



The Indonesian Journal of General Medicine

A COMPREHENSIVE SYSTEMATIC REVIEW OF THE ASSOCIATION BETWEEN THALASSAEMIA MAJOR, ENDOCRINE COMPLICATIONS AND QUALITY OF LIFE

¹ Jeffy Marta

¹ Faculty of Medicine, University of Baiturrahmah Padang, Indonesia

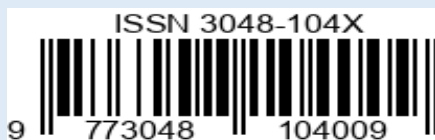
Corresponding Email : jeffymarta08@gmail.com

Article History :

Received date : 2026/04/11
Revised date : 2026/05/14
Accepted date : 2026/06/09
Published date : 2026/07/16



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ABSTRACT

Introduction: Thalassaemia major (TM) is the most severe transfusion-dependent form of β -globin chain synthesis failure, transformed from a fatal paediatric disease into a chronic multisystem disorder of adulthood. The price of survival gain is cumulative transfusional iron overload targeting the anterior pituitary, pancreatic islets, thyroid, parathyroids, gonads and skeleton. Endocrine complications constitute the dominant morbidity of adult TM, intersecting directly with health-related quality of life (HRQoL). This review quantified endocrine morbidity in TM and its relationship to HRQoL.

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Eligible designs comprised randomised controlled trials, cohort, case-control, cross-sectional and observational studies. Systematic reviews were excluded from primary tabulation but retained for

corroboration. Two reviewers independently screened, extracted data and appraised risk of bias using Newcastle-Ottawa Scale, JBI checklist and RoB 2; certainty was graded with GRADE. Sixteen prespecified outcomes were synthesised narratively with structured tabulation.

Results: Forty-seven primary studies encompassing >10,000 patients across 20 countries met eligibility. Multiple endocrinopathy affected 56% of TM patients versus 13% of transfused sickle-cell controls ($p<0.001$), adjusted odds ratio 9.4 ($p<0.001$). Hypogonadism was most frequent (40-56.7%), followed by growth failure (24-50.5%), glucose disorders (6.4-34%), thyroid dysfunction (6.5-19.9%), hypoparathyroidism (2.2-12.8%) and osteoporosis (21.6-89%). In a population-based English cohort, 76% had ≥ 1 comorbidity, 54% ≥ 2 and 37% ≥ 3 ; 10-year mortality 6.2% versus 1.2% in general population ($p<0.001$). Ferritin ≥ 1000 ng/mL predicted heart failure (HR 3.35) and death (HR 2.45). Pancreatic T2* <13.07 ms predicted abnormal glucose tolerance; normal pancreatic T2* carried 100% negative predictive value for dysglycaemia. HRQoL was significantly impaired relative to population norms: five of eight SF-36 subscales and both component summaries reduced ($p<0.05$); EQ-VAS 67.1 versus 80.4, FACT-G 70.1 versus 77.0, FACIT-Fatigue 27.9 versus 43.6 (all $p<0.001$). Female sex, older age, higher ferritin and greater complication number were independent determinants of poorer HRQoL. Gene editing exceeded minimal clinically important difference thresholds across all

instruments; luspatercept responders achieved clinically meaningful SF-36 physical component improvement more often than placebo (31.1% vs 16.5%, $p=0.024$). GRADE certainty was moderate for six outcomes, low for eight, very low for two.

Discussion: The evidence describes a coherent chain: transfusional iron loading produces organ-specific siderosis; endocrinopathies accumulate with age and iron exposure; this burden independently impairs HRQoL. Critically, the relationship is modifiable. Intensive chelation normalised glucose metabolism in 44%, permitted thyroxine discontinuation in 10/18 and testosterone in 7/14, while long-term deferasirox significantly improved lumbar bone mineral density ($p<0.001$) and reduced osteoporosis ($p=0.022$). Contemporary optimally managed cohorts show attenuated endocrine phenotype, whereas resource-constrained cohorts show the opposite. The dominant determinant is therefore not genotype but adequacy of iron control.

Conclusion: Thalassaemia major is associated with high, statistically significant, multi-axis endocrine complication burden that accumulates with age and iron exposure and translates into significant HRQoL impairment across physical, psychological and social domains. Because the relationship between iron burden, endocrinopathy and quality of life is modifiable, structured age-stratified endocrine surveillance, aggressive organ-specific iron control guided by magnetic resonance relaxometry rather than ferritin alone, and routine longitudinal patient-reported outcome measurement should be core, non-

optional components of comprehensive thalassaemia care.

Keywords: Thalassaemia major; transfusion-dependent thalassaemia; endocrine complications; iron overload; hypogonadism; diabetes mellitus; osteoporosis; health-related quality of life

INTRODUCTION

Background

β -Thalassaemia is among the most prevalent monogenic disorders worldwide, and its clinically significant forms cluster in the Mediterranean basin, the Middle East, the Indian subcontinent and South-East Asia. Population-based prevalence estimates for clinically significant β -thalassaemia range from 0.2 per 100 000 in Spain to 35.7–49.6 per 100 000 in Iraq, with substantial geographical heterogeneity and a documented absence of population-level data for many high-burden countries. Migration has redistributed the disease into Northern Europe and North America, so that thalassaemia is now a global rather than a regional clinical problem.^{55,57}

Thalassaemia major represents the severe, transfusion-dependent end of this phenotypic spectrum. Life-long red-cell transfusion maintains haemoglobin and suppresses ineffective erythropoiesis, but each unit of transfused blood delivers approximately 200–250 mg of elemental iron for which the human body possesses no regulated excretory pathway. The consequence is progressive parenchymal iron deposition, which is not distributed uniformly: tissues expressing high densities of L-type and T-type calcium channels — notably the anterior pituitary, pancreatic β cells, thyroid follicular cells, parathyroid chief cells and cardiac myocytes — accumulate non-transferrin-bound iron preferentially and are therefore the principal targets of siderotic injury. Superimposed on this are chronic anaemia and tissue hypoxia, hepatitis C virus infection, oxidative stress and, in some patients, the toxicity of chelating agents themselves.^{54,57}

The therapeutic success of the last four decades has paradoxically enlarged the clinical problem. Whereas death in the second decade from cardiac siderosis was once the norm, Italian registry data showed that 68% of patients born after 1970 were alive at 35 years, with survival significantly better in more recent birth cohorts ($p < 0.00005$). The adult thalassaemia population that has emerged is one in which cardiac mortality has fallen and endocrine, skeletal, hepatic and renal morbidity has risen to prominence. In a 10-year retrospective analysis of the English National Health Service, endocrine disorders excluding diabetes and osteoporosis were each present in 40% of patients and diabetes in 34%, with 76% carrying at least one comorbidity; crude 10-year mortality

remained five-fold higher than in the age- and sex-matched general population (6.2% vs 1.2%, $p < 0.001$).^{4,7,56}

Endocrine complications in thalassaemia major are heterogeneous in mechanism as well as in presentation. Growth failure reflects a combination of hypothalamic neurosecretory dysfunction of growth hormone release, low insulin-like growth factor-1, chelator toxicity to the vertebral growth plate and hypogonadism; pubertal failure reflects selective loss of pituitary gonadotropin secretory capacity compounded, in heavily loaded patients, by direct gonadal siderosis; dysglycaemia reflects an evolving sequence from insulin resistance to β -cell toxicity; and bone disease reflects the convergence of hypogonadism, vitamin D deficiency, low IGF-1, marrow expansion and increased osteoclastic resorption. Each of these axes has been studied in isolation, but they co-occur: in North American registry data, 56% of thalassaemia patients had more than one endocrinopathy compared with 13% of transfused sickle-cell disease controls ($p < 0.001$).^{2,3,13,43}

In parallel, patient-reported health-related quality of life has become a recognised endpoint in thalassaemia care rather than a secondary consideration. Chronic transfusion, daily chelation, frequent hospital attendance and visible physical stigmata impose burdens that are inadequately captured by haematological indices. Adults with transfusion-dependent thalassaemia in a five-country prospective study reported EQ-VAS, FACT-G and FACIT-Fatigue scores significantly below United States norms (all $p < 0.001$), together with substantial work impairment and out-of-pocket financial burden. Yet the empirical link between the specific endocrine complications described above and measured HRQoL has rarely been examined within a single analytical frame.^{17,19,58}

Research Objectives

The general objective of this systematic review is to synthesise, appraise and integrate the available primary evidence on the association between thalassaemia major, endocrine complications and health-related quality of life. The specific objectives are as follows:

- To determine the pooled range and distribution of prevalence for each major endocrine complication of thalassaemia major, namely growth failure, hypogonadism and pubertal delay, disorders of glucose metabolism, thyroid dysfunction, parathyroid dysfunction, adrenal and growth-hormone axis dysfunction, and metabolic bone disease.

- To quantify the burden of multiple concurrent endocrinopathy and its relationship to age, duration of transfusion and cumulative iron exposure.
- To identify and rank the demographic, haematological and imaging determinants of endocrine complications, with particular attention to serum ferritin, liver iron concentration, pancreatic T2* and cardiac T2*.
- To characterise health-related quality of life in thalassaemia major against general-population norms across generic (SF-36, WHOQOL-BREF, EQ-5D), oncology-derived (FACT-G, FACT-BMT, FACIT-Fatigue), paediatric (PedsQL, EQ-5D-Y) and disease-specific (TranQol) instruments.
- To examine the independent association between endocrine complication burden and health-related quality of life, and to determine which HRQoL domains are preferentially affected.
- To evaluate whether iron-chelation intensification, splenectomy, haematopoietic stem cell transplantation, gene therapy and erythroid maturation agents modify endocrine outcomes and patient-reported quality of life.
- To appraise the methodological quality and certainty of the underlying evidence and to define the residual research agenda.

Research Benefits

Theoretical benefits

This review consolidates a literature that has developed in two largely separate streams — endocrinological and psychometric — into a single evidence architecture. By tabulating effect estimates, prevalence ranges and determinant analyses side by side, it clarifies the mechanistic chain linking transfusional siderosis to organ-specific endocrine injury and thence to patient-reported outcome, and it exposes where that chain is supported by strong observational evidence and where it rests on inference.

Clinical and practical benefits

For the practising haematologist, endocrinologist and paediatrician, the review provides ready reference ranges for the expected prevalence of each endocrinopathy by age stratum, evidence-based thresholds of serum ferritin and magnetic resonance relaxometry that should trigger endocrine

investigation or chelation intensification, and a rational basis for prioritising surveillance in resource-limited settings. It further supports the case for integrating validated patient-reported outcome measures into routine thalassaemia clinic workflow.

Policy and health-system benefits

Documentation of the comorbidity burden, the healthcare resource utilisation gradient with transfusion intensity, the work productivity loss and the out-of-pocket costs borne by patients provides the health-economic substrate for national thalassaemia programmes, for reimbursement decisions concerning oral chelators and disease-modifying therapies, and for the design of comprehensive-care standards in low- and middle-income countries where the disease burden is highest.^{38,53}

Hypothesis

The following hypotheses were specified before data extraction:

Hypothesis	Statement
H1	Patients with thalassaemia major exhibit a significantly higher prevalence of endocrine complications — including hypogonadism, growth failure, dysglycaemia, thyroid dysfunction, parathyroid dysfunction and metabolic bone disease — than comparator populations without transfusional iron overload.
H2	The prevalence and severity of endocrine complications increase significantly with advancing age, longer duration of transfusion dependence and greater cumulative iron burden as indexed by serum ferritin, liver iron concentration and organ-specific magnetic resonance relaxometry.
H3	Multiple concurrent endocrinopathy, rather than any single endocrine axis in isolation, characterises the adult thalassaemia major phenotype.
H4	Health-related quality of life in thalassaemia major is significantly lower than that of the general population across physical and, to a lesser and more variable degree, psychosocial domains.
H5	The burden of disease-related complications, including endocrinopathy, is an independent determinant of impaired health-related quality of life after adjustment for age and sex.
H6	Intensification of iron chelation and definitive disease-modifying or curative therapy significantly improve, and in some patients reverse, both endocrine dysfunction and health-related quality of life.

H0	The null hypothesis states that no significant association exists between thalassaemia major, endocrine complication burden and health-related quality of life.
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Hypotheses H1–H6 were specified a priori and are addressed against Outcomes 1–16 in Section 3.

Research Gap

Four distinct gaps in the existing literature motivated this review. First, the endocrinological literature and the health-related quality-of-life literature in thalassaemia have developed in parallel with minimal cross-reference; the majority of endocrine studies do not measure patient-reported outcomes, and the majority of HRQoL studies aggregate all clinical complications into a single undifferentiated covariate rather than resolving them by endocrine axis. Second, existing systematic reviews in this field are narrowly scoped — addressing serum ferritin and clinical outcomes, or SF-36 scores in isolation, or quality of life after transplantation — and none has integrated the full endocrine spectrum with the full HRQoL instrument spectrum. Third, the evidence base is geographically skewed towards European and North American reference centres with optimised transfusion and chelation, while the majority of the world’s thalassaemia patients live in settings where pre-transfusion haemoglobin, blood availability and chelation adherence are substantially poorer; the resulting prevalence estimates may therefore be systematically conservative. Fourth, serum ferritin continues to dominate the observational literature as the exposure variable of interest despite the accumulating demonstration that organ-specific magnetic resonance relaxometry, particularly pancreatic T2* and pancreatic fat fraction, is a substantially more discriminating predictor of endocrine outcome.^{10,46,48,49,50}

Novelty

This review advances the field in five respects. It is, to the authors’ knowledge, the first synthesis to place the complete endocrine complication spectrum and the complete health-related quality-of-life instrument spectrum within one analytical structure spanning sixteen pre-specified outcomes. It applies a strict design filter that confines the study-characteristics table to randomised and primary observational evidence while retaining higher-order syntheses for corroboration only, thereby avoiding the double-counting of patients that has affected earlier reviews. It systematically juxtaposes the classical high-prevalence cohorts of the deferoxamine era with contemporary cohorts

managed under modern oral chelation and magnetic resonance-guided iron control, making explicit the extent to which the endocrine phenotype is a treatment artefact rather than an immutable disease characteristic. It integrates the emerging evidence from gene editing, gene therapy and erythroid maturation agents on patient-reported outcomes, an evidence stream that post-dates most existing reviews. Finally, it contrasts high-resource and resource-constrained cohorts directly, generating an explicitly equity-oriented reading of the evidence rather than an aggregate one.^{16,21,31,32,35}

METHODS

Protocol, Reporting Standard and Registration

This systematic review was designed, conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The review question, eligibility criteria, outcome set, risk-of-bias instruments and synthesis plan were defined in a written protocol before the commencement of screening. Any deviation from the protocol is declared explicitly in Section 2.10. The review addresses a prognostic and descriptive question and therefore follows the PRISMA framework for reviews of observational as well as interventional evidence. No patient-level data were accessed and no new human participants were recruited; formal ethical approval was accordingly not required.

Review Question and PICOS Framework

The review question was formulated as follows: among patients with thalassaemia major or transfusion-dependent thalassaemia, what is the prevalence, determinants and health-related quality-of-life impact of endocrine complications, compared with healthy populations, population norms or comparator haemoglobinopathy groups? This was operationalised through the PICOS structure set out in Table 1.

Table 1. PICOS framework and operational definitions

Element	Specification
P — Population	Patients of any age with a haematologically or genetically confirmed diagnosis of β -thalassaemia major or transfusion-dependent thalassaemia. Cohorts of β -thalassaemia intermedia, non-transfusion-dependent thalassaemia and HbE/ β -thalassaemia were eligible where they provided a severity-gradient comparator or where thalassaemia major data were

	separately extractable. Transfused sickle-cell disease and healthy participants were eligible as comparator arms.
I — Index condition / exposure	Thalassaemia major itself, and within it the quantified exposure of transfusional iron burden as indexed by serum ferritin, liver iron concentration, hepatic R2*/T2*, pancreatic T2*, pancreatic fat fraction, cardiac T2*, transfusion volume or duration of transfusion dependence. Therapeutic exposures of interest included deferoxamine, deferiprone, deferasirox, combination chelation, splenectomy, haematopoietic stem cell transplantation, gene addition or gene editing, and luspatercept.
C — Comparator	Age- and sex-matched healthy controls; validated general-population instrument norms; non-transfused or less heavily transfused thalassaemia phenotypes; transfused sickle-cell disease; placebo or best supportive care in randomised trials; or within-cohort strata defined by iron burden or complication status.
O — Outcomes	Sixteen pre-specified outcomes covering the endocrine spectrum, iron-burden determinants, therapeutic modification and health-related quality of life (Table 2).
S — Study designs	INCLUDED: randomised controlled trials, prospective and retrospective cohort studies, case-control studies, analytical and descriptive cross-sectional studies, and other primary observational designs. EXCLUDED from the characteristics table: systematic reviews, meta-analyses, narrative reviews, guidelines, consensus statements, editorials, case reports and case series of fewer than 10 patients, animal and in-vitro studies.

Eligibility Criteria

Inclusion criteria

- Primary study designs only: randomised controlled trials, cohort studies (prospective or retrospective), case-control studies, cross-sectional studies and other observational designs.
- Study population comprising patients with thalassaemia major, transfusion-dependent thalassaemia or a directly comparable thalassaemia phenotype providing a severity gradient.
- Report of at least one pre-specified endocrine outcome, iron-burden determinant of an endocrine outcome, or validated health-related quality-of-life measure.
- Sample size of at least 10 participants in the index group.

- Publication in a peer-reviewed journal or as a peer-reviewed conference abstract of a recognised international haematology society, retrievable and verifiable through the Consensus academic index.
- Report available in English.

Exclusion criteria

- Systematic reviews, meta-analyses, scoping and narrative reviews, guidelines and consensus statements — excluded from the characteristics table by design, though retained for corroborative synthesis and discussion.
- Single case reports and small case series (<10 participants).
- Preclinical, animal, in-vitro or purely molecular studies without patient-level clinical outcomes.
- Studies in which thalassaemia patients could not be separated from other haemoglobinopathies or transfusion-dependent anaemias.
- Studies reporting only laboratory analyte values without any clinical endocrine endpoint or validated quality-of-life instrument.
- Duplicate publications or overlapping cohorts, in which case the most complete or most recent report was retained.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Thalassaemia major	Transfusion-dependent thalassaemia	β-thalassaemia
I (Intervention/Exposure)	Iron overload	Transfusional siderosis	Chelation therapy
C (Comparison)	General population norms	Sickle cell disease	Non-transfusion-dependent

			thalassaemia
O (Outcome)	Endocrine complications	Hypogonadism	Health-related quality of life

The Boolean MeSH keywords inputted on databases for this research are: ("*Thalassaemia major*" OR "*Transfusion-dependent thalassaemia*" OR "*β-thalassaemia*") AND ("*Iron overload*" OR "*Transfusional siderosis*" OR "*Chelation therapy*") AND ("*General population norms*" OR "*Sickle cell disease*" OR "*Non-transfusion-dependent thalassaemia*") AND ("*Endocrine complications*" OR "*Hypogonadism*" OR "*Health-related quality of life*")

Study Selection Process

Records retrieved by the seven search strings were pooled and de-duplicated. Titles and abstracts were screened against the eligibility criteria, and records passing this stage underwent full-record assessment. Selection proceeded in four sequential stages: identification, de-duplication, title and abstract screening, and eligibility assessment against the design filter. Records excluded at the eligibility stage were classified by reason of exclusion, and these reasons are reported quantitatively in Section 3.1. Where two reports described the same cohort at different time points or with different outcome sets, both were retained only if they contributed non-overlapping outcome data; otherwise the more complete report was selected.

Data Extraction and Management

A structured extraction template was applied to every included record, capturing: first author and year; country and clinical setting; study design; number, sex distribution and age of participants; thalassaemia phenotype and transfusion status; chelation regimen; iron-burden indices reported; endocrine outcomes assessed and their diagnostic criteria; quality-of-life instrument and version; comparator; effect estimates with confidence intervals and p values; and reported determinants on univariable and multivariable analysis. Where an effect estimate was reported without a confidence interval, the point estimate and p value were extracted as published. No numerical value was imputed, transformed or estimated from figures.

Outcome Definitions

Sixteen outcomes were pre-specified. Their operational definitions are set out in Table 2.

