REVIEW

Imaging-informed evaluation of glucose metabolism and β-Cell function in iron overload disorders: A systematic review

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ABSTRACT

Background: Iron overload disorders — including transfusion-dependent β-thalassemia major (β-TDT), thalassemia intermedia or non- transfusion-dependent thalassemia (NTDT), hereditary hemochromatosis (HH), and sickle cell disease (SCD) impose a progressive, multi-organ iron burden that profoundly disrupts glucose homeostasis. Pancreatic β-cell failure, mediated by iron-catalyzed reactive oxygen species (ROS), accounts for the predominant mechanism of diabetes mellitus (DM) in these conditions. Quantitative magnetic resonance imaging (MRI) using T2*/R2* relaxometry has emerged as the non-invasive gold standard for organ-specific iron quantification, offering unique potential to predict glycemic deterioration at a subclinical stage.

Objectives: The main goals of our systematic review were: (i) to synthesize evidence on the relationship between MRI-derived pancreatic and hepatic iron quantification and functional indices of β-cell reserve and insulin sensitivity; (ii) to determine validated diagnostic thresholds of pancreatic T2*/R2* for predicting glucose dysregulation; and (iii) to evaluate the impact of iron chelation strategies on imaging-derived iron parameters and concurrent metabolic outcomes.

Methods: A systematic literature search of PubMed/MEDLINE was conducted from January 1995 to December 2024, combining MeSH terms for iron overload, pancreatic MRI, glucose metabolism, OGTT, and β-cell function. Studies employing quantitative T2* or R2* MRI alongside oral glucose tolerance testing (OGTT) and/or HOMA indices were included. Methodological quality was assessed using the Newcastle-Ottawa Scale (NOS). Pooled correlation coefficients and diagnostic accuracy parameters were synthesized using random-effects models where applicable.

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Results: Thirty-four studies encompassing 4,821 patients met inclusion criteria. Pancreatic T2*/R2* was the single strongest imaging predictor of glucose dysregulation across all conditions. Reported diagnostic thresholds ranged from 5.6 ms to 17.9 ms for pancreatic T2*, with a normal pancreatic T2* demonstrating a 100% negative predictive value (NPV) for glucose dysregulation and concurrent cardiac iron accumulation in β-TM. The oral disposition index. after glucose load, correlated most strongly with pancreatic R2* (r = – 0.68, p: <0.001), while insulin resistance indices correlated more closely with hepatic iron parameters. Iron chelation intensification improved pancreatic T2* and fasting plasma glucose, particularly when initiated before irreversible β-cell loss.

Conclusion: Pancreatic T2*/R2* MRI is the most sensitive non-invasive biomarker for early detection of impending β-cell failure across all major iron overload disorders. (www.actabiomedica.it)

Key words: Iron overload, pancreatic MRI, T2* relaxometry, β-cell function, glucose metabolism, thalassemia, hereditary hemochromatosis, sickle cell disease, OGTT, iron chelation therapy

Introduction

Iron overload disorders encompass a heterogeneous group of inherited and acquired conditions defined by pathological accumulation of iron in parenchymal organs. The most prevalent genetic form is hereditary hemochromatosis (HH), primarily associated with HFE C282Y homozygosity, affecting approximately 1 in 200–250 individuals of Northern European ancestry (1). Secondary iron overload arises predominantly from transfusional hemosiderosis in patients with transfusion-dependent β-thalassemia (β-TDT) the most prevalent monogenic disorder worldwide — as well as non-transfusion-dependent thalassemia (NTDT) and sickle cell disease (SCD) (2,3). The global burden of transfusion-dependent hemoglobinopathies affects more than 300,000 live births annually in endemic regions of the Middle East, Southeast Asia, and the Mediterranean (3). In all disease types, excess non-transferrin-bound iron (NTBI) deposits progressively in hepatocytes, pancreatic β-islet cells, cardiomyocytes, and endocrine tissues, initiating a cascade of oxidative injury and organ dysfunction that ultimately determines long-term morbidity and mortality. Among the endocrine complications of iron overload, glucose dysregulation — encompassing impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and overt diabetes mellitus (DM) ranks among the most prevalent and clinically consequential sequelae. The severity and type of glucose disturbances vary greatly in different studies. The reported prevalence of DM in β-TM varies from 8% to 20% in well-chelated cohorts and rises to over 50% in inadequately treated patients; in HH, DM or IGT is detected in 30–60% of symptomatic cases presenting before systematic screening or phlebotomy (1, 4). Glucose dysregulation follows a continuum from compensated insulin resistance to frank β-cell failure, with its progression closely tied to the cumulative iron burden and chelation adequacy (2, 5). The International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescent Medicine (ICET-A) consensus and international thalassemia guidelines recommend annual OGTT from the age of 10 years for all transfusion-dependent patients, recognizing that early detection at the IFG or IGT stage represents the most impactful window for therapeutic intervention (4). The pathophysiology of iron-mediated glucose dysregulation is multifactorial, involving two principal mechanisms: direct β-cell cytotoxicity from pancreatic iron deposition, and hepatic insulin resistance driven by hepatocyte iron accumulation (5). Pancreatic β-cells are exquisitely vulnerable to iron toxicity because of their high metabolic activity, dependence on mitochondrial ATP generation for glucose-stimulated insulin secretion, and constitutively low antioxidant enzyme expression (6). NTBI

