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SYSTEMATIC REVIEWS

Tipping the balance: Haemoglobinopathies and the risk of diabetes

Henry J Baldwin, Aislinn E Green, Kayleigh M Spellar, Philip J Arthur, Hannah G Phillips, Jeetesh V Patel

Henry J Baldwin, Aislinn E Green, Kayleigh M Spellar, Philip J Arthur, Hannah G Phillips, Jeetesh V Patel, University of Nottingham Medical School, Nottingham NG7 2UH, United Kingdom

Jeetesh V Patel, University of Birmingham Centre for Cardiovascular Sciences, Sandwell and West Birmingham Hospitals NHS Trust, West Midlands B18 7QH, United Kingdom

Jeetesh V Patel, Sandwell Medical Research Unit, Lyndon, Sandwell General Hospital, West Midlands B71 4HJ, United Kingdom

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Correspondence to: Dr. Jeetesh V Patel, Sandwell Medical Research Unit, Lyndon, Sandwell General Hospital, West Bromwich, West Midlands B71 4HJ,
United Kingdom. jeeteshp@gmail.com
Telephone: +44-121-5073971
Fax: +44-121-5073216

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Abstract

AIM: To establish a link between the risk of diabetes with haemoglobinopathies by examining available evidence of the effects of iron and blood glucose homeostasis from molecular to epidemiological perspectives.

METHODS: A systematic literature search was performed using electronic literature databases using various search terms. The International Diabetes Federation World Atlas was used to generate a list of populations with high rates of diabetes. PubMed, Scopus and Google Scholar were used to identify which of these populations also had a reported prevalence of haemoglobin abnormalities.

RESULTS: Abnormalities in iron homeostasis leads to increases in reactive oxygen species in the blood. This promotes oxidative stress which contributes to peripheral resistance to insulin in two ways: (1) reduced insulin/insulin receptor interaction; and (2) β-cell dysfunction. Hepcidin is crucial in terms of maintaining appropriate amounts of iron in the body and is in turn affected by haemoglobinopathies. Hepcidin also has other metabolic effects in places such as the liver but so far the extent of these is not well understood. It does however directly control the levels of serum ferritin. High serum ferritin is found in obese patients and those with diabetes and a meta-analysis of the various studies shows that high serum ferritin does indeed increase diabetes risk.

CONCLUSION: From an epidemiological standpoint, it is plausible that the well-documented protective

effects of haemoglobinopathies with regard to malaria may have also offered other evolutionary advantages. By contributing to peripheral insulin resistance, haemoglobinopathies may have helped to sculpt the so-called "thrifty genotype", which hypothetically is advantageous in times of famine. The prevalence data however is not extensive enough to provide concrete associations between diabetes and haemoglobinopathies - more precise studies are required.

Key words: Diabetes; Ferritin; Haemoglobinopathy; Iron metabolism; Malaria

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Core tip: Are diabetes and haemoglobinopathies linked? There is strong evidence to suggest that the processes involved in both iron and blood glucose homeostasis interact with one another. Metabolic disorders involving iron appear to contribute to the pathological process of diabetes at least on a cellular level. This article also examines prevalence data of diabetes and various haemoglobinopathies in certain populations to establish whether there is an association from an epidemiological perspective.

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INTRODUCTION

There are a number of postulated theories that suggest that there were once evolutionary benefits of certain gene variants that are known to cause disease in modern populations. One such association is demonstrated by the protective nature of Sickle-cell trait in terms of the interruption of the life cycle of *Plasmodia*, which lessens the impact of malaria infection on an individual with such a phenotype[1]. It does not seem unreasonable to suggest that there may be other associations that are yet to be discovered. The evolutionary advantages of having higher blood glucose concentrations have been suggested by the "thrifty genotype" hypothesis, *i.e.*, peripheral insulin resistance acting to ration energy in times of famine[2]. This article focuses on the associations between iron metabolism and type 2 diabetes mellitus by examining the available evidence. The pathological link between haemoglobin abnormalities and diabetes is investigated in addition to the molecular mechanisms that may be involved. The prevalence of type 2 diabetes has risen in populations who live in regions with antecedentally high rates of malaria infection and in ethnic groups who have emigrated from these areas[3,4]. Prevalence data of haemoglobinopathies, iron transport abnormalities and diabetes are examined in order to establish whether populations with high rates of diabetes are more likely to have haemoglobin abnormalities.

