# Serum hepcidin concentrations and type 2 diabetes

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## Abstract

Hepcidin is a peptide hormone with both paracrine and endocrine functions that help in maintaining body iron stores. Type 2 diabetes (T2D) is one of the sequelae of excess body iron stores; thus, iron regulatory hormone hepcidin may have a direct or at least an indirect role in the aetiopathogenesis of T2D. Both human and animal studies at molecular and genetic levels have attempted to establish a role for hepcidin in the development of T2D, and a few epidemiologic studies have also showed a link between hepcidin and T2D at population level, but the findings are still inconclusive. Recent data have suggested different pathways in which hepcidin could be associated with T2D with much emphasis on its primary or secondary role in insulin resistance. Some of the suggested pathways are *via* transcription modulator of hepcidin (STAT3); ferroportin 1 expression on the cells involved in iron transport; transmembrane protease 6 enzyme; and pro-inflammatory cytokines, interleukin (IL)-1, IL-6, tumor necrosis factor-$\alpha$ and IL-10. This review briefly reports the existing evidence on the possible links between hepcidin and T2D and concludes that more data are needed to confirm or refute hepcidin's role in the development of T2D. Examining this role could provide a further evidence base for iron in the aetiopathogenesis of T2D.

Key words: Serum hepcidin; Body iron; Diabetes; Type 2 diabetes; Insulin resistance

Core tip: Excess body iron has been demonstrated as an independent risk factor of type 2 diabetes (T2D). Lately, manipulation of serum hepcidin concentrations through the use of hepcidin agonist is being suggested in the management of iron overload diseases, of which T2D is one. However, little is known about the role of hepcidin in the development of T2D; hence, the need for a review of the existing evidence linking hepcidin and T2D. We discuss some of the main mechanisms through which hepcidin could be associated with T2D.

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## INTRODUCTION

Recently, attention has been shifting towards the iron-regulatory hormone hepcidin and its possible role in the aetiopathogenesis of type 2 diabetes (T2D). Hepcidin is primarily a hepatic peptide synthesized as a preprohepcidin, which is a 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[1-3]. Tissues of the kidney[4], pancreatic beta cell[5], macrophages[6] and adipocytes[7] have also been reported to produce hepcidin, but the role of this extra hepatic contribution to serum hepcidin is still unclear.

Hepcidin's role is to maintain iron homeostasis[8,9]. It performs this action by regulating the expression and function of cell membrane-embedded ferroportin (FPN)[10], the cellular iron exporter in iron-transporting cells[8,9]. 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.

Among the known diseases associated with the iron overload syndrome is T2D[11,12]. Even mildly elevated body iron has been demonstrated as a risk factor of T2D[13]. Some recent epidemiologic studies have tried to explore the association between serum hepcidin and T2D, with inconsistent findings[14-16]. Also, serum glucose concentration has been shown to regulate serum hepcidin[17]. As the underlying mechanisms between body iron stores and T2D still need further clarifications, hepcidin could provide some answers. Therefore, we reviewed the emerging links between hepcidin and T2D.

## ROLE OF HEPCIDIN IN IRON METABOLISM

Iron is a transition metal that is predominantly absorbed in the duodenum and upper jejunum[18]. The intestinal absorption of iron is in two waves of uptake of iron from intestinal lumen into the intestinal mucosa and from mucosa into the blood[19]. The two known forms of dietary iron are heme and non-heme iron. The heme iron is well absorbed by the body while the non heme iron predominantly in ferric form $Fe^{3+}$ is reduced to ferrous $Fe^{2+}$ form by the duodenal cytochrome b reductase[20]. This is transported by the divalent-cation transporter 1, a member of the natural- resistance-associated macrophage protein family, across the intestinal apical membrane[21], and later stored in the cytosol of ferritin or exported from the basolateral membrane of the enterocytes *via* FPN1. Because of its numerous health effects due to excess or deficiency, there is a need to strictly regulate iron within the physiological range.