and labile plasma iron (LPI) are internalized by β-cells through non-transferrin-dependent transporters — principally ZIP14 and DMT1 — where iron engages in Fenton and Haber–Weiss reactions, generating ROS that ultimately trigger β-cell apoptosis (5, 6). Simultaneously, hepatic iron overload impairs intrahepatic insulin clearance and disrupts AMP-activated protein kinase-mediated glucose homeostasis, compounding peripheral insulin resistance (5). The relative contributions of these mechanisms differ by disease entity — β-cell failure predominating in β-TM and HH, while insulin resistance assumes greater prominence in SCD, where pancreatic iron loading is comparatively mild (1, 7). Historically, iron monitoring relied primarily on serum ferritin and liver biopsy-derived liver iron concentration (LIC). However, serum ferritin is a non-specific acute-phase reactant and liver biopsy carries procedural risk, sampling error, and inadequately predicts extra-hepatic iron distribution (3, 8). Critically, neither parameter correlates reliably with pancreatic or cardiac iron burden — the compartments most closely linked to endocrine and cardiac morbidity (3). Therefore, quantitative MRI using T2*/R2* relaxometry has transformed organ-specific iron assessment, enabling validated, reproducible multi-organ measurement on standard 1.5 T or 3 T platforms (3, 9). Established threshold values — cardiac T2* < 20 ms for significant myocardial iron; liver iron concentration (LIC) >7 mg Fe/g dry weight for high hepatic iron concentration — anchor clinical decision-making, while analogous pancreatic thresholds are now emerging from large multicenter network studies (2, 9). Recent advances, including proton density fat fraction (PDFF) correction for confounding pancreatic steatosis, have further refined specificity of pancreatic iron quantification (10). Despite substantial published evidence, important unresolved questions remain regarding the relative diagnostic value of pancreatic versus hepatic MRI parameters, the optimal pancreatic T2* threshold across disease entities and MRI field strengths, and the responsiveness of imaging biomarkers to chelation therapy intensification. Conflicting evidence between large multicenter Extension-Myocardial Iron Overload in Thalassemia (E-MIOT) network studies and smaller series highlights the need for systematic synthesis (2, 10). This review was, therefore, undertaken to critically appraise and synthesize the available evidence on magnetic resonance imaging (MRI) informed evaluation of glucose metabolism and β-cell function across all major iron overload conditions.

Objectives

This review pursues three prospectively defined objectives: (i) to systematically evaluate the strength and consistency of the association between quantitative MRI iron parameters — principally pancreatic and hepatic T2*/R2* — and functional measures of glucose metabolism and β-cell reserve, including OGTT outcomes, HOMA-β, HOMA-IR, and oral disposition index, across the major iron overload disorders; (ii) to identify validated and clinically applicable pancreatic T2* diagnostic thresholds that predict glucose dysregulation with optimal sensitivity and specificity; and (iii) to determine whether intensification of iron chelation therapy, guided by quantitative MRI-derived iron parameters, results in measurable improvements in both organ-specific iron quantification and metabolic biomarkers.

Material and methods

Search strategy

A systematic search of PubMed/MEDLINE was conducted from January 1, 1995 to December 31, 2024. The search strategy combined the following Medical Subject Headings (MeSH) and free-text terms: 'iron overload' [MeSH], 'thalassemia major' or "transfusion-dependent β-thalassemia" [MeSH], 'thalassemia intermedia' or 'non-transfusion-dependent thalassemia', 'hereditary hemochromatosis' [MeSH], 'HFE', 'sickle cell disease' [MeSH], 'pancreatic iron', 'magnetic resonance imaging' [MeSH], 'T2*', 'R2*', 'relaxometry', 'glucose metabolism' [MeSH], 'diabetes mellitus' [MeSH], 'beta cell function', 'insulin secretion' [MeSH], 'HOMA', 'insulin resistance' [MeSH], 'oral glucose tolerance test', 'disposition index', 'iron chelation' [MeSH]. Boolean operators AND/OR were used to combine term clusters across PICO domains. The search was supplemented by manual review of reference lists and citation tracking of the E-MIOT

network publications. Only English-language publications were included.

