Endocrine Disorders in Sickle-Cell Disease

Cresio Alves* and Zilda Braid

Pediatric Endocrinology Service, Hospital Universitario Professor Edgard Santos, Faculty of Medicine, Federal University of Bahia, Salvador, Bahia, Brazil

Abstract: *Background*: Sickle cell disease is a hemoglobinopathy of global importance due to its worldwide high prevalence. Endocrine and metabolic disorders may be associated with this disease, aggravating its clinical course. *Objective*: Evaluate the current knowledge about metabolic and endocrine derangements related to sickle cell anemia. *Source*: Literature search was performed in MEDLINE and SciELO databases, in the last 20 years, combining in different compositions the following terms: sickle cell disease, short stature, delayed puberty, diabetes mellitus, osteoporosis, hypothyroidism and adrenal dysfunction. *Results*: Endocrine disorders in sickle cell disease have multifarious causes: tissue hypoxia, chronic anemia, iron overload, high energy demand, genetic influence and malnourishment. Slow speed of growth and delayed puberty are frequent. The most common endocrine disorders in sickle cell disease are: growth delay, osteopenia and hypogonadism. Diabetes mellitus, thyroid and adrenal disorders are overall rare in this population. *Conclusion*: Recognition of an endocrine disturbance is of utmost importance in the follow-up of sickle cell disease patients. Thus, preventive measures, early diagnosis and replacement of specific hormonal deficiencies may be implemented contributing to a better quality of life for these patients.

Keywords: Sickle cell disease, growth and pubertal disorders, diabetes mellitus, adrenal gland diseases, thyroid diseases, metabolic bone diseases.

INTRODUCTION

Sickle cell disease is an autosomal recessive hemoglobinopathy caused by a mutated beta-globin and subsequent hemoglobin polymerization, causing deformation of red blood cells [1]. These so-called sickle cells are destroyed in the spleen precipitating chronic hemolytic anemia. The clumping of these sickle cells also brings about intermittent small vessel occlusion, leading to tissue ischemia and organ dysfunctions [1]. Its more frequent genotypes are HbSS (sickle cell disease), HbSC (SC hemoglobinopathy) and S/β-thalassemia (Sβ hemoglobinopathy) [2]. The sickle cell syndromes are among, epidemiologically, the most important genetic diseases in Brazil and in the world. According to the World Health Organization (WHO), about 300,000 children are born as carriers of sickle cell disease every year [3]. In Brazil, according to its Ministry of Health, 3,500 new cases of sickle cell anemia are diagnosed every year, with an incidence from 1:650 to 1:13,500, depending on the region of the country [4].

Packed red blood cell transfusion is the standard of care for acute vascular disease in sickle cell disease. Although the body is able to limit its absorption of iron, it does not have the ability to control its excretion. Therefore, sequential transfusions are related to iron overload and, eventually, to organ damage [1,5]. Endocrine dysfunction is one of the most precocious complications [1,5,6]. The high energetic expenditure, malnourishment and ischemic events are other factors that contribute to the overt endocrine derangements in sickle cell disease [1,7,8].

*Address correspondence to this author at the Rua Plínio Moscoso, 222/601. CEP: 40157-190. Salvador – Bahia, Brazil; Tel: (+) (55) (71) 9178-4055; Fax: (+) (55) (71) 3393-1021; E-mail: cresio.alves@uol.com.br

Acknowledging the high prevalence of this hemoglobinopathy and the increasing longevity of its carriers, and thus a higher risk of developing endocrinopathies, the goal of this study is to make a critical review of the main endocrine derangements associated with sickle cell disease.

ENDOCRINE DYSFUNCTION AND SICKLE CELL DISEASE

Fig. (**1**) summarizes the pathophysiology of the development of endocrine disease in sickle cell disease patients.

Short Stature

The slower speed of growth is the most common endocrine derangement in children with sickle cell disease [1,5,9,10]. Although the length at birth is normal, the growth deficit is already observed as of 2 years-old [11-13], where the weight is more compromised than the height [8-13]. The decrease in the speed of growth is progressive, achieving its nadir during adolescence [12,14].