Following a feedback mechanism, hepcidin is either up- or down-regulated by hepatocytes, depending on the level of body iron. Genetically, the mRNA of the gene (*HEPC*) coding for hepcidin increases with increase in body iron stores. At molecular level, hepcidin regulates iron transport from iron-exporting tissue into plasma by inhibiting intestinal iron absorption[9], release of iron from macrophages[22] and the placental passage of iron[23]. It performs these functions by binding to FPN1, which is expressed on the duodenal enterocytes, hepatocytes, placental syncytiotrophoblasts and the reticuloendothelia macrophages. It later internalizes and degrades FPN1 leading to a reduction in the ability of these cells to export iron into the plasma[8]. Conversely, there is re-expression of FPN1 on these iron-exporting cells in iron deficiency. However, it must be noted that body iron is not the only stimulus for hepcidin release. Hepcidin also responds to inflammation, infection, or both; as such, hepcidin appears to be a link between iron and inflammation. The antimicrobial properties of hepcidin would require conditions inconsistent with those observed in the serum, further emphasizing its iron-regulatory role rather than its broad-spectrum antibiotic activity[24].

## MECHANISMS LINKING HEPCIDIN AND T2D

Insulin resistance is a feature of T2D, and the relationship between iron metabolism and insulin resistance has been suggested to be bidirectional[25]. However, the association between hepcidin and insulin resistance remains vague. Molecular studies have showed that insulin stimulates hepcidin *via* STAT3, which is a novel transcription modulator of hepcidin[26]. A study by Wang *et al*[26], in which they induced diabetes in rats using streptozotocin with or without high-fat diet, showed a significant reduction in hepcidin expression in the liver, mediated by STAT3, causing abnormal elevation of FPN in the intestine, leading to serum iron elevation. Le Guenno *et al*[27] showed a 3.5-fold reduction in hepcidin mRNA in the group with higher insulin resistance when compared to the control group. Some previous studies[15,28,29] also have shown reduced hepcidin and prohepcidin concentrations in T2D subjects, suggesting insulin signal loss among T2D subjects with elevated iron stores.

Another mechanistic link between hepcidin and insulin is through glucose stimulation. One of the extrahepatic sources of serum hepcidin is the beta cell of the pancreas[5]. Insulin and hepcidin release have also been localized to beta cell granules where hepcidin may evoke its paracrine function. Thus, as glucose stimulates insulin release, there is a concomitant production of hepcidin. In the trial arm of a study by Aigner *et al*[17] in which they assessed the effect of glucose on serum iron and hepcidin, they found an increase in serum hepcidin in glucose-treated subjects compared to the control group treated with only water.

To further strengthen the association between hepcidin and T2D, a genome-wide association study (GWAS) by Gan *et al*[30] evaluated the association of transmembrane protease serine 6 (TMPRSS6) variants