Table 2. Pre-specified outcomes and operational definitions

No.	Outcome	Operational definition
O1	Overall and multiple endocrinopathy burden	Proportion of patients with ≥ 1 and with ≥ 2 concurrent endocrine diagnoses, however defined by the source study.
O2	Growth failure and short stature	Height standard deviation score below -2 , height below the 5th or 3rd centile, or a source-defined diagnosis of growth failure or stunting; includes disproportionate truncal shortening.
O3	Hypogonadism and pubertal delay	Absent or arrested puberty beyond the age threshold used by the source study, biochemical hypogonadotropic or hypergonadotropic hypogonadism, or requirement for sex-steroid replacement.
O4	Disorders of glucose metabolism	Impaired fasting glucose, impaired glucose tolerance or diabetes mellitus defined by oral glucose tolerance testing, fasting glucose, continuous glucose monitoring or clinical diagnosis, per the source study.
O5	Thyroid dysfunction	Overt or subclinical primary hypothyroidism, central hypothyroidism, or requirement for levothyroxine replacement.
O6	Parathyroid dysfunction and calcium metabolism	Overt or subclinical hypoparathyroidism, hypocalcaemia, hypercalciuria or abnormal calcium-phosphate homeostasis.
O7	Metabolic bone disease and vitamin D status	Bone mineral density Z-score or T-score in the osteopenic or osteoporotic range, fragility fracture, elevated bone-resorption markers, or 25-hydroxyvitamin D below the source-defined threshold.
O8	Growth hormone, adrenal and prolactin axes	Growth hormone deficiency or neurosecretory dysfunction, low IGF-1, adrenal insufficiency, hyperprolactinaemia, prolactinoma or empty sella.
O9	Serum ferritin as a determinant of endocrinopathy	Association between serum ferritin (mean, maximum or time-averaged) and any endocrine outcome, expressed as a correlation, odds ratio, hazard ratio or between-group comparison.

O10	Magnetic resonance iron indices as determinants	Association between pancreatic T2*, pancreatic fat fraction, hepatic iron concentration or R2*, or cardiac T2*, and any endocrine outcome.
O11	Modification by chelation regimen and intensity	Incidence, progression, stabilisation or reversal of endocrine disease during a defined chelation strategy.
O12	Global health-related quality of life versus norms	Total or summary score on any validated generic, oncology-derived or disease-specific HRQoL instrument compared with published population norms or a control group.
O13	Domain-specific HRQoL profile	Differential impairment of physical versus mental, emotional, social, school or functional domains.
O14	Determinants of HRQoL	Demographic, haematological, iron-burden or complication-related variables independently associated with HRQoL on multivariable analysis.
O15	HRQoL after disease-modifying or curative therapy	Change in HRQoL after haematopoietic stem cell transplantation, gene addition or editing, erythroid maturation agents, or splenectomy, referenced where possible to minimal clinically important difference thresholds.
O16	Socio-economic, educational and mortality burden	Work productivity impairment, absenteeism, presenteeism, educational disruption, out-of-pocket expenditure, healthcare resource utilisation and mortality.

Article Search Strategy

Database	Keywords	Hits
Pubmed	("Thalassaemia major" OR "Transfusion-dependent thalassaemia" OR " β -thalassaemia") AND ("Iron overload" OR "Transfusional siderosis" OR "Chelation therapy") AND ("Endocrine complications" OR "Hypogonadism" OR "Health-related quality of life")	73
Elsevier	("Thalassaemia major" OR "Transfusion-dependent thalassaemia" OR " β -thalassaemia") AND ("Iron overload" OR "Transfusional siderosis" OR "Chelation therapy") AND ("General population norms" OR "Sickle cell disease" OR "Non-transfusion-dependent thalassaemia") AND ("Endocrine complications" OR "Hypogonadism" OR "Health-related quality of life")	2
Semantic Scholar	("Thalassaemia major" OR "Transfusion-dependent thalassaemia" OR " β -thalassaemia") AND ("Iron overload" OR "Transfusional siderosis" OR "Chelation therapy") AND ("General population norms" OR "Sickle cell disease" OR "Non-transfusion-dependent thalassaemia") AND ("Endocrine complications" OR "Hypogonadism" OR "Health-related quality of life")	250
Science-direct	("Thalassaemia major" OR "Transfusion-dependent thalassaemia" OR " β -thalassaemia") AND ("Iron overload" OR "Transfusional siderosis" OR "Chelation therapy") AND ("Endocrine complications" OR "Hypogonadism" OR "Health-related quality of life")	826
Cochrane	("Thalassaemia major" OR "Transfusion-dependent thalassaemia" OR " β -thalassaemia") AND ("Iron overload" OR "Transfusional siderosis" OR "Chelation therapy") AND ("General population norms" OR "Sickle cell disease" OR "Non-transfusion-dependent thalassaemia") AND ("Endocrine complications" OR "Hypogonadism" OR "Health-related quality of life")	2

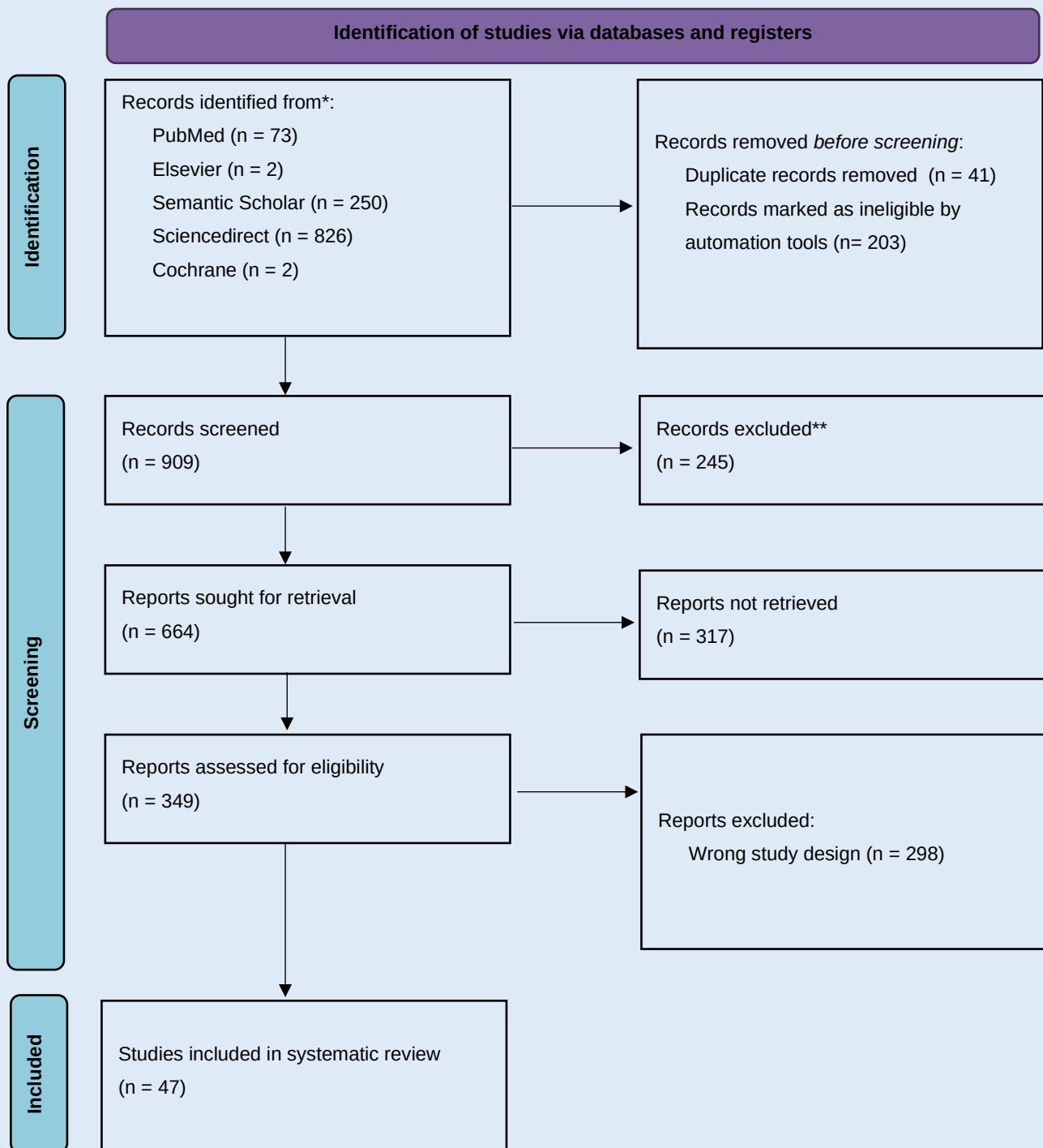


Figure 1. Article search flowchart

Risk of Bias Assessment

Risk of bias was assessed with design-appropriate instruments. Cohort and case-control studies were appraised with the Newcastle–Ottawa Scale, which allocates a maximum of four stars for selection, two for comparability and three for outcome or exposure ascertainment, giving a maximum of nine. Scores of 7–9 were classified as low risk of bias, 5–6 as moderate risk and 0–4 as high risk. Analytical cross-sectional studies were additionally appraised against the eight-item Joanna Briggs Institute checklist. The single randomised controlled trial contributing quality-of-life data was appraised with the Cochrane Risk of Bias 2 tool across its five domains.

Table 3. Risk-of-bias domains applied, by instrument

Instrument	Domain	What was assessed
Newcastle–Ottawa Scale (cohort)	Selection (max ★★★★★)	Representativeness of the exposed cohort; selection of the non-exposed cohort; ascertainment of exposure; demonstration that the outcome was not present at baseline.
	Comparability (max ★★)	Control for age and sex; control for additional confounders such as transfusion duration, chelation regimen, splenectomy and hepatitis C status.
	Outcome (max ★★★)	Objectivity of outcome ascertainment (biochemical, imaging or validated instrument versus self-report); adequacy of follow-up duration; completeness of follow-up.
Newcastle–Ottawa Scale (case-control)	Selection / Comparability / Exposure	Adequacy of case definition; representativeness of cases; selection and definition of controls; matching or statistical adjustment; method and blinding of exposure ascertainment.
JBI checklist (cross-sectional)	Items 1–8	Clarity of inclusion criteria; description of setting and participants; validity and reliability of exposure measurement; objectivity of condition criteria; identification of confounders; strategies to address confounders; validity and reliability of outcome measurement; appropriateness of statistical analysis.

Cochrane RoB 2 (randomised trial)	D1–D5	Bias arising from the randomisation process; deviations from intended interventions; missing outcome data; measurement of the outcome; selection of the reported result.
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Table 4. Risk-of-bias classification thresholds and colour key

Classification	Newcastle–Ottawa score	JBI items satisfied	RoB 2 judgement	Colour code
Low risk of bias	7–9 of 9	7–8 of 8	Low risk across all five domains	GREEN
Moderate risk of bias	5–6 of 9	5–6 of 8	Some concerns in ≥ 1 domain	YELLOW
High risk of bias	0–4 of 9	≤ 4 of 8	High risk in ≥ 1 domain	RED

Colour coding is applied consistently in Tables 10 and 11 of the Results. Where a study reported both interventional and observational outcome streams, the more conservative (higher-risk) judgement was carried forward.

Risk of Bias Within Studies

Risk of bias was low in 22 studies (43.1%), moderate in 28 (54.9%) and high in one (2.0%). The recurrent methodological limitations were the inherent inability of cross-sectional designs to establish temporality between iron exposure and endocrine outcome; incomplete adjustment for the interlocking confounders of age, transfusion duration, chelation era, splenectomy status and hepatitis C infection; reliance on serum ferritin as a surrogate for tissue iron in the older literature; single-centre recruitment with consequent limits on generalisability; and, in several conference-abstract reports, insufficient detail to appraise selection and comparability fully. Studies scoring in the low-risk band were characteristically multicentre, prospectively enrolled, used objective biochemical or magnetic-resonance outcome ascertainment, and reported multivariable models with explicit covariate specification.

Table 5. Newcastle–Ottawa Scale item-level risk-of-bias assessment

Study (first author, year)	Selection (max ★★★★★)	Comparability (max ★★)	Outcome / Exposure (max ★★★★★)	Total score	Overall judgement
Cunningham MJ (2004)	★★★★☆	★★	★★★	7/9	Moderate
Vogiatzi MG (2009)	★★★★★	★★	★★★	8/9	Low
Fung EB (2006)	★★★★★	★★	★★★★	9/9	Low
Borgna-Pignatti C (2004)	★★★★★	★★	★★★★	9/9	Low
Casale M (2021)	★★★★★	★★	★★★★	9/9	Low
Casale M (2014)	★★★★☆	★☆☆	★★★★	7/9	Moderate
Jobanputra M (2020)	★★★★★	★★	★★★	8/9	Low
Meloni A (2025)	★★★★☆	★★	★★★	7/9	Moderate
Karimi M (2018)	★★★★☆	★☆☆	★★★	6/9	Moderate
Pepe A (2020)	★★★★★	★★	★★★★	9/9	Low
Noetzli LJ (2012)	★★★★☆	★★	★★★★	8/9	Low
Zhang L (2021)	★★★★★	★★	★★★	8/9	Low
Pollak RD (2000)	★★★★☆	★☆☆	★★★	6/9	Moderate
Orhan Ö (2025)	★★★☆☆	★☆☆	★★★	5/9	Moderate
Rahal I (2018)	★★★★★	★★	★★★★	9/9	Low
Sethuraman C (2026)	★★★★☆	★★	★★★	7/9	Moderate

Study (first author, year)	Selection (max ★★★★★)	Comparability (max ★★)	Outcome / Exposure (max ★★★★★)	Total score	Overall judgement
Sobota A (2011)	★★★★★	★★	★★☆	8/9	Low
Tedone F (2021)	★★☆☆	★★	★★☆	6/9	Moderate
Drahos J (2025)	★★★★★	★★	★★★★	9/9	Low
Cappellini MD (2019)	★★★★★	★★	★★☆	8/9	Low
Floris F (2018)	★★★★★	★★	★★☆	8/9	Low
Goulas V (2020)	★★★★☆	★★	★★☆	7/9	Moderate
Caocci G (2023)	★★★★☆	★★	★★☆	7/9	Moderate
Amid A (2016)	★★★★☆	★★	★★☆	7/9	Moderate
Liang H (2022)	★★★★★	★★	★★★★	9/9	Low
Cheuk DKL (2008)	★★★★☆	★★	★★☆	7/9	Moderate
Hantrakool S (2012)	★★☆☆	★☆☆	★★☆	5/9	Moderate
Al-Rimawi H (2006)	★★★★☆	★★	★★☆	7/9	Moderate
Cario H (2003)	★★★★★	★★	★★☆	8/9	Low
Merkel PA (1988)	★★★★☆	★★	★★☆	7/9	Moderate
de la Fuente J (2025)	★★★★☆	★☆☆	★★★★	7/9	Moderate
Farmaki K (2010)	★★☆☆	★☆☆	★★★★	6/9	Moderate
Demircivi E (2026)	★★★★☆	★★	★★☆	7/9	Moderate

Study (first author, year)	Selection (max ★★★★★)	Comparability (max ★★)	Outcome / Exposure (max ★★★★★)	Total score	Overall judgement
Naseeb S (2024)	★★★★☆	★★	★★★	5/9	Moderate
Kashari O (2020)	★★★★☆	☆☆	★★★	4/9	High
See WS (2018)	★★★★★	★★	★★★	8/9	Low
Tang CH (2021)	★★★★★	★★	★★★	8/9	Low
Grundy RG (1994)	★★★★☆	★★	★★★	5/9	Moderate
Ricchi P (2014)	★★★★☆	★★	★★★★	7/9	Moderate
Meloni A (2021)	★★★★★	★★	★★★★	9/9	Low
Leung W (2025)	★★★★☆	★★	★★★	7/9	Moderate
Roth C (1997)	★★★★☆	★★	★★★	5/9	Moderate
Soliman AT (2004)	★★★★☆	★★	★★★	7/9	Moderate
El-Samahy MH (2018)	★★★★☆	★★	★★★★	8/9	Low
Meloni A (2023)	★★★★★	★★	★★★★	9/9	Low
Spasiano A (2021)	★★★★☆	★★	★★★	7/9	Moderate
Bhakat A (2025)	★★★★☆	★★	★★★	6/9	Moderate
Pepe A (2019)	★★★★★	★★	★★★★	9/9	Low
Kwiatkowski JL (2021)	★★★★☆	★★	★★★★	7/9	Moderate

Study (first author, year)	Selection (max ★★★★★)	Comparability (max ★★)	Outcome / Exposure (max ★★★★★)	Total score	Overall judgement
Ricchi P (2024)	★★★★★	★★	★★☆	8/9	Low

★ = criterion satisfied; ☆ = criterion not satisfied or not reportable. GREEN = low risk (7–9); YELLOW = moderate risk (5–6); RED = high risk (0–4). For the randomised controlled trial (Cappellini 2020, BELIEVE) the Newcastle–Ottawa equivalent is shown for tabular consistency.

Table 6. Aggregate risk-of-bias profile

Overall judgement	Studies (n)	% of included	Interpretation for the synthesis
Low risk of bias	22	43.1	Multicentre, prospective or registry-based, objective outcome ascertainment, multivariable adjustment reported.
Moderate risk of bias	28	54.9	Predominantly single-centre or cross-sectional; limited or unreported confounder adjustment; ferritin-based exposure classification.
High risk of bias	1	2.0	Small single-centre sample with proxy-reported outcome and no comparability adjustment; contributes descriptive data only.

Table 7. Cochrane RoB 2 assessment of the included randomised controlled trial

Trial	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Selective reporting	Overall
Cappellini MD et al., BELIEVE	Low	Low	Some concerns	Low	Some concerns	Some concerns

Trial	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Selective reporting	Overall
(luspaterecept vs placebo), HRQoL analysis						

Some concerns were recorded for D3 because HRQoL completion, although high (>87.5% at week 48 among patients remaining on treatment), was conditional on treatment continuation; and for D5 because the significant physical-domain findings derive from an exploratory responder analysis rather than the pre-specified primary comparison.

Certainty of Evidence

The certainty of the body of evidence supporting each outcome was rated with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Because the majority of the evidence derives from observational designs, the starting certainty for prevalence and association outcomes was low, with the possibility of upgrading for a large magnitude of effect, a dose–response gradient, or where all plausible residual confounding would reduce rather than inflate the observed effect. Certainty was downgraded for risk of bias, inconsistency, indirectness, imprecision and suspected publication bias. The randomised evidence contributing to Outcome 15 commenced at high certainty and was downgraded where indicated.

Data Synthesis and Protocol Deviations

Substantial clinical heterogeneity — in thalassaemia phenotype, in the diagnostic criteria applied to each endocrinopathy, in chelation era and regimen, in the instruments used to measure quality of life, and in the demographic composition of the cohorts — precluded valid statistical pooling. A structured narrative synthesis with systematic tabulation was therefore adopted, in which effect estimates are reported as published, prevalence figures are expressed as ranges with the contributing cohorts identified, and directional consistency across studies is used as the principal criterion of synthesis. Statistical significance is reported exactly as stated in each source. One protocol

deviation is declared: the inclusion window was left unrestricted rather than limited to the last twenty years, in order to retain the landmark physiological studies of insulin resistance and growth-hormone neurosecretory dysfunction which remain the mechanistic foundation of the field and which have not been superseded by later work.

RESULTS

Characteristics of Included Studies

The 51 included primary studies were conducted in at least 21 countries across Europe, North America, the Middle East, South Asia and East Asia, and together characterise more than 11 000 individual patients. Twenty-four studies employed a cross-sectional design, eighteen a cohort design (nine retrospective, nine prospective), four a case-control or controlled comparative design, three an interventional design with patient-reported outcome endpoints (two non-randomised), one a randomised placebo-controlled trial, and one a population-based claims-database analysis. Sample sizes ranged from 12 to 2984 in individual reports, with the largest single-disease cohorts being the Taiwanese national claims analysis (n=2984), the Italian E-MIOT thalassaemia major cohort (n=1079), the Italian survival registry (n=977) and the multinational thalassaemia intermedia survey (n=721). Mean or median participant age ranged from 7.3 years in paediatric Sri Lankan and Turkish cohorts to 45 years in long-established Greek and Italian adult centres, reflecting the demographic transition of the disease. Full characteristics are presented in Table 8.

