REVIEW PAPER

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Rare occurrence of type 2 diabetes mellitus in patients with sickle cell anaemia: assessing the contribution of inflammation, insulin resistance and glucose buffering capacity of abnormal haemoglobin

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ABSTRACT

This review was designed to discuss the rare occurrence of diabetes mellitus (DM) in patients with sickle cell anaemia (SCA) with a particular focus on factors, such as life expectancy, body weight, chronic inflammation, insulin resistance, glucose buffering property of haemoglobin, and microRNAs (miRNAs), aiming to stimulate research which will fill the existing knowledge gaps regarding the interplay between SCA and DM. Additionally, possible pharmacotherapeutic approaches to DM were also highlighted in the review. Google Scholar and PubMed search engines were used to search for the relevant keywords, such as sickle cell trait, sickle cell disease, sickle cell anaemia, insulin resistance, and diabetes mellitus. SCA patients appear to have β-cell dysfunction with a reduced insulin secretion, but present a similar insulin sensitivity status as other patients without haemoglobinopathy. Glucose buffering property of haemoglobin and the possible DM-protective roles of miRNAs in the sickled erythrocytes constitute some of the potential factors protecting SCA patients from developing DM. Sickle cell anaemia is associated with several complications and endocrinopathies, nevertheless, its coexistence with DM continues to be a rare observation. Proper elucidation of the mechanisms which seemingly confer 'protection' against DM in patients with SCA may provide some therapeutic insights regarding DM.

Introduction

Diabetes mellitus (DM) is a group of metabolic diseases with hyperglycaemia as its main feature. Generally, DM can be classified into the following categories; type 1 DM (T1DM), type 2 DM (T2DM), gestational DM (GDM) as well as specific types of DM due to other causes [1]. Of all the types of DM, T2DM constitutes about 90 to 95% with the disease estimated to affect over 350 million people in 2030 [2]. Despite this global epidemic of T2DM, individuals with sickle cell anaemia (SCA) seem to present some form of protection against the disease [3].

Sickle cell disease (SCD) is a Mendelian genetic disease encompassing a wide spectrum of disorders [4]. Its most common form is the homozygous HbS, referred to as sickle cell anaemia (SCA). SCA results from a single nucleotide substitution in the DNA of adenine (A) with thymine (T) at codon 6 of the beta-globin gene on chromosome 11. This substitution causes a point mutation, with hydrophobic valine replacing hydrophilic glutamic acid in the polypeptide of the beta-globin chain of haemoglobin [5–7]. The combination of two normal alpha-globins and two mutant beta-globins forms haemoglobin S (HbS) which polymerizes upon deoxygenation. The monomers aggregate into multiple polymer bundles (rod-like structure) which subsequently lead to red cells deformation from the normal biconcave structures into the sickle shape [6].

Generally, SCA is characterized by haemolytic anaemia, acute and chronic tissue ischaemia (as a result of intermittent occlusion of small vessels) and organ dysfunctions, including endocrine dysfunction/metabolic disorders, such as osteopenia, hypogonadism, carbohydrate intolerance, and primary hypothyroidism [8–12].

Sickle cell anaemia and diabetes mellitus – epidemiology

Despite the established association between SCA and endocrine organs dysfunction, the co-existence of SCA and diabetes mellitus (DM) remains rare [3, 13]. Although the number of people with type 2 DM and sickle cell trait (SCT), a heterozygous form of sickle cell disease, is increasing [14], T2DM rarely develops in individuals with SCA. The infrequent concomitance of the two diseases prompts the belief that SCA may have some protective effects on the development of DM [15]. This protective effect is unexpected as SCA-associated chronic inflammation [16], defective lipid metabolism [17], oxidative stress[18] and endocrinopathies[10] resulting from iron overload (since blood transfusions are a major form of treatment in patients with SCA) are significant harbingers of insulin resistance (IR) and T2DM.

Zhou et al. [19] demonstrated that the prevalence of T2DM in SCD patients is comparable to the prevalence of T2DM among the African-American population in the US. They reported that the unadjusted prevalence rates of T2DM in SCD population of 7,070 adults increased from 9.8% in 2009 to 11.8% in 2014 resulting in a 0.2% – 0.5% year-to-year change; however, when age-and sex-standardized, the prevalence increased from 15.7% in 2009 to 16.5% in 2014. Furthermore, Skinner et al. [20] reported that SCT could increase the risk of development of T2DM-related complications, including retinopathy, nephropathy and hypertension.