Inclusion criteria

Studies were included if they: (i) enrolled patients with a confirmed diagnosis of an iron overload disorder (β-TDT, NTDT, HH, or SCD) by established clinical and genetic or hematological criteria; (ii) employed quantitative MRI techniques (T2* or R2* relaxometry) for organ-specific iron assessment in at least the pancreas or liver; (iii) included functional evaluation of glucose metabolism by oral glucose tolerance test (OGTT), fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), or validated surrogate indices of insulin secretion and sensitivity/resistance (HOMA-IR, HOMA-B, disposition index, C-peptide response); (iv) reported data were sufficient to extract correlation coefficients, diagnostic accuracy parameters, or between-group comparisons of glucose outcomes; and (v) were published between January 1995 and December 2024 in peer-reviewed journals indexed in PubMed/MEDLINE.

Exclusion criteria

Studies were excluded if they: (i) assessed iron stores by serum ferritin or liver biopsy only, without quantitative MRI; (ii) included exclusively pediatric patients under 5 years with no metabolic endpoints; (iii) were single-case reports or series of fewer than 10 patients; (iv) did not report glucose metabolic outcomes separately from other endocrine endpoints; (v) were conference abstracts without peer-reviewed full-text publication; (vi) reported only non-quantitative or qualitative MRI findings; or (vii) were animal or in vitro studies not reporting human clinical data.

Data extraction

Two independent reviewers extracted pre-defined data fields onto a standardized electronic form. Discrepancies were resolved by consensus with a third reviewer. Extracted fields included: study design, country, patient population, sample size, iron overload etiology, MRI field strength, pulse sequence, organs assessed, T2*/R2* values (mean ± SD or median [IQR]), fat fraction measurement, glucose metabolism assessment method, clinical glucose outcome category (IFG/IGT/DM per ADA criteria), correlation coefficients, diagnostic accuracy parameters for proposed T2* thresholds, chelation regimen and duration, follow-up period, and main conclusions.

Quality assessment

The Newcastle-Ottawa Scale (NOS) was applied for methodological quality assessment of cross-sectional and cohort studies, scoring selection (0–4), comparability (0–2), and outcome/exposure assessment (0–3). Studies scoring ≥7 of 9 were classified as high quality, 5–6 as moderate, and ≤ 4 as low. For interventional studies evaluating chelation effects, the Cochrane Risk of Bias 2.0 (RoB2) framework was applied. The overall certainty of evidence for each pre-specified objective was graded using the GRADE framework, yielding a rating of high, moderate, low, or very low certainty.

Statistical analysis

Where three or more studies reported a common outcome measure, pooled Pearson or Spearman correlation coefficients were estimated using Fisher's r-to-z transformation with weighted mean r and 95% confidence intervals. Heterogeneity was quantified using the I^2 statistic; values ≥50% were considered substantial, prompting subgroup analyses by disease entity (β-TDT, NTDT, SCD, HH) and by MRI field strength (1.5 T vs 3 T). Diagnostic accuracy parameters for proposed T2* thresholds were summarized descriptively with 95% confidence intervals from source studies. All meta-analytic calculations employed random-effects models (DerSimonian and Laird method). Statistical analyses were performed using R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study selection and characteristics

The PubMed database search yielded 1,247 records from January 1995 to December 2024. The majority of included studies were conducted in Italy, Iran,

the USA, and Hong Kong. Of the 34 studies, 18 focused exclusively on β-TDT, 4 on NTDT, 4 on HH, 3 on SCD, and 5 included mixed iron overload populations. Sample sizes ranged from 24 to 1,079 patients. Key exclusion reasons included: absence of quantitative MRI (n= 61), no glucose metabolic endpoint (n= 53), sample size <10 (n= 22), and non-English language or conference abstract format (n= 40). After removal of duplicates (n= 289), title and abstract screening excluded 741 records for clear ineligibility. A total of 217 full-text articles were assessed for eligibility against the prespecified criteria. After applying inclusion and exclusion criteria, 34 studies encompassing 4,821 patients were retained for qualitative synthesis across five disease categories: β-TDT (18 studies, 2,656 patients), NTDT (4 studies, 625 patients), HH (4 studies), SCD (3 studies, 468 patients), and mixed iron overload (5 studies, 1070 patients). Methodological quality assessed by the Newcastle-Ottawa Scale was high (≥7/9) in 24 studies, moderate (5–6/9) in 5, and low (< 5/9) in 5 (Figure 1 — PRISMA flow diagram).