The bone maturation is also delayed [11,15], rendering some recovery of final adult stature in adulthood [6,13]. Nevertheless, the weight at adulthood is inferior compared to a control group, with a lower BMI (Body Mass Index) for a particular age and gender [8,14,16]. As adults, the patients usually are slim, relatively tall, with long extremities, short trunk and narrow shoulders and hips [17]. The growth curves devised from Jamaican children with sickle cell anemia confirm this growth pattern [16]. The short stature in sickle cell disease follows more of a constitutional growth delay pattern. The SS and $S\beta^0$ hemoglobinopathy carriers present with a higher weight and height deficit, compared to SC and $S\beta^+$ hemoglobinopathy carriers [8,12,17].

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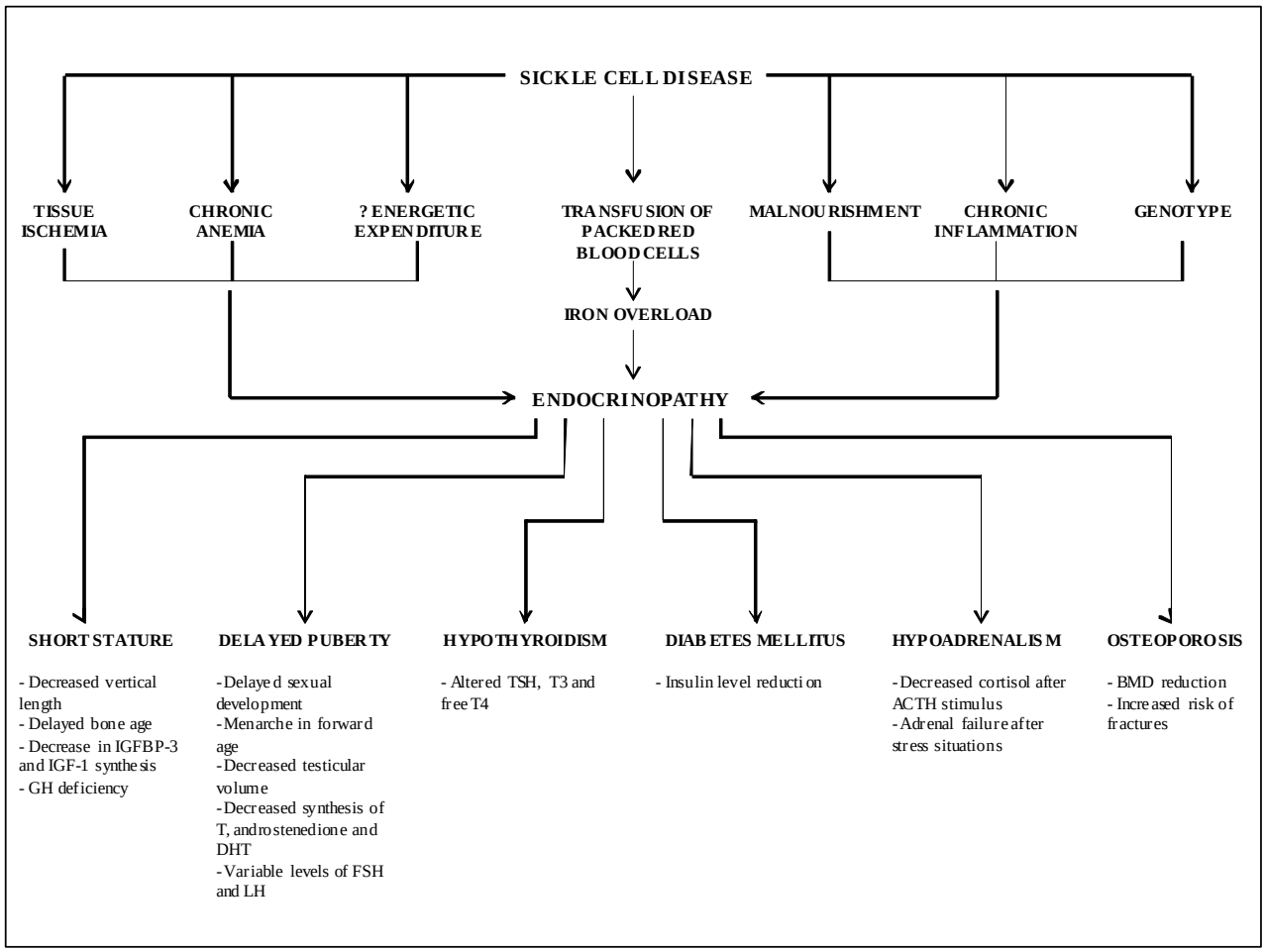

Fig. (1). Pathophysiology of the development of endocrinopathies in sickle cell anemia patients.