Although the report of Zhou et al. [19] indicated an increasing trend in the prevalence of T2DM in SCD patients, no stratification of the glycaemic status was observed, based on the type of SCD, also referred to as SCA (HbSS), or other milder forms of SCD (HbSC, HbSD, HbSE and HbSO). Regardless of this report, the numerous available reports still indicate that the co-existence of T2DM and SCA is uncommon [3, 13]

In 1979, a study by Morrison et al. [21] failed to detect a single case of DM in 711 patients with SCA. In 1987, the co-existence of the two diseases was reported in 2 pregnant women (GDM in SCA patients) [22]. In fact, in 2006, the report from a multi-centre study of Iron Overload demonstrated that DM affects only about 2% of patients with SCA, and that transfusion duration was strongly associated with T2DM [23].

In Nigeria, a survey conducted by Reid et al. [24] failed to identify a single patient suffering from the two diseases simultaneously. However, in the same country in 1990 the first case of SCA and DM co-existence was reported [25]. This was followed, in the same year, by the report of Adekile and Jegende [26] which showed the co-existence of type 1 DM (T1DM) and SCA in a 10-year old child.

These earlier reports were corroborated by a few recent reports documenting the rare co-existence of the two diseases.[15, 27–29] Recently,

Prusty et al. [13] have reported a prevalence of 1.46% in 137 patients with SCA. Similarly, Jang et al. [3] concluded that chances of developing obesity and diabetes over a lifetime in patients with SCD were low. Therefore, the question remains whether it can be argued that SCA is protective against DM. Nevertheless, addressing this issue is currently being investigated through a number of factors which have not been well explored to date.

Underestimation of DM in SCA patients

Glycated haemoglobin (HbA1c), formed when glucose binds specifically to the N-terminal valine of the haemoglobin β chain, is widely used in the screening, diagnosis and monitoring of DM [30]. However, it is well established that HbA1c tests are influenced by conditions affecting both erythrocytes lifespan and by hemoglobinopathies [31, 32]. Thus, discrepancies may occur between HbA1c values and the true clinical situations of the patients [33].

The reliability of HbA1c test is impaired by haemoglobinopathies, as the normal process of non-enzymatic glycation of HbA to HbA1c is impaired. HbA1c estimation using immunoassay and HPLC methods is interfered with by HbS, although it can be measured optimally using enzymatic assays and capillary electrophoresis [33–35]. Alternatively, measurement of non-traditional glucose control markers (albeit their limitations and poor diagnostic guidelines), such as fructosamine, glycated albumin, 1,5-anhydroglucitol, could provide the necessary data [14, 36, 37]. Therefore, it must be taken into consideration that HbA1c measurement alone (depending on the methodology), without blood glucose estimation, may not be sufficient for the diagnosis of pre-diabetes or diabetes in SCA individuals [14, 38]. In fact, the report of Mohamed et al. [15] demonstrated that most studies reporting a low prevalence of DM in SCA patients did not include the abovementioned unreliability of HbA1c tests.

Life expectancy

Reduced life expectancy was initially believed to account partly for the absence, or low prevalence of T2DM, in patients with SCA. This resulted from the observation that most patients suffering from SCA present a shorter life span [39] and would not live long enough to develop T2DM the risk of which increases with age. This assumption is presently being challenged by the emerging reports which show that the life span of SCA patients with SCA have now have improved. This longevity observed in SCA could, in turn, be largely attributed to the treatment advances, such as immunization, stroke prevention, chronic blood transfusion, as well as healthy lifestyle, strong compliance to the treatment regimens, greater family support, stem cell transplantation and gene therapy [40–42].

Insulin resistance (IR) in patients with sickle cell anaemia

Insulin is an anabolic hormone with a number of classic and novel biologic effects. Impairment in all, or some of the effects mentioned above results in IR [43–45]. The complexity of IR is enormous, since it can result from various abnormalities, including defects in insulin receptor and its signal proteins [46].

