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Nutrition and sickle cell disease

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ABSTRACT

A common observation in sickle cell disease is growth retardation, in particular, wasting. Wasting is associated with increased hospitalization and possibly poorer clinical outcomes. Therefore understanding the mechanism of wasting is crucial and reducing the degree of wasting by improving the nutritional status, holds the potential for modifying the course of the disease.

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1. Introduction

Sickle cell disease (SCD) refers to a group of autosomal recessive disorders in which the inheritance of the haemoglobin S allele in a homozygous state (sickle cell anaemia [SCA]), or in combination with one other variant allele, most commonly haemoglobin C, or with a β-thalassaemic allele results in the presence of greater than 50% haemoglobin S concentration in blood. This group of chronic diseases poses significant public health challenges in Jamaica and many Caribbean countries.

A common observation in SCA is growth retardation, in particular, wasting. The poor growth results from a combination of relative hypophagia and increased metabolic demands driven by increased whole body protein turnover, glucose and lipid fluxes and resting metabolic rate. Sickle cell related complications exacerbate the metabolic demand and in addition, imposes specific ones, e.g., arginine for nitric oxide production and cysteine.

The subsequent metabolic adaptation to mismatch between energy intake and demand is complex and involves changes in body composition manifested as wasting and a repartitioning of the components of energy expenditure. The importance of understanding the mechanism of wasting resides in the observation that wasting, a marker of negative energy balance is associated with increased hospitalization and possibly poorer clinical outcomes.

2. Background

Human nutrition is the science that deals with the interaction between metabolic demand and dietary intake. There are many factors that modulate this interaction including socioeconomic, genetic, disease factors [1] and more recently "metabolic set" [2]. Current nutritional doctrine posits that metabolic demand drives dietary intake [3]. The metabolic demand consists of basal demand which is defined as the energy expended to maintain homeostasis at rest after a 12 h fast in a thermoneutral environment and a variable component which comprises energy associated with thermic effect of food, growth and activity [4,5].

Nutritional research in sickle cell anaemia (SCA) has focused on relating clinical features of sickle cell anaemia to nutritional abnormalities as well as nutritional strategies to modulate or improve clinical manifestations. The focus of this article will be on the growth retardation, in particular, the wasting observed in SCA and its nutritional correlates.

3. Pathophysiology of sickle cell anaemia

The nutritional and metabolic context of homozygous S sickle cell disease (sickle cell anaemia) is determined by pathophysiologic processes initiated by the high

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intra-erythrocytic concentration of HbS and includes haemolysis, compensatory haematopoeisis, vaso-occlusion, reperfusion injury and inflammation [6]. The initiating event is polymerization of HbS, which promotes pathological changes in erythrocytes that in turn cause vascular occlusion. Several metabolic and physiological mechanisms are activated in response to the pathophysiological cascade [7]. In response to activation and increased turnover in these systems, whole body protein turnover [8–10], glucose and lipid fluxes [11] and resting metabolic rate are all increased [9,10,12–16]. Sickle cell related complications will exacerbate these metabolic demands and in addition, place specific ones, e.g., for arginine – immediate precursor of nitric oxide [17] and cysteine [8]. This increase in the metabolic demand has to be met from the diet in order to maintain body cell mass.

Although the birth weight of newborns with SCA is not different from AA controls [18], numerous studies [19,20] from the Caribbean [21], Latin America [22], the USA [23] and Africa [24] have reported growth deficits beginning in childhood. For example in the Jamaican Sickle Cell Cohort Study (JSCCS), a longitudinal observational study of sickle cell disease and its clinical manifestations, children with SCA had significantly lower weight and height compared with the NCHS growth reference standard from as early as 3 months of age [25] and significantly lower weight and height velocity compared with age matched HbAA controls from 2 years of age [26]. The deficit in weight persists through adolescence and adulthood and at age 17 years, the mean weight deficit was $\sim$ 10 kg.

Wasting or under nutrition has long been recognized as a marker of impaired survival in free living individuals with primary malnutrition [27] as well as in chronic diseases such as cystic fibrosis [28], congestive heart failure, cancer cachexia and HIV [29]. In SCA, the reported predictors of morbidity were an episode of dactylitis prior to age 1, a haemoglobin < 7 g/dL and leukocytosis [30]. However, the clinical utility of these predictors is unclear [31]. Notwithstanding, the emphasis on the role of clinical and haematological factors as predictors of morbidity has distracted attention from the role that sup-optimal nutrition may have on the natural history of SCA. For example, recently Cox et al. have reported that wasting was related to increased frequency of hospitalization but not to mortality in non-birth cohort of African children [32].

