitivity C-reactive protein (hsCRP) levels did not differ significantly between participants with or without Type 2 diabetes, making acute inflammation as a confounding factor unlikely (Jerzak, Lohmann et al. 2020). In addition, the fact that participants with Type 2 diabetes and polycystic ovary syndrome had lower circulating hepcidin levels than control subjects suggest that inflammation is not the predominant factor regulating hepcidin levels in these individuals. Indeed, a recent population study has shown that CRP is not a significant determinant of hepcidin-25 (Sam, Busbridge et al. 2013).

It is tempting to speculate that the reduction in hepcidin levels observed in individuals with Type 2 diabetes is attributable to reduced production associated with hyper insulinaemia. Insulin inhibits production of liver proteins, including sex hormone binding globulin and insulin-like growth factor-binding protein 1. However, the differences observed in our study may reflect changes in hepcidin clearance, or in both production and clearance (Le, Nestler et al. 2012).

In summary, participants with conditions associated with insulin resistance (i.e. Type 2 diabetes and polycystic ovary syndrome) had inadequate hepcidin concentrations for their iron load compared with weight-matched control subjects. The results of this small,

preliminary study require verifying in larger studies, and the significance of the altered hepcidin levels in the obese are currently unclear, complicating interpretation. However, given increased iron may play a role in the pathogenesis of Type 2 diabetes, these findings have implications for the treatment of insulin resistance and Type 2 diabetes (Aydın and Winters 2016).

6. Conclusion

The role of hepcidin in type 2 diabetes (T2D) remains uncertain despite its potential link to insulin resistance and T2D development. While hepcidin is involved in regulating body iron stores, its association with pro-inflammatory cytokines linked to T2D suggests a broader impact. Studies show varying hepcidin concentrations in different T2D populations, indicating a potential role in insulin resistance. However, it is inconclusive whether serum hepcidin independently contributes to T2D's development. Further experimental and clinical research is necessary to confirm or refute hepcidin's specific role in T2D pathogenesis.

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