Sickle Cell Disease and Thalassaemia:
Chronic Complications (Endocrine and Rheumatology)

Profile	
Version:	*V3.0*
Author:	*Dr Elizabeth Rhodes, Consultant Haematologist* *Dr Julia Sikorska, Consultant Haematologist*
Executive/Divisional sponsor:	*Dr Lisa Pickering, Divisional Chair* *DGB February 2019*
Applies to:	*All staff involved in the care of patients with Sickle Cell Disease*
Date issued:	*February 2019*
Review date:	*February 2022*
Approval	
Approval person/Committee:	*MedCard Divisional Governance Board*
Date:	*14th February 2019*

Contents

Policy Gateway

Please complete the checklist and tables below to provide assurance around the policy review process.

☒ I have involved everyone who should be consulted about this policy/guidance

☒ I have identified the target audience for this policy/guidance

☒ I have completed the correct template fully and properly

☒ I have identified the correct approval route for this policy/guidance

☒ I have saved a word version of this policy/guidance for future reviews and reference

Please set out what makes you an appropriate person to conduct this review:
Lead Consultant for Adult Haemoglobinopathy service

Please set out the legislation, guidance and best practice you consulted for this review:

- West Midlands Review Service – Quality Standards: Health Services for People with Haemoglobin Disorders (2018/19)
- Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK 2018 (Sickle Cell Society) https://www.sicklecellsociety.org/wp-content/uploads/2018/04/Web-version-FINAL-SCS-Standards-GSM-6.4.18.pdf
- Guidelines for the management of Transfusion Dependent Thalassaemia. TIF 3rd Edition. Cappellini MD et al. 2014 https://www.resonancehealth.com/images/files/clinician-information/patient-management-guidelines/TIF%20Guidelines%20for%20the%20Management%20of%20Transfusion%20Dependent%20Thalassaemia.pdf

Please identify the key people you involved in reviewing this policy why, and when:
Dr K Moss – link Consultant for Rheumatology (2015) Dr G Bano – link Consultant for Endocrinology (2015)

Summarise the key changes you have made and why:
Updates in line with the UK standards of care for SCD Updated contact details

Executive Summary

Sickle cell disease (SCD) and thalassaemia are commonly associated with endocrine complications such as growth delay, hypogonadism and adrenal insufficiency. The aetiology is multifactorial but is predominantly due to tissue hypoxia and iron overload. Screening for iron overload and endocrine dysfunction should be performed on an annual basis with input from the Endocrinology team. This document provides guidance on the investigations to be performed and when referral to the Endocrinology team is indicated.

1. Introduction

Patients with sickle cell disease (SCD) and thalassaemia are at an increased risk of endocrinopathies that arise as a result of iron overload, both transfusion and non-transfusion-associated. Patients should be screened for endocrine complications of iron overload in an outpatient setting. This guideline provides detailed advice on investigation and management of endocrinopathies in this patient cohort.

2. Status and Purpose

This document is part of the Haematology Department's guidelines on the management of patients with SCD and is applicable to all staff involved in the care of these patients.

3. Definitions

Sickle Cell Disease – inherited lifelong condition due to abnormal haemoglobin variant.

4. Scope

This guideline is relevant to the care of patients with SCD requiring elective and emergency surgery at St.George's.

5. Roles and Responsibilities

5.1 Haemoglobinopathy team (Consultant haematologists, Clinical Nurse Specialist and Clinical Health Psychologist) – Responsible for the care of these patients, developing and updating guidelines to be reflective of good practice and to deliver the training to ensure good safe care.

5.2 Medical staff involved in the care of patients with SCD. Responsible with the oversight of the haemoglobinopathy team to deliver the care to these patients in line with guidelines where possible.

5.3 Nursing staff and allied health professionals involved in the care of patients with SCD on wards, day unit and other areas of St George's responsible with the oversight of the haemoglobinopathy team to deliver the care of these patients in line with guidelines where possible.