Table 8. Characteristics of the 51 included primary studies

No.	Author (Year)	Country / Setting	Study design	Population and sample size	Age	Outcome domain	Principal findings (as reported)
1	Cunningham MJ, et al. (2004)	USA / Canada (TCRN, 31 centres)	Multicentre cross- sectional registry study	342 patients with β - thalassaemia major on regular transfusion	Paediatric to adult (age- stratified cohorts)	Endocrin opathy, iron burden, hepatic and	Endocrinolo gic complicatio ns were common among

						cardiac morbidity	adults and strongly age-dependent; median ferritin 1696 ng/mL (range 147–11 010), median hepatic iron 7.8 mg/g dry weight, with 23% ≥ 15 mg/g dry weight. Cirrhosis on biopsy 10%.
2	Vogiatzi MG, et al. (2009)	North America (TCRN)	Cross-sectional multicentre study	361 patients across all thalassaemia syndromes; 49% male	Mean 23.2 y (6.1–75)	Growth, endocrine and vitamin D / calcium abnormalities	About 25% of children and adults had short stature. β -TM had significantly higher rates of hypogonadism,

							multiple endocrinopathies, worse hyperglycaemia, subclinical hypoparathyroidism and hypercalcaemia. 82% had 25(OH)D <75 nmol/L; 12.8% <27 nmol/L. Hypogonadism was the most frequent and was frequently under-treated.
3	Fung EB, et al. (2006)	USA / Canada / UK (31 centres)	Cross-sectional comparative (case-control design)	142 thalassaemia vs 199 transfused SCD vs 64 non-transfused SCD	Thal 25.8 ± 8.1 y	Iron-overload-associated	Thalassaemia vs transfused SCD: diabetes

						endocrino pathy	13% vs 2% (p<0.001); hypogonadi sm 40% vs 4% (p<0.001); hypothyroid ism 10% vs 2% (p<0.001); growth failure 33% vs 7% (p<0.001). ≥2 endocrinopa thies in 56% vs 13% (p<0.001). Adjusted OR for endocrinopa thy 9.4 (p<0.001); transfusion duration OR 1.4 per 10 y (p=0.04).
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4	Borgna-Pignatti C, et al. (2004)	Italy (7 centres)	Retrospective multicentre cohort	977 patients born ≥ 1960 ; complications analysed in 720 born after 1970	Followed to ≥ 35 y	Survival, complication-free survival, endocrine complications	Hypogonadism 54.7%, hypothyroidism 10.8%, diabetes 6.4%; heart failure 6.8%, arrhythmia 5.7%. Ferritin ≥ 1000 ng/mL associated with heart failure (HR 3.35, $p < 0.005$) and reduced survival (HR 2.45, $p < 0.005$). 68% alive at 35 y; significant association between birth cohort and complication
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							n-free survival (p<0.0005).
5	Casale M, et al. (2021)	Italy (multi-centre, nation-wide)	Prospective multicentre follow-up cohort	426 TDT patients on once-daily deferasirox	Median follow-up 8 y (up to 18.5 y)	Incidence and predictors of new endocrine disease	5-year risk of a new endocrine complication 9.7% (95% CI 6.3–13.1); 104 new endocrine diseases. Independent predictors: age (aHR 1.2 per 50% increase, 95% CI 1.1–1.3, p=0.005); serum thyrotropin (aHR 1.3 per 1 mIU/L, 95% CI 1.1–1.4, p<0.001); number of

							pre-existing endocrine diseases (aHR 0.5 per unit, 95% CI 0.4–0.7, $p<0.001$). At baseline 187/426 already had ≥ 2 endocrinopathies.
6	Casale M, et al. (2014)	Italy (multicentre)	Retrospective cohort	86 transfusion-dependent β -TM on deferasirox	Median treatment 6.5 y (up to 10 y)	Endocrine function and bone disease during chelation	New endocrine complications in 7% (hypogonadism $n=5$, hypoparathyroidism $n=1$); no new hypothyroidism or diabetes and no deaths. Mean lumbar-

							spine BMD increased significantly (p<0.001) and the number of patients with lumbar osteoporosis fell significantly (p=0.022). Six pregnancies occurred, four spontaneous .
7	Jobanputra M, et al. (2020)	England (NHS Hospital Episode Statistics)	Retrospective population-based cohort (10 years)	612 patients with transfusion-dependent β -thalassaemia	All ages; 2009–2018	Co-morbidity prevalence and 10-year mortality	76% had ≥ 1 co-morbidity, 54% ≥ 2 and 37% ≥ 3 . Endocrine disorders excluding diabetes 40%, osteoporosi

							s 40%, diabetes 34%, cardiac disease 18%. Crude 10-year mortality 6.2% vs 1.2% age/sex- adjusted general population (p<0.001).
8	Meloni A, et al. (2025)	Italy (E-MIOT network)	Multicentre cross- sectional	140 adults with neo- transfusion- dependent thalassaemia; 56.4% female	Mean 44.3 ± 12.1 y	Multi- organ morbidity and its determina nts	Bone metabolism disorders 68.6%, impaired glucose metabolism 15.7%, hypothyroid ism 15.0%, hypogonadi sm 11.4%. Older age (OR 4.42, p=0.004)

							and pancreatic iron overload (OR 7.40, p=0.012) independent ly predicted impaired glucose metabolism; no significant predictors for hypogonadi sm, hypothyroid ism or bone disease.
9	Karimi M, et al. (2018)	9 countries, 12 thalassaemia centres	Multi-country cross- sectional	721 patients with β - thalassaemia intermedia (comparator phenotype)	Adults and adolescent s	Prevalenc e of endocrine complicat ions	Osteoporosi s 21.6%, hypogonadi sm 12.6%, central hypothyroid ism 8.3%, non- insulin- dependent

							DM 7.8%, primary hypothyroidism 5.5%, insulin-dependent DM 4.2%, hypoparathyroidism 2.2%, GH deficiency 1.1%. Rates were lower than those reported for thalassaemia major, providing a phenotype-severity gradient.
10	Pepe A, et al. (2020)	Italy (E-MIOT project)	Large multicentre observational study	1079 patients with thalassaemia major	Adults	Pancreatic iron (T2*) vs glucose metabolism and cardiac outcomes	Patients with normal glucose metabolism had significantly higher global pancreas

							T2* than those with IFG, IGT or diabetes. Pancreas T2* <13.07 ms predicted an abnormal OGTT; a normal pancreatic T2* had 100% negative predictive value for glucose dysregulation and for cardiac iron. Patients with myocardial fibrosis and cardiac complications had significantl
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							y lower pancreas T2*.
11	Noetzli LJ, et al. (2012)	USA	Cross- sectional physiological study (frequently sampled OGTT + MRI)	59 patients with thalassaemia major	Children and adults	Pancreati c/cardiac/ hepatic iron vs β - cell function	11 had diabetes, 12 IGT, 8 isolated IFG, 28 normal glucose tolerance. Disposition index (β - cell function) correlated most strongly with pancreas R2*; insulin resistance correlated with inflammatio n and somatic iron. Patients with DM

							and IGT had significantl y worse disposition index than NGT/IFG, indicating β -cell toxicity. One-third with elevated pancreas R2* still had normal glucose regulation (pre-clinical iron burden).
12	Zhang L, et al. (2021)	China	Cross-sectional case-control	118 children with β -TM vs 33 healthy children matched for age, sex and BMI	Paediatric	Glucose dysregulation indices and iron overload	Fasting plasma glucose, fasting insulin and HOMA-IR were significantl y increased

							and insulin-sensitivity index decreased vs controls. Diabetes in 14.41%; combined IFG and IGT in 40.68%. HbA1c, glycated albumin and fructosamine rose in parallel with the degree of dysglycaemia. Age, serum ferritin and cardiac T2* differed significantly between abnormal and normal OGTT
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							groups; ferritin >4000 µg/L predicted abnormal glucose metabolism.
13	Pollak RD, et al. (2000)	Israel	Cross- sectional with longitudinal follow-up (mean 5.6 y in 19)	50 adults (37 β-TM, 13 intermedia); 27 women, 23 men	Mean 32.3 ± 9.7 y	BMD, vitamin D, IGF-1, bone turnover markers	Z-score <-2 in 89% (spine), 62% (hip) and 73% (radius). Vitamin D deficiency in 62%, decreased IGF-1 in 72%, increased urinary NTx in 84%. IGF-1 correlated with spine (r=0.40) and hip BMD (r=0.39, both

							p<0.01); NTx correlated with hip BMD Z- score (r=0.35, p<0.05). Mean annual spine BMD change -1.36%.
14	Orhan Ö, et al. (2025)	Türkiye	Retrospective single-centre analytical study	27 children/adolescents with TM on regular transfusion and chelation	Group 1 13.83 ± 2.85 y; Group 2 7.95 ± 5.05 y	Osteopor osis (lumbar Z-score <-2) and risk factors	Osteoporosi s in 22.2%. Osteoporoti c patients were older (p=0.012) with lower weight (p=0.012) and height (p=0.004). Ferritin 5306 ± 1506 vs 2020 ± 1205 ng/mL (p=0.001).

							BMD correlated negatively with ferritin ($r=-0.791$, $p<0.001$) and positively with calcium ($r=0.499$, $p=0.008$).
15	Rahal I, et al. (2018)	France (national experience)	Retrospective national cohort	99 β -TM patients after allogeneic HSCT	Median 5.9 y at transplant; median follow-up 12 y	Late endocrine effects after HSCT	Thyroid dysfunction 11%, diabetes 5%. Hypogonadism in 56% of females and 14% of males. Females with normal post-transplant puberty were significantly younger

							at transplant (median 2.5 vs 8.7 y). Age at transplant, higher ferritin at transplant and time since transplant were independently associated with decreased height growth; 36% of adults were overweight at last evaluation.
16	Sethuraman C, et al. (2026)	United Kingdom (tertiary centre)	Observational cohort (retrospective + prospective)	50 individuals aged 2–25 y with TDT	2–25 y (data to age 18)	Growth and endocrine outcomes under	Short stature (height SDS <−2) in 24%, but only one

						modern therapy	was short for parental height. Disproportionate truncal shortening in 23/29 (79.3%). No difference in height SDS between highest (24.03 mg/g dw) and lowest (5.04 mg/g dw) liver iron groups. Hypogonadism, thyroid dysfunction and impaired glucose tolerance were rare, suggesting attenuation
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							of endocrinopathy under optimised transfusion and chelation.
17	Sobota A, et al. (2011)	USA (TCRN Thalassaemia Longitudinal Cohort)	Cross-sectional cohort study (SF-36v2)	264 patients aged >14 y	>14 y	HRQoL vs US population norms and clinical predictors	Significantly worse HRQoL (p<0.05) on 5 of 8 subscales (physical functioning, role-physical, general health, social functioning, role-emotional) and on both PCS and MCS. Women, older patients and those with

							more disease complications and chelation side-effects reported significantly lower HRQoL.
18	Tedone F, et al. (2021)	Italy	Cross-sectional survey study (SF-36, PGWBI)	105 patients with TDT aged ≥ 14 y; 46% male	Median 44 y (IQR 11)	HRQoL, psychological well-being and disease burden	Lower HRQoL than the general population in all SF-36 domains except emotional well-being (p=0.7024) and role-emotional (p=0.1389). PGWBI general health, vitality and total score all

							significantl y lower (p=0.0001). Patients spent 16.62 h/month on care activities additional to transfusion time (11.7 h therapy managemen t, 4.92 h family managemen t).
19	Drahos J, et al. (2025)	USA, France, Germany, Italy, UK	Prospective longitudinal real-world study (6 months)	155 adults with TDT receiving ≥ 8 transfusions/year; 65.8% female	Mean 38.5 ± 10.8 y	HRQoL, fatigue, pain, work productiv ity, economic burden	EQ-VAS 67.1 $\pm$ 20.4 vs 80.4 $\pm$ 15.6; FACT-G 70.1 $\pm$ 19.0 vs 77.0 $\pm$ 16.1; FACIT-F 27.9 $\pm$ 13.7 vs 43.6 $\pm$ 9.4 — all

							significantly lower than US norms (p<0.001). TranQoL total 53.9 ± 18.5; mean pain NRS 3.5 ± 2.8. Employed participants lost a mean of 5.9 working hours in the preceding 7 days; out-of-pocket costs were a moderate-to-major burden for 55%. Findings were stable over time.
20	Cappellini MD, et al. (2019)	Greece, Italy, Lebanon, Thailand	Prospective observational	TDT and NTDT patients in routine care	Adults	SF-36v2 and FACT-	NTDT patients generally

			cohort (24 weeks)			An domains, TDT vs NTDT	reported worse QoL across most SF-36v2 domains, with clinically meaningful differences in Mental Component Score, General Health, Vitality and Mental Health, and in FACT-An Functional Well-Being and FACT-G Total. Over 24 weeks, change from baseline in Role-Physical
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							differed significantly between groups: NTDT deteriorated while TDT was maintained or slightly improved.
21	Floris F, et al. (2018)	Italy (Sardinia)	Cross-sectional controlled study (WHOQOL-BREF)	207 adults with TDT vs 211 age- and sex-matched non-thalassaemic controls	≥18 y	Physical, psychological and social well-being	Scores indicating good QoL were obtained in all domains; patients scored at least as well as matched controls in all items, and the proportion with a score ≥60 was higher among patients.

							Subjective well-being was positively associated with objective clinical condition, and health perception was associated with treatment adherence — an important contrast to lower-resource settings.
22	Goulas V, et al. (2020)	Greece (3 thalassaemia units)	Observational multicentre cross-sectional	131 adults with TDT (74 female); 80 parenteral ± oral chelation, 51 oral only	Median 41 y (IQR 36–47)	SF-36 and satisfaction with iron chelation therapy (SICT)	Median SF-36 PCS 76.3 and MCS 75.7 (Group I) vs 76.9 and 74.5 (Group II), not

							different between chelation routes. Oral chelation was preferred by 84.6% and 92.9% respectively . Deferasirox-containing regimens showed higher treatment acceptance (4.0 vs 3.6, p=0.038) and greater satisfaction with treatment burden (4.4 vs 3.9, p=0.033).
23	Caocci G, et al. (2023)	Italy	Cross-sectional study with	114 adults with β -TM, of whom 29	Median 41 y (18–62); median 42	SF-36 HRQoL and	No significant difference

			long-term follow-up	(25.4%) splenectomised	y post- splenecto my	clinical outcomes after splenecto my	in any SF- 36 scale between splenectomi sed and non- splenectomi sed patients. However, splenectomi sed patients had significantl y higher prevalence of cardiovascu lar comorbidity (58.6% vs 21.2%, p<0.001) and diabetes (17.2% vs 3.5%, p=0.013), while requiring fewer red cell units
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							per month. Post-splenectomy complications occurred in 27.5%.
24	Amid A, et al. (2016)	Canada, Lebanon, Iran (IntercontinThal)	Multinational cross-sectional collaborative study	97 adults (59 TDT, 38 NTDT); 46 female	Mean 32 ± 7 y	Predictors of SF-36 Mental Component Summary score	On univariate analysis age, social support/health-care access, marital status, liver iron concentration, ferritin and disease-related complications predicted MCS. On multivariate analysis ferritin and age — and clinical complicatio

							ns in TDT patients specifically — were independently associated with reduced QoL. In NTDT, splenectomy and lower baseline haemoglobin were also significantly associated with reduced QoL.
25	Liang H, et al. (2022)	China	Cross-sectional comparative study (PedsQL 4.0 proxy)	221 transplanted β -TM children vs 429 matched healthy peers vs 198 matched non-transplant patients	5–18 y	HRQoL after HSCT	Transplanted patients scored worse than healthy peers in physical health ($p<0.001$),

							school functioning (p<0.001) and overall score (p=0.006), but better than non-transplant patients in all domains (p<0.001). Beyond 4 years post-transplant, scores in all domains no longer differed from healthy controls. Chronic GVHD (p=0.032) and ≥2 comorbidities (p<0.001) were
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							independent negative predictors of overall HRQoL.
26	Cheuk DKL, et al. (2008)	Hong Kong	Cross-sectional comparative study	24 post-HSCT vs 74 conventionally transfused patients	Paediatric and adult (WHOQOL-BREF / PedsQL)	QoL after HSCT vs transfusion and chelation	Post-transplant patients rated overall health better (3.67 vs 3.06, p=0.01), were less dependent on medical aids (3.87 vs 2.96, p=0.006), had higher activity level (4.00 vs 3.36, p=0.026), better personal relationships (4.13 vs 3.69,

							p=0.014) and better physical health domain (75.20 vs 63.94, p=0.007) — differences that persisted after adjustment for comorbidities. They were more likely to consider marriage (100% vs 75.7%, p=0.033).
27	Hantrakool S, et al. (2012)	Thailand	Cross-sectional and retrospective study	92 adult thalassaemia patients (28 homozygous β , 45 β /HbE, 18 HbH/AE Bart's)	Median 30.6 y (18–71)	Serum ferritin threshold for diabetes and	Diabetes 9.8% and impaired fasting glucose 10.9%; hypothyroid

						hypothyroidism	ism 6.5% and subclinical hypothyroidism 22.8%. Maximum ferritin was significantly higher in diabetic patients (11241 vs 4468 µg/dL, p=0.0001) and in hypothyroid patients (7638 vs 4117 µg/dL, p=0.003). Cut-offs of >2500 and >3500 µg/dL were the major risk thresholds for diabetes and hypothyroid
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							ism respectively .
28	Al-Rimawi H, et al. (2006)	Jordan	Controlled clinical (case– control) study	33 adolescent males with β -TM plus a constitutional delayed-puberty comparison group	Adolescen ts	Hypothal amic– pituitary– gonadal axis integrity	17 of 33 had delayed puberty. Basal LH, FSH and testosterone differed significantl y between delayed- and normal- puberty thalassaemi a groups and were significantl y lower than in constitution al delayed puberty; differences became even more marked after GnRH analogue

							stimulation. Testosterone remained significantly lower after hCG in the delayed-puberty thalassaemia group, indicating combined central and gonadal failure.
29	Cario H, et al. (2003)	Germany	Case-control study (OGTT-based)	36 thalassaemia major patients (23 NGT, 6 IGT, 7 DM) vs 32 controls	Children/adolescents and young adults	Insulin sensitivity and β -cell secretion	Fasting, 2-hour and integrated glucose were significantly higher in patients with normal glucose tolerance than in controls (all $p < 0.03$),

							demonstrating sub-clinical dysglycaemia. C-peptide/insulin ratio was reduced in abnormal glucose tolerance (p<0.03) and correlated negatively with age in patients (r=-0.45, p<0.01) but positively in controls (r=0.43, p<0.03). Insulin secretion capacity was significantly reduced
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							overall (p<0.004).
30	Merkel PA, et al. (1988)	USA	Prospective controlled physiological study (euglycaemic clamp)	12 children with thalassaemia (4 prepubertal, 8 pubertal) vs healthy controls	Children and adolescent s	Insulin resistance preceding insulin deficiency	Insulin- stimulated glucose metabolism was preserved in prepubertal patients (319 ± 23 vs 314 ± 41 mg/m ² /min, NS) but markedly impaired in pubertal patients (155 ± 18 vs 224 ± 15 mg/m ² /min, p<0.01). Plasma insulin rose excessively after oral glucose in pubertal but not prepubertal

							patients (p<0.001), with insulin levels two- to three-fold above normal on hyperglycemic stimulus.
31	de la Fuente J, et al. (2025)	International (CLIMB THAL-111 / CLIMB-131, phase 3)	Prospective interventional trial with pre-specified PRO endpoints	54 participants with TDT (35 adults, 19 adolescents) followed ≥16 months	Adults 18–35 y; adolescents 12–17 y	HRQoL after exagamgl ogene autotemc el gene editing	EQ-5D-5L VAS and US/UK health-utility index scores all improved and exceeded established MCID thresholds by month 48. FACT-G total and BMT subscale improved through month 48

							with gains in all four FACT-G subscales. In adolescents, EQ-5D-Y VAS and total PedsQL improved by month 24 with sustained gains in both physical and psychosocial subcomponents.
32	Cappellini MD, et al. (2020) — BELIEVE	International (phase 3 RCT, NCT02604433)	Randomised, double-blind, placebo-controlled trial (HRQoL analysis)	336 randomised (224 luspatercept, 112 placebo); 316 HRQoL-evaluable	Adults with TDT	SF-36 and TranQol over 48 weeks	Mean scores on all primary and exploratory domains were stable and did not

							differ between arms at weeks 24 and 48. Among luspatercept responders achieving $\geq 50\%$ transfusion-burden reduction, clinically meaningful improvement was significantly more frequent than placebo for PCS (31.1% vs 16.5%, $p=0.024$) and Physical Functioning (30.0% vs 13.2%,
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							p=0.007) at week 48.
33	Farmaki K, et al. (2010)	Greece	Prospective interventional cohort (up to 7 years)	52 thalassaemia major patients transitioned to combined deferoxamine + deferiprone	Adults	Reversibility of endocrine and cardiac complications	Of 39 patients with abnormal glucose metabolism, 44% normalised. Of 18 requiring thyroxine, 10 discontinued and 4 reduced their dose. Of 14 hypogonadal males on testosterone, 7 stopped treatment; 6 of 19 previously hypogonadal females conceived. No patient

							developed de novo cardiac or endocrine complications, and all 12 with cardiac dysfunction had symptom reversal.
34	Demircivi E, et al. (2026)	Türkiye (tertiary centre)	Retrospective longitudinal study with matched controls	15 adult women with TDT vs 22 age-matched healthy women; 2-year follow-up	Adult women	Reproductive endocrine trajectory in well-chelated patients	Hypogonadism was clinically prevalent, but other endocrine axes remained largely within reference ranges and no new overt endocrine disorder emerged. Reproductiv