**Table 1 Studies linking hepcidin/prohepcidin and type 2 diabetes (n = 6)**

| Ref. | Subject/study design | Measurement of hepcidin/prohepcidin | Assessment of T2D | Results |
|---|---|---|---|---|
| Sam et al[15] | British men and women/case-control | Active serum hepcidin-25 and serum hepcidin-ferritin ratio measured using RIA | HbA1c = 73.17 ± 4.12, mean ± SEM | Student's t-test/Mann-Whitney U-test to compare hepcidin (ng/mL) and hepcidin-ferritin ratio in T2D vs control showed: 20.00 (10.00-41.00) vs 33.00 (18.05-54.00), P < 0.05 and 0.22 (0.15-0.32) vs 0.45 (0.26-0.58), P < 0.01 |
| Guo et al[16] | Chinese men and women/case-control | Serum hepcidin measured using ELISA | Fasting plasma glucose > 7 mmol/L | Wilcoxon rank test to compare hepcidin (ng/mL) in T2D vs control showed: 34.44 ± 26.98 vs 32.34 ± 22.75, P = 0.72. Logistic regression analysis showed no significant association between serum hepcidin concentrations and onset of T2D: OR = 1.03, 95%CI: 0.87-1.22, P = 0.75 |
| Gan et al[30] | Chinese men and women/prospective cohort | Two TMPRSS6 SNPs [rs855791 (V736A) and rs4820268 (D521D)] of hepcidin by DNA genotyping | WHO 1999 criteria or previous history of T2D. Fasting plasma glucose < 5.6 mmol/L = normoglycemia | Logistic regression analysis showed both 2 TMPRSS6 SNPs to be significantly associated with decreased risk of T2D:OR$_{rs855791 (V736A)}$ = 0.801, 95%CI: 0.654-0.98, P = 0.0314 and OR$_{rs4820268(D521D)}$ = 0.802, 95%CI: 0.656-0.98, P = 0.0311 |
| Jiang et al[14] | Chinese men and women/case-control | Serum hepcidin measured using ELISA | Fasting glucose ≥ 7.0 mmol/L, non-fasting glucose ≥ 11.1 mmol/L, use of diabetes medication, or a self-reported physician diagnosis | Kruskal-Wallis test/student's t-test to compare hepcidin (μg/L) in T2D vs control showed: 778.91 ± 175.22 vs 513.44 ± 281.73, P < 0.001 |
| Aso et al[29] | Japanese men and women/case-control | Serum prohepcidin measured using ELIA | Not reported | Mann-Whitney U test to compare prohepcidin (ng/mL) in T2D vs control showed: 141 ± 42.6 vs 198.1 ± 36.7, P < 0.0001 |
| Fernández-Real et al[28] | Spanish men/cross-sectional and intervention | Serum prohepcidin measured using ELISA | Oral glucose tolerance test | Pearson's test showed significant correlation between circulating prohepcidin and fasting glucose (r = 0.27; P = 0.002) and HbA1c (r = 0.31; P < 0.0001). After phlebotomy, prohepcidin decreased significantly in T2D (P = 0.04) and in HFE gene mutation carrier (0.03) with a negative correlation between serum prohepcidin and insulin sensitivity (r = -0.50, P = 0.04) |

HbA1c: Glycated hemoglobin; T2D: Type 2 diabetes; RIA: Radioimmunoassay; ELISA: Enzyme linked immunosorbent assay; TMPRSS6: Transmembrane protease serine 6; SNPs: Single nucleotide polymorphisms; WHO: World Health Organization.

with risk of T2D. TMPRSS6 is an enzyme that inhibits the expression of hepcidin and its iron-lowering variants were used in their study. They found a reduced risk between the two TMPRSS6 variants and T2D (P = 0.0277). It is at least plausible to report that lower hepcidin concentration exacerbates insulin resistance seen in T2D, if causal relationship is yet to be fully established.

T2D is a dysmetabolic state characterized by low-grade chronic inflammation, and some authors have suggested a role for pro-inflammatory cytokines such as interleukins (IL)-1, IL-6 and tumor necrosis factor-α, in the development of insulin resistance[31], and in addition, IL-10 in T2D[32]. Increased circulating concentrations of these pro-inflammatory cytokines have also been observed in T2D subjects[33]. IL-6 is the most important inflammatory cytokine regulating hepcidin, and it performs this function during STAT3 phosphorylation, thus activating STAT3 for hepcidin gene expression[24]. STAT3 has been reported as necessary and sufficient for IL-6 responsiveness of the hepcidin promoter[34]. Thus, a low hepcidin concentration could stimulate IL-6, thereby enhancing its role in the development of T2D. A population-based study by Spranger et al[35] showed that IL-1β and IL-6 concentrations predict the risk of T2D. It is therefore enticing to speculate from the available evidence that hepcidin has a role in insulin resistance, the hallmark of T2D, through iron regulation from interrelated signals of STAT3, pro-inflammatory cytokines and the TMPRSS6 enzyme.