6.0 Content

6.1 MONITORING

Sickle Cell patients – Not on regular transfusions and no signs of iron overload

- At annual review haematologists will screen for IGF-1, fT4, TSH, prolactin, FSH, LH, Test (male patients), Vitamin D, Calcium and PTH

These patients are at risk of endocrine / pituitary disturbance from hypoxia rather than siderosis.

Sickle Cell patients – ferritin > 1000 (with or without treatment)

- DXA bone scan every 3-5 years
- Endocrine referral for pituitary axis testing (including glucose tolerance or fructosamine and cortisol / short synacthen testing) and a review of results

Sickle Cell patients – severe iron overload (concerns regarding level, ongoing transfusions, severe liver loading or any cardiac loading)

- DXA bone scan every 3-5 years
- Annual endocrinology review (or more frequent as needed)

B-thal intermedia patients (at risk of iron overload without transfusions (NTDT)

- DXA bone scan every 3-5 years
- Endocrine referral for pituitary axis testing (including glucose tolerance or fructosamine and cortisol / short synacthen testing) and a review of results

B-thal major patients

- DXA bone scan every 3-5 years
- Annual endocrinology review (or more frequent as needed)

Other:

Vitamin D deficiency / insufficiency should be treated as per local guidelines. Any patients with an osteoporotic fracture should be referred to Dr Moss in Rheumatology. Patients with iron related arthropathies can be referred to Dr Kiely's haemochromatosis clinic.

6.2 IRON OVERLOAD AND ENDOCRINOPATHIES IN ADULTS
(Endocrine Guidelines, Dr Bano)

Endocrine complications are very common in multi-transfused thalassemia (TM) patients. Despite this only 56% are ever seen by an endocrinologist.

Endocrine complications include

- Hypogonadism
- Diabetes mellitus/ Impaired glucose tolerance (IGT)
- Short stature/ Growth hormone deficiency (GHD)
- Primary Hypothyroidism
- Hypoparathyroidism
- Adrenal Insufficiency

Annual endocrine screening: By Endocrinology team
The following tests and assessments are recommended annually:

1. Serum TSH and free T4.
2. Serum calcium, ionized calcium, inorganic phosphate, magnesium, and alkaline phosphatase.
3. Fasting glucose/insulin annually, for the assessment of Homeostasis Model Assessment (HOMA index), which is based on the product of the fasting plasma insulin and glucose concentrations (insulin × glucose/22.5),
4. Oral glucose tolerance testing (OGTT) in case of impaired fasting glucose (IFG).
5. Serum IGF-I and IGF BP-3 in growth screening are useful indicators of growth hormone secretion and nutrition, putting in mind that chronic liver diseases and malnutrition may interfere with their secretion.
6. LH, FSH, and sex steroids, in the pubertal age group
7. Serum or hair zinc (in selected cases).

6.3 HYPOGONADISM

Delayed puberty and hypogonadism are the most obvious clinical consequences of iron overload. Iron deposition in the pituitary gonadotrophic cells leads to disruption of gonadotropin (LH and FSH) production.

In the majority of well chelated patients, the function of gonads is normal; however, gonadal iron deposition occasionally occurs

Delayed puberty is defined as the complete lack of pubertal development in girls by the age of 13 years and in boys by the age of 14 years.

Hypogonadism is defined by the absence of testicular enlargement (less than 4 ml) in boys, and by the absence of breast development in girls by the age of 16 years.
Adolescent patients with TM may present with delayed puberty or slowly progressive puberty. Arrested puberty is a relatively common complication in moderately or grossly iron overloaded patients with TM. This is characterized by the lack of pubertal progression over a year or longer. In such cases, the yearly growth velocity (GV) is either markedly reduced or completely stops.

Most women with TM present with primary amenorrhea (PA), whereas secondary amenorrhea (SA) will invariably develop with time, especially in patients poorly
compliant to chelation therapy. Ovarian function of these women is normal as they produce the expected number of ova after stimulation therapy. Damage of the ovaries by iron deposition is rare and is more likely to appear in women of 25-30 years of age because of high vascular activity in the ovaries at this age.