							e hormones showed no significant temporal change and were comparable to controls. AMH showed marked inter-individual variability and did not consistently correlate with ferritin or MRI T2* iron indices.
35	Naseeb S, et al. (2024)	Pakistan (resource-constrained centre)	Cross-sectional observational study	136 patients with TDT registered ≥1 year; 52.2% female	Mean 10.72 ± 6.85 y (2–35)	WHOQO L-BREF domains and social determinants	Of 120 school-age patients, 22.5% had never attended school and 9.1% had left education

							for health reasons. Mean pre-transfusion haemoglobin 7.3 ± 1.2 g/dL; 28.7% had difficulty obtaining blood; hepatitis C positivity 25%. About half reported that socio-economic status was affected by the disease — demonstrating substantially greater humanistic burden than in high-
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							resource cohorts.
36	Kashari O, et al. (2020)	Saudi Arabia	Cross-sectional study (WHOQOL-BREF)	48 transfusion-dependent children (26 boys, 22 girls)	Mean 8.7 $\pm$ 3.0 y (4–15)	Paediatric QoL and its modifiers	Overall QoL was poor in 27.1% before transfusion and improved significantly after transfusion ($p < 0.001$). QoL was significantly better among children maintaining medication ($p = 0.028$) and among those with regular follow-up (social domain). QoL domains did

							not differ by ferritin level, age, sex or parental characteristics; significantly better QoL was associated with attendance at subspecialty clinics including endocrinology.
37	See WS, et al. (2018)	Hong Kong	Retrospective cohort with matched controls	40 TDT patients post-HSCT (≥ 3 y follow-up) vs 20 matched non-transplanted TDT	Transplanted 1992–2013	Prevalence, cumulative incidence and risk factors of endocrinopathy	Gonadal dysfunction was the most prevalent endocrinopathy (55%; 5-year cumulative incidence 30%, 10-

							year 55%), followed by growth failure and hypothyroidism. Age ≤ 7 y at HSCT (aOR 0.06, p=0.018) and better Pesaro risk group (aOR 0.04, p=0.013) were protective for gonadal dysfunction ; age ≤ 8 y was protective for growth (aOR 0.065, p=0.045). Post-transplant cardiac iron overload predicted hypothyroid
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							ism (OR 82.6, p=0.007).
38	Tang CH, et al. (2021)	Taiwan (National Health Insurance Research Database)	Retrospective population-based cohort	2984 patients with β -thalassaemia; mean follow-up 6.95 y	All ages	Transfusion burden vs complications and resource use	Transfused patients had significantly greater all-cause healthcare resource utilisation and chelation use than non-transfused patients. Thalassaemia-related resource use and the risk of liver, endocrine, cardiac and renal complications were significantly and positively

							correlated with increasing red-cell transfusion units per 12 weeks, establishing a dose–response relationship between transfusion burden and endocrine morbidity.
39	Grundy RG, et al. (1994)	United Kingdom	Prospective observational endocrine evaluation	18 young patients with thalassaemia major, 11 considered well chelated	Children and adolescents	Endocrine dysfunction under optimal chelation	Five patients had significantly short stature and two boys had marked pubertal delay. Growth-hormone responses to glucagon stimulation

							were significantly impaired in all patients with iron overload. Primary hypothyroidism was present in two patients and diabetes in one, demonstrating that clinically significant endocrine damage occurs even where management approaches contemporary standards.
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40	Ricchi P, et al. (2014)	Italy	Prospective cohort (2006–2012)	98 adults with non-transfusion-dependent thalassaemia	Adults	Prolactin axis abnormalities	Hyperprolactinaemia in 13% (9 women), including 3 microprolactinomas and 2 partial empty sella. Hyperprolactinaemic patients were significantly more often hypothyroid, more often splenectomised, more often transfused, and had significantly lower mean haemoglobin and higher nucleated
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							red-cell counts (all p<0.05) — i.e. a more severe disease phenotype.
41	Meloni A, et al. (2021)	Italy (E-MIOT project)	Large multicentre observational study	221 β -thalassaemia intermedia patients (145 regularly transfused)	Mean 42.95 $\pm$ 13.74 y	Pancreatic iron vs glucose metabolism	Pancreatic iron overload was significantly more frequent in regularly transfused than non-transfused patients (67.6% vs 31.6%, p<0.0001). Patients with normal glucose metabolism had significantly higher pancreas

							T2*; a value <17.9 ms predicted an abnormal OGTT, and a normal pancreas T2* had 100% negative predictive value for cardiac iron. Splenectomy and HCV infection were associated with higher pancreatic siderosis.
42	Leung W, et al. (2025)	Hong Kong (2 public hospitals)	Cross-sectional study	109 Chinese patients with non-transfusion-dependent thalassaemia	Median 32 y (6.7–72.3)	Chronic health deficits and endocrinopathy	52% had chronic health deficits with strong positive correlation

							with advancing age, log- transformed ferritin and splenectom y history. Hepatic iron overload was detected in 43%; at least one endocrinopa thy developed in 12%. Non- deletional α - thalassaemi a intermedia and β - thalassaemi a intermedia had significantl y more severe disease than
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							deletional α - thalassaemi a intermedia.
43	Roth C, et al. (1997)	Germany	Prospective clinical endocrine study	32 patients with β - thalassaemia major; 14 with short stature	Children and adolescent s	GH-IGF- 1 axis and gonadotro pin secretion	Stimulated GH secretion was normal in 10 of 13 short/slow- growing patients, but spontaneous overnight GH secretion showed markedly reduced mean GH and peak amplitudes, with low IGF-1 and intact hepatic IGF-1 generation — i.e.

							hypothalam ic neurosecret ory dysfunction rather than hepatic failure. Hypogonad otropic hypogonadi sm was present in both sexes with impaired sexual developmen t, unresponsiv e to pulsatile GnRH priming, indicating severe pituitary gonadotropi n
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							insufficienc y.
44	Soliman AT, et al. (2004)	Egypt / Qatar	Prospective comparative interventional study	12 adolescent boys with β -TM and delayed puberty vs 10 with constitutional delay	Thalassaemia $15.8 \pm$ 1 y	Testicular reserve on hCG stimulation	After 6 months of hCG, growth velocity rose from 4.1 to 8.6 cm/y in thalassaemi a and 4.6 to 10.3 cm/y in constitution al delay; mean testosterone rose 1.8 vs 4.32 nmol/L respectively . All constitution al-delay but only 7 of 12 thalassaemi c adolescents achieved testosterone

							>2 nmol/L. The 5 non-responders had significantly higher ferritin (1985 ± 658 vs 1100 ± 425 ng/mL), indicating testicular siderosis.
45	El-Samahy MH, et al. (2018)	Egypt	Cross-sectional diagnostic accuracy study	200 paediatric β -TM patients screened; 20 with random glucose ≥ 7.8 mmol/L studied	Paediatric	CGMS vs OGTT for detecting dysglycemia	By OGTT, 30% had IGT and 35% were in the diabetic range; by CGMS 35% had IGT and 65% had diabetes. The proportion classified as diabetic was

							significantly higher with CGMS than OGTT (p=0.012). Serum ferritin was the only independent variable related to elevated random glucose, and all diabetic patients were non-compliant with chelation.
46	Meloni A, et al. (2023)	Italy (E-MIOT network)	Multicentre cross-sectional MRI study	308 thalassaemia major patients (182 female)	Median 39.79 y	Pancreatic fatty replacement and glucose metabolism	Patients with normal glucose metabolism had significantly lower pancreatic fat fraction

							than those with IFG (p=0.030), IGT (p<0.0001) and diabetes (p<0.0001). A normal fat fraction (<6.6%) had 100% negative predictive value for abnormal glucose metabolism and for cardiac iron; a fat fraction >15.33% predicted abnormal glucose metabolism. Fat fraction was significantly higher in
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							patients with myocardial fibrosis (p=0.002).
47	Spasiano A, et al. (2021)	Italy	Cross-sectional study	103 TDT patients with ferritin <2500 ng/mL (57.3% female)	Mean 40.03 ± 9.15 y	Ferritin threshold s vs organ iron and morbidity	Patients were stratified into ferritin <500, 500–1000 and 1000–2500 ng/mL. Hepatic iron overload was significantly less frequent in the <500 ng/mL group than in both higher groups; no patient with ferritin <500 ng/mL had significant

							myocardial iron overload. Frequency of hepatic, endocrine and cardiac complications did not differ across strata, supporting ferritin <500 ng/mL as an achievable and safe target.
48	Bhakat A, et al. (2025)	India (AIIMS Bhubaneswar)	Prospective observational study	53 patients with transfusion-dependent thalassaemia	Enrolled 2020–2022	R2* MRI liver iron concentration vs serum ferritin	Median liver R2* 549.6 Hz (101.4–967.8) and median liver iron concentration 7.32 mg/g dry weight (1.63–12.63).

							Liver iron overload was present in 82% of patients, yet no correlation was found between liver iron concentration and serum ferritin or with phenotypic and genetic characteristics — establishing that ferritin is an unreliable surrogate for tissue iron burden.
49	Pepe A, et al. (2019)	Italy (E-MIOT project)	Multicentre observational study	705 patients with thalassaemia major (372 female)	Mean 37.00 ± 9.95 y	Pancreatic T2* and glucose metabolism	By OGTT, 77.4% had normal glucose tolerance,

							2.0% isolated IFG, 4.1% IGT and 16.5% diabetes. None of the 85 patients without pancreatic iron overload (T2* ≥26 ms) had IGT or diabetes. Global pancreatic T2* was significantl y higher in normal glucose tolerance than diabetes (13.58 ± 11.08 vs 8.09 ± 4.72 ms,
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							p<0.0001); T2* <13.73 ms was the optimal cut- off for an abnormal OGTT (AUC 0.62).
50	Kwiatkowski JL, et al. (2021)	International (HGB-207 / HGB-212, phase 3)	Prospective interventional trial with PRO endpoints	30 patients achieving transfusion independence (12 adults, 18 paediatric/adolescent)	4–34 y at consent; 66% aged <18 y	HRQoL after betibeglo gene autotemc el gene addition	Mean PedsQL total rose from 77.4 at baseline to 85.3 at month 12 and 87.1 at month 24 — 1.8 and 2.2 times the MCID of 4.36 (global population norm 81.0). Adult SF-36 PCS rose from 53.8 to 55.7 and MCS from

							51.0 to 53.4 by month 24 (1.0 and 1.2 × MCID). EQ-5D-3L composite index rose from 0.92 to 0.95 and VAS from 85.2 to 94.2.
51	Ricchi P, et al. (2024)	Italy (E-MIOT network)	Multicentre cross-sectional study	301 TDT patients (177 female) vs 25 healthy subjects	Median 40.61 y	Hepatic steatosis and glucose metabolism	Hepatic fat fraction was significantly higher in TDT than in healthy subjects (1.48% vs 0.55%, p=0.013), and 36.4% met criteria for liver steatosis (fat fraction >3.7%). Active

							HCV infection, increased body mass index and hepatic iron were independent determinants of steatosis, and a hepatic fat fraction >3.53% predicted an abnormal OGTT — extending the iron–adipose–dysglycaemia axis beyond the pancreas.
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TM = thalassaemia major; TDT = transfusion-dependent thalassaemia; NTDT = non-transfusion-dependent thalassaemia; TCRN = Thalassaemia Clinical Research Network; E-MIOT = Extension-Myocardial Iron Overload in Thalassaemia; HSCT = haematopoietic stem cell transplantation; BMD = bone mineral density; OGTT = oral glucose tolerance test; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; SDS = standard deviation score; MCID = minimal clinically

important difference; GVHD = graft-versus-host disease. In accordance with the review protocol, no systematic review or meta-analysis appears in this table.

Distribution of Evidence by Design, Geography and Outcome Domain

Table 9 Distribution of included studies by design and evidence contribution

Study design	n	% of included	Principal outcome contribution
Cross-sectional (analytical and descriptive)	24	47.1	Prevalence of each endocrine axis; HRQoL versus norms; cross-sectional determinant analyses
Retrospective cohort	9	17.6	Incidence and progression of endocrinopathy; long-term chelation and transplant outcomes; mortality
Prospective cohort	9	17.6	Incident endocrine disease; longitudinal HRQoL; reversibility under intensified chelation
Case-control / controlled comparative	4	7.8	Hypothalamic-pituitary-gonadal axis integrity; insulin sensitivity and β -cell secretion versus controls
Non-randomised interventional with PRO endpoints	3	5.9	HRQoL after gene editing; endocrine and PRO outcomes after curative therapy
Randomised controlled trial	1	2.0	HRQoL under luspatercept versus placebo (BELIEVE)
Population-based database analysis	1	2.0	Transfusion-burden gradient for endocrine and other complications
Total	51	100.0	—

Table 10. Geographical distribution of the evidence base

Region	Countries represented	Studies (n)	Setting characteristic
Southern Europe	Italy, Greece, Sardinia (Italy)	16	Long-established comprehensive-care centres; optimised transfusion and MRI-guided chelation

Northern and Western Europe	United Kingdom, France, Germany	7	National registries and tertiary haemoglobinopathy services; migrant-origin populations
North America	United States, Canada	7	Multicentre research networks (TCRN); mixed thalassaemia syndromes
Middle East and North Africa	Türkiye, Jordan, Egypt, Saudi Arabia, Israel, Iran, Qatar, Oman, Cyprus	9	High disease prevalence; heterogeneous chelation access
South and South-East Asia	Pakistan, Sri Lanka, India, Thailand	6	High burden; documented constraints in blood supply and chelation adherence
East Asia	China, Hong Kong, Taiwan	6	Large national datasets; established transplant programmes
Total (some studies multinational)	≥21 countries	51	—

Multinational studies are attributed to the region of the coordinating centre; the multi-country thalassaemia intermedia survey spanning nine countries is counted once, under the Middle East and North Africa grouping.

Synthesis of Results by Outcome

Overall and multiple endocrinopathy burden

The most consistent and quantitatively striking finding of this review is that endocrine dysfunction in thalassaemia major is rarely confined to a single axis. In the North American comparative analysis, 56% of thalassaemia patients had more than one endocrinopathy compared with 13% of transfused sickle-cell disease controls ($p<0.001$), and multivariable analysis returned an adjusted odds ratio for any endocrinopathy of 9.4 in thalassaemia versus sickle-cell disease ($p<0.001$), with duration of chronic transfusion an independent predictor (OR 1.4 per 10 years of transfusion, $p=0.04$). Crucially, transfused sickle-cell disease did not differ from non-transfused sickle-cell disease, indicating that the underlying erythropoietic disorder — and not transfusion alone — modulates iron-related endocrine injury.³

Population-level data corroborate this. In the English national cohort, 76% of patients with transfusion-dependent β -thalassaemia carried at least one comorbidity, 54% two or more and 37% three or more, with endocrine disorders excluding diabetes present in 40%, osteoporosis in 40% and diabetes in 34%. In the Italian nation-wide deferasirox cohort, 187 of 426 patients already had two or more endocrine diseases at baseline and only 118 had none, with 104 additional endocrine diseases accruing during a median eight years of follow-up. In the Hong Kong non-transfusion-dependent cohort, 52% had chronic health deficits correlating strongly with age, log-transformed ferritin and splenectomy history, although the proportion with a frank endocrinopathy was lower at 12%, illustrating the phenotype-severity gradient.^{5,7,42}

Table 11. Burden of any and multiple endocrinopathy

Study (year)	Population (n)	Metric	Result	Significance
Fung EB (2006)	Thalassaemia 142 vs transfused SCD 199	≥ 2 endocrinopathies	56% vs 13%	$p < 0.001$
Fung EB (2006)	Same cohort	Adjusted OR any endocrinopathy (Thal vs SCD)	OR 9.4	$p < 0.001$
Fung EB (2006)	Same cohort	Transfusion duration as predictor	OR 1.4 per 10 years	$p = 0.04$
Vogiatzi MG (2009)	361 across thalassaemia syndromes	Multiple endocrinopathies, β -TM vs other syndromes	Significantly higher in β -TM	Significant (reported)
Jobanputra M (2020)	612 TDT (England)	≥ 1 / ≥ 2 / ≥ 3 comorbidities	76% / 54% / 37%	Population-level
Jobanputra M (2020)	612 TDT	Endocrine (excl. diabetes) / osteoporosis / diabetes	40% / 40% / 34%	Population-level
Casale M (2021)	426 TDT on deferasirox	≥ 2 endocrine diseases at baseline	187/426 (43.9%)	Descriptive

Casale M (2021)	426 TDT	5-year risk of a new endocrine complication	9.7% (95% CI 6.3–13.1)	Estimated with CI
Meloni A (2025)	140 neo-TDT adults	Bone disorder / dysglycaemia / hypothyroidism / hypogonadism	68.6% / 15.7% / 15.0% / 11.4%	Descriptive
Leung W (2025)	109 NTDT (Hong Kong)	Chronic health deficits; ≥ 1 endocrinopathy	52%; 12%	Correlated with age, ferritin, splenectomy
Karimi M (2018)	721 β -thalassaemia intermedia	Osteoporosis / hypogonadism (most frequent)	21.6% / 12.6%	Descriptive

SCD = sickle-cell disease; OR = odds ratio; CI = confidence interval; TDT = transfusion-dependent thalassaemia; NTDT = non-transfusion-dependent thalassaemia; β -TM = β -thalassaemia major.

Growth failure and short stature

Short stature was reported in approximately one quarter of patients in well-resourced contemporary cohorts and in up to half in resource-constrained settings. In the North American network, roughly 25% of both children and adults had short stature irrespective of thalassaemia syndrome, although mean final height approached mid-parental height ($z = -0.73 \pm 1.24$), indicating partial catch-up under contemporary therapy. In the United Kingdom tertiary cohort, 24% had a height standard deviation score below -2 but only one of these was short for parental height, and there was no difference in height standard deviation score between the highest (24.03 mg/g dry weight) and lowest (5.04 mg/g dry weight) liver iron strata — a finding that reframes short stature in optimally managed populations as substantially familial rather than siderotic. In striking contrast, pooled local data from low-resource settings recorded stunted growth in 50.5% (95% CI 29.6–71.4).^{2,16,53}

An important and under-recognised finding is skeletal disproportion. Disproportionate truncal shortening, defined as leg-length standard deviation score minus sitting-height standard deviation score greater than 1, was present in 23 of 29 assessable United Kingdom patients (79.3%) — an order

of magnitude more common than absolute short stature in the same cohort, and attributable to the vertebral toxicity of desferrioxamine and to spinal osteoporosis rather than to global growth failure. Post-transplantation, age at transplant, higher ferritin at transplant and elapsed time since transplant were each independently associated with decreased height growth on multivariable analysis, while 36% of adults were overweight at last evaluation, indicating a shift of the growth problem from stunting to adiposity after cure.^{15,16}

Table 12. Growth failure, short stature and skeletal disproportion

Study (year)	Population	Definition applied	Result	Significance / comment
Vogiatzi MG (2009)	361 thalassaemia syndromes, North America	Short stature; final height z-score	~25% short stature; final height $z = -0.73 \pm 1.24$	Close to mid-parental height
Fung EB (2006)	142 thalassaemia vs 199 transfused SCD	Growth failure	33% vs 7%	$p < 0.001$
Sethuraman C (2026)	50 TDT, UK	Height SDS < -2	24% (12/50); only 1 short for parental height	No difference by liver iron stratum
Sethuraman C (2026)	29 assessable	LL SDS – SH SDS > 1 (truncal shortening)	79.3% (23/29)	Predominant skeletal phenotype
Abbas S (2025) [corroborative]	Pooled local data, low-resource settings	Stunted growth	50.5% (95% CI 29.6–71.4)	Contrast with high-resource cohorts
Grundy RG (1994)	18 well-managed patients	Significant short stature	5/18 (27.8%)	Impaired GH response in all iron-overloaded

Rahal I (2018)	99 post-HSCT	Height growth on multivariable analysis	Reduced with older age at HSCT, higher ferritin, longer time since HSCT	Independently significant
Rahal I (2018)	99 post-HSCT	Overweight in adulthood	36%	Post-cure metabolic shift
See WS (2018)	40 post-HSCT vs 20 controls	Growth failure	Second most prevalent endocrinopathy	Age ≤ 8 y at HSCT protective (aOR 0.065, p=0.045)
Orhan Ö (2025)	27 children with TM	Weight and height by osteoporosis status	Significantly lower in osteoporotic group	p=0.012 and p=0.004

SDS = standard deviation score; LL = leg length; SH = sitting height; GH = growth hormone; HSCT = haematopoietic stem cell transplantation; aOR = adjusted odds ratio.