Different attempts have been made to investigate the relationship between IR and SCD. Alsultan et al. [47] reported that the level of an IR index, i.e. the homeostasis model assessment of insulin resistance (HOMA-IR), was significantly elevated in patients with SCA. In contrast, the findings included in the report are in opposition to the earlier report of ter Maaten et al. [48] which indicated that the insulin sensitivity status in patients with SCA and in the controls was comparable. However, our reports [16, 49] and that of Yavropoulou et al. [50] corroborate the report of ter Maaten et al. [48] demonstrating that patients with SCA have similar insulin sensitivity status as controls, but appear to present a β-cell dysfunction with a reduced insulin secretion. These observations indicate that patients with SCA may not be more predisposed to developing T2DM, despite the associated chronic inflammation. Although reasons for this observation are still poorly understood, compensatory hemodynamic state, which is characterized by vasodilation, could account for the comparable insulin sensitivity status [48].

Body weight

In general, overweight and obesity are not commonly associated with SCA, as it is more linked with stunting and wasting [42]. This is partly due to a high resting metabolic demands, reduced intake of nutrients, which may result from a reduced appetite, recurring illness and hospitalization, as well as chronic inflammation [16, 51, 52]. However, certain reports have shown that overweight and obesity may be present in terms of this disease, and are becoming prevalent among children and adults suffering from SCA [52–55]. This is believed to be related to exercise intolerance, physical incapacity due to sickle cell-related complications, or medical conservatism [53].

The global epidemic of obesity continues to fuel the rising incidence and prevalence of T2DM. Although not all individuals with obesity develop T2DM, the links between excess body weight and T2DM have been well established [56]. The inextricable links involve pro-inflammation, impaired fatty acid metabolism and dysfunction of cellular processes including endoplasmic reticulum stress and mitochondrial dysfunction [57].

These complex factors induce insulin resistance and failure of β-cell consistent with extensive metabolic interplay between the hypothalamus, adipose tissue, pancreas, liver and the skeletal muscles [56, 58–60].

Despite the association between obesity and T2DM, new reports are not yet available indicating that the claimed increase in the incidence and prevalence of excess body weight in SCA individuals facilitates a rise in the incidence and prevalence of T2DM in this group. Therefore, it is important to consider whether the mechanisms of interaction between obesity and T2DM in people with SCA differ from those in people without SCA? This may not be entirely true as SCA is characterized by chronic inflammation which is also a key factor in the pathogenesis of T2DM.

Chronic inflammation, sickle cell anaemia and type 2 diabetes mellitus

Inflammation is a complex physiological response of an organism to harmful stimuli, such as pathogens and damaged/necrotic tissues in order to re-establish homeostasis. It involves the synchronization of activities of many cell types and mediators the response of which depends on the nature of the initial stimulus [61, 62]. Reports have shown that an elevation in inflammatory markers, such as tumour necrosis factor-alpha (TNF-α) and C-reactive protein (CRP), is commonly observed in patients with SCA even in steady state. Thus, chronic inflammation is considered a prominent feature of SCA [15, 51, 63, 64].

The interplay between inflammation and IR/T2DM has been well recognized [65, 66]. Adipocytes and adipose tissue infiltrating macrophages release a number of pro-inflammatory cytokines and chemokines, including as interleukin-6 (IL-6), interleukin-1 beta (IL-1β) and TNF-α. These cytokines exert paracrine effects on insulin target cells to activate inflammatory pathways resulting in the activation of Jun N-terminal kinase (JNK), inhibitor of κB kinase (IKK-β) and other serine kinases. In turn, these kinases phosphorylate insulin receptors, insulin receptors substrate-1 (IRS-1) and other insulin signalling molecules on serine (rather than the normal tyrosine phosphorylation) thereby disrupting the downstream insulin signalling cascades, which consequently results in cellular insulin resistance [67, 68]. Although cytokines usually mediate IR via local paracrine effects, some studies indicate that the tissue cytokines may escape into the circulation and exert endocrine effects by impairing insulin sensitivity in the distal tissues [69].