## STUDIES LINKING HEPCIDIN AND T2D

Existing data across different populations suggest a link between hepcidin and T2D (Table 1). There are four case-control studies[14-16,29]. In Sam et al[15] study, the authors measured serum hepcidin and serum hepcidin:ferritin ratio, which has been suggested as a marker of adequate hepcidin production for a particular iron dosage[36]. Aso et al[29] also measured serum ferritin, prohepcidin and adiponectin, and both studies showed decrease in serum hepcidin/prohepcidin in T2D subjects when compared with the healthy control[15,29]. Because of the confounding effect of obesity and renal status in serum hepcidin measurement, Sam et al[15] matched their control subjects for body mass index (BMI) and serum creatinine. Aso et al[29] assessed the correlation between adiponectin and prohepcidin in T2D subjects on the basis that adiponectin has a beneficial role in

glucose homeostasis[37]; hence, in glucose dysregulation observed in T2D, adiponectin and prohepcidin were expected to be low. In keeping with their hypothesis, Aso *et al*[29] found low concentrations of adiponectin and prohepcidin and a positive correlation between them in T2D subjects. The other two case-control studies[14,16] showed increased hepcidin/prohepcidin in T2D subjects when compared with the control group. In Jiang *et al*[14] study, T2D subjects had higher BMI and creatinine than the controls, thus suggesting obesity and renal impairment as possible reasons for the elevated serum hepcidin. Further, inflammatory markers, *i.e.*, IL-6, C-reactive protein and white cell counts, were elevated in T2D subjects compared to the controls, speculating inflammatory signals as the cause of the elevated hepcidin. One factor that could be responsible for the contradictory findings in the hepcidin-T2D association study is the wide range of assays with varying degrees of limitation that were used in evaluating serum hepcidin and serum prohepcidin. The lack of an accurate assay to evaluate serum hepcidin in the past may have influenced some investigators to choose prohepcidin, which is thought to be easier to measure due to its higher immunogenicity. Although some studies have shown that prohepcidin does not accurately reflect iron status and iron absorption[38], others have claimed that it is an indicator of endogenous hepcidin levels[39] in healthy subjects. This could be the reason why some studies used hepcidin while others used prohepcidin in examining the association between hepcidin and T2D. This is of particular interest in chronic renal disease patients in end-stage renal failure, where there is cross-reactivity in serum hepcidin-25 measurement with that of other hepcidins, *i.e.*, hepcidin-20 and hepcidin-22[40]. The question then arises whether the concentration of hepcidin in T2D subjects is primary or secondary to elevated body iron stores. The GWAS with a prospective design by Gan *et al*[30] at least provided further insight into the role of hepcidin as they showed a decreased risk in developing T2D with the iron-lowering variants of TMPRSS6. Also, in the trial arm of the three-in-one study by Fernández-Real *et al*[28], a negative correlation was observed between prohepcidin and insulin sensitivity after phlebotomy to reduce body iron stores, suggesting an association between prohepcidin and body iron in insulin sensitivity.

## CONCLUSION

In conclusion, we have briefly reviewed the emerging evidence pertaining to the role of hepcidin in T2D. Although the causative role of body iron in insulin resistance and T2D has been documented in both observational[41] and interventional studies[42], the role of hepcidin in this process is still uncertain. However, in addition to the regulatory role in body iron stores, serum hepcidin concentrations have been linked to pro-inflammatory cytokines, STAT3, and TMPRSS6, all of which have been associated with T2D. Data gathered in this review showed that hepcidin concentrations vary in different populations with T2D. Further, hepcidin has either a primary or secondary role in insulin resistance which characterizes T2D. However, it is still inconclusive from these accumulated data that serum hepcidin is an independent risk factor in the aetiopathogenesis of T2D. Thus, more experimental and clinical studies are needed to confirm or refute the claim that hepcidin has a role in T2D.

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