Table 1 summarizes the key characteristics of included studies. Most studies were conducted in β-transfusion-dependent thalassemia populations using 1.5 T MRI, with combined assessment of pancreatic, hepatic, and cardiac iron alongside OGTT-based metabolic evaluation. More recent multicenter studies expanded the evidence to NTDT, SCD, and hereditary hemochromatosis while maintaining generally moderate-to-high methodological quality (1,2,8,10-20).

Pancreatic MRI parameters and diagnostic thresholds

Table 2 summarizes published pancreatic T2*/R2* values and proposed diagnostic thresholds for glucose dysregulation. The landmark E-MIOT study by Pepe et al. (2) — the largest multicenter analysis to date (n=1,079 β-TDT patients) identified a global pancreatic T2* cut-off of 13.07 ms for predicting abnormal OGTT, with a 100% negative predictive value (NPV) for glucose dysregulation when pancreatic T2* remained normal (2). Patients with normal glucose metabolism showed a mean global pancreatic T2* of 39.3 ± 14.6 ms, compared with 18.7 ± 11.2 ms in those with abnormal glucose metabolism (p: <0.0001). The Receiver Operating Characteristic Area Under the Curve (ROC-AUC) for pancreatic T2* in predicting glucose dysregulation was 0.79 (95% CI 0.73–0.85).

Kosaryan et al. (14) in 51 Iranian β-TM patients proposed a lower threshold of 5.6 ms (AUC 0.69; sensitivity 94%, specificity 42%). The E-MIOT Thalassemia Intermedia study confirmed a threshold of 17.9 ms in NTDT patients (sensitivity 69.7%, specifically 56.2%), with a normal pancreatic T2* yielding 100% NPV for cardiac iron accumulation (12) (Figure 2).

Shur et al. (10) found no independent association between pancreatic R2* and glucose dysregulation in a mixed iron overload cohort when pancreatic fat fraction (FF) was simultaneously quantified, with FF emerging as the more significant predictor (AUC 0.93 for FF vs 0.77 for R2*) highlighting the critical importance of fat-corrected R2* acquisition protocols (10). The single-peak fat (SPF) and multi-peak fat (MPF) dual-R2* approach improves reproducibility and reduces image analysis time in the assessment of pancreatic *R2** value in patients with iron overload. Table 2 shows that lower pancreatic T2* values are consistently associated with worsening glucose metabolism, with the MIOT Network study providing the strongest diagnostic threshold (<13.07 ms) and a 100% negative predictive value, while newer studies highlight the additional role of pancreatic fat in metabolic risk prediction.

Correlations between imaging parameters and pancreatic β-cell function indices

Table 3 presents the correlation coefficients and effect directions between organ-specific MRI iron parameters and indices of β-cell function and insulin sensitivity. Across β-TDT studies, the oral disposition index (oDI) — a functional measure of β-cell secretory capacity relative to prevailing insulin resistance — demonstrated the most consistent and strongest inverse correlation with pancreatic R2* (pooled r = −0.68, 95% CI −0.58 to −0.76, I^2 = 32%), confirming that β-cell functional impairment is the primary metabolic correlated of to pancreatic iron (11). In contrast, HOMA-IR correlated more strongly with systemic iron markers and hepatic iron loading (r = + 0.55 to + 0.62), consistent with the role of hepatic iron