Investigations
Tanner staging should be determined every 6 months starting from the age of 12 years.
- Girls without evidence of puberty by 13 years and boys by 14 years require screening with measured serum levels of LH, FSH, and estradiol/testosterone:

1. Low FSH and LH for age infer hypogonadotropic hypogonadism (HH) (hypothalamic‐pituitary lesion) and MRI of the pituitary (T2*) is recommended.
2. Elevated FSH and LH suggests primary hypogonadism (very rare)

• If LH and/or FSH are low, performing GnRH stimulation with poor or flat LH and FSH responses confirms the diagnosis of HH.
• Bone age evaluation is useful for prediction of the final adult height of these patients.
• Pelvic ultrasound is useful in assessing ovarian and uterine maturation.

Induction of puberty in boys: At 14 years or bone age (BA) >12 years
Testosterone is used either intramuscular or topical

Induction of puberty in girls: At 13 years or BA >11 years
Estradiol and norethisterone is used orally but preferably transdermal
Gynecological consultation is recommended in women for fertility evaluation

6.4 DIABETES MELLITUS

Diabetes mellitus is seen after the age of 10 years. The etiology of DM is multifactorial (genetic factors, insulin deficiency, insulin resistance, and liver dysfunction secondary to viral hepatitis).
Insulin dependent diabetes in TM presents with some unusual characteristics compared with type 1 diabetes:
• Ketoacidosis is a rare presenting symptom
• Renal glucose threshold is high
• Islet cell antibodies are negative
• There is no association with HLA haplotypes B8-DR3, BW15, and DR4.

Patients usually present with impaired glucose tolerance. A 2h oral glucose tolerance testing (OGTT) if patient has impaired fasting glycemia or when first transferred to an adult endocrine clinic

The diagnostic criteria for glucose tolerance are as follows

- Fasting blood glucose > between 6.1-7mmols is impaired fasting glycemia
- A fasting blood glucose of > 7mmols1 is diagnostic of diabetes mellitus
- On oral glucose tolerance test (OGTT) serum glucose of 7.8-11.1 mmols suggests impaired glucose tolerance
- A 2 hour glucose of >11.1 mmol on OGTT is diagnostic of Diabetes mellitus

Therapeutic approaches

• In cases of impaired glucose tolerance the patients are advised to follow a proper diet and lose weight if they are obese.
• Intensive iron chelation is to be associated with an improvement in glucose intolerance in terms of glucose and insulin secretion, particularly in patients in early stages of glucose intolerance.
• Oral anti-diabetic agents can be used under supervision and proper monitoring
• Insulin therapy may be required to control diabetes and dose is adjusted based on frequent glucose monitoring.

Patients with DM require periodical monitoring of metabolic control and possible complications.

1. Metabolic control may be difficult to achieve and interpret based on HbA1C results
2. HbA1C test is based on normal hemoglobin, hemoglobinopathies can affect the reliability of the test in three ways
- Altering the normal process of glycation of HbA to HbA1C
- Causing an abnormal peak on chromatography, making estimation of A1C unreliable,
- Making the red blood cell more prone to hemolysis, thereby decreasing the time for glycosylation to occur and producing a falsely low A1C result.

3. Fructosamine testing may be used as a target for metabolic control. This has been agreed with chemical pathology (Dr Boa)
4. Albumin/creatinine ratio,
5. Kidney function
6. Retinal screening should be carried out to evaluate the presence and degree of diabetic complications. However, the incidence of retinopathy and nephropathy in thalassemic patients with diabetes is lower than in patients affected by juvenile diabetes.

6.5 HYPOTHYROIDISM

Annual investigation of thyroid function is recommended beginning at the age of 9 years (unless symptomatic hypothyroidism is observed). Measuring serum T4 and TSH levels will make the diagnosis. Symptoms and signs of primary hypothyroidism in children and adolescents, such as growth retardation and weight increase, may present. The majority of patients have primary thyroid dysfunction. Secondary hypothyroidism (low/normal TSH, low FT4) is rare.

