

The Effects of Treatment with Blood Transfusion, Iron Chelation and Hydroxyurea on Puberty, Growth and Spermatogenesis in Sickle Cell Disease (SCD): A short update

Ashraf T Soliman^{1,2}, Nada Alaaraj¹, Mohamed Yassin^{1,2}

¹Department of Pediatrics, Division of Endocrinology, Hamad General Hospital, Doha, Qatar; ²Department of Hematology and Oncology, National Centre for Cancer Care and Research, Hamad Medical Corporation, Weill Cornell Medicine, Qatar (WCMCQ)

Abstract. Sickle cell disease (SCD) is traditionally associated with growth failure and delayed puberty. Wasting and stunting are still prevalent in children and adolescents with SCD, especially in developing countries. In addition, sperm abnormalities are frequent in males with SCD, with high rates of low sperm density, low sperm counts, poor motility, and increased abnormal morphology. Severe anaemia, vaso-occlusive attacks with ischemic injury to different organs including the pituitary gland and testis, and nutritional factors are incriminated in the pathogenesis of defective growth, puberty, and spermatogenesis. There is great phenotypic variability among patients with SCD. The variability in the clinical severity of SCD can partly be explained by genetic modifiers, including HbF level and co-inheritance of α -thalassaemia. In the past, severe disease led to early mortality. Advancements in treatment have allowed patients with SCD to have a longer and better quality of life. For most patients, the mainstays of treatment are preventive and supportive. For those with severe SCD, three major therapeutic options are currently available: erythrocyte transfusion or exchange, hydroxyurea and hematopoietic stem cell transplantation. In this mini review the authors tried to recognize, delineate, and update knowledge on abnormalities due to SCD from those created by the use of different treatment modalities. (www.actabiomedica.it)

Key words: Sickle cell disease, growth, puberty, spermatogenesis, hydroxyurea, treatment.

Introduction

Sickle cell disease (SCD) is one of the commonest inherited diseases. It is an encompassing term for all variants of hemoglobinopathy which include at least one copy of hemoglobin S with another abnormal hemoglobin. It is most common among people from Africa, India, the Caribbean, the Middle East, and the Mediterranean, but population movement has made this a worldwide problem (1).

Before 1970, patients with SCD rarely survived past childhood. With the introduction of the

pneumococcal vaccine, universal screening of newborns, and early penicillin prophylaxis, these patients are living long enough to have children and grandchildren. In addition, advancements in treatment have allowed patients with SCD to have a better quality of life. There is great phenotypic variability among patients with SCD. The variability in the clinical severity of SCD can partly be explained by genetic modifiers, including HbF level and co-inheritance of α -thalassaemia. For most patients, the mainstays of treatment are preventative and supportive. For those with severe SCD, three major therapeutic options

are currently available: erythrocyte transfusion (simple or exchange), hydroxyurea and hematopoietic stem cell transplantation. Chronic transfusion therapy, prescribed in high-resource countries primarily to the roughly 10% of SCD patients at high risk for stroke, can ameliorate and prevent stroke and vaso-occlusive crisis; however, several potential adverse effects, including iron overload, alloimmunization (an immune response to foreign antigens that are present in the donor's blood) and haemolytic transfusion reactions, limit its potential benefits. Iron chelation therapy, particularly the second-generation oral agents, employed to prevent and treat iron overload in chronically transfused SCD patients appears to be associated with improved overall and event free survival (1,2).

The various effects of SCD on linear growth, pubertal development, and gonadal maturation (spermatogenesis) have been modified by the above-mentioned modes of treatment. The aim of this mini review is to update the physicians on the variable effects of SCD and pros and cons of using different modes of therapy on linear growth, puberty, and spermatogenesis.

Effect of SCD on Growth and Puberty

The Cooperative Study of Sickle Cell Disease (CSSCD), which included 2,115 patients with SCD from 2 to 25 years old, reported that boys and young men with SCD were significantly shorter than their peers and weighed significantly less across all ages. They found that children with SCD reached a pubic hair and genitalia development at an older age than expected (3).