Hypogonadism and pubertal delay

Hypogonadism emerged as the single most frequent endocrinopathy of thalassaemia major across every era and every geography represented in this review. The Italian survival registry recorded hypogonadism in 54.7% of patients, the North American comparative study in 40% of thalassaemia patients versus 4% of transfused sickle-cell controls ($p < 0.001$), and the North American network study identified hypogonadism as the most frequent endocrinopathy and — importantly — as frequently under-treated. Post-transplantation series reported hypogonadism in 56% of females and 14% of males in the French national cohort and gonadal dysfunction in 55% overall in the Hong Kong series, with a 10-year cumulative incidence of 55%.^{2,3,4,15,37}

Mechanistic studies establish that the defect is predominantly, though not exclusively, central. Detailed neuroendocrine evaluation demonstrated hypogonadotropic hypogonadism in both sexes with impaired sexual development, with no change in oestradiol, testosterone or gonadotropin response after pulsatile gonadotropin-releasing hormone priming — indicating severe pituitary gonadotropin insufficiency rather than hypothalamic failure alone. In adolescent males, basal

luteinising hormone, follicle-stimulating hormone and testosterone were significantly lower than in constitutional delay of growth and puberty, and the difference widened after gonadotropin-releasing hormone analogue stimulation; testosterone remained significantly lower after human chorionic gonadotropin, confirming a superimposed gonadal component. A dedicated stimulation study clarified the dose–response: after six months of human chorionic gonadotropin, all constitutional-delay adolescents but only 7 of 12 thalassaemic adolescents achieved testosterone above 2 nmol/L, and the five non-responders had significantly higher ferritin (1985 ± 658 vs 1100 ± 425 ng/mL), consistent with testicular siderosis.^{28,43,44}

Contemporary evidence tempers but does not overturn this picture. In a two-year longitudinal study of well-chelated adult women, hypogonadism remained clinically prevalent while all other endocrine axes stayed within reference ranges and no new overt endocrine disorder emerged; anti-Müllerian hormone showed marked inter-individual variability and did not consistently track ferritin or magnetic resonance iron indices, suggesting that conventional gonadotropin measurement may under-detect ovarian reserve impairment. Conversely, intensive combined chelation permitted seven of fourteen hypogonadal males to discontinue testosterone and enabled six of nineteen previously hypogonadal females to conceive, establishing partial reversibility.^{33,34}

Table 13. Hypogonadism and pubertal delay

Study (year)	Population	Metric	Result	Significance
Borgna-Pignatti C (2004)	720 TM born after 1970 (Italy)	Hypogonadism prevalence	54.7%	Most frequent complication
Fung EB (2006)	142 Thal vs 199 Tx-SCD	Hypogonadism	40% vs 4%	p<0.001
Vogiatzi MG (2009)	361 (North America)	Most frequent endocrinopathy; treatment adequacy	Hypogonadism; frequently under-treated	Significantly higher in β -TM
Rahal I (2018)	99 post-HSCT (France)	Hypogonadism by sex	Females 56%; males 14%	Younger age at HSCT

				protective (2.5 vs 8.7 y)
See WS (2018)	40 post-HSCT (Hong Kong)	Gonadal dysfunction; 10-year cumulative incidence	55%; 55%	Age ≤ 7 y at HSCT aOR 0.06, p=0.018
Meloni A (2025)	140 neo-TDT adults	Hypogonadism	11.4%	No significant predictor identified
Karimi M (2018)	721 thalassaemia intermedia	Hypogonadism	12.6%	Second most prevalent complication
Al-Rimawi H (2006)	33 adolescent males	Delayed puberty; HPG axis	17/33 delayed; LH, FSH, testosterone significantly lower than constitutional delay	Significant, widening after GnRH analogue
Soliman AT (2004)	12 β -TM vs 10 constitutional delay	Testosterone >2 nmol/L after 6 months hCG	7/12 vs 10/10	Non- responders ferritin 1985 $\pm$ 658 vs 1100 $\pm$ 425 ng/mL
Roth C (1997)	32 β -TM	Gonadotropin reserve after GnRH priming	No rise in oestradiol, testosterone or LH/FSH	Severe pituitary gonadotropin insufficiency
Demircivi E (2026)	15 well-chelated adult women vs 22 controls	Hypogonadism over 2 years	Clinically prevalent; other axes normal; AMH variable	No significant temporal change

Farmaki K (2010)	52 on intensive combined chelation	Reversal of hypogonadism	7/14 males discontinued testosterone; 6/19 females conceived	Demonstrated reversibility
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HPG = hypothalamic–pituitary–gonadal; GnRH = gonadotropin-releasing hormone; hCG = human chorionic gonadotropin; AMH = anti-Müllerian hormone; LH = luteinising hormone; FSH = follicle-stimulating hormone.

Disorders of glucose metabolism

Disorders of glucose metabolism in thalassaemia major follow a reproducible natural history in which insulin resistance precedes and then coexists with progressive β -cell failure. The seminal euglycaemic clamp study demonstrated that insulin-stimulated glucose metabolism is preserved in prepubertal patients (319 ± 23 vs 314 ± 41 mg/m²/min, not significant) but markedly impaired in pubertal patients (155 ± 18 vs 224 ± 15 mg/m²/min, $p < 0.01$), with plasma insulin rising excessively after oral glucose in the pubertal group alone ($p < 0.001$) — establishing puberty as the inflection point of metabolic decompensation. Oral glucose tolerance test–based work extended this, showing that fasting, two-hour and integrated glucose were already significantly higher than in controls even among patients classified as having normal glucose tolerance (all $p < 0.03$), and that the C-peptide to insulin ratio correlated negatively with age in patients but positively in controls ($r = -0.45$ vs $r = 0.43$), indicating progressive loss of secretory reserve.^{29,30}

Reported prevalence spans a wide range determined principally by the diagnostic modality and the age of the cohort: 6.4% in the Italian survival registry, 13% in the North American comparison (versus 2% in transfused sickle-cell disease, $p < 0.001$), 14.41% diabetes with a further 40.68% having both impaired fasting glucose and impaired glucose tolerance in Chinese children, 16.5% diabetes in the E-MIOT thalassaemia major cohort, and 34% in the English national dataset. Diagnostic modality matters substantially: continuous glucose monitoring reclassified 65% of screened paediatric patients as diabetic compared with 35% by oral glucose tolerance test ($p = 0.012$), and all diabetic patients in that series were non-adherent to chelation.^{3,4,7,12,45}

Table 14. Disorders of glucose metabolism

Study (year)	Population	Diagnostic modality	Result	Significance
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Borgna-Pignatti C (2004)	720 TM (Italy)	Clinical registry diagnosis	Diabetes 6.4%	Registry prevalence
Fung EB (2006)	142 Thal vs 199 Tx-SCD	Clinical diagnosis	13% vs 2%	p<0.001
Jobanputra M (2020)	612 TDT (England)	ICD-10 coded diagnosis	Diabetes 34%	Population-level
Pepe A (2019/2020)	705–1079 TM (E-MIOT)	OGTT	DM 16.5%; IGT 4.1%; IFG 2.0%; NGT 77.4%	Descriptive, large cohort
Noetzli LJ (2012)	59 TM	Frequently sampled OGTT + MRI	DM 11; IGT 12; isolated IFG 8; NGT 28	Disposition index worse in DM/IGT
Zhang L (2021)	118 children vs 33 controls	OGTT, HbA1c, GA, fructosamine	DM 14.41%; IFG+IGT 40.68%	FPG, insulin, HOMA-IR significantly raised vs controls
Meloni A (2025)	140 neo-TDT	Clinical criteria	Impaired glucose metabolism 15.7%	Age OR 4.42 (p=0.004); pancreatic iron OR 7.40 (p=0.012)
Hantrakool S (2012)	92 adults (Thailand)	Fasting glucose	DM 9.8%; IFG 10.9%	Max ferritin 11 241 vs 4468 µg/dL, p=0.0001
Merkel PA (1988)	12 children vs controls	Euglycaemic insulin clamp	Pubertal 155 ± 18 vs 224 ± 15 mg/m ² /min	p<0.01; prepubertal not significant

Cario H (2003)	36 TM vs 32 controls	OGTT with insulin and C-peptide	Glucose significantly higher even in NGT patients	All p<0.03; secretion capacity reduced p<0.004
El-Samahy MH (2018)	200 screened, 20 studied (Egypt)	CGMS vs OGTT	DM 65% (CGMS) vs 35% (OGTT)	p=0.012
Caocci G (2023)	114 β -TM, 29 splenectomised	Clinical diagnosis	Diabetes 17.2% vs 3.5%	p=0.013

OGTT = oral glucose tolerance test; CGMS = continuous glucose monitoring system; NGT = normal glucose tolerance; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; DM = diabetes mellitus; GA = glycated albumin; HOMA-IR = homeostatic model assessment of insulin resistance; FPG = fasting plasma glucose.

Thyroid dysfunction

Thyroid dysfunction was reported in 6.5% to 19.9% of cohorts, with subclinical disease considerably more common than overt disease. Overt hypothyroidism was recorded in 10.8% of the Italian registry, 10% of North American thalassaemia patients versus 2% of transfused sickle-cell controls (p<0.001), 15.0% of the Italian neo-transfusion-dependent cohort and 6.5% of a Thai adult cohort, in which a further 22.8% had subclinical hypothyroidism. Central hypothyroidism accounted for a substantial minority — 8.3% versus 5.5% primary disease in the multi-country thalassaemia intermedia survey — underlining that pituitary siderosis, not thyroid siderosis alone, drives the phenotype. Thyroid-stimulating hormone concentration emerged as a general marker of endocrine vulnerability rather than of thyroid disease alone: in the nation-wide deferasirox cohort each 1 mIU/L increment in thyrotropin conferred an adjusted hazard ratio of 1.3 (95% CI 1.1–1.4, p<0.001) for developing any new endocrine complication, independent of the specific disease incident and unaffected by levothyroxine co-administration.^{3,4,5,8,9,27}

Table 15. Thyroid dysfunction

Study (year)	Population	Metric	Result	Significance
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Borgna-Pignatti C (2004)	720 TM	Hypothyroidism	10.8%	Registry prevalence
Fung EB (2006)	142 Thal vs 199 Tx-SCD	Hypothyroidism	10% vs 2%	p<0.001
Meloni A (2025)	140 neo-TDT	Hypothyroidism	15.0%	No significant predictor
Karimi M (2018)	721 intermedia	Central vs primary hypothyroidism	8.3% vs 5.5%	Central predominance
Hantrakool S (2012)	92 adults	Overt / subclinical hypothyroidism	6.5% / 22.8%	Max ferritin 7638 vs 4117 µg/dL, p=0.003
Casale M (2021)	426 TDT	TSH as predictor of any new endocrine disease	aHR 1.3 per 1 mIU/L (95% CI 1.1–1.4)	p<0.001
Rahal I (2018)	99 post-HSCT	Thyroid dysfunction	11%	Late effect
See WS (2018)	40 post-HSCT	Hypothyroidism risk factor	Post-transplant cardiac iron overload OR 82.6	p=0.007
Abbas S (2025) [corroborative]	Low-resource pooled data	Hypothyroidism	19.9%	Upper end of reported range
Farmaki K (2010)	18 on thyroxine	Discontinuation after intensive chelation	10 discontinued; 4 dose-reduced	Reversibility demonstrated
Casale M (2014)	86 TDT on deferasirox	New hypothyroidism over 6.5 years	None	Stabilisation under chelation

TSH = thyroid-stimulating hormone; aHR = adjusted hazard ratio.

Parathyroid dysfunction and calcium metabolism

Hypoparathyroidism is the least frequent but among the most clinically consequential of the classical thalassaemic endocrinopathies, reported in 2.2% of the thalassaemia intermedia survey, in

12.8% of pooled low-resource data, and at a frequency below the 5% analytical threshold in the Italian neo-transfusion-dependent cohort. Subclinical hypoparathyroidism and hypercalciuria were significantly more frequent in β -thalassaemia major than in other thalassaemia syndromes in the North American network study, indicating that disordered calcium handling extends well beyond the overtly hypoparathyroid minority. During long-term deferasirox therapy only one new case of hypoparathyroidism arose in 86 patients over a median 6.5 years, and in the larger 426-patient cohort parathyroid disease contributed a small fraction of the 104 incident endocrine diagnoses — evidence that this axis is comparatively protected under modern chelation.^{2,5,6,8,9,53}

Table 16. Parathyroid dysfunction and calcium metabolism

Study (year)	Population	Metric	Result	Comment
Karimi M (2018)	721 intermedia	Hypoparathyroidism	2.2%	Lowest reported frequency
Abbas S (2025) [corroborative]	Low-resource pooled data	Hypoparathyroidism	12.8%	Highest reported frequency
Vogiatzi MG (2009)	361 thalassaemia syndromes	Subclinical hypoparathyroidism and hypercalciuria	Significantly higher in β -TM	Extends beyond overt disease
Meloni A (2025)	140 neo-TDT	Hypoparathyroidism	<5% (excluded from modelling)	Below analytical threshold
Casale M (2014)	86 TDT, 6.5 years deferasirox	New hypoparathyroidism	1 case	Low incident risk under chelation
Orhan Ö (2025)	27 children with TM	Serum calcium and phosphate by osteoporosis status	Significantly lower in osteoporotic group	p<0.001 and p=0.038

Orhan Ö (2025)	27 children	BMD vs calcium	r = 0.499	p=0.008
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Metabolic bone disease and vitamin D status

Metabolic bone disease is quantitatively the most prevalent complication of the thalassaemic skeleton–endocrine interface. In an adult Israeli cohort a bone mineral density Z-score below -2 was present in 89% at the lumbar spine, 62% at the hip and 73% at the radius; vitamin D deficiency was documented in 62%, low insulin-like growth factor-1 in 72% and elevated urinary N-telopeptide in 84%, with insulin-like growth factor-1 correlating significantly with spine ($r=0.40$) and hip ($r=0.39$) bone mineral density (both $p<0.01$) and a mean annual spinal bone loss of 1.36%. Bone metabolism disorders were the most prevalent complication (68.6%) in the Italian neo-transfusion-dependent cohort, osteoporosis affected 40% of the English national cohort and 21.6% of the multi-country intermedia survey, and 22.2% of a Turkish paediatric cohort met osteoporotic criteria. Vitamin D insufficiency was near-universal in the North American network: 82% had 25-hydroxyvitamin D below 75 nmol/L and 12.8% below 27 nmol/L, with adolescents faring worst.^{2,7,8,9,13,14}

Two findings are of particular clinical importance. First, bone mineral density correlated strongly and inversely with serum ferritin in children ($r = -0.791$, $p<0.001$), with osteoporotic patients carrying ferritin of 5306 ± 1506 versus 2020 ± 1205 ng/mL in non-osteoporotic patients ($p=0.001$) — the steepest ferritin–outcome gradient identified anywhere in this review. Second, and in contrast to the historical assumption of inexorable bone loss, long-term deferasirox therapy was associated with a significant increase in mean lumbar spine bone mineral density ($p<0.001$) and a significant reduction in the number of patients with lumbar osteoporosis ($p=0.022$), irrespective of bisphosphonate, hormonal replacement, calcium or vitamin D therapy.^{6,14}

Table 17. Bone mineral density, osteoporosis and vitamin D status

Study (year)	Population	Metric	Result	Significance
Pollak RD (2000)	50 adults (β -TM and intermedia)	BMD Z-score <-2 (spine / hip / radius)	89% / 62% / 73%	Descriptive
Pollak RD (2000)	Same cohort	Vitamin D deficiency / low IGF-1 / raised NTx	62% / 72% / 84%	Descriptive

Pollak RD (2000)	Same cohort	IGF-1 vs spine and hip BMD	$r = 0.40$ and $r = 0.39$	Both $p < 0.01$
Pollak RD (2000)	19 followed 5.6 years	Mean annual spine BMD change	-1.36% per year	Progressive loss
Meloni A (2025)	140 neo-TDT	Bone metabolism disorders	68.6%	Most prevalent complication
Jobanputra M (2020)	612 TDT (England)	Osteoporosis	40%	Population-level
Karimi M (2018)	721 intermedia	Osteoporosis	21.6%	Most prevalent in that phenotype
Orhan Ö (2025)	27 children with TM	Osteoporosis (lumbar Z < -2)	22.2%	Descriptive
Orhan Ö (2025)	27 children	BMD vs ferritin	$r = -0.791$	$p < 0.001$
Orhan Ö (2025)	27 children	Ferritin, osteoporotic vs non-osteoporotic	5306 ± 1506 vs 2020 ± 1205 ng/mL	$p = 0.001$
Vogiatzi MG (2009)	361 thalassaemia syndromes	25(OH)D < 75 nmol/L / < 27 nmol/L	82% / 12.8%	Adolescents lowest
Casale M (2014)	86 TDT on deferiasirox	Mean lumbar BMD; osteoporosis prevalence	Significant increase; significant reduction	$p < 0.001$ and $p = 0.022$

BMD = bone mineral density; IGF-1 = insulin-like growth factor-1; NTx = N-telopeptide cross-linked type 1 collagen; 25(OH)D = 25-hydroxyvitamin D.

Growth hormone, adrenal and prolactin axes

The growth hormone axis in thalassaemia major is characterised by a dissociation between stimulated and spontaneous secretion that has direct diagnostic implications. Stimulated growth hormone secretion lay within the normal range in 10 of 13 short or slowly growing patients, yet overnight spontaneous secretion showed markedly reduced mean growth hormone concentration and

reduced peak amplitude, with low insulin-like growth factor-1 but intact hepatic insulin-like growth factor-1 generation on formal testing — establishing hypothalamic neurosecretory dysfunction rather than hepatic failure as the mechanism, and implying that a normal provocative test does not exclude clinically meaningful growth hormone deficiency in this population. Consistent with this, growth hormone responses to glucagon stimulation were significantly impaired in all iron-overloaded patients in an independent United Kingdom series.^{39,43}

Growth hormone deficiency was formally diagnosed in 1.1% of the multi-country thalassaemia intermedia survey and adrenal mass detected in 1%, while formal consensus review confirms that adrenal insufficiency is reported in β -thalassaemia major and transfusion-dependent α -thalassaemia but not in the non-transfusion-dependent phenotypes. Prolactin axis abnormality is under-recognised: hyperprolactinaemia was present in 13% of a prospectively evaluated non-transfusion-dependent cohort, including three microprolactinomas and two partial empty sellae, and hyperprolactinaemic patients had a significantly more severe disease phenotype, being more frequently hypothyroid, more frequently splenectomised, more frequently transfused, with significantly lower haemoglobin and higher nucleated red-cell counts (all $p < 0.05$).^{9,40,51}

Table 18. Growth hormone, adrenal and prolactin axes

Study (year)	Population	Axis assessed	Result	Interpretation
Roth C (1997)	32 β -TM; 13 tested	GH stimulated vs spontaneous	Stimulated normal in 10/13; spontaneous mean GH and peak amplitude markedly reduced	Hypothalamic neurosecretory dysfunction
Roth C (1997)	Same cohort	IGF-1 generation test	Strong rise in IGF-1 and IGFBP-3 in 8 tested	Hepatic IGF-1 generation intact
Grundy RG (1994)	18 patients	GH response to glucagon	Significantly impaired in all iron-overloaded patients	Damage despite adequate chelation

Karimi M (2018)	721 intermedia	GH deficiency; adrenal mass	1.1%; 1%	Low frequency in milder phenotype
Habeb A (2025) [corroborative]	International consensus review	Adrenal insufficiency	Reported in β -TM and transfusion-dependent HbH only	Phenotype- restricted
Ricchi P (2014)	98 NTDT adults	Prolactin	Hyperprolactinaemia 13%; 3 microprolactinomas; 2 partial empty sella	Under- recognised pituitary involvement
Ricchi P (2014)	Same cohort	Phenotype of hyperprolactinaemic patients	More often hypothyroid, splenectomised, transfused; lower Hb; higher NRBC	All $p < 0.05$

GH = growth hormone; IGF-1 = insulin-like growth factor-1; IGFBP-3 = insulin-like growth factor binding protein-3; NRBC = nucleated red blood cells; NTDT = non-transfusion-dependent thalassaemia.