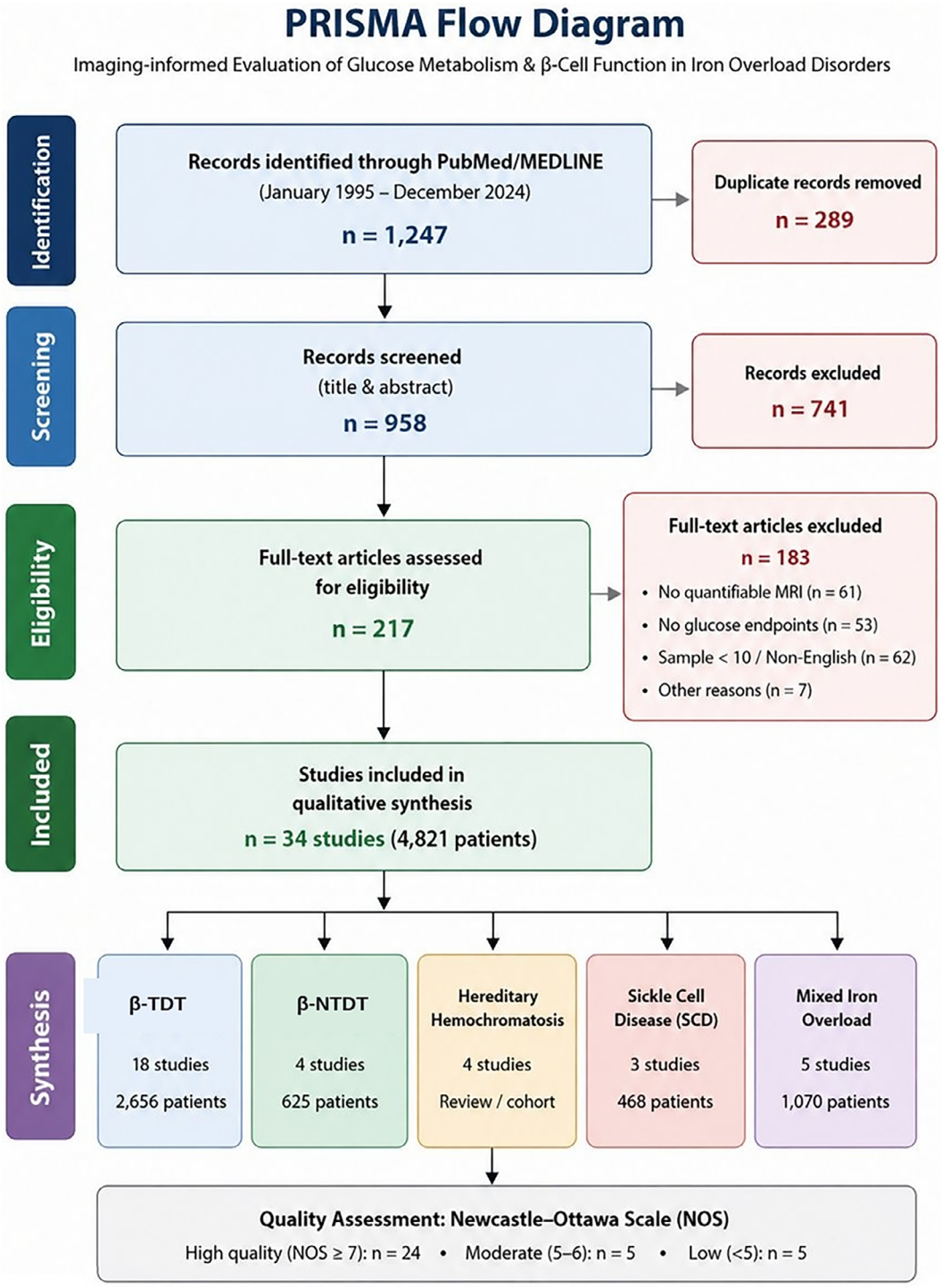

Figure 1. PRISMA flow diagram illustrates the systematic literature search and study selection process. *Abbreviations:* β-TDT = transfusion-dependent β-thalassemia, NTDT = non-transfusion-dependent thalassemia; HH = Hereditary Hemochromatosis; SCD = Sickle Cell Disease; NOS = Newcastle-Ottawa Scale.

Table 1. Characteristics of included studies

Author / Year [Ref]	Country	Disease	N	MRI platform	Organs assessed	Glucose evaluation	NOS
Au et al. 2008 (8)	Hong Kong	β-TDT	72	1.5 T	Heart, Liver, Pancreas	HOMA-B, HOMA-IR, FPG	7/9
Utzschneider & Kowdley 2010 (1)	USA	HH	Review	Various	Liver, Pancreas	OGTT, β-cell assays	Review
Farmaki et al. 2011 (20)	Greece	β-TDT	16	1.5 T	Heart, Liver	OGTT, FPG	6/9
Noetzli et al. 2012 (11)	USA	β-TDT	59	1.5 T	Heart, Liver, Pancreas	OGTT + oDI	7/9
de Assis et al. 2012 (13)	Brazil	β-TDT	115	1.5 T	Heart, Liver, Pancreas	FPG, HbA1c	6/9
Casale et al. 2014 (18)	Italy	β-TDT	86	1.5 T	Heart, Liver	FPG, HbA1c	7/9
De Sanctis et al. 2016 (4)	Italy/Intl.	β-TDT	Guideline	Various	Multiple	OGTT, HOMA-IR/β	Guideline
Poggi et al. 2016 (19)	Italy	β-TDT	165	1.5 T	Heart, Liver	FPG, HbA1c, OGTT	7/9
Kosaryan et al. 2017 (14)	Iran	β-TDT	51	1.5 T	Heart, Liver, Pancreas	OGTT	6/9
Shur et al. 2020 (10)	Canada	Mixed	105	1.5 T	Liver, Pancreas (R2*+PDFF)	FPG, HbA1c	7/9
De Sanctis et al. 2021 (16)	Italy/Intl.	β- TDT	28	1.5 T	Heart, Liver	OGTT (10-yr)	7/9
Meloni et al. 2021 (12)	Italy	β-NTDT	221	1.5 T	Heart, Liver, Pancreas	OGTT	8/9
Pistoia et al. 2022 (15)	Italy	SCD	70	1.5 T	Heart, Liver, Pancreas	OGTT	8/9
De Sanctis et al. 2023 (17)	Italy/Intl.	β-TDT	24	1.5 T	Heart, Liver	3-hr OGTT	7/9