Soliman et al. (4) studied 110 children and adolescents with SCD. The height standard deviation score (Ht-SDS), growth velocity (GV:cm/yr), and growth velocity standard deviation score (GV-SDS) of children and adolescents with SCD were significantly decreased compared to normal children. 27 per cent of patients with SCD had Ht-SDS less than -2, and 67% had Ht-SDS less than -1. Girls with SCD, aged between 13 and 21 years, had markedly delayed age at breast development and menarche. Twenty-five per cent of boys with SCD, above the age of 14 years, had absence of testicular development. Males with SCD

who had spontaneous testicular development had significantly smaller testicular volume than did normal controls (4). An impaired pubertal development and testicular hormone function in adolescents and adult males has been reported also by other researchers (5-8).

Rhodes et al. (9) in a longitudinal study found that the rate of height growth in 19 boys with SCD was lower than controls one and two years after the beginning of the study. After two years, the percent increase in height values were 6.46 vs. 8.86% ($p < 0.05$). Weight increased at a similar rate in both groups. Boys with SCD had lower gain in fat free mass.

A review, including 46 studies, performed on growth in children with SCD, found a consistent pattern of growth failure among affected children from all geographic areas, with good evidence linking growth failure to endocrine dysfunction, metabolic derangement, and specific nutrient deficiencies (10).

Increased energy requirements have been reported for children, teenagers, and adults with SCD in their usual state of health. Increased protein turnover adds an additional nutritional burden. Nutrient deficiencies based on biomarkers have been reported for vitamins B6, D, E, retinol, and zinc. In a 12-mo trial, zinc supplementation was shown to increase linear growth in children with SCD-SS. However, there are remarkably few supplementations or general nutrition intervention studies aimed at improving growth or nutritional status in children with SCD (11,12).

SCD effect on hormonal control of growth and puberty

Defective growth appears to be mediated partially through defective GH-IGF-I secretion and hypothalamic-pituitary gonadal axis. Soliman et al. (13) investigated 15 short children with SCD (Ht-SDS < -2). Eight out of the 15 children with SCD did not mount an appropriate GH response to clonidine provocation ($< 10 \mu\text{g/L}$). Computed tomographic (CT) scanning of the hypothalamic-pituitary area in those eight children with SCD revealed a partial or complete empty sella in all of them, suggesting a defective GH release, and consequently low IGF-I production. Therefore, the slow growth velocity in children with SCD might be secondary to hypoxic-vascular insults to their

hypothalamic-pituitary axis during one or more of the sickling episodes.

In a later study, the authors investigated 21 children with SCD and found that 9 had defective GH response to both clonidine and glucagon provocation. These children differed from the 12 others in having slower linear growth velocity, lower circulating concentrations of IGF-I and IGFBP-3, and either partial or complete empty sellae in CT scans of the hypothalamic-pituitary area (14). A GH deficiency has been recently confirmed in 2 out of 52 (3.8%) Italian patients with SCD (15). A significant improvement of growth velocity has been reported in 5 patients treated for 3 or more years with recombinant human GH (rhGH) (16).

Ozen et al. (17) studied a group of 50 Turkish children with SCD between 4 and 18 years old. Of the 35 boys included in the study, one had hypergonadotropic hypogonadism, with elevated basal LH and FSH and decreased testosterone levels as compared to normal values; three of the boys had small testes and decreased testosterone levels, but LH levels within normal limits.

Singhal et al. (18) studied 10 Jamaican boys with SCD who had shown no signs of puberty by age 16. Subjects were found to have high basal FSH levels compared to normal adults, suggesting primary testicular failure. Five out of the 10 boys also had impaired or no response of testosterone levels to human chorionic gonadotropin (hCG) stimulation. The presence of a hypergonadotropic hypogonadism or damage of Leydig cells to hCG stimulation test were not confirmed by Taddesse et al. (19) and Martins et al. (20).

In summary SCD has a variable negative effect on linear growth and pubertal development. Defective growth appears to be mediated partially through defective GH-IGF-I secretion, delayed pubertal maturation and nutritional deficiencies.