MATERIALS AND METHODS

A systematic literature search was performed using electronic literature databases, PubMed, Web of Knowledge and Cochrane Library. The search terms used included: "diabetes", "diabetes mellitus", "diabetes mellitus type 2", "iron", "free radicals", "glucose tolerance", "insulin resistance", "insulin", "resistance", "sensitivity", "hepcidin", "ferritin". Relevant references from selected articles were also reviewed. The International Diabetes Federation World Atlas was used to generate a list of populations with high rates of diabetes. PubMed, Scopus and Google Scholar were used to identify which of these populations also had a reported prevalence of haemoglobin abnormalities.

RESULTS

Putative link between haemoglobin metabolism and diabetes

Oxidative stress, iron and diabetes: The production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) due to iron overload in humans has been attributed to the Fenton Reaction. This occurs due to the ability of iron to convert between its two oxidative states, Fe^{2+} and Fe^{3+}[5]. Alternative proposed mechanisms include the Haber-Weiss reaction, with haem iron acting as a catalyst and Fe^{2+} as a reactant[6]. Antioxidants and detoxifying enzymes are required to maintain careful control of ROS and RNS production. Iron overload can tilt this balance, leading to oxidative stress[6]. Oxidants have in turn been shown to cause the release of catalytic iron resulting in the formation of yet more ROS and RNS forming a vicious cycle[7]. Oxidative stress is one mechanism speculated to be linked to insulin resistance and abnormal glucose tolerance, as a novel explanation of the link between diabetes and iron overload.

Pancreatic β-cells in fact show particular sensitivity to oxidative stress due to their low expression of antioxidants such as catalase and SOD2[8]. The resulting β-cell dysfunction as a consequence of this stress causes decreased expression of transcription factors required for cell maintenance and insulin production[8]. Further research has demonstrated that circulating insulin is also directly affected by ROS, affecting the ability of insulin to bind to the insulin receptor[9]. The combination of these factors consequently leads to hyperglycaemia and ultimately, the development of diabetes.

Homeostatic mechanisms for preventing damage from iron overload include both the regulation of cytosolic iron by binding to iron regulatory proteins (IRP) and production of the peptide hormone Hepcidin[8].

Table 1 Comparison of studies examining Hepcidin, Prohepcidin and Serum Ferritin concentrations in individuals with type II diabetes

Ref.	No. of patients with type II diabetes	No. of total participants	Hepcidin concentration	Prohepcidin concentration	Serum Ferritin concentration
Aso *et al*[16], 2010	104	169	-	Significantly lower than control	Significantly higher than control
Jiang *et al*[24], 2011	34	64	Significantly higher than control	-	Significantly higher than control
Guo *et al*[25], 2013	555	1259	No significant difference from control	-	Significantly higher than control
Sam *et al*[26], 2013	33	66	Significantly lower hepcidin than control	-	Not significantly higher than control

Binding of IRP results in a decrease in iron uptake into the body and an increase in the translation of ferritin, a molecule that sequesters iron within cells[8]. High serum ferritin levels are associated with obesity, metabolic syndrome and cardiovascular risk and more recent studies have demonstrated it to be directly associated with diabetes[10-12]. Care must be taken however in attributing causality to this relationship. Diabetes is known to be a chronic inflammatory state, and this finding may simply be explained by the fact that ferritin is an acute phase reactant and therefore simply produced as a result of inflammation[13].

Hepcidin has been shown to inhibit cellular iron efflux by binding to ferroportin, an important iron exporter, causing the internalisation and degradation of iron[14,15]. Subsequently, hepcidin decreases intestinal iron absorption and prevents the release of iron from macrophages[16]. The hepcidin-ferroportin axis is essential to maintaining iron homeostasis, however is still not completely understood[17]. Hepcidin is modulated by its inversely proportional relationship to both serum and tissue iron, with iron concentrations being inversely proportional to hepcidin concentration. This balance is essential to maintain iron as demonstrated clinically in patients with hereditary hemochromatosis who have low hepcidin levels and hence have toxic accumulation of iron[18].