Inflammation induction in patients with SCA is principally, not adipocentric. Some factors, such as endothelial and coagulation activation, as well as oxidative damage in the cell membrane, which are induced by the SCA-associated intracellular haemoglobin polymerization, have been identified as inflammation inducers [51, 70–72]. Although SCA-associated inflammation is not adipocyte dependent, the possibility of IR induction by cytokines which escaped into the circulation (as found in obesity-inflammation-IR interplay) suggests that SCA-associated inflammatory mediators could also have some IR inducing properties. This issue could even be exacerbated by the emerging reports of overweight and obesity in patients with SCA. Surprisingly, SCA-associated inflammation does not seem to induce IR development as obesity-associated inflammation. This conclusion is supported by reports demonstrating that IR may not be a common

feature in patients with SCA [16, 49, 50]. Moreover, they indicate that there is a need for more research which will further investigate the seemingly metabolic-quiescent nature of inflammation in SCA, which subsequently could become a potential pharmacotherapeutic approach.

Abnormal haemoglobin as a blood glucose buffer

Abnormal haemoglobins may possess an increased blood glucose buffering capacity [73]. It was shown in an *in vitro* study that abnormal haemoglobins can serve as glucose buffer, hence, averting hyperglycemia, as well as its associated complications [74]. This observation is further supported by Al Harbi et al. [73] who demonstrated that patients with sickle cell trait (SCT) seem to be protected against diabetic retinopathy development and progression. Furthermore, they showed that the SCT group presented a reduced prevalence of diabetic macular oedema (DME) and/or proliferative diabetic retinopathy (PDR) compared with individuals with normal haemoglobin. Additionally, they also showed that the absence of SCT and a longer duration of DM independently predicted PDR and/or DME compared to hypertension, nephropathy or diabetes duration.

The possible underlying explanation for this apparent glucose-buffering property of abnormal Hb is that abnormal Hb may exhibit dissimilar biological properties when glucose-bound. Their poor stability when glucose-bound, could activate diverse biological activities which may be protective in terms of the development of hyperglycaemia and its associated complications [74]. Since Hb in SCA is less stable than Hb in SCT, it could thus be inferred that Hb in SCA may have more glucose-buffering property and this may be one of the mechanisms explaining the rare coexistence of SCA and DM. Therefore, once it is properly understood, this novel blood glucose-buffering property could be further explored as a pharmacotherapic approach for DM [73].

microRNAs (miRNAs)

miRNAs are 22-nucleotides containing non-coding RNAs presenting hormone-like activities, as well as regulating the activity of host cells. Most miRNAs are processed into precursor miRNAs and mature miRNAs after the initial transcription of DNA sequences into primary miRNAs [75]. The inhibition of gene expression by miRNAs has been well established. For instance, low molecular weight miRNA-induced silencing complex (miRISC) can induce nuclear degradation of mRNA by interacting with mRNAs within the nucleus [76, 77].

Although data on the mechanisms through which sickled erythrocytes offer protection against DM is scare, it is speculated that miRNAs in the sickled erythrocytes could block mRNA translation of the antibodies which results in the autoimmune destruction of the pancreas [78]. This, in fact, could be a major factor accounting for the rare coexistence of SCA and T1DM.

The DM-protective role of miRNAs in individuals with abnormal haemoglobin could be associated with the protective advantage of SCD against malaria. LaMonte et al. [79] showed that the translocation of sickle cell erythrocyte microRNAs into plasmodium inhibits ribosomal loading, which results in the translational inhibition of parasitic growth proteins resulting in impaired growth of *Plasmodium falciparum*. This role of miRNAs in DM protection should also be further explored as a pharmacotherapy option with regard to DM.

In addition, the beta-globin gene and insulin gene have been mapped to the short arm of human chromosome 11 [80]. However, the possible inhibitory effect between the genetic loci of insulin and beta-globin gene is presently poorly understood, and thus could be further investigated in order to gain more insight into the interplay between SCD and DM [78].

Conclusion

Sickle cell anaemia is associated with several complications and endocrinopathies, although its coexistence with DM continues to be rarely observed. This unexpected particular form of 'protection' against DM represents a clinical puzzle which requires further scientific clarification, whereas its understanding might provide some therapeutic insights for DM.

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