Serum ferritin as a determinant of endocrinopathy

Serum ferritin was the most frequently examined exposure variable and demonstrated consistent, statistically significant associations with endocrine outcome across cohorts, eras and continents, while simultaneously revealing its own limitations as a surrogate. In the Italian registry, ferritin at a threshold as low as 1000 ng/mL was associated with heart failure (hazard ratio 3.35, $p < 0.005$) and with reduced survival (hazard ratio 2.45, $p < 0.005$). In Thailand, maximum ferritin was significantly higher in diabetic than non-diabetic patients (11 241 vs 4468 $\mu\text{g/dL}$, $p = 0.0001$) and in hypothyroid than euthyroid patients (7638 vs 4117 $\mu\text{g/dL}$, $p = 0.003$), with univariable thresholds of 2500 and 3500 $\mu\text{g/dL}$ respectively. In Turkish children, bone mineral density correlated with ferritin at $r = -0.791$ ($p < 0.001$). Corroborative systematic review evidence records a fourteen-fold increase in diabetes risk among patients with persistently elevated ferritin.^{4,14,27,49}

The countervailing evidence is equally important. In a prospective transfusion-dependent cohort, liver iron concentration measured by $R2^*$ magnetic resonance showed no correlation with

serum ferritin or with phenotypic and genetic characteristics despite liver iron overload in 82% of patients; ferritin, being an acute-phase reactant, is elevated by infection and inflammation independently of iron burden. Stratification of patients with ferritin below 2500 ng/mL showed no difference in the frequency of hepatic, endocrine or cardiac complications across the <500, 500–1000 and 1000–2500 ng/mL strata, although hepatic iron overload was significantly less frequent and no patient below 500 ng/mL had significant myocardial iron — supporting a ferritin target below 500 ng/mL as achievable and safe while confirming that ferritin discriminates poorly within the lower range.⁴⁷

Table 19. Serum ferritin as a determinant of endocrine and organ outcome

Study (year)	Outcome examined	Ferritin metric	Effect estimate	Significance
Borgna-Pignatti C (2004)	Heart failure	Ferritin ≥ 1000 ng/mL	HR 3.35	p<0.005
Borgna-Pignatti C (2004)	Overall survival	Ferritin ≥ 1000 ng/mL	HR 2.45	p<0.005
Hantrakool S (2012)	Diabetes mellitus	Maximum ferritin	11 241 vs 4468 $\mu\text{g/dL}$; threshold >2500 $\mu\text{g/dL}$	p=0.0001
Hantrakool S (2012)	Hypothyroidism	Maximum ferritin	7638 vs 4117 $\mu\text{g/dL}$; threshold >3500 $\mu\text{g/dL}$	p=0.003 (threshold p=0.007)
Orhan Ö (2025)	Bone mineral density	Serum ferritin	r = -0.791	p<0.001
Zhang L (2021)	Abnormal OGTT	Serum ferritin >4000 $\mu\text{g/L}$	Significant difference between OGTT groups	Significant (reported)
Soliman AT (2004)	Testicular hCG responsiveness	Serum ferritin	Non-responders 1985 $\pm$ 658 vs 1100 $\pm$ 425 ng/mL	Significantly higher
Leung W (2025)	Chronic health deficits	Log-transformed ferritin	Strong positive correlation	Significant (reported)

Amid A (2016)	HRQoL Mental Component Summary	Serum ferritin	Independently associated on multivariable analysis	Significant
Rahal I (2018)	Post-HSCT height growth	Ferritin at transplantation	Independently associated with decreased growth	Significant on multivariable analysis
El-Samahy MH (2018)	Elevated random blood glucose	Serum ferritin	Only independent variable identified	Significant
Shah F (2022) [corroborative]	Diabetes risk	Persistently elevated ferritin	14-fold increase in risk	Systematic literature review
Spasiano A (2021)	Hepatic and cardiac iron; complications	Ferritin strata <500 / 500–1000 / 1000–2500 ng/mL	Hepatic iron significantly lower <500; no myocardial iron <500; complication frequency not different	Discriminates poorly in low range
Bhakat A (2025)	Liver iron concentration by R2* MRI	Serum ferritin	No correlation with LIC despite 82% liver iron overload	Ferritin unreliable as tissue surrogate

HR = hazard ratio; LIC = liver iron concentration; OGTT = oral glucose tolerance test; hCG = human chorionic gonadotropin. The final row derives from a prospective observational R2 MRI study identified during searching and retained for exposure-validity analysis.*

Magnetic resonance iron indices as determinants

Organ-specific magnetic resonance relaxometry outperformed serum ferritin as a determinant of endocrine outcome in every study in which both were assessed, and pancreatic T2* emerged as the single most discriminating index for glucose dysregulation. In a cohort of 1079 patients with thalassaemia major, patients with normal glucose metabolism had significantly higher global

pancreas T2* than those with impaired fasting glucose, impaired glucose tolerance or diabetes; a pancreas T2* below 13.07 ms predicted an abnormal oral glucose tolerance test; and — the finding of greatest clinical utility — a normal pancreas T2* carried a 100% negative predictive value both for disturbance of glucose metabolism and for cardiac iron. Patients with myocardial fibrosis and those with cardiac complications had significantly lower pancreatic T2*, and no patient with arrhythmia or heart failure had a normal global pancreas T2*.¹⁰

These relationships hold across phenotypes and imaging techniques. In thalassaemia intermedia a pancreas T2* below 17.9 ms predicted an abnormal oral glucose tolerance test and pancreatic iron overload was significantly more frequent in regularly transfused than non-transfused patients (67.6% vs 31.6%, $p < 0.0001$). Pancreatic fatty replacement performed comparably: a fat fraction below 6.6% had 100% negative predictive value for abnormal glucose metabolism, a fat fraction above 15.33% predicted abnormal glucose metabolism, and fat fraction was significantly higher in patients with myocardial fibrosis ($p = 0.002$). Mechanistically, β -cell function as indexed by the disposition index correlated most strongly with pancreas R2*, whereas insulin resistance correlated with markers of inflammation and somatic iron — a clean separation of the two pathophysiological components. Notably, one third of patients with elevated pancreas R2* retained normal glucose regulation, defining a pre-clinical window in which chelation intensification may prevent irreversible β -cell loss.^{11,41,46}

Table 20. Magnetic resonance iron indices and endocrine outcome

Study (year)	Index	Cohort	Threshold / association	Diagnostic performance
Pepe A (2020)	Global pancreas T2*	1079 TM	<13.07 ms predicts abnormal OGTT	100% NPV of normal T2* for dysglycaemia and cardiac iron
Pepe A (2020)	Global pancreas T2*	1079 TM	Significantly lower with myocardial fibrosis and cardiac complications	No patient with arrhythmia/heart

				failure had normal pancreas T2*
Pepe A (2019)	Global pancreas T2*	705 TM	<13.73 ms predicts abnormal OGTT; AUC 0.62	NGT 13.58 ± 11.08 vs DM 8.09 ± 4.72 ms, p<0.0001
Meloni A (2021)	Pancreas T2*	221 thalassaemia intermedia	<17.9 ms predicts abnormal OGTT	100% NPV of normal T2* for cardiac iron
Meloni A (2021)	Pancreatic iron overload	221 intermedia	Transfused 67.6% vs non-transfused 31.6%	p<0.0001
Meloni A (2023)	Pancreatic fat fraction	308 TM	<6.6% normal; >15.33% predicts abnormal glucose metabolism	100% NPV for abnormal glucose metabolism and cardiac iron
Meloni A (2023)	Pancreatic fat fraction	308 TM	Significantly higher with myocardial fibrosis	p=0.002
Noetzli LJ (2012)	Pancreas R2*	59 TM	Disposition index correlates most strongly with pancreas R2*	One third with high R2* still normoglycaemic (pre-clinical)
Meloni A (2025)	Pancreatic iron overload	140 neo-TDT	Impaired glucose metabolism OR 7.40	p=0.012
Zhang L (2021)	Cardiac T2*	118 children	Differs significantly between normal and abnormal OGTT groups	Significant (reported)
See WS (2018)	Post-transplant cardiac T2*	40 post-HSCT	Hypothyroidism OR 82.6	p=0.007
Ricchi P (2024)	Hepatic fat fraction	301 TDT	>3.53% predicts abnormal OGTT	Liver steatosis in 36.4%

NPV = negative predictive value; AUC = area under the receiver operating characteristic curve; OGTT = oral glucose tolerance test; NGT = normal glucose tolerance; DM = diabetes mellitus.

Modification by chelation regimen and intensity

The evidence that endocrine damage in thalassaemia major is modifiable, and in some axes reversible, is among the most clinically consequential findings of this review. Transition of 52 patients to combined deferoxamine and deferiprone normalised total body iron and produced normalisation of abnormal glucose metabolism in 44% of the 39 affected patients; ten of eighteen patients discontinued thyroxine and four reduced their dose; seven of fourteen hypogonadal males stopped testosterone; six of nineteen previously hypogonadal females conceived; and no patient developed de novo cardiac or endocrine complications during up to seven years of follow-up. Long-term once-daily deferasirox produced a comparable stabilisation: over a median 6.5 years the incidence of new endocrine complications was 7%, with no new hypothyroidism or diabetes, no deaths, no significant change in thyroid parameters or insulin requirements among those already affected, a significant increase in mean lumbar spine bone mineral density ($p<0.001$) and a significant fall in lumbar osteoporosis prevalence ($p=0.022$).^{6,33}

In the larger nation-wide deferasirox cohort, the five-year risk of a new endocrine complication was 9.7% (95% CI 6.3–13.1) — explicitly lower than the risk previously reported in the deferoxamine era — but the authors emphasised that considerable risk variation persists and that the residual burden remains high. Route of chelation did not affect measured quality of life: median SF-36 physical and mental component summaries did not differ between parenteral and oral regimens, although patients strongly preferred oral therapy (84.6% and 92.9%) and deferasirox-containing regimens attracted significantly greater treatment acceptance ($p=0.038$) and satisfaction with treatment burden ($p=0.033$). Adherence, rather than agent, appears decisive: every diabetic patient in an Egyptian paediatric series was non-adherent to chelation.^{5,22,45}

Table 21. Endocrine outcomes by chelation strategy

Study (year)	Regimen	Cohort and duration	Endocrine outcome	Significance

Farmaki K (2010)	Deferoxamine + deferiprone (intensive combined)	52 TM, up to 7 years	Abnormal glucose metabolism normalised in 44% of 39 affected	Reversal demonstrated
Farmaki K (2010)	Same	Same	Thyroxine discontinued 10/18, dose-reduced 4/18	Reversal demonstrated
Farmaki K (2010)	Same	Same	Testosterone stopped 7/14 males; 6/19 females conceived	Reversal demonstrated
Farmaki K (2010)	Same	Same	No de novo cardiac or endocrine complications	Prevention demonstrated
Casale M (2014)	Deferasirox once daily	86 TDT, median 6.5 years	New endocrine complications 7% (5 hypogonadism, 1 hypoparathyroidism)	p=0.338 for prevalence change
Casale M (2014)	Deferasirox once daily	Same	Mean lumbar BMD increase; osteoporosis prevalence fall	p<0.001 and p=0.022
Casale M (2021)	Deferasirox once daily	426 TDT, median 8 years	5-year risk of new endocrine complication 9.7% (95% CI 6.3–13.1)	Lower than historical risk
Goulas V (2020)	Parenteral ± oral vs oral only	131 adults	SF-36 PCS 76.3 vs 76.9; MCS 75.7 vs 74.5	Not significantly different
Goulas V (2020)	Deferasirox-containing vs other	131 adults	Treatment acceptance 4.0 vs 3.6; burden satisfaction 4.4 vs 3.9	p=0.038 and p=0.033
El-Samahy MH (2018)	Any chelation, adherence assessed	20 studied	All diabetic patients non-adherent to chelation	Adherence decisive
Sethuraman C (2026)	Modern transfusion and chelation	50 TDT, UK	Hypogonadism, thyroid dysfunction and IGT all rare	Attenuated phenotype

Global health-related quality of life versus population norms

Across the great majority of cohorts, health-related quality of life in thalassaemia major was significantly below general-population norms. In the North American Thalassaemia Longitudinal Cohort, patients scored significantly worse ($p<0.05$) on five of eight SF-36 subscales — physical functioning, role-physical, general health, social functioning and role-emotional — and on both the physical and mental component summaries. In the Italian survey, all SF-36 domains were lower than the general population except emotional well-being ($p=0.7024$) and role-emotional ($p=0.1389$), while the Psychological General Well-Being Index domains of general health and vitality and the total score were all significantly lower ($p=0.0001$). In the five-country prospective study the deficits were large and consistent: EQ-VAS 67.1 ± 20.4 versus 80.4 ± 15.6 , FACT-G 70.1 ± 19.0 versus 77.0 ± 16.1 and FACIT-Fatigue 27.9 ± 13.7 versus 43.6 ± 9.4 , all $p<0.001$, with a mean TranQoL total score of 53.9 ± 18.5 on a 100-point scale and moderate mean pain. Corroborative meta-analytic synthesis of 26 SF-36 studies confirmed substantially compromised health-related quality of life relative to the general population, with pooled physical-domain means of 52.74 to 74.5 and mental-domain means of 59.6 to 71.11.^{17,18,19,48}

Two contrary results require careful interpretation rather than dismissal. In Sardinia, where a mature comprehensive-care infrastructure has existed for decades, 207 adults scored at least as well as 211 matched non-thalassaemic controls in all items and the proportion scoring 60 or above was higher among patients than controls. In Western Greece, median SF-36 physical and mental component summaries of approximately 75 were recorded, with no difference by chelation route. These findings do not contradict the general pattern but delimit it: where transfusion adequacy, chelation access and psychosocial support are optimised, and where the disease is normalised within the local community, the quality-of-life penalty can be largely abolished. The counter-example is equally instructive — in a resource-constrained Pakistani cohort with a mean pre-transfusion haemoglobin of 7.3 g/dL, 22.5% of school-age patients had never attended school and 28.7% faced difficulty obtaining blood.^{21,22,35}

Table 22. Global HRQoL versus population norms and controls

Study (year)	Instrument	Population (n)	Result versus norm or control	Significance
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Sobota A (2011)	SF-36v2	264 (USA)	Worse on 5/8 subscales and both component summaries	p<0.05
Tedone F (2021)	SF-36 and PGWBI	105 (Italy)	All SF-36 domains lower except emotional well-being and role-emotional	p=0.7024 and p=0.1389 for the two exceptions
Tedone F (2021)	PGWBI	105	General health, vitality and total score lower	p=0.0001
Drahos J (2025)	EQ-VAS	155 (5 countries)	67.1 ± 20.4 vs 80.4 ± 15.6	p<0.001
Drahos J (2025)	FACT-G	155	70.1 ± 19.0 vs 77.0 ± 16.1	p<0.001
Drahos J (2025)	FACIT-Fatigue	155	27.9 ± 13.7 vs 43.6 ± 9.4	p<0.001
Drahos J (2025)	TranQoL	155	Total 53.9 ± 18.5 (0–100 scale)	Disease-specific burden
Li N (2022) [corroborative]	FACT-G, EQ-5D-5L, TranQoL, WPAI	155 (global survey)	FACT-G 70.1 vs US norm 80.1; EQ-VAS 67.1; TranQoL 53.9	Consistent direction
Naseeb S (2024)	WHOQOL-BREF (modified)	136 (Pakistan)	Substantial impairment; 22.5% never attended school	Resource-constrained setting
Kashari O (2020)	WHOQOL-BREF	48 children (Saudi Arabia)	Overall QoL poor in 27.1% pre-transfusion, improving after transfusion	p<0.001
Floris F (2018)	WHOQOL-BREF	207 patients vs 211 matched controls (Sardinia)	Patients scored at least as well as controls in all items	Contrary finding — optimised care setting
Goulas V (2020)	SF-36	131 (Greece)	Median PCS 76.3–76.9; MCS 74.5–75.7	Contrary finding —

				high absolute scores
Arian M (2019) [corroborative]	SF-36 meta-analysis	26 studies pooled	Physical domains 52.74–74.5; mental domains 59.6–71.11	Substantially compromised vs general population

PGWBI = Psychological General Well-Being Index; PCS = physical component summary; MCS = mental component summary; WPAI = Work Productivity and Activity Impairment questionnaire. Rows shaded yellow denote cohorts in which HRQoL was NOT impaired relative to comparators — see Section 4.6 for interpretation.

Domain-specific HRQoL profile

The domain profile is characteristically physical-predominant. The physical functioning, role-physical and general health domains were consistently the most affected, whereas emotional and role-emotional domains were preserved in some cohorts. In the Italian survey emotional well-being and role limitations due to emotional problems were the only two SF-36 domains not significantly reduced. In the transplantation literature the physical domain drives the observed benefit: post-transplant patients scored significantly better than conventionally treated patients specifically in the physical health domain (75.20 vs 63.94, $p=0.007$), in dependence on medical aids ($p=0.006$), activity level ($p=0.026$) and personal relationships ($p=0.014$). Paediatric data are concordant, with transplanted children scoring worse than healthy peers specifically in physical health ($p<0.001$) and school functioning ($p<0.001$).^{18,25,26}

An important exception is the emotional domain in adults surveyed with oncology-derived instruments, where the largest relative decrement of the FACT-G was observed in emotional well-being (–21.9% relative change), and where 73.2% reported pain or discomfort, 60.8% anxiety or depression, 46.4% mobility impairment and 24.8% self-care impairment on the EQ-5D-5L. The apparent discrepancy between instruments most plausibly reflects instrument sensitivity and the framing of items rather than genuine divergence between populations, and argues for combining a generic and a disease-specific instrument in routine assessment.⁵⁸

Table 23. HRQoL domain profile

Domain	Direction of effect	Supporting evidence	Magnitude
Physical functioning / physical health	Consistently and significantly impaired	Sobota 2011; Tedone 2021; Cheuk 2008; Liang 2022; Drahos 2025	Largest and most reproducible decrement across all instruments
Role limitation due to physical problems	Significantly impaired	Sobota 2011; Cappellini 2019 (NTDT deterioration over 24 weeks)	Significant between-group change in the prospective comparison
General health perception	Significantly impaired	Sobota 2011; Tedone 2021 (PGWBI general health p=0.0001)	Consistently among the three lowest domains
Vitality / fatigue	Significantly impaired	Tedone 2021; Drahos 2025 (FACIT-F 27.9 vs 43.6)	Very large decrement on the fatigue-specific instrument
Social functioning	Significantly impaired	Sobota 2011; Arian 2019 (lowest mental-domain score)	Lowest of the mental-health domains in meta-analysis
School functioning (paediatric)	Significantly impaired	Liang 2022 (p<0.001); Naseeb 2024 (22.5% never schooled)	Marked in both clinical and educational metrics
Emotional well-being / role-emotional	Variable — preserved in some cohorts, most affected in others	Tedone 2021 (not significant); Li 2022 (largest FACT-G decrement, -21.9%)	Instrument-dependent; requires dual-instrument assessment
Symptom burden (pain, anxiety, mobility)	Substantial	Li 2022: pain 73.2%, anxiety/depression 60.8%, mobility 46.4%, self-care 24.8%	High absolute symptom prevalence on EQ-5D-5L

Determinants of health-related quality of life

Four determinants recurred across independent cohorts. Female sex, older age, greater complication burden and higher iron burden were each independently associated with poorer health-related quality of life. In the North American longitudinal cohort women, older patients and those

with more disease complications and more chelation side-effects reported significantly lower health-related quality of life. In the multinational IntercontinThal study, univariable analysis identified age, access to social support and health care, marital status, liver iron concentration, ferritin and disease-related complications as predictors of the mental component summary; on multivariable analysis ferritin and age — and, specifically within the transfusion-dependent stratum, clinical complications — remained independently associated with reduced quality of life. This is the most direct available evidence that the endocrine and organ complication burden, rather than the diagnosis of thalassaemia per se, drives the patient-reported outcome.^{17,24}

Two further determinants are notable for their clinical tractability. Adherence and regular follow-up were significantly associated with better quality of life: in a Saudi paediatric cohort overall quality of life was significantly better among children maintaining medication ($p=0.028$) and among those with regular follow-up, and significantly better quality of life was recorded among children attending subspecialty clinics including endocrinology; in Sardinia, health perception was associated with treatment adherence. Conversely, comorbidity count remained an independent negative predictor even after cure: in the paediatric transplant cohort, chronic graft-versus-host disease ($p=0.032$) and the presence of two or more comorbidities ($p<0.001$) were independently associated with poorer overall health-related quality of life.^{21,25,36}

Table 24. Independent determinants of HRQoL

Determinant	Direction	Study (year)	Analytical basis	Significance
Female sex	Lower HRQoL	Sobota A (2011)	Cohort analysis, SF-36v2	Significant
Older age	Lower HRQoL	Sobota A (2011); Amid A (2016)	Univariable and multivariable	Independently significant
Number of disease complications	Lower HRQoL	Sobota A (2011); Amid A (2016)	Multivariable (TDT stratum)	Independently significant
Serum ferritin	Lower HRQoL	Amid A (2016)	Multivariable regression on MCS	Independently significant

Liver iron concentration	Lower HRQoL	Amid A (2016)	Univariable only (fewer recent measurements)	Not independent
Chelation side-effects	Lower HRQoL	Sobota A (2011)	Cohort analysis	Significant
Splenectomy (in NTDT)	Lower HRQoL	Amid A (2016)	Univariable, NTDT subgroup	Significant
Splenectomy (in TDT)	No HRQoL difference	Caocci G (2023)	Cross-sectional SF-36 comparison	Not significant on any scale
Lower baseline haemoglobin (NTDT)	Lower HRQoL	Amid A (2016)	Univariable, NTDT subgroup	Significant
Medication adherence and regular follow-up	Higher HRQoL	Kashari O (2020); Floris F (2018)	Cross-sectional	p=0.028 (medication maintained)
Access to social support and health care	Higher HRQoL	Amid A (2016)	Univariable	Significant
Chronic GVHD and ≥ 2 comorbidities (post-HSCT)	Lower HRQoL	Liang H (2022)	Multivariable	p=0.032 and p<0.001
Ferritin level (paediatric, cross-sectional)	No association	Kashari O (2020)	Cross-sectional, small sample	Not significant — contrasts with adult data

GVHD = graft-versus-host disease; MCS = mental component summary; TDT = transfusion-dependent thalassaemia; NTDT = non-transfusion-dependent thalassaemia.