Effect of treatment on growth and pubertal development

a. Effects of blood transfusion and iron chelation on growth and puberty

A prospective study compared the height, weight, and body mass index (BMI) of 53 children with SCD

receiving long-term transfusions vs. 41 receiving standard care. Both groups were below average height, weight, and BMI as compared to normal children. Researchers found that after 2 years, those children receiving transfusions, every 3–5 weeks, approached normal average values in height and weight, whereas children who did not receive transfusions did not experience the same increase in growth velocity. Height growth velocity in children receiving transfusions was 0.56 cm/mo vs. 0.47 cm/mo in children receiving standard care (P: NS), while the difference of weight growth velocity was statistically significant (0.41 kg/mo vs. 0.25 kg/mo; P: < 0.05) (21).

Yassin et al. (22) evaluated growth parameters and endocrine disorders in relation to the liver iron concentration (LIC) assessed by the Ferriscan® method in a cohort of 40 adults with SCD receiving blood transfusions and iron chelation therapy since early childhood. Patients with SCD with LIC > 8 mg Fe/g dry weight (moderate iron overload) had significantly shorter stature, lower IGF-I SDS and higher alanine aminotransferase (*ALT*) compared to SCD patients with lower LIC.

Treatment with blood transfusion (23) or iron chelation therapy (24) seem to have not significant influence on pubertal development. On the other hand, Soliman et al. (25) measured testosterone, LH, and FSH levels in male SCD patients before and 7 days after packed red cell transfusion. All the patients had been receiving transfusions from childhood and were on regular chelation therapy. After transfusion, there was a significant increase in all three hormones ($p < 0.05$). Therefore, these data suggest that the correction of anemia may have a role on the function of hypothalamic pituitary testicular axis.

b. Effects of hydroxyurea on growth and puberty

Hydroxyurea (HU) has been used for more than 20 years because of its anti-sickling potential. Higher levels of fetal hemoglobin (HbF) diminish deoxygenated sickle globin polymerization in vitro and clinically reduce the incidence of disease morbidities (26). Two studies had a prolonged follow-up (approximately 17 years) and both showed elevated HbF,

reduced acute events, and decreased mortality during HU utilization (27,28).

Regarding the potential detrimental effects of HU on growth due to its antimetabolite properties, Wang et al. (29) studied the effects of treatment in children with SCD. Height and weight were similar between children who were on pre-treatment and treatment, and there was no significant difference in growth velocity between the two groups. In another study, the same Authors (30) reported that children treated with HU had no adverse effect on pubertal development.

c. Effect of hematopoietic stem cell transplantation (HSCT) on growth and puberty

Hematopoietic stem cell transplantation (HSCT) remains the only curative treatment currently in use for patients with SCD, but access is limited for several reasons, including donor availability and sociocultural and economic barriers. However, some controversy remains about which patients should undergo the procedure and a debate about the long-term toxicities from HSCT. HCT for SCD has been typically reserved for patients with severe complications of SCD, such as stroke or who were considered to be at risk of long-term disease-related complications. The risk of infertility after HSCT depends on many factors, most notably the inclusion of radiation, in the conditioning regimen, gonadotoxic chemotherapeutic agents, and stage of pubertal development at the time of HSCT.

However, recent advances including more novel approaches such as reduced toxicity conditioning and the use of alternative allogeneic donors, including matched unrelated donor, unrelated cord blood donors, and familial haploidentical donors are very encouraging (31).

Growth velocity has been measured after HSCT for patients with SCD. In general linear growth does not appear to be adversely affected by myeloablative doses of busulfan in the preparative regimen. However, recipient age and stage of pubertal development influence the effect of busulfan on growth and prepubertal children who were near the onset of the adolescent growth spurt experienced a decrease in linear growth velocity after busulfan administration. In contrast, younger children did not experience decreased

growth velocity during the 2 years after transplantation (32,33).

The comparison of height and weight velocities in males and females after HSCT in comparison to the Cooperative Study of Sickle Cell Disease (CSSCD) and pediatric hydroxyurea groups showed an higher linear growth velocity in males of CSSCD group (34).