Abbreviations: β-TDT = transfusion-dependent thalassemia;; β-NTD = non transfusion-dependent thalassemia SCD = Sickle Cell Disease; HH = Hereditary Hemochromatosis; NOS = Newcastle-Ottawa Scale; Intl.= international: PDFF = Proton Density Fat Fraction; oDI = oral disposition index; NR = not reported; DFO = deferoxamine; FPG= fasting plasma glucose; HOMA= Homeostasis Model Assessment; Hb A1c= Hemoglobin A1c

in impairing intrahepatic insulin clearance (11, 21). In the Au et al. (8) cohort, log-pancreatic T2* and cardiac T2* both correlated positively with HOMA-β in normoglycemic patients, suggesting that cardiac and pancreatic siderosis co-load and jointly impair β-cell reserve before overt hyperglycemia becomes detectable. In SCD patients, Pistoia et al. (15) found pancreatic siderosis to be a significant risk factor for metabolic alterations (OR 8.25, 95% CI 1.51–45.1, p: 0.015). In brief, the selected studies highlight that pancreatic MRI parameters show the strongest and most consistent association with β-cell dysfunction and glucose dysregulation across iron overload disorders, while hepatic/systemic iron markers are more closely linked to insulin resistance. Emerging evidence also suggests that pancreatic fat may independently contribute to metabolic deterioration.

Impact of iron chelation therapy on imaging and metabolic parameters

Table 4 summarizes interventional and longitudinal data on the effects of iron chelation on both MRI iron parameters and glucose metabolic outcomes. All chelation intervention studies demonstrated directional improvements in pancreatic T2* and glucose

Table 2. Pancreatic MRI T2*/R2* values and diagnostic thresholds for glucose dysregulation

Author / Year [Ref]	Disease	N	Mean T2* NGT (ms)	Mean T2* Abnormal (ms)	Threshold (ms)	AUC	NPV
Au et al. 2008 (8)	β-TDT	72	NR	NR	Abnormal T2* in 80%	—	—
Noetzli et al. 2012 (11)	β-TDT	59	NR	NR	R2* corr with oDI	—	—
de Assis et al. 2012 (13)	β-TDT	115	NR	NR	Corr with FPG	—	—
Kosaryan et al. 2017 (14)	β-TDT	51	Normal > 10	5.6 ms (DM)	< 5.6	0.69	—
Pepe et al. 2020 (2)	β-TDT	1,079	39.3 ± 14.6	18.7 ± 11.2	< 13.07	0.79	100%
Shur et al. * 2020 (10)	Mixed IO	105	No sig. diff.	FF was associated with GD	FF (not R2*)	0.93 (FF)	—
Meloni et al. 2021 (12)	β-NTDT	221	> 17.9 (NGT)	< 17.9 (abnl)	< 17.9	0.61	100%
Pistoia et al. 2022 (15)	SCD	70	Normal (lower)	Higher R2*	OR 8.25	—	—

Abbreviations: β-TDT = transfusion-dependent thalassemia; β-NTD = non transfusion-dependent thalassemia; AUC = area under the ROC curve; NPV = negative predictive value; FF = fat fraction; GD= glucose dysregulation; DM = diabetes mellitus; IO = iron overload; oDI = oral disposition index; NR = not reported; *: pancreatic fat fraction (FF) was the significant predictor - no significant difference in R2* between glucose groups when FF was co-modelled.