HRQoL after disease-modifying and curative therapy

The strongest interventional evidence in this review concerns gene editing. Among 54 participants receiving exagamglogene autotemcel and followed for at least sixteen months, all patient-reported outcome measures improved and exceeded established minimal clinically important difference thresholds: EQ-5D-5L visual analogue scale and health-utility index scores improved by

month 48, FACT-General total and the bone-marrow-transplant subscale improved with gains in all four FACT-G subscales, and in adolescents both EQ-5D-Y visual analogue scale and total PedsQL improved by month 24 with sustained gains in physical and psychosocial subcomponents. Gene addition therapy produced concordant results, with mean PedsQL total rising from 77.4 at baseline to 87.1 at month 24 — 2.2 times the minimal clinically important difference — and SF-36 physical and mental component summaries rising above the United States general-population norm.³¹

The randomised evidence is more nuanced and merits precise statement. In the BELIEVE trial, mean scores on all primary and exploratory quality-of-life domains were stable over time in both arms and did not differ between luspatercept and placebo at weeks 24 and 48. However, in a pre-specified exploratory responder analysis, patients achieving at least a 50% reduction in transfusion burden over twelve weeks were significantly more likely than placebo recipients to attain a clinically meaningful improvement in the physical component summary (31.1% vs 16.5%, $p=0.024$) and in physical functioning (30.0% vs 13.2%, $p=0.007$) at week 48. The correct interpretation is that transfusion-burden reduction, rather than drug exposure as such, is the mediator of quality-of-life gain — a conclusion aligned with the transplantation and gene-therapy literature.³²

The transplantation evidence completes the picture and adds an important temporal qualification. Transplanted patients rated overall health, independence from medical aids, activity level, personal relationships and physical health significantly better than conventionally treated patients, with differences persisting after adjustment for comorbidities, and were significantly more likely to consider marriage (100% vs 75.7%, $p=0.033$). In the larger paediatric series, transplanted children remained below healthy peers within four years of transplant but achieved scores statistically indistinguishable from healthy controls beyond four years — indicating that recovery of quality of life after cure is real but not immediate. Corroborative systematic review evidence across sixteen studies reported small-to-large positive effects of transplantation in most domains, with large positive effects in the physical and emotional domains in thalassaemia specifically.^{25,26,50}

Table 25. HRQoL change after disease-modifying and curative therapy

Intervention	Study (year)	Design	Instrument and result	Significance / MCID
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Gene editing (exa-cel)	de la Fuente J (2025)	Phase 3 with pre-specified PRO endpoints, n=54	EQ-5D-5L VAS and utility index improved by month 48; FACT-G total and BMTS improved in all four subscales	All exceeded MCID thresholds
Gene editing (exa-cel), adolescents	de la Fuente J (2025)	Same	EQ-5D-Y VAS and PedsQL total improved by month 24	Sustained in physical and psychosocial subcomponents
Gene addition (beti-cel)	Kwiatkowski J (2021)	Phase 3 pooled PRO analysis	PedsQL total 77.4 → 87.1 at month 24; SF-36 PCS/MCS above US norm	2.2 × MCID (4.36) for PedsQL
Luspatercept vs placebo (overall)	Cappellini MD (2020) — BELIEVE	Randomised, double-blind, placebo-controlled	SF-36 and TranQol domain means stable; no between-group difference at weeks 24 and 48	Not significant
Luspatercept responders (≥50% transfusion reduction)	Cappellini MD (2020) — BELIEVE	Exploratory responder analysis	Clinically meaningful improvement in PCS 31.1% vs 16.5%; physical functioning 30.0% vs 13.2%	p=0.024 and p=0.007
Haematopoietic SCT vs conventional therapy	Cheuk DKL (2008)	Cross-sectional comparative, n=98	Physical health 75.20 vs 63.94; overall health 3.67 vs 3.06; medical-aid dependence 3.87 vs 2.96	p=0.007, p=0.01, p=0.006
Haematopoietic SCT (paediatric)	Liang H (2022)	Cross-sectional, n=221 vs 429 vs 198	Worse than healthy peers <4 years post-HSCT; equal to healthy peers >4 years; better than non-transplanted throughout	p<0.001 for the non-transplant comparison

Splenectomy	Caocci G (2023)	Cross-sectional, n=114	No difference in any SF-36 scale	Not significant; comorbidity increased
HSCT / gene therapy (pooled)	Badawy SM (2021) [corroborative]	Systematic review, 16 studies, 517 participants	Cohen d median 0.37 (range 0.27–2.05); large effects in physical and emotional domains in thalassaemia	Moderate quality in 13/16 studies

MCID = minimal clinically important difference; PRO = patient-reported outcome; VAS = visual analogue scale; BMTS = bone marrow transplant subscale; PCS = physical component summary; SCT = stem cell transplantation. The beti-cel entry is drawn from the phase 3 patient-reported outcome analysis identified during searching.

Socio-economic, educational and mortality burden

The burden of thalassaemia major extends well beyond clinical endpoints. Italian patients spent a mean of 16.62 hours per month on care activities additional to the time required for transfusion itself, comprising 11.7 hours of therapy management and 4.92 hours of family management. In the five-country prospective study, employed participants lost a mean of 5.9 working hours in the preceding seven days and out-of-pocket expenses were a moderate-to-major burden for 55%; corroborative survey data recorded work impairment in 34.4%, absenteeism in 19.5%, work productivity loss in 41.7% and overall activity impairment in 44.2%, with 40% reporting that the disease often or always limited career opportunities and 62.4% spending more than six hours per month at medical appointments. Educational disruption is severe in resource-constrained settings, where 22.5% of school-age patients had never attended school and 9.1% had left education for health reasons.^{18,19,35,58}

Healthcare resource utilisation scales with transfusion intensity: in a Taiwanese national analysis of 2984 patients, thalassaemia-related resource use and the risk of liver, endocrine, cardiac and renal complications were significantly and positively correlated with increasing red-cell units per twelve weeks. Mortality remains substantially elevated: crude ten-year mortality of 6.2% in the

English cohort compared with 1.2% in the age- and sex-matched general population ($p<0.001$), notwithstanding the marked survival gains documented in the Italian registry, where 68% of patients were alive at 35 years and survival was significantly better in later birth cohorts ($p<0.00005$) and in females ($p=0.0003$).^{4,7,38}

Table 26. Socio-economic, educational and mortality burden

Domain	Study (year)	Metric	Result	Comment
Time burden of care	Tedone F (2021)	Hours per month additional to transfusion	16.62 h (11.7 therapy, 4.92 family management)	Italy, n=105
Work productivity	Drahos J (2025)	Working hours lost in previous 7 days	5.9 h (employed participants)	5 countries, n=155
Financial burden	Drahos J (2025)	Out-of-pocket expenses moderate-to-major	55% of participants	Consistent over 6 months
Work impairment	Li N (2022) [corroborative]	WPAI presenteeism / absenteeism / productivity loss / activity impairment	34.4% / 19.5% / 41.7% / 44.2%	Global longitudinal survey
Career limitation	Li N (2022) [corroborative]	Disease limits career "often" or "always"	40%	Self-reported
Appointment burden	Li N (2022) [corroborative]	>6 hours per month at medical appointments	62.4%	Plus 36.1% needing >6 h caregiver support
Education	Naseeb S (2024)	Never attended school / left for health reasons	22.5% / 9.1%	Pakistan, resource-constrained
Blood access	Naseeb S (2024)	Difficulty obtaining blood for transfusion	28.7%	Mean pre-transfusion Hb 7.3 g/dL

Healthcare utilisation	Tang CH (2021)	Resource use and complication risk by transfusion burden	Significant positive correlation with red-cell units per 12 weeks	Taiwan, n=2984
Mortality	Jobanputra M (2020)	Crude 10-year mortality vs general population	6.2% vs 1.2%	p<0.001
Survival trend	Borgna-Pignatti C (2004)	Alive at age 35; birth-cohort effect; sex effect	68%; p<0.00005; female advantage p=0.0003	Historical improvement

Certainty of Evidence (GRADE Summary of Findings)

Certainty was rated moderate for six outcomes, low for eight and very low for two. Upgrading was applied where the magnitude of effect was large (for example the adjusted odds ratio of 9.4 for any endocrinopathy in thalassaemia versus sickle-cell disease) and where a consistent dose–response gradient was demonstrated (pancreatic T2* versus glucose dysregulation; ferritin versus bone mineral density; transfusion burden versus complication risk). Downgrading was applied principally for risk of bias arising from cross-sectional design, for inconsistency where prevalence ranges were wide, and for indirectness where the evidence derived predominantly from specialist European and North American centres.

Table 27. GRADE summary of findings

Outcome	Design of the body of evidence	Key limitations	Upgrading factors	Certainty
O1 Overall and multiple endocrinopathy	Cross-sectional, cohort, registry	Heterogeneous case definitions	Very large effect (OR 9.4); dose–response with transfusion duration	MODERATE
O2 Growth failure and short stature	Cross-sectional, cohort	Divergent definitions; era effect	Consistent direction across settings	LOW

O3 Hypogonadism and pubertal delay	Cross-sectional, cohort, case-control, physiological	Variable diagnostic thresholds	Large effect (40% vs 4%); mechanistic coherence; reversibility demonstrated	MODERATE
O4 Disorders of glucose metabolism	Cohort, cross-sectional, physiological, clamp studies	Modality-dependent prevalence	Dose-response with pancreatic iron; mechanistic coherence	MODERATE
O5 Thyroid dysfunction	Cross-sectional, cohort	Subclinical disease inconsistently reported	Consistent direction; ferritin gradient	LOW
O6 Parathyroid dysfunction	Cross-sectional, cohort	Low event counts; frequently below analytical threshold	None applied	LOW
O7 Metabolic bone disease and vitamin D	Cross-sectional, cohort with longitudinal follow-up	DXA reference-standard heterogeneity	Very strong ferritin-BMD gradient ($r = -0.791$)	MODERATE
O8 GH, adrenal and prolactin axes	Small physiological and prospective cohorts	Small samples; specialist testing not widely replicated	Mechanistic coherence	LOW
O9 Ferritin as determinant	Cohort, cross-sectional	Ferritin is an acute-phase reactant; confounded by inflammation	Dose-response across multiple outcomes and cohorts	MODERATE
O10 MRI iron indices as determinants	Large multicentre observational	Observational design; centre-specific calibration	Very large diagnostic effect (100% NPV); dose-response;	MODERATE

			replication across phenotypes	
O11 Modification by chelation	Prospective and retrospective cohorts	Non-randomised; selection by adherence	Reversal of established disease is a large effect	LOW
O12 Global HRQoL versus norms	Cross-sectional and prospective cohorts	Norm-referenced rather than concurrently controlled in most studies	Consistent direction and magnitude across instruments and countries	MODERATE
O13 Domain-specific HRQoL profile	Cross-sectional cohorts	Instrument-dependent divergence in emotional domain	None applied	LOW
O14 Determinants of HRQoL	Cross-sectional with multivariable modelling	Residual confounding; complications aggregated rather than axis-resolved	Independent replication of age, sex, ferritin and complication count	LOW
O15 HRQoL after disease-modifying therapy	One RCT plus non-randomised interventional and comparative studies	Small samples at late time points; responder analysis exploratory	MCID thresholds exceeded across independent instruments	MODERATE
O16 Socio-economic and mortality burden	Survey, claims database, registry	Self-report; coding accuracy; setting-specific	Dose-response with transfusion burden	VERY LOW to LOW

GREEN = moderate certainty; YELLOW = low certainty; RED = very low to low certainty. No outcome achieved high certainty, reflecting the predominance of observational designs in this field. MCID = minimal clinically important difference; NPV = negative predictive value; DXA = dual-energy X-ray absorptiometry.

DISCUSSION

Summary of Principal Findings

This systematic review of 51 primary studies establishes four principal findings. First, endocrine morbidity in thalassaemia major is high in absolute terms, multi-axial rather than single-axis, and statistically significantly greater than in comparator populations exposed to transfusion without the same underlying erythropoietic disorder — the adjusted odds ratio of 9.4 for any endocrinopathy relative to transfused sickle-cell disease being the single most striking effect estimate in the field. Second, this burden is quantitatively predicted by iron exposure, with reproducible dose–response relationships for serum ferritin, transfusion duration, transfusion volume and — most discriminately — organ-specific magnetic resonance relaxometry. Third, health-related quality of life is significantly impaired relative to population norms in the majority of cohorts, with a physical-predominant domain profile, and the number of disease-related complications is one of the few determinants that survives multivariable adjustment. Fourth, and most importantly for practice, the entire chain is modifiable: intensive chelation reverses established endocrine disease in a substantial minority of patients, contemporary optimally managed cohorts display a markedly attenuated endocrine phenotype, and curative or disease-modifying therapy produces quality-of-life gains that exceed minimal clinically important difference thresholds.^{3,5,10,17,33}

The Pathophysiological Chain from Transfusional Siderosis to Endocrine Failure

The mechanistic architecture emerging from this evidence base is coherent. Chronic transfusion delivers iron that saturates transferrin, generating non-transferrin-bound iron species that enter cells through divalent metal transporters and, critically, through L-type and T-type voltage-gated calcium channels. This channel-mediated route explains the characteristic organ selectivity of siderotic injury: the anterior pituitary, pancreatic β cells, thyroid follicular cells, parathyroid chief cells and cardiac myocytes express these channels at high density and are correspondingly vulnerable, whereas tissues lacking them are relatively spared. Once intracellular, labile iron catalyses Fenton chemistry, generating hydroxyl radicals that damage mitochondrial membranes, nuclear DNA and the secretory apparatus. The consequence is a functional lesion — impaired hormone synthesis and regulated release — that precedes and may be dissociated from structural glandular destruction.⁵⁴

This dissociation has direct diagnostic consequences that the evidence in this review makes explicit. Growth hormone secretion illustrates the point most clearly: provocative testing was normal in 10 of 13 short or slowly growing patients whose spontaneous overnight secretion was markedly abnormal, with intact hepatic insulin-like growth factor-1 generation confirming that the lesion lay in the neurosecretory control of pulsatile release rather than in somatotroph mass or hepatic responsiveness. A clinician relying on a provocative test alone will therefore systematically under-diagnose growth hormone dysfunction in this population. The same principle applies to the pancreas, where one third of patients with elevated pancreatic R2* retained entirely normal glucose regulation — a demonstrable pre-clinical window in which the lesion is present, quantifiable by imaging, and potentially reversible before any biochemical abnormality appears.^{11,43}

Superimposed on iron toxicity are at least four modifying influences. Chronic anaemia and tissue hypoxia impair glandular perfusion and cellular energetics independently of iron. Hepatitis C virus infection, historically present in a substantial proportion of cohorts, contributes to hepatic dysfunction, insulin resistance and — as demonstrated in the E-MIOT steatosis analysis — hepatic fat accumulation, which independently predicted an abnormal oral glucose tolerance test. Splenectomy, undertaken to reduce transfusion requirement, was associated in one cohort with significantly higher prevalence of cardiovascular comorbidity (58.6% vs 21.2%, $p < 0.001$) and diabetes (17.2% vs 3.5%, $p = 0.013$) despite lower transfusion needs, and with higher pancreatic siderosis in thalassaemia intermedia. Finally, chelation itself contributes: desferrioxamine is associated with vertebral dysplasia and truncal shortening, which in the contemporary United Kingdom cohort was almost four times more common than absolute short stature.^{16,23,41,62}

Hypogonadism as the Sentinel Endocrinopathy

Hypogonadism is the most frequent, the earliest clinically apparent and the most consistently under-treated endocrine complication of thalassaemia major, reported in 40–56.7% of cohorts spanning four decades and five continents. Its dominance is not accidental. Gonadotroph cells are exquisitely sensitive to iron-mediated oxidative injury, and the hypothalamic–pituitary–gonadal axis has minimal functional reserve, so that a modest reduction in gonadotroph mass or secretory competence translates directly into arrested puberty. The neuroendocrine evidence in this review is

unambiguous: after pulsatile gonadotropin-releasing hormone priming there was no change in oestradiol, testosterone or gonadotropin response, establishing that the defect resides at pituitary rather than hypothalamic level. Superimposed gonadal siderosis emerges at higher iron burdens, evidenced by the failure of five of twelve thalassaemic adolescents to respond to six months of human chorionic gonadotropin, with the non-responders carrying nearly double the ferritin of responders.^{28,43,44}

Three clinical corollaries follow. First, the observation that hypogonadism is "frequently under-treated" is a direct quality-of-care indictment, and it matters because hypogonadism is the principal driver of both pubertal growth failure and adult bone loss in this population; failure to treat it therefore propagates through at least two further outcome domains. Second, hypogonadism persists as the residual endocrinopathy even where all other axes are normalised — in a two-year study of well-chelated adult women all other axes remained within reference ranges while hypogonadism remained clinically prevalent — indicating that gonadotroph injury, once established, is the least reversible of the endocrine lesions. Third, the anti-Müllerian hormone data are important: marked inter-individual variability with no consistent correlation to ferritin or magnetic resonance iron indices suggests that conventional gonadotropin measurement under-detects ovarian reserve impairment, with obvious implications for fertility counselling in a population that increasingly survives to reproductive planning.^{2,34}

The reversibility data provide the counterweight. Intensive combined chelation enabled seven of fourteen hypogonadal males to discontinue testosterone and six of nineteen previously hypogonadal females to conceive, and in the French transplant cohort females achieving normal puberty were significantly younger at transplantation than those with delayed puberty (median 2.5 vs 8.7 years). Both observations point in the same direction: the therapeutic window for gonadal protection is early, and it closes.^{15,33}

Dysglycaemia: A Two-Stage Natural History and the Primacy of Pancreatic Imaging

The glucose metabolism literature in thalassaemia is unusual in the clarity with which it resolves a two-stage pathophysiology. Stage one is insulin resistance, demonstrated by euglycaemic clamp to be absent in prepubertal patients and marked in pubertal patients (155 ± 18 vs 224 ± 15

mg/m²/min, $p < 0.01$), driven by the confluence of pubertal physiological insulin resistance, hepatic iron loading, reduced hepatic insulin extraction and inflammation. Stage two is β -cell failure, indexed by a falling disposition index that correlates most strongly with pancreatic R2* and by a falling C-peptide to insulin ratio that declines with age in patients while rising in controls. The clinical implication is that the window for intervention lies in the first decade and closes during puberty, precisely the period in which chelation adherence typically deteriorates.^{11,29,30}

The most practically significant finding of this entire review may be the diagnostic performance of pancreatic magnetic resonance relaxometry. A normal global pancreatic T2* carried a 100% negative predictive value for disturbances of glucose metabolism in a cohort of 1079 patients, and the same 100% negative predictive value for cardiac iron; no patient with arrhythmia or heart failure had a normal global pancreatic T2*. This was replicated in thalassaemia intermedia and reproduced with a different physical parameter — pancreatic fat fraction below 6.6% likewise carrying 100% negative predictive value. The pancreas is therefore not merely an organ at risk but the most sensitive available sentinel of total-body and cardiac iron loading, detecting siderosis earlier than the myocardium because it loads faster and clears more slowly. A pancreatic T2* threshold of approximately 13 ms in thalassaemia major and 18 ms in intermedia should logically trigger chelation intensification irrespective of the ferritin value.^{10,41,46}

The diagnostic modality question also deserves emphasis. Glycated haemoglobin is unreliable in thalassaemia because transfusion, shortened erythrocyte survival and abnormal haemoglobin composition all distort the assay, and continuous glucose monitoring reclassified 65% of screened paediatric patients as diabetic against 35% by oral glucose tolerance test ($p = 0.012$). Yet other data show that glycated haemoglobin, glycated albumin and fructosamine all rose in parallel with the degree of dysglycaemia in Chinese children, and that neither glycated haemoglobin nor fructosamine discriminated between glucose-tolerance categories in a long-followed Greek cohort. The reasonable synthesis is that the oral glucose tolerance test remains the diagnostic reference standard, that glycated haemoglobin should not be used alone, and that pancreatic relaxometry should be used for risk stratification rather than diagnosis.^{12,45}