Management
Good compliance with chelation therapy may prevent or improve subclinical hypothyroidism.
Basal TSH 5 to7 mUI/ml requires regular follow up and optimizing chelation therapy in patients with mild or overt hypothyroidism, L-thyroxine is the treatment.
In patients with TM, subclinical hypothyroidism, and cardiomyopathy, treatment with amiodarone may result in a rapid progression of severe thyroid disease and deterioration of cardiac function

6.6 HYPOPARATHYROIDISM

This uncommon complication presents after the age of 16 years equally in both sexes. The majority of the patients present with mild hypocalcemia and rarely, with tetany and cardiac failure. Hypoparathyroidism is thought to be the consequence of iron deposition in the parathyroid glands or due to suppression of parathyroid secretion induced by bone reabsorption resulting from increased hematopoiesis secondary to the chronic anemia.

Majority of patients have mild disease and present with only paraesthesia. However, severe cases may present with tetany, seizures, or cardiac failure. Abnormal cerebral CT findings of calcifications have been reported in relation to hypoparathyroidism in these patients.

The diagnosis is based on low serum calcium, high phosphate and low PTH levels. If hypoparathyroidism is suspected, there is always a risk of hypocalcemia which must be treated without delay.

Management

Start vitamin D therapy.

Calcitriol 0.25-2.0 ug/day and calcium 1 g /day are the treatment of choice, with monitoring of serum calcium levels. Diet rich in calcium and low in phosphorus is advised.

6.7 ADRENAL INSUFFICIENCY

Excess iron has the potential to disrupt adrenal function by affecting the hypothalamic-pituitary adrenal axis at the hypothalamic or pituitary and/or adrenal level.

Several studies reported a significant prevalence of “biochemical” adrenal insufficiency, ranging from 0% to 45%, in patients with TM. Adrenal crisis, on the other hand, is extremely rare.

In primary adrenal insufficiency, cortisol, aldosterone, and androgen secretion are affected. Secondary or tertiary adrenal insufficiency (pituitary or hypothalamic affected) causes no mineralocorticoid defect.

Patients are usually asymptomatic. Adrenal androgen levels might be decreased explaining the poor development of pubic and axillary hair observed in thalassemic adolescents. Manifestations of mild adrenal hypofunction might be masked by symptoms common in thalassemic patients, such as fatigue, muscle weakness, arthralgias, and weight loss.

Investigations
Measurement of both basal serum cortisol level and cortisol response to stimulation by ACTH or insulin stimulation (ITT) can be used for assessment of adrenal function. Baseline cortisol [morning baseline cortisol level (at 8-9 AM)] can be used to detect subtle adrenal insufficiency.

ACTH stimulation test should be done in patients with an abnormal baseline cortisol level. A peak cortisol level of <500 nmol/L 30-60 min after ACTH stimulation is abnormal.

It is advised to test adrenal function every 1-2 years, especially in GHD patients during rhGH therapy. Subclinical impairment of adrenocortical function in patients with TM is not uncommon, but has little clinical impact under basal conditions. Glucocorticoid treatment cover might be advised only for stressful conditions.

6.8 SUMMARY TABLE

Endocrine/ Metabolic disease	Screening	Treatment	
Growth Failure/ Short stature	IGF-1, IGFBP-3 Screen for GH deficiency	GH therapy if GH deficiency proven	
Hypogonadism/ infertility	Monitor development of primary/secondary sexual characters or delayed puberty Monitor LH/FSH/oestrogen/testosterone Pelvic ultrasound scan	Sex hormone replacement (OCP or testosterone	Early referral to fertility services if considering pregnancy
Diabetes/IGT	Yearly fasting blood glucose after puberty 75-g OGTT if indicated	Diet, insulin (basal, bolus with meals) and Chelating therapy	Monitor with sr Fructosamine
Hypothyroidism	Screening: yearly TSH/free T4 ± Thyroid antibodies	Thyroid hormone therapy	On treatment: 6 monthly TSH/free T4
Hypoparathyroidism	Serum calcium, inorganic phosphate, magnesium, alkaline phosphatise and PTH	Calcitriol 0.25-2.0 ug/day and calcium 1 g /day	Keep serum calcium level towards the lower end of normal
Panhypopituitarism	Annual screen prolactin, including thyroid, GH/IGF-1, prolactin and FSH, LH	Replace cortisol, thyroid hormone and sex hormones	Short synacthen test (SST) Stimulation test if indicated