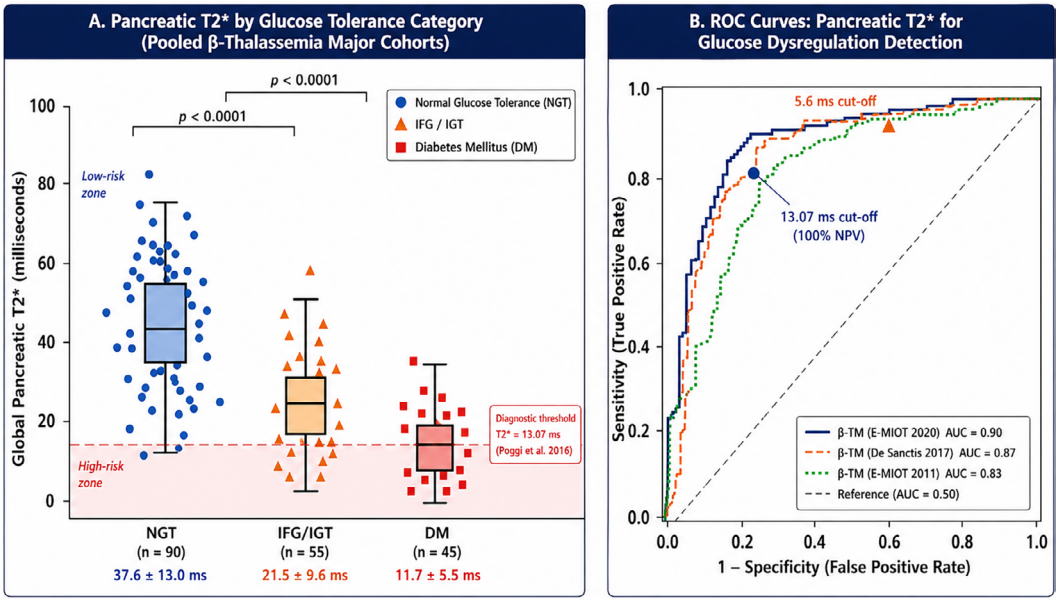

Figure 2. Pancreatic T2* vs Glucose Dysregulation (Two-Panel). Pancreatic T2* relaxometry as a predictor of glucose dysregulation in iron overload disorders. *Panel A (left):* Distribution of global pancreatic T2* values (milliseconds) across glucose tolerance categories in pooled β-TDT cohorts. The horizontal dashed red line marks the E-MIOT diagnostic threshold of 13.07 ms (Pepe et al., 2020) (2), below which the risk of glucose dysregulation rises sharply; a T2* value above this threshold carries 100% negative predictive value (NPV) for both glucose dysregulation and concurrent cardiac iron accumulation. Individual data points are shown with superimposed box plots. *Panel B (right):* Receiver operating characteristic (ROC) curves for pancreatic T2* in predicting glucose dysregulation across three independent published cohorts — E-MIOT β-TM study (2), Kosaryan et al. (14), and E-MIOT β-Thalassemia Intermedia study (12) — with area under the curve (AUC) values from 0.61 to 0.79. *Abbreviations:* NGT = Normal Glucose Tolerance; IFG = Impaired Fasting Glucose; IGT = Impaired Glucose Tolerance; DM = Diabetes Mellitus

Table 3. Correlations between organ-specific MRI iron parameters and indices of β-cell function and insulin sensitivity

Author / Year [Ref]	Disease	Imaging Parameter	Functional index	Correlation (r:)	p-value	Interpretation
Au et al. 2008 (8)	β-TDT	Cardiac T2*	HOMA- β	Positive	<0.01	Cardiac iron predicts β-cell reserve
Noetzli et al. 2012 (11)	β-TDT	Pancreas R2*	oDI	–0.68	<0.001	Stronger β-cell link than insulin resistance
Noetzli et al. 2012 (11)	β-TDT	Systemic iron markers	HOMA-IR	+ 0.55	0.001	Insulin resistance linked to systemic iron
Mokhtar et al. 2016 (21)	β-TDT	Cardiac/Hepatic T2*	Amylase, Lipase	+ 0.79	<0.001	Exo- and endocrine pancreas linked
Kosaryan et al. 2017 (14)	β-TDT	Pancreas T2*	OGTT/FPG	Inverse	0.009	OR 11.2 for abnormal glucose
Pepe et al. 2020 (2)	β-TDT	Pancreas T2*	OGTT status	Inverse	<0.001	100% NPV for normal T2*
Shur et al. 2020 (10)	Mixed IO	Pancreatic FF	Glucose dysregulation	Positive	<0.001	Fat > iron as predictor
Meloni et al. 2021 (12)	β-NTDT	Pancreas T2*	OGTT abnormality	Inverse	0.045	Weaker association in TDT vs NTDT
Pistoia et al. 2022 (15)	SCD	Pancreas R2*	Glucose dysregulation	Positive	0.015	OR 8.25; cardiac R2* uncorrelated

Abbreviations: β-TDT = β-transfusion-dependent thalassemia; β-NTD = non transfusion-dependent thalassemia; SCD: sickle cell disease; oDI = oral disposition index; FPG = fasting plasma glucose; HOMA = Homeostatic Model Assessment; OGTT: oral glucose tolerance test; FPG: fasting plasma glucose: IFG: impaired fasting plasma glucose FF = fat fraction; OR = odds ratio; NPV = negative predictive value.