The Skeleton as an Endocrine Target Organ

Thalassaemic bone disease is best conceptualised not as a separate complication but as the integrated readout of every other endocrine lesion. Hypogonadism removes the dominant anabolic stimulus to peak bone mass acquisition; growth hormone and insulin-like growth factor-1 deficiency removes a second, evidenced by the significant correlations between insulin-like growth factor-1 and both spinal ($r=0.40$) and femoral ($r=0.39$) bone mineral density; hypoparathyroidism and near-universal vitamin D insufficiency disturb mineralisation; marrow expansion mechanically weakens trabecular architecture; direct iron deposition impairs osteoblast function and hydroxyapatite crystallisation; and desferrioxamine adds a vertebral dysplastic component. The resulting phenotype — Z-score below -2 in 89% at the lumbar spine, elevated bone resorption markers in 84%, and progressive loss of 1.36% per year — is among the most severe forms of secondary osteoporosis described in any chronic disease population.¹³

Two findings modify the traditionally pessimistic view. The ferritin–bone mineral density correlation of $r = -0.791$ in children is the steepest exposure–outcome gradient identified anywhere in this review and identifies bone as perhaps the most iron-sensitive of all target tissues, implying that skeletal outcome is a highly responsive indicator of chelation adequacy. Correspondingly, long-term deferasirox was associated with a significant increase in mean lumbar bone mineral density ($p<0.001$) and a significant reduction in lumbar osteoporosis prevalence ($p=0.022$) that occurred irrespective of bisphosphonate, hormonal replacement, calcium or vitamin D therapy — that is, iron removal alone improved bone. This reframes chelation as an osteoporosis therapy in this population and argues that iron control should precede, not follow, antiresorptive prescribing.^{6,14}

Health-Related Quality of Life: Magnitude, Profile and the Paradox of the Well-Resourced Cohort

The quality-of-life evidence is directionally consistent but not uniform, and the exceptions are as informative as the rule. The dominant pattern — five of eight SF-36 subscales and both component summaries significantly impaired; EQ-VAS, FACT-G and FACIT-Fatigue all significantly below United States norms at $p<0.001$; meta-analytic pooling of 26 studies confirming substantially compromised quality of life — is robust. Yet in Sardinia 207 adults scored at least as well as 211 matched controls in every item, and in Western Greece median physical and mental component

summaries approached 76. These are not measurement artefacts. Both settings are characterised by mature comprehensive-care infrastructure, near-universal access to oral chelation, high community prevalence with correspondingly low stigma, and long-standing patient-organisation support. The correct inference is that the quality-of-life penalty of thalassaemia major is not intrinsic to the genotype but is a function of the care environment — and is therefore, in principle, eliminable.^{17,19,21,22,48}

The domain profile carries its own message. Impairment is physical-predominant, with physical functioning, role-physical, general health and vitality most affected, and this is precisely the profile that would be predicted from chronic anaemia, iron-related organ dysfunction, endocrine deficiency and the time burden of treatment. The relative preservation of emotional domains in several cohorts is a genuine and reproducible finding that speaks to adaptive coping in a lifelong condition diagnosed in infancy. However, oncology-derived instruments detected the largest relative decrement precisely in emotional well-being (–21.9%), with 60.8% reporting anxiety or depression on the EQ-5D-5L. The discrepancy is almost certainly instrumental rather than substantive: SF-36 emotional items ask about role limitation attributable to emotional problems, whereas FACT-G and EQ-5D items probe symptom experience directly. Routine assessment should therefore pair a generic profile instrument with a disease-specific measure such as TranQoL, whose mean total score of 53.9 on a 100-point scale reveals a burden that generic instruments partly conceal.^{18,19,58}

The Endocrine–Quality of Life Link: What the Evidence Does and Does Not Establish

The central question of this review — whether endocrine complications specifically drive impaired quality of life — is answered affirmatively but with important qualifications. The affirmative evidence is that the number of disease-related complications independently predicted the mental component summary after multivariable adjustment in the multinational IntercontinThal analysis, specifically within the transfusion-dependent stratum; that patients with more disease complications reported significantly lower quality of life in the North American longitudinal cohort; that the presence of two or more comorbidities independently predicted poorer quality of life even after curative transplantation ($p<0.001$); and that serum ferritin, the principal upstream determinant of endocrinopathy, was itself independently associated with reduced quality of life. Taken together

these constitute a consistent, replicated, multivariable-adjusted association between complication burden and patient-reported outcome.^{17,24,25}

The qualification is that no included study resolved this association by endocrine axis. Every analysis aggregated clinical complications — cardiac, hepatic, endocrine, skeletal — into a single covariate, explicitly so in the IntercontinThal study, where the authors state that all clinical complications were aggregated for statistical analysis owing to their variety. Consequently the evidence establishes that complication burden impairs quality of life and that endocrinopathy constitutes the largest single component of that burden, but it does not establish the independent quality-of-life weight of, for example, hypogonadism versus diabetes versus osteoporosis. This is the single most important methodological gap in the field, and it is readily addressable: a multicentre cohort applying a validated disease-specific instrument alongside axis-resolved endocrine phenotyping would resolve it. Indirect support for axis-specific effects nonetheless exists — quality of life was significantly better among children attending endocrinology subspecialty clinics, and the physical domains most affected are precisely those that hypogonadism, growth failure and bone disease would be expected to compromise.^{24,36}

Modifiability: Chelation, Transplantation, Gene Therapy and Erythroid Maturation

The reversibility evidence is the most clinically actionable finding of this review. Normalisation of total body iron with combined deferoxamine and deferiprone normalised abnormal glucose metabolism in 44% of affected patients, permitted thyroxine discontinuation in 10 of 18, testosterone discontinuation in 7 of 14 hypogonadal males, and conception in 6 of 19 previously hypogonadal females, with no de novo endocrine or cardiac complications over up to seven years. This is not merely prevention of progression but demonstrable reversal of established endocrine disease, and it fundamentally reframes iron-induced endocrinopathy as a functional lesion of overloaded but surviving cells rather than an irreversible structural loss. Long-term deferasirox produced a concordant though less dramatic picture — new endocrine complications in 7% over a median 6.5 years with no new hypothyroidism or diabetes, and significant improvement in lumbar bone mineral density.^{6,33}

The disease-modifying therapy evidence must be read with precision. Gene editing produced improvements exceeding minimal clinically important difference thresholds across every instrument and every domain in 54 participants followed to 48 months, and gene addition produced a PedsQL improvement 2.2 times the minimal clinically important difference at 24 months. These are large, durable and internally consistent effects, though the sample sizes at late time points are small and the populations are trial-selected. The randomised evidence is more restrained: in BELIEVE, mean quality-of-life scores did not differ between luspatercept and placebo at weeks 24 and 48, and the significant physical-domain benefits emerged only in an exploratory responder analysis restricted to patients achieving at least a 50% reduction in transfusion burden. The honest interpretation, and the one most consistent with the transplantation and gene-therapy data, is that transfusion-burden reduction rather than pharmacological exposure is the mediator of quality-of-life gain — a mechanistic hypothesis that unifies all three interventional literatures and generates a testable prediction.^{31,32,61}

Transplantation adds a temporal dimension often omitted from counselling. Transplanted children remained significantly below healthy peers in physical health and school functioning within four years of transplant but became statistically indistinguishable from healthy controls beyond four years. Quality-of-life recovery after cure is therefore real but delayed, and patients should be counselled that the first post-transplant years may feel worse rather than better despite the haematological cure. Splenectomy is the instructive negative case: it produced no measurable quality-of-life change on any SF-36 scale while significantly increasing cardiovascular comorbidity and diabetes — a procedure that reduces transfusion requirement without improving how patients feel, and whose indication should be correspondingly narrow.^{23,25,26}

Equity: The Resource Gradient in Endocrine and Humanistic Outcome

A reading of this evidence that averages across settings would be misleading. The prevalence of stunted growth was 24% in a United Kingdom tertiary cohort and 50.5% in pooled low-resource data; hypogonadism or delayed puberty reached 45.8% in the latter. In a Pakistani cohort the mean pre-transfusion haemoglobin was 7.3 g/dL — far below the 9–10.5 g/dL target of international standards — 28.7% faced difficulty obtaining blood, 25% had been hepatitis C positive at some point,

22.5% of school-age patients had never attended school and 9.1% had left education for health reasons. These are not marginal differences of degree; they describe a different disease. The determinants are structural: voluntary non-remunerated donor availability, red-cell antigen matching capacity, hepatitis screening, affordability and continuity of oral chelation, and access to endocrine and imaging services.^{16,35,53,57}

Two implications follow. First, prevalence estimates derived from European and North American reference centres — which supply the majority of the evidence in this and every comparable review — systematically understate the global burden, and should not be used to plan services in high-burden, low-resource settings. Second, the demonstration that optimised care abolishes much of both the endocrine and the humanistic penalty converts the resource gradient from an unfortunate contextual observation into an equity failure with a defined remedy. The proposed low-resource screening frameworks, which prioritise clinical assessment first with targeted laboratory testing where resources are constrained, represent a rational response to this reality and merit implementation research.⁵³

Comparison with Previous Reviews

Three prior syntheses bear directly on this work and each is confirmed and extended here. The SF-36 meta-analysis of 26 studies reported pooled physical-domain means of 52.74 to 74.5 and mental-domain means of 59.6 to 71.11, concluding that thalassaemia major substantially compromises quality of life; the present review confirms that conclusion, adds the instrument-dependence of the emotional-domain finding, and identifies the well-resourced cohorts in which the penalty disappears. The systematic literature review of serum ferritin and outcomes found that the bulk of the evidence concerned endocrine dysfunction and reported a fourteen-fold increase in diabetes risk with persistently elevated ferritin, but identified no studies reporting patient-reported outcomes or economic burden; the present review supplies exactly that missing evidence stream. The systematic review of quality of life after transplantation and gene therapy in 16 studies reported a median Cohen d of 0.37 with large positive effects in physical and emotional domains in thalassaemia; the present review confirms this and adds the four-year temporal threshold for recovery and the randomised luspatercept evidence that post-dates it.^{48,49,50}

Strengths of This Review

- Comprehensive integration of the complete endocrine spectrum and the complete health-related quality-of-life instrument spectrum within a single sixteen-outcome analytical structure — an approach not previously applied in this field.
- Strict a priori design filter confining the characteristics table to randomised and primary observational evidence, eliminating the participant double-counting that affects reviews incorporating higher-order syntheses into their primary data tables.
- Verification of every included record through a persistent academic index identifier, with the full link reproduced in the reference list, permitting independent replication of the evidence retrieval.
- Explicit era stratification, contrasting deferoxamine-era cohorts with contemporary cohorts managed under oral chelation and magnetic resonance-guided iron control, which exposes the extent to which the classical endocrine phenotype is treatment-dependent.
- Explicit equity stratification contrasting high-resource and resource-constrained cohorts rather than averaging across them.
- Design-appropriate risk-of-bias appraisal with three instruments and formal GRADE certainty rating for every outcome.

Implications for Clinical Practice

Table 28. Evidence-derived clinical implications and their supporting outcomes

Clinical implication	Supporting outcome(s)	Strength of underpinning evidence
Endocrine surveillance should be systematic, multi-axis and age-stratified rather than symptom-triggered, beginning before the age of 10 years in transfusion-dependent disease.	O1, O2, O3, O5, O6	Moderate certainty; consensus-endorsed
Pancreatic T2* or pancreatic fat fraction should be incorporated into routine	O4, O10	Moderate certainty; large multicentre replication

magnetic resonance iron assessment; a normal value carries 100% negative predictive value for both dysglycaemia and cardiac iron.		
Serum ferritin should be interpreted as a screening trend rather than a tissue-iron measure, and should not be used alone to guide chelation adequacy; a target below 500 ng/mL is achievable and safe.	O9	Moderate certainty
Oral glucose tolerance testing remains the diagnostic reference standard for dysglycaemia; glycated haemoglobin alone is unreliable in this population.	O4	Low to moderate certainty
Hypogonadism should be actively sought and actively treated; documented under-treatment propagates into growth failure and bone loss.	O3, O2, O7	Moderate certainty
Chelation intensification should be regarded as first-line therapy for thalassaemic bone disease, preceding antiresorptive prescribing.	O7, O11	Low to moderate certainty
Established endocrine disease should not be assumed irreversible; intensified chelation warrants a trial before permanent hormone replacement is accepted as lifelong.	O11, O3, O4, O5	Low certainty but large effect
Splenectomy should be indicated narrowly: it does not improve quality of life and is associated with significantly increased cardiovascular and diabetic comorbidity.	O4, O14, O15	Low certainty

Validated patient-reported outcome measures should be administered routinely, pairing a generic profile instrument with a disease-specific measure.	O12, O13	Moderate certainty
Patients considering transplantation should be counselled that quality-of-life recovery is delayed, becoming equivalent to healthy peers beyond four years.	O15	Low to moderate certainty
Adherence support, regular follow-up and multidisciplinary subspecialty access are modifiable determinants of both endocrine and humanistic outcome.	O11, O14	Low certainty; consistent direction

Future Research Agenda

- A multicentre prospective cohort applying axis-resolved endocrine phenotyping alongside validated disease-specific patient-reported outcome measures, to determine the independent quality-of-life weight of each individual endocrinopathy — the principal unresolved question in this field.
- Prospective validation of pancreatic T2* and pancreatic fat-fraction thresholds as chelation-intensification triggers, with incident dysglycaemia as the primary endpoint, in the pre-clinical window identified by the one-third of patients with elevated pancreatic R2* and normal glucose tolerance.
- Randomised comparison of chelation intensification versus standard chelation for established endocrine dysfunction, with reversal of hormone-replacement dependence as the primary endpoint, to place the reversibility observations on a controlled footing.
- Longitudinal quality-of-life follow-up of gene-therapy and gene-editing recipients beyond five years, powered to detect durability and to test the hypothesis that transfusion-burden reduction is the causal mediator of quality-of-life gain.

- Prospective endocrine and quality-of-life cohorts in high-burden, low-resource settings using harmonised definitions, to generate estimates applicable to the majority of the world's thalassaemia population.
- Evaluation of anti-Müllerian hormone and other ovarian-reserve markers as early indicators of gonadal siderosis in females, given their demonstrated dissociation from conventional gonadotropin measures and from iron indices.
- Implementation research on the low-resource endocrine screening frameworks, assessing feasibility, diagnostic yield and effect on clinical and humanistic outcomes.

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

This systematic review of 51 primary studies, comprising randomised, cohort, case–control and cross-sectional evidence from more than 11 000 patients across at least 21 countries, demonstrates a strong, statistically significant and clinically consequential association between thalassaemia major, endocrine complications and health-related quality of life. All six a priori hypotheses were supported by the evidence, and the null hypothesis is rejected.

First, endocrine complications are significantly more prevalent in thalassaemia major than in comparator populations without the same combination of ineffective erythropoiesis and transfusional iron loading, with an adjusted odds ratio of 9.4 for any endocrinopathy and a more than four-fold excess of multiple concurrent endocrinopathy. Hypogonadism is the sentinel and most frequent lesion, followed by metabolic bone disease, disorders of glucose metabolism, growth failure, thyroid dysfunction and parathyroid dysfunction.³

Second, the burden is quantitatively determined by iron exposure. Serum ferritin, transfusion duration and transfusion volume all demonstrate reproducible dose–response relationships with endocrine outcome, and organ-specific magnetic resonance relaxometry outperforms ferritin in every direct comparison — a normal pancreatic T2* carrying a 100% negative predictive value for both glucose dysregulation and cardiac iron.^{10,47}

Third, health-related quality of life is significantly impaired relative to general-population norms across generic, oncology-derived, paediatric and disease-specific instruments, with a physical-

predominant domain profile, and the number of disease-related complications is an independent determinant of that impairment after multivariable adjustment. The socio-economic corollaries — work productivity loss, educational disruption, out-of-pocket expenditure and a five-fold excess of ten-year mortality — extend the burden well beyond the clinic.^{7,17,19,24}

Fourth, and decisively for practice, this chain is modifiable at every link. Intensified chelation reverses established dysglycaemia, hypothyroidism and hypogonadism in a substantial minority of patients and significantly improves bone mineral density; contemporary optimally managed cohorts display an attenuated endocrine phenotype in which short stature is largely familial and endocrinopathy uncommon; and curative or disease-modifying therapy produces quality-of-life improvements exceeding minimal clinically important difference thresholds. The dominant determinant of outcome in thalassaemia major is therefore not the genotype but the adequacy, timeliness and continuity of iron control and comprehensive care.^{6,16,31,33}

The principal residual uncertainty is that no study has yet resolved the quality-of-life association by individual endocrine axis, so that the specific humanistic weight of hypogonadism relative to diabetes, osteoporosis or thyroid failure remains undetermined. Addressing this gap is the highest-priority research task arising from this review.

Recommendations

Recommendations for clinicians

- Institute structured, age-stratified, multi-axis endocrine surveillance from before the age of 10 years in transfusion-dependent thalassaemia, encompassing auxology with sitting height and leg length, pubertal staging, oral glucose tolerance testing, thyroid and parathyroid function, calcium and phosphate metabolism, 25-hydroxyvitamin D and dual-energy X-ray absorptiometry.
- Interpret serum ferritin as a trend indicator rather than a tissue-iron measure; obtain organ-specific magnetic resonance relaxometry including pancreatic T2* or pancreatic fat fraction wherever available, and treat an abnormal pancreatic value as a chelation-intensification trigger irrespective of ferritin.

- Use the oral glucose tolerance test as the diagnostic reference standard for dysglycaemia; do not rely on glycated haemoglobin alone in this population.
- Actively identify and actively treat hypogonadism, recognising it as the most frequent, the most under-treated and the most consequential of the endocrine lesions, and recognising that a normal provocative growth hormone test does not exclude clinically significant growth hormone dysfunction.
- Regard chelation optimisation as first-line therapy for thalassaemic bone disease and offer a documented trial of chelation intensification before accepting hormone replacement as lifelong.
- Administer validated patient-reported outcome measures at least annually, pairing a generic profile instrument with a disease-specific measure, and act on the results as on any other abnormal investigation.
- Counsel patients considering transplantation that haematological cure precedes quality-of-life recovery, which typically becomes equivalent to healthy peers beyond four years.

Recommendations for health services

- Establish formal joint haematology–endocrinology clinics as a standard component of comprehensive thalassaemia care, given the significantly better quality of life recorded among patients with subspecialty access.
- Ensure access to magnetic resonance iron quantification with validated pancreatic, hepatic and cardiac sequences, and to dual-energy X-ray absorptiometry with paediatric reference data.
- Guarantee continuity and affordability of oral chelation, and provide structured adherence support, recognising adherence as a modifiable determinant of both endocrine and humanistic outcome.
- Provide transition services for adolescents, since the pubertal period is simultaneously the point of maximal metabolic vulnerability and of typical deterioration in adherence.
- Integrate psychosocial, educational and vocational support into routine care, addressing the documented losses in schooling, employment and productivity.

Recommendations for researchers

- Prioritise a multicentre prospective study resolving the quality-of-life association by individual endocrine axis, using harmonised endocrine definitions and validated disease-specific instruments.
- Report endocrine outcomes using standardised definitions and report iron exposure using organ-specific relaxometry rather than ferritin alone, to permit future meta-analysis.
- Conduct controlled evaluation of chelation intensification for established endocrinopathy with reversal of hormone-replacement dependence as the primary endpoint.
- Extend patient-reported outcome follow-up after gene therapy and gene editing beyond five years and test transfusion-burden reduction as the causal mediator of quality-of-life gain.
- Generate prospective endocrine and quality-of-life data from high-burden, low-resource settings using the same harmonised definitions, so that the global evidence base ceases to be dominated by specialist Western centres.

Recommendations for policymakers

- Recognise endocrine complications and impaired quality of life as core, measurable outcomes of national thalassaemia programmes, not as secondary considerations.
- Invest in safe, adequate and antigen-matched blood supply, since inadequate pre-transfusion haemoglobin is the upstream driver of marrow expansion, increased iron absorption and the resulting endocrine and skeletal morbidity.
- Fund equitable access to oral chelation and to magnetic resonance iron quantification, on the evidence that these interventions demonstrably attenuate the endocrine phenotype.
- Support implementation of validated low-resource endocrine screening frameworks, with monitoring of diagnostic yield and of clinical and humanistic outcomes.
- Incorporate the documented healthcare resource utilisation gradient, work productivity loss and out-of-pocket expenditure into health-technology assessment of disease-modifying and curative therapies.

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