Dallas et al. (33) monitored endocrine function in all survivors after Allo-HSCT. All patients were of age ≥ 12 yr at the last evaluation. Five out of 9 males exhibited normal gonadal function, with normal LH, FSH and testosterone levels. Three males had evidence of hypogonadism, with elevated gonadotropins but normal testosterone levels. One patient developed primary hypogonadism and received testosterone therapy. Two out of 4 females developed ovarian failure with elevated gonadotropins and low estradiol levels requiring replacement therapy. The other two females had normal laboratory results and menstrual cycles, and one of the women was 5 months pregnant at her last evaluation.

Despite the occurrence of spontaneous puberty in girls transplanted at a younger age and the birth without treatment of several babies from females transplanted several years ago during infancy, demonstrating some reversibility of ovarian dysfunction, it remains crucial to maximize the chances of fertility and to recommend pre-transplant cryopreservation of ovarian and testis tissues before SCT with myeloablative conditioning regimen (35-37).

d. Effects of SCD and its treatment on spermatogenesis

Few studies have been published on the analyses of sperm parameters in patients with SCD. Some have reported an alterations of spermatozoa concentration, motility and morphology, others a decrease in ejaculate volume and sperm vitality (38,39). In addition to testicular dysfunction, there may be abnormalities in the accessory sex organs, such as the seminal vesicle and prostate that negatively affect the ejaculate volume (40).

The risk of impaired fertility depends on many factors, including: anemia (25), testicular infarction or hypogonadism (41,42), iron overload (43), HU treatment (44), exposure to gonadotoxic chemotherapeutic

agents, and stage of pubertal development at the time of transplantation (45).

Blood transfusion has been shown to be beneficial, at least in the short term, for semen quality. Seven days after packed red cell transfusion, patients had significantly increased sperm count and motility ($p < 0.05$), which was correlated with the increased in testosterone ($p = 0.01$) (25). Blood transfusions can treat and prevent complications of severe SCD and lower the risk of stroke in infants and children. The major and unavoidable complication of transfusions in SCD is iron overload. Therefore, chelation therapy is routinely employed to prevent and treat iron overload in chronically transfused SCD patients. However, inadequate iron chelation leads to iron overload and end organ toxicity involving the endocrine glands, liver and heart (43).

Although the impact of HU in reducing acute complications and improving survival suggests that HU may have a positive effect at limiting SCD-related organ dysfunction long term and

some clinicians have suggested that HU has a positive impact on Vaso occlusive events may limit testicular infarction and improve spermatogenesis, there is a theoretical risk of HU affecting sperm development given that it is an antimetabolite (iv). HU is a ribonucleotide reductase inhibitor primarily acting as an S-phase-specific cytotoxic agent that impairs DNA synthesis. These effects are relatively short lived once the drug is removed. Therefore once-daily administration of HU has brief, intermittent cytotoxic effects on dividing cells (43,44).

Garozzo et al. (46) reported the first case of azoospermia following HU use and Grigg (47) concluded that HU therapy made lead to decreased sperm production and/or altered sperm morphology both during and after therapy, and these effects are at least partially reversible with the cessation of therapy.

However, data are inconsistent as to whether this reduction in sperm counts is partially or fully reversible. In addition, the timing of recovery after discontinuation of HU is unclear. In summary, given that sperm abnormalities exist at baseline in the SCD population and the unclear impact of HU on male fertility, clinicians have little information regarding potential azoospermia or oligospermia when counselling patients or

families of young children starting HU. Nevertheless, more information is needed on the impact of HU on male fertility and sperm production. Counselling patients before HU initiation is challenging given this lack of information. Consensus reports on HU use in SCD suggest that sperm banking (44) or cryopreservation of testicular tissue be offered before starting HU (44,48,49).

Close monitoring for sperm abnormalities during HU therapy with serial sperm analyses every 6-12 months has been suggested (44) However, little guidance is given as to how this information should alter clinical management with respect to temporarily halting or permanently discontinuing HU.