IGFBP-3: insulin-like growth factor binding protein 3**; IGF-1:** insulin-like growth factor 1**; GH:** growth hormone**; T:** testosterone**; DHT:** dihydrotestosterone**; FSH:** follicle-stimulant hormone; **LH:** luteinizing hormone**; TSH:** thyroid-stimulating hormone**; T3:** triiodothyronine; **T4:** thyroxine**; ACTH:** corticotrophin**; BMD:** Bone Mineral Density.

Despite Buison *et al.*, had demonstrated that boys presented with height, weight and BMI values that were significantly lower than girls [18]; Al-Saqladi *et al.* have shown that the severity of sickle cell disease was related to smaller growth in the female gender, probably due to differences in hemoglobin levels and fetal hemoglobin, energy consumption and hormonal changes [17]. These controversial studies expose how unclear the influence of gender is in growth retardation.

Several studies have shown a prebubertal plummet in IGF-1 (insulin-like growth factor) [1,8,14,19,20] and IGFBP-3 (insulin-like growth factor binding protein 3) hepatic synthesis [12,19]. Collett-Soberg *et al.* reported mean serum levels of IGF-1 and IGFBP-3 in sickle cell disease patients below the normal range for age, exposing a positive correlation between IGF-1 serum levels and speed of growth [21]. In this study, sickle cell disease patients with short stature presented with a larger amount of IGFBP-3 cleaved by proteases, decreasing its affinity by IGF-1 [21].

The peak of growth hormone (GH) in response to clonidine is significantly smaller in sickle cell disease, defining deficiency of this hormone in this subset of patients [20]. The reduction of the GH response to the stimulus may be attributed to vaso-occlusive phenomena that lead to ischemic-hypoxic injury of the hypothalamic-hypophyseal axis [8,12,20] or by local iron deposition [21]. However, Luporini *et al*. did not find a relationship between decreasing growth speed and any element of the GH/IGF-1 axis, suggesting that short stature in these patients is caused by other intrinsic factors in this disease [13].

The influence of transfusion therapy on growth is questionable. Some studies show a smaller delay in bone age, better nutritional status and even a considerable increase in the speed of growth in sickle cell disease patients undergoing transfusion [8,11]. According to Wang *et al*., children who underwent long-term transfusions had significant improvement in growth compared to those who underwent conventional treatment [22]. On the other hand, Fung *et al*. did not find any statistical difference in growth deficit

between transfused and non-transfused sickle cell disease patients [5].

Although hypogonadism may be associated with growth retardation, the observed growth deficit in prepubertal age suggests that the sexual steroid deficiency does not constitute a primary cause of short stature in these children [21].

Therefore, the growth deficit linked to sickle cell disease is multifarious, probably a consequence of the integrated and synergic action of several mechanisms. Besides the aforementioned variables, we may add bone marrow hyperactivity resulting in a higher basal metabolism, chronic inflammation, micronutrient deficiency (especially zinc) and the premature closure of the epiphyses owing to local ischemic events [1,8,12,15,23]. Concerning therapy, Soliman *et al.* [19] and Nunlee-Bland *et al*. [12] have proven benefits when GH is replaced in sickle cell anemia patients. Nutritional therapy is questionable since studies demonstrate adequate calories and nutrition ingesting among children with sickle cell disease and growth retardation [12,19]. However, nutrient supplementation can reduce clinical illness resulting in an improvement in growth [17].

Delayed Puberty

The delayed pubertal onset and progression is frequent [1,8,11,24,25]. The SS and $S\beta^0$ hemoglobinopathy carriers present a more prominent delay in puberty when compared to SC and $S\beta^+$ hemoglobinopathy carriers [8,15,17].

The girls present with delayed breast development and menarche [22,26]. At adulthood, infertility, delayed first pregnancy, higher incidence of miscarriage and premature delivery are common [17]. According to studies performed by Serjeant *et al.*, the age of menarche in Jamaican girls is delayed by 0.5 years in SC hemoglobinopathy patients and by 2.4 years in sickle cell disease patients [27].

The boys also have delayed sexual development, starting after 16 years of age [28]. The hypogonadal patients present with eunuchoid habitus, decrease or absence of secondary sex characteristics, small testicular volume and higher predisposition to infertility, including seminal derangements [1,29,30].