The synthesis of hepcidin is mainly within hepatocytes, but has also been noted in pancreatic β cells and the adipose tissue of obese patients[19,20]. This may suggest that pancreatic β cells also have a role in iron metabolism in addition to the regulation of glucose and insulin[19]. Whilst several studies have investigated levels of circulating hepcidin or prohepcidin (a precursor of hepcidin) in patients with diabetes (Table 1), there is currently no consensus or large scale-studies available, and data relating to the role of hepcidin in this context is limited. Cell culture studies have revealed that glucose induces secretion of hepcidin in INS-1E cultures (a pancreatic β cell model) yet has no effect on HepG2 cell cultures (a hepatocyte model)[21]. In contrast, insulin up-regulates hepcidin secretion in HepG2 cell cultures. There was no data found for the effect of insulin on hepcidin secretion by pancreatic β cells[22]. A single murine study looked at hepcidin activity during starvation. It proposed that the increased hepcidin secretion seen in such states has a role in preserving tissue iron and supporting gluconeogenesis in the liver[23]. As gluconeogenesis is abnormally induced in obese individuals and those with diabetes, a link between diabetes and hepcidin is possible[23]. Whilst it seems likely that hepcidin has a role in the glucose-insulin axis, no firm conclusions are possible with the data currently available. Further exploration of the role of hepcidin could explain whether an elevated serum ferritin is the likely cause or effect of the chronic inflammation seen in diabetes.

The link between abnormal iron metabolism and diabetes is established in those with Sickle-cell disease and haemochromatosis[27,28]. However, the effect of iron intake on the risk of healthy individuals developing diabetes and its subsequent clinical progression is much less clear.

Haemochromatosis is known to result from the dysregulation of the body's finely balanced iron metabolism[29]. The resulting free iron is known to be toxic when present in sufficiently high concentrations although the exact mechanisms behind its role in both health and disease are still not fully understood. The ubiquitous nature of iron *in vivo*, from oxygen transport and energy metabolism to DNA synthesis, explains the systemic and wide ranging tissue types affected by this disease. Traditional explanations of the resulting diabetes have cited iron as a purely diabetogenic influence[30]. However, a recent paper by Abbas *et al*[31] challenges the traditional thinking regarding the role that increased iron deposition plays in haemochromatosis. Indeed, iron overload in hereditary haemochromatosis was found to exhibit both pro-diabetic influences, mediated *via* beta-cell toxicity as well as an anti-diabetic effect caused predominately by weight loss[31].

Research targeted at a link between abnormal iron metabolism and diabetes in those who are otherwise healthy has repeatedly produced conflicting results. Jiang *et al*[32] conducted a prospective study that followed up a cohort of initially healthy males for 12 years. Total haem and/non-haem iron intake was compared between those who developed diabetes in this time period, and those who remained healthy. Only haem iron was positively associated with diabetes although other lifestyle factors could not be excluded as contributors[33]. This result has been backed up by similar research, including data from the Nurses' Health

Study Ⅱ and other large cohort studies[34,35].

In contrast, an African study demonstrated that there was no link between serum ferritin and diabetes prognosis in those with patients without additional health complications[36]. However, with a small sample size (n = 60), and the fact that these were not newly diagnosed diabetics this conclusion must also be treated with caution. A study in India concluded there was no link between raised serum ferritin and the risk of developing diabetes. However, it did not look at any other indices of iron status, which would have allowed comparison with the current literature[37].

Orban *et al*[33] recently attempted to make sense of these conflicting results with a meta-analysis of studies of indices of iron status in those without haemochromatosis or thalassemia[32]. It concluded that a significant link between a raised ferritin level and an increased risk of diabetes does indeed exist. Other indices such as transferrin saturation and soluble transferrin receptor number were also implicated but a methodology which failed to address the confounding effect of inflammation and a low statistical power means these conclusions must be met with caution[32].

It has been highlighted that these results indicate the very immediate need for further, high quality research regarding the effect of iron intake on the progression of diabetes in those without abnormal iron metabolism[38]. For example, looking at the effect of iron supplementation on diabetes progression in newly diagnosed patients. To date only the risk of developing the disease has been looked at in detail epidemiologically. Additionally, the mechanistic studies are generally in their infancy, *i.e.*, are only based on animal models at this stage. This area of research would need to be advanced to human based studies to yield more significant data.

Epidemiology of Fe transport/haemoglobin abnormalities and association with diabetes in populations

The worldwide distribution of the common haemoglobinopathies coincides with that of malaria, and indeed confers resistance from its more severe expressions[1,39]. Inherited haemoglobin disorders (Sickle-cell disorders and thalassaemias) were originally characteristic of the tropics and subtropics but are now common worldwide due to migration[40]. However, the main regions with the highest rates of Sickle-cell disease are sub-Saharan Africa, the Mediterranean[41], the Middle East[42,43] and the Indian subcontinent. Additionally, the Sickle-cell gene variants are extremely common in some of the Caribbean Islands and in North America[44].