Conclusions

Advancements in treatment have allowed patients with SCD to have a longer and better quality of life. For most patients, the mainstays of treatment are preventative and supportive. For those with severe SCD, three major therapeutic options are currently available: blood transfusion (simple or exchange), hydroxyurea and hematopoietic stem cell transplantation. Blood transfusions can treat and prevent complications of severe SCD and lower the risk of stroke in infants and children. The major and unavoidable complication of transfusions in SCD is iron overload. Therefore, chelation therapy is routinely employed to prevent and treat iron overload in chronically transfused SCD patients. However, inadequate iron chelation leads to iron overload and end organ toxicity involving the endocrine glands, liver and heart. Hydroxyurea, a myelosuppressive agent, is the only effective drug proven to reduce the frequency of painful episodes, raises the level of HbF and the haemoglobin level. However, there is a concern that hydroxyurea may have a detrimental effect on growth and spermatogenesis because of its antimetabolite properties. In addition, stem-cell transplantation has many unwanted effects on growth and sperm production because of the use of immune-suppressant and cytotoxic drugs. Sometimes it is difficult, although very important, to be able to distinguish between abnormalities caused by treatment versus those due to the disease process. Therefore. more studies are needed

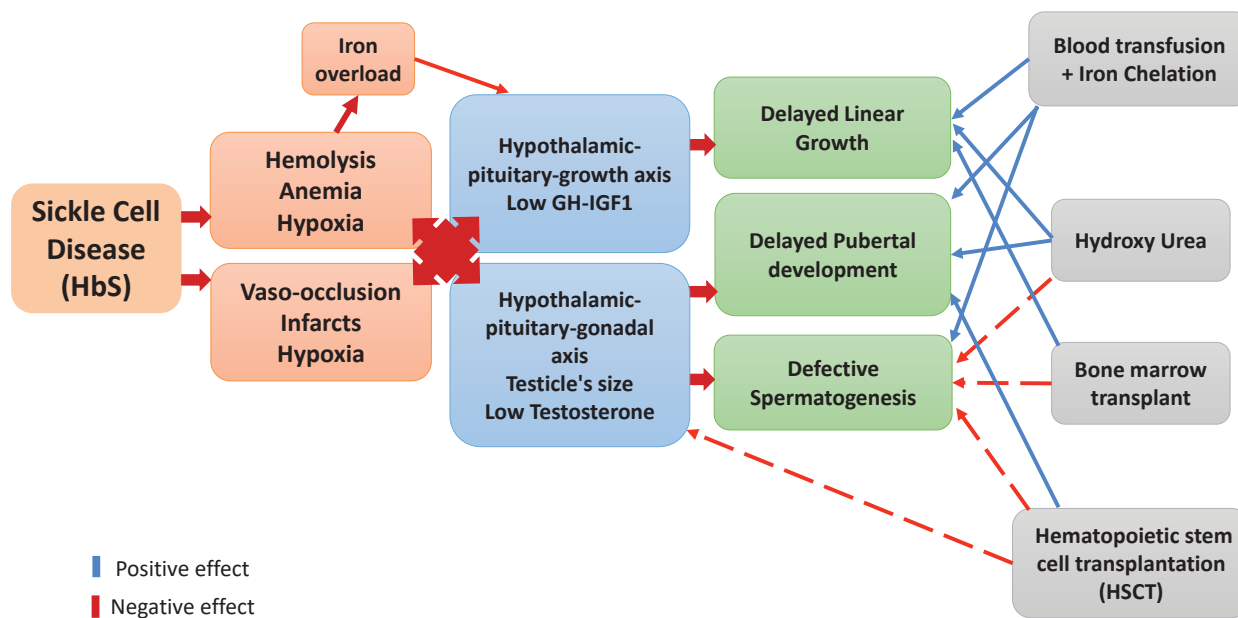


Figure 1. Effects of SCD and different modes of therapy on growth, puberty, and spermatogenesis

to clarify and quantify the extent of different SCD treatment effect/s on sex organs, hormone production, and semen quality. It is also important be able to distinguish between abnormalities caused by treatment versus those due to the disease process (Figure 1).

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Correspondence:

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Prof. Ashraf T Soliman, MD PhD FRCP

Department of Pediatrics

Division of Endocrinology

Hamad General Hospital

Doha, Qatar

E-mail: atsoliman56@gmail.com