The delayed puberty and hypogonadism, despite its frequency, do not have a defined etiology [1]. The primary gonadal failure, hypothalamic-hypophyseal dysfunctions and even the zinc deficiency may be responsible for hypogonadism [29,31]. The FSH (follicle-stimulant hormone) and LH (luteinizing hormone) levels are variable [1,29]. In the male gender, the low serum levels of testosterone, DHT (dihydrotestosterone) and androstenedione with high levels of LH and FSH before and after stimulus with GnRH (gonadotropin-releasing hormone) suggest a primary hypogonadism [17,28]. The reduced testosterone levels after stimulus with chorionic gonadotropin confirm the gonadal hypofunction in boys who are SS hemoglobin carriers [28]. In an older study, it was shown that LH and other serum levels of sex steroids were decreased indicating hypogonadotropic hypogonadism [32].

The periodic transfusions neither altered pubertal evolution nor affected the development of hypogonadotropic hypogonadism in sickle cell disease carriers [8].

Hypothyroidism

Hypothyroidism is regarded as the rarest endocrinopathy in sickle cell anemia patients [5]. Its etiology in these patients remains elusive [1,33]. It is believed that the primary hypothyroidism is probably secondary to iron deposition, based on TSH (thyroid-stimulating hormone) elevation after stimulus with TRH (thyrotropin-releasing hormone) and in necropsy data [1,33]. Isolated case reports imply that primary thyroid failure should be considered in adult sickle cell disease patients [33]. As in diabetes, the transfusion duration is considered the most evident predictive factor for the development of hypothyroidism. According to Fung *et al.* [5], 1.5% of patients with sickle cell disease have hypothyroidism. In the general population it has variable frequency of 1-5% depending on age. The relative risk of hypothyroidism in sickle cell disease is 1.9 for every 10 years of transfusion [5]. On the other hand, some authors did not find significant difference in the levels of T3 (triiodothyronine), T4 (thyroxine), free T4 or TSH (thyroid stimulating hormone) among the SS and AA hemoglobin carriers [7,20,32].

Impaired Glucose Tolerance and Diabetes Mellitus

Glucose intolerance and impaired fasting glucose have been reported in sickle cell disease patients, indicating the presence of hypoinsulinism in these individuals [34]. According to studies by Fung *et al.* [5], 2% of patients with SCD presents with diabetes mellitus. However, the manifestation of actual type 1 or type 2 diabetes mellitus in sickle cell anemia carriers is rare [1,35,36].

Feasible explanations for disorders of carbohydrate metabolism are iron overload rendering damage to pancreatic beta cells and decline in the production of insulin [1]. Corroborating this data, the transfusion duration is considered the most evident predictive factor for the development of diabetes. For every 10 years of transfusion, there is an increase of 2.5 in the risk of diabetes in the sickle cell disease carriers [5]. Nevertheless, current studies show evidence that insulin levels are similar between sickle cell disease children and their healthy controls [7]. In order to explain this rare association, studies try to prove that there is some type of influence of the mutated β-globin gene on the insulin gene. As both genes share a location in the short arm of the chromosome 11, it was proposed that inhibitory effects may affect the inheritance or penetrance of each other [35]. A possible explanation for the low frequency of diabetes in the sickle cell population is that the life expectancy of these patients can overshadow the development of overt diabetes [35].

The interpretation of glycated hemoglobin (HbA_1C) in diabetic patients with sickle cell disease should be done cautiously due to false-negative results affording lower values than what is expected [1,37,38]. This stems from a lower period of exposure, due to the limited red blood cell survival of 10-14 days, of the terminal amino group (NH_2) of valine in the β-globin chain to the irreversible, non-enzymatic glycosylation process [37-39]. The effect of the hemoglobinopathy in the HbA_1C measurement also depends on the employed laboratory method and the expression of HbF [37,40,41]. The hemoglobin variant should be identified

before the dosage of HbA_1C in order to choose the laboratorial method that affords more reliable results. The colorimetric method is the standard procedure for measuring glycated hemoglobin in both patients with sickle cell disease and sickle cell trait [39].

The frutosamine level may be taken as an alternative in assessing the glucose control of sickle cell disease patients, as its values reflect the glycosylation of serum proteins, without interference by hemoglobin variants [1,37,38,41].