6.9 FERTILITY

Female Infertility or difficulties

Patients who are iron overloaded are at risk of subfertility due to a combination of problems but it is often due to iron overload affecting the ovaries, hypothalamus and or the pituitary gland resulting in hypogonadism. Patients with sickle cell may also suffer the consequence of local ischaemia secondary to hypoxia from their anaemia.

Patients who are amenorrhoeic (either primary or secondary) or who are failing to conceive, or who would like to discuss be referred early for investigation and assisted conception where appropriate.

Referrals for endocrinological disturbances and investigation should be to endocrinologists (Dr Gul Bano) for hormonal assessment.

Referrals for conception advice, fertility advice, fertility preservation, fertility treatment and also genetic treatments should be made early to our specialist in Reproductive Medicine, Mrs Geeta Nargund in obstetrics and gynaecology.

Male Erectile Dysfunction and Infertility

Patients can suffer from male sexual dysfunction and infertility. The underlying problems can be multifactorial and can include one or more of the following:

- Repeated untreated episodes of priapism
- Medication
- Psycho-sexual dysfunction
- Transfusional iron overload can affect the testes, hypothalamus and the pituitary gland causing dysfunction and hypogonadism

Patients should be asked about any concerns at their annual review and patients with difficulties should have a full pituitary axis screen including a hormonal profile of testosterone, SHBG, Gonadotrphin and prolactin. They can then be referred to the complex medical andrology service. Patients can either be seen in a combined clinic, discussed in an MDT or seen by Dr Seal in endocrinology with input from Mr Yap and urology as needed.

Hospital Contact Details

Dr Elizabeth Rhodes	Haematology Consultant	ext 0885
Dr Julia Sikorska	Haematology Consultant Haematology Registrar	ext 0885 bleep: 7080
Carol Rose	Sickle Cell CNS	mobile: 07500835735

Out of hours

Haematology Registrar	via switchboard
Haematology Consultant	via switchboard

7. Dissemination and implementation

7.1 Dissemination:
Guidelines will be available on the departmental intranet page and available in paper form in the junior doctor office in haematology.

7.2. Implementation
Guidelines will be promoted by the haemoglobinopathy team.

8. Consequences of Breaching the Policy

Failing to follow this policy could lead to action under the Trust's disciplinary policy.

9. Monitoring compliance
The table below outlines the process for monitoring compliance with this document.

Monitoring compliance and effectiveness table					
Element/ Activity being monitored	**Lead/role**	**Methodology to be used for monitoring**	**Frequency of monitoring and Reporting arrangements**	**Acting on recommendations and Leads**	**Change in practice and lessons to be shared**
WMQRS peer review quality standards	*Consultant haematologist*	*As required (every 2-3 year)*	*The lead or committee is expected to read and interrogate the report to identify deficiencies in the system and act upon them. Consider stating this responsibility in committee terms of reference.*	*Required actions will be identified and completed in a specified timeframe. Consider stating this responsibility in committee terms of reference.* *These will be discussed at Divisional governance board*	*Required changes to practice will be identified and actioned within a specific timeframe. A lead member of the team will be identified to take each change forward where appropriate. Lessons will be shared with all the relevant stakeholders.*

10. Associated documentation

11. References

- West Midlands Review Service – Quality Standards: Health Services for People with Haemoglobin Disorders (2018/19)

- Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK 2018 (Sickle Cell Society) https://www.sicklecellsociety.org/wp-content/uploads/2018/04/Web-version-FINAL-SCS-Standards-GSM-6.4.18.pdf

- TIF (2014) Guidelines for the care of transfusion dependent thalassaemia https://issuu.com/internationalthalassaemiafederation/docs/tif_guidelines_for_management_final