4. Why are subjects with sickle cell anaemia wasted?

4.1. Energy intake

The long-term gain or loss of body weight indicates positive or negative energy balance, respectively. Therefore, in the presence of wasting relative to AA controls, two questions arise:

- is energy intake lower in SCA?
- is energy expenditure greater in SCA?

We have measured energy intake in a random sample of 50 adults with SCA (29 males and 21 females), aged 19–25 years using a 24 h dietary recall and a three-day diet diary. The energy intake in this sample was 11.6 ± 3.9 MJ/d, (males) and 8.8 ± 1.6 MJ/d (females) whilst the protein intakes were 88.3 ± 31.2 g/d and 64.8 ± 16.4 g/d for males and females respectively (unpublished). These intakes in absolute terms tended to be lower than the intake of energy (12.2 ± 4.3 MJ/d, males; 9.7 ± 3.9 MJ/d, females) and protein (93.9 ± 36.7 g/d, males; 75.7 ± 35.9 females) among Jamaican adults [33], but when weight normalized are actually comparable. Similarly Singhal et al. [16] and others [13,34,35] have reported that energy and protein intake in children were not different compared with age matched controls. Most estimates of energy intake in SCA have been performed in the steady state, but the natural history of SCA is characterized by frequent acute crises [36] accompanied by anorexia and/or reduced physical activity. Energy intake is likely to fall and energy expenditure to rise in a crisis, producing a negative energy balance. The presence of wasting on the background of high REE implies that energy intake is inappropriately low at steady state in SCA. This relative hypophagia may be due to suppression of appetite from early in life. This is supported by the results of the study by Heyman et al. [37]. In this study, nutritional supplementation with increased energy and protein by the nasogastric route which effectively bypassed the normal appetite regulatory mechanism, produced a rapid and sustained increase in growth rate, associated with striking reductions in pain crises and infections in children. However, the available evidence suggests that application of this technique as a regular component of clinical care is not advisable as the administration of inappropriate amounts of energy and protein is associated with increased risk of the overfeeding syndrome and death [38].

The relative hypophagia of SCA might be produced by inflammatory mediators e.g. IL6. The control of appetite involves the interaction of short-term and long-term regulatory systems [39]. The short-term regulation of appetite is thought to mediated by overlapping and redundant neurohumoral systems [40]. For example, changes in circulating glucose concentrations will elicit meal initiation and termination by regulating activity of specific hypothalamic neurons that respond to glucose [41]. Other nutrients (e.g., amino acids and fatty acids), gastrointestinal peptide hormones, most notably ghrelin, PYY and cholecystokinin, as well as autonomic afferents signaling gastric distension are also involved in short-term regulation of food intake. The set points of these neurohumoral systems vary among individuals leading to significant meal-to-meal variation in intake and thus short-term gain or loss of weight. They are also integrated with longer-term humoral regulators of appetite such as insulin, and leptin, a protein hormone produced mainly by adipocytes, and possibly also other adipocytokines to maintain energy homeostasis. Insulin and leptin, are transported into the brain where they inhibit the secretion of the orexigenic hypothalamic neuropeptide Y and agouti-related peptide (AGRP) which stimulate food intake and decrease energy expenditure thereby regulating feeding behaviour and body weight [40]. Circulating insulin and leptin concentrations are proportional to body fat content. Insulin and leptin secretion and circulating levels are also influenced by recent energy intake and dietary macronutrient content. Insulin and leptin

concentrations decrease during fasting and energy-restricted diets, independent of body fat changes, ensuring that feeding is triggered before body energy stores become depleted [42]. In SCA the roles of leptin and insulin in modulating appetite are unclear. Individuals with SCA have lower fat mass (FM) compared to age matched controls [13]. Further, plasma leptin concentration normalized for differences in fat mass have been reported to be lower in patients with SCA compared with controls [43]. Additionally blood glucose levels in response to an oral glucose tolerance test have been reported to be higher [44] and C-peptide to be lower in SCA [45] compared with controls suggesting an impairment of insulin secretion in SCA. On the other hand peripheral insulin sensitivity is similar in SCA and controls [46]. Taken together, the lower leptin concentration and relative insulinopenia represent a physiological signal to stimulate appetite. However it is likely that the chronic inflammation of SCA is associated with increased production of cytokines such as TNF-a and IL6, which inhibit the actions of leptin and insulin both at the level of the hypothalamus and peripherally thereby contributing to the relative hypophagia and wasting observed in SCA. Indeed, IL6 concentrations and other proinflammatory cytokines have been shown to be increased in the steady state in children and adults with SCA [47–50]. In contrast the reduction of inflammation by feeding a high protein diet at weaning in the Berkeley transgenic sickle cell mice model was associated with improved rate of weight gain [51] supporting the theory that the relative hypophagia is due to elevated inflammatory mediators.

4.2. Energy expenditure

The components of total energy expenditure are:

- resting energy expenditure (REE) – energy required for basal and post-absorptive metabolism;
- thermic effect of food (TEF) – energy to digest and metabolise food;
- physical activity energy expenditure (PAEE).

Thus, at balance, and hence weight neutrality, total energy intake (TEI) = REE + TEF + PAEE. In normal adults, REE is the largest component, comprising of 60–80% of TEE, with TEF accounting $< 10\%$ of the TEE. Physical activity energy expenditure (PAEE) is the most variable component of TEE contributing 10–30% in fairly sedentary populations [52].

Total energy expenditure and REE have been examined simultaneously in two reports [13,53]. Both reported lower absolute TEE in SCA (13.8 MJ/d versus 10.5 MJ), but differences disappeared after adjustment for fat-free mass (FFM). In children, adolescents and non-wasted adults with SCA, REE is increased even after adjusting for differences in FFM [9,10,13–16]. Although FFM is a better predictor of REE than body weight, it only accounts for 53–88% of the variability in REE because metabolically inactive components are included [54]. In the JSCCS, we have found that FFM accounted for 57% of the variability of REE.

A relative increase in REE/FFM could be due to an increase in the size of the metabolically active components, or increases in the metabolic rate of the individual tissues. In none of the studies reported here [13,53] were the components of FFM measured directly as this is difficult; rather FFM, was either estimated from anthropometry or deuterium dilution. However, the composition of FFM is not constant across the range of body composition [55], and the relative proportions of its metabolically active components namely, muscle mass and organ mass, as well as their hydration are likely to vary as individuals become more wasted [56,57]. Since visceral components of the FFM (liver, heart, kidney, intestine) utilize nearly half of the total oxygen consumption at rest while skeletal muscle, which comprises up to 50% of the body weight, contributes 18–22% of REE [54,58]. Thus an increase in the organ mass: FFM ratio in SCA compared with controls would result in an increase in REE adjusted for FFM.

Increased REE per FFM could also result from an increased energy flux rate through metabolically active tissues [59]. This increased metabolic flux may be driven by the high rates of red cell turnover as a result of chronic haemolysis [7], increased cardiac output [60,61] and protein turnover [9,10,12,14,62,63] that occurs in sickle cell anaemia. The contribution of glucose turnover and lipid metabolism to the hypermetabolism of SCA is unclear. In other models of hypermetabolism and wasting such as cancer cachexia increased glucose turnover and altered lipid metabolism play a role in the associated hypermetabolism [64].

In the two studies in which TEE and REE were measured simultaneously [13,53], physical activity was not directly measured but was computed as the difference between TEE and REE. This is technically incorrect as this assumes that TEF is constant and similar in magnitude between individuals with SCA and controls. Nevertheless, the calculated PAEE from these two studies was reportedly lower in children with SCA compared to controls, suggesting that they had adapted to their level of energy intake by limiting physical work [13,53].

Diet induced thermogenesis contributes the least quantitatively to TEE. However, in chronic energy deficient adults TEF is increased and this is associated with substrate oxidation rates suggestive of the predominant utilization of carbohydrate as fuel both in the fasted and the fed states [65]. If the metabolic adaptation of the wasted individual with SCA is comparable to wasting associated with chronic energy deficient adults then TEF would be expected to increase also.

5. Summary

In summary, I have argued that the wasting in SCA is due to multiple causes including:

- inappropriately low energy intake due to appetite suppression by inflammatory mediators;
- elevated energy expenditure related to:
  - physiological adaptations to haemolysis,
  - changes in body composition resulting in a relative increase in visceral FFM,
  - inflammation.

The metabolic adaptation to mismatch between energy intake and demand is complex and undoubtedly involves

changes in body composition and a repartitioning of the components of energy expenditure. The adaptive response will be dependent upon prior nutritional status, the magnitude of the mismatch, and the duration of exposure to the mismatch. The studies to date have failed to fully elucidate the physiological adaptations in individuals with SCA especially in the wasted adult with SCA. The importance of understanding the mechanism of wasting resides in the observation that wasting, a marker of negative energy balance, is associated with poor clinical outcome. Because the wasting of SCA shares the functional impairments noted in other high metabolic demand chronic disease states complicated by wasting, then improvement of nutritional status by reducing the degree of wasting, holds the potential for ameliorating the course of sickle cell anaemia.

Disclosure of interest

The author declares that he has no conflicts of interest concerning this article.

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