Adrenal Dysfunction

Adrenal dysfunction in the sickle cell population is caused by hemorrhage and/or thromboembolism to the adrenal glands [1]. Their frequency in patients with sickle cell disease although uncommon is not established. The iron deposition may also lead to the hypothalamic-hypophyseal-adrenal axis changes [1]. In adrenal lesions, the morning serum cortisol becomes low only with progression of the adrenal injury. Thus, the most precocious derangements will only be detected by the stimulus of the corticotropin (ACTH) test [42]. Therefore, sickle cell disease patients manifesting mild hypoadrenalism may be asymptomatic, developing adrenal failure only when in stress situations [1]. Some studies have shown drop in the cortisol serum levels in sickle cell anemia patients when compared to healthy controls [17,32,34], while other studies have not evidenced this difference [42].

Osteoporosis

The prevalence of reduced bone mineral density (BMD) in sickle cell anemia patients is extremely high [2], beginning in childhood and affecting both genders [1,8,43]. Miller *et al*. have shown a higher prevalence in males than in the females (92% *vs*. 55%) [2]. In the study performed by Sadat-Ali *et al.*, the decrease in bone mass was detected in 62.2% of the men and in 67.06% of the women [44]. Concerning the genotype of sickle cell anemia, there was no difference in the presence of BMD reduction among the SS and SC hemoglobin carriers [2]. The bone mineralization is significantly compromised in patients with severe course of sickle cell anemia [43].

The risk factors for osteopenia include chronic anemia, delayed puberty, bone microinfarcts, immobilization, calcium and vitamin D deficiency and deficiency of IGF-1 [1,22,45,46]. The chronic hemolytic anemia and the decreased erythropoiesis diminish the cortical layer width and dilate the marrow cavity and inter-trabecular spaces [22,45,46]. Buison *et al.* pinpointed that calcium and vitamin D consumption is below the normal requirements in sickle cell anemia patients, which contributes to the deficiency of these nutrients [8]. However, some studies did not show significant correlations between the intake of these nutrients and bone density [43]. Sickle cell disease patients with GH deficiency present with lower BMD and bony formation than SCD patients with normal levels of this hormone [22]. There is also a significant correlation between BMD reduction and decreased zinc, IGF-1 and IGFBP3 serum levels, as well as lower BMI [1,2,22]. GH replacement in these patients intensifies bone turnover and bone density within 6-12 months [22]. No meaningful differences were detected in the serum levels of bone formation markers (bone-specific alkaline phosphatase, osteocalcin) and bone reabsorption markers (N-telopeptide of collagen type I) between sickle cell disease patients with low BMD and those with normal bone density [43].

The patients with sickle cell anemia manifest osteopenia with a decrease in the total bone body area, resulting in bone fractures [18]. The BMD reduction is usually observed in the lumbar spine followed by the head of the femur [43]. In spite of the lumbar spine being the most susceptible region for bone density changes [1,2], most of the fractures happen in the upper limbs, followed by the lower [45,46]. The fractures are caused by bone mineral density reduction and vitamin D deficiency [45]. As children with sickle cell anemia are forced to decrease physical activity, either due to bone pain or immobilization, despite potent painkillers [47], this leads to a decline in the risk of fracture from fall [45]. According to Fung *et al.*, no significant difference was found comparing prevalence of fractures in transfused and in non-transfused sickle cell anemia patients, although the transfused group had less fractures [45].

CONCLUSION

The etiology of the metabolic and endocrine disorders of sickle cell anemia is multifactorial with their manifestations interacting synergistically. Among them, stand out chronic anemia, hemoglobinopathy genotype ($SS > S\beta^0 > S\beta^+ > SC$), iron overload (high number and duration of transfusions), age (positive association with age) malnourishment, and predominance of clinical manifestations of higher severity and specific hormonal derangements.

The most frequent endocrine disturbances are growth delay, delayed puberty, hypogonadism and osteopenia.

Diabetes mellitus, adrenal insufficiency and hypothyroidism are uncommon. The treatment of these endocrinopathies involves the specific replacement of hormonal deficiencies, treatment of anemia, decrease of energy expenditure and reestablishment of the nutritional needs. Chelating agents in patients with iron overload do not reverse the established endocrine deficiency.

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All authors acknowledge that they have participated sufficiently in the work to take public responsibility for its content.

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