The prevalence of diabetes in sub-Saharan Africa is reported as being between 1% (rural Uganda) and 12% (Nairobi)[45]. A paediatric study of 860 individuals in Western Kenya reported 38.5% were heterozygous and 9.5% homozygous for α-thalassaemia. Sickle-cell trait was present in 17.2% and Sickle-cell disease in 1.8%[46]. This demonstrates a relatively high prevalence of both diabetes and haemoglobinopathies, calling for the need for further investigation to directly compare diabetes and haemoglobinopathies in each of these populations. Prevalence of diabetes in India is 9.1%, with the cumulative gene frequency of haemo globinopathies being 4.2%, with large variation between different ethnic groups[47]. Again, direct study of both conditions in these individual ethnic groups is needed in order to draw more meaningful comparison. Turkey is of particular interest as the prevalence of diabetes is 14.8%, but Sickle-cell disease is only found in 0.3%, which suggests much less of a correlation than that seen in India and Africa. However, in some areas of Turkey, (*i.e.*, Çukurova) the prevalence of carriers of HbAS is as high as 44%[48,49]. A similar affect has been reported in Madang in Papa New Guinea, where 97% of the population tested were either heterozygous or homozygous for α-thalassaemia[50]. The overall prevalence of diabetes in Papa New Guinea is 5.2%[51], however it would be interesting to examine the populations of Madang and Çukurova for diabetes prevalence specifically due to the extremely high rates of α-thalassaemia and HbAS. The United States provides interesting data. The overall prevalence of diabetes is 9.2%, with 13.2% of African Americans affected[52]. The highest rates of diabetes in the United States are actually amongst American Indians and Alaskan natives (15.9%)[52], where the prevalence of Sickle-cell disease is 36.2/100000 live births, making these ethnic groups the third most affected by Sickle-cell disease behind African Americans (289/100000) and Hispanics (89.1/100000)[53,54]. Hb-E occurs widely throughout the eastern half of the Indian subcontinent, Bangladesh, Myanmar, and East and Southeast Asia. Most notably in the Northern parts of Thailand and Cambodia, where the region is referred to as the "Hb-E Triangle" where up to 70% are carriers. The prevalence of diabetes in these areas is 8.5% (Thailand)[55] and 2.6% (Cambodia)[56].

Although, on the whole, it is difficult to determine any firm correlations using the above sources, the existing data certainly summons enough intrigue to warrant further investigation.

DISCUSSION

Examining the epidemiological evidence for an association between diabetes and the various haemoglobinopathies is not straightforward. The main issue is the complex interplay of various environmental and biological factors that all contribute to the development of diabetes, making a clear association between certain factors difficult to prove. There is clear evidence on a molecular level of an interaction between glucose homeostasis and haem abnormalities, however the epidemiological perspective remains unclear due to a lack of specific studies in this area. Focussed diabetes prevalence data from the groups with extremely high carrier rates of the various haemoglobinopathies would be extremely beneficial, as a link between the molecular

evidence and the epidemiological picture could be demonstrated. Other issues include the large number of individuals with diabetes who are undiagnosed. Improvements in screening and healthcare education programs seem to be the answer here, although these are not without their own problems. The Center for Disease Control and Prevention estimates this figure to be 8.1 million people (27.8% of those with diabetes) in the United States[53], making true prevalence data difficult to obtain. It remains plausible however that in the face of various selective pressures there was once an evolutionary advantage in having a higher blood glucose level. This could help to explain why there are a number of ethnic groups who are at greater risk of developing diabetes than others. It is also possible that these genetic predispositions to higher blood glucose levels developed in tandem with the haem abnormalities that are known to be protective against malaria. However with a lack of studies directly examining the two conditions, a concrete association is difficult to prove.

COMMENTS

Background

A putative pathophysiological mechanism exists between diabetes and blood born disorders. These processes involve both iron and blood glucose metabolism and there is a high potential for the two to interact with one another.

Research frontiers

Metabolic disorders involving iron contribute to diabetes on a cellular level. Evidence at a clinical or population level is less clear and is reviewed here.

Innovations and breakthroughs

The evidence reviewed here provides a putative link between diabetes and haemoglobinopathies which carries clinical ramifications (with respect to risk) for populations that have an antecedental risk of blood born disorders. The role of iron metabolism and its impact on diabetogenic risk is also considered here.

Peer-review

This article is based on a literature search, focusing on correlations between iron metabolism and type 2 diabetes, and on epidemiological data in search for a possible link between diabetes and haemoglobinopathies. It is a potentially useful paper for discussion of an important subject that could be of use to the clinicians and researchers in the field as an overview, where many studies are compared with their strong and weak points, and suggestions are given.

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