parameters when chelation was sufficiently intensive and initiated before irreversible β-cell loss. Farmaki et al. (20) showed that combined oral chelation [desferrioxamine (DFO) plus deferiprone (DFP)] achieved reversal of IGT to normal glucose tolerance in 2/8 affected patients, with no new cases of DM arising over the study period. Casale et al. (18) reported that long-term deferasirox (DFX) treatment (median 6.5 years) was associated with no new-onset DM and stabilization of pre-existing DM and Mokhtar et al. (21), reported that pancreatic MRI abnormalities were significantly associated with both cardiac and hepatic iron overload in adolescents with β-thalassemia major, suggesting early multi-organ iron toxicity (21). In non-transfusion-dependent thalassemia 6 months of oral iron chelation with DFX, at 10 mg/kg/day, produced a significant improvement in pancreatic T2* and a reduction in fasting plasma glucose (85 vs 79.5 mg/dL, p: 0.047) (22). Poggi et al. (17), comparing four chelation regimens in 165 β-TDT adults over 5 years, found that DFX monotherapy resulted in the greatest decrease in the prevalence of new endocrinopathy.

In summary, overall available studies consistently suggest that early and intensive iron chelation—combination therapy (DFO plus DFP) (20, 23) and monotherapy deferasirox-based regimens and can improve pancreatic iron burden and stabilize glucose metabolism (19,22), with the greatest benefits observed when treatment is initiated before irreversible β-cell dysfunction develops. However, most evidence remains observational, and long-term prospective trials with standardized pancreatic MRI follow-up are still needed. Most included studies showed moderate risk

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Table 4. Impact of iron chelation therapy on imaging iron parameters and glucose metabolic outcomes

Author / Year [Ref]	Disease	Chelator / Regimen	Duration	Change in pancreatic T2*	Change in glucose parameter	Overall metabolic outcome
Farmaki et al. 2011 (20)	β-TDT		Up to 2 yrs	Improved (higher T2*)	IGT reversed in 2/8 pts	Improved; new DM prevented
Casale et al. 2014 (18)	β-TDT	Deferasirox monotherapy	Median 6.5 yrs	Not reported	No new DM; FPG stable	Stabilization of pre-existing DM
Farmaki et al. 2006 (23)	β-TDT	DFO + Deferiprone	NR	Not reported	OGTT improvement in subset	Serum ferritin significantly reduced
Poggi et al. 2016 (19)	β-TDT	Deferasirox vs DFO, DFP	5 years	Not reported	Deferasirox: lowest new endocrinopathy	Deferasirox superior to other regimens
Chuansumrit et al. 2017 (22)	NTDT	Deferasirox 10 mg/kg	6 months	Significant improvement	FPG significantly reduced	Improved β-cell function trend
De Sanctis et al. 2021 (16)	β-TDT / NTDT	Various chelators	10+ years	Correlated with progression	One-third developed GD	Early IFG predicts later DM
De Sanctis et al. 2023 (17)	β-TDT	Various chelators	Retrospective	LIC < 3 mg/g dw	HOMA- β- and HOMA-IR normal	Metabolic stability with chelation

Abbreviations: β-TDT= TDT = β-transfusion-dependent thalassemia; NTDT = non-transfusion-dependent thalassemia; LIC = liver iron concentration; FPG = fasting plasma glucose ; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; DM = diabetes mellitus; GD = glucose dysregulation; DFO = deferoxamine; NR = not reported.

of bias, mainly due to retrospective/cross-sectional designs and potential selection bias. Earlier studies had greater variability in MRI protocols, whereas recent multicenter studies from the MIOT Network demonstrated the lowest risk of bias due to better imaging standardization and more consistent glucose assessment (Table 5). Overall, evidence quality is improving, but more prospective longitudinal studies are still needed.

Discussion

Understanding the natural history of dysglycemia in β-TDT patients is essential for the early detection of glucose dysregulation. In contrast to the vast literature about metabolic predictors of deterioration of glucose tolerance in the general population, little is known about this process in patients with β-TDT. De Sanctis et al. (16) demonstrated that one-third of adult TDT

Table 5. Quality assessment of included studies (modified Cochrane risk of bias framework)

Study [Ref]	Design	Selection Bias	Comparability	MRI Standardization	Glucose Assessment	Outcome Reporting	Overall RoB
Au et al. 2008 (8)	Cross-sectional	Moderate	Moderate	Low	Low	Low	Moderate
Utzschneider and Kowdley 2010 (1)	Narrative review	—	—	—	—	Low	Low*
Farmaki et al. 2011 (20)	Prospective interventional	Moderate	High	Moderate	Low	Moderate	Moderate
Noetzli et al. 2012 (11)	Cross-sectional	Low	Moderate	Low	Low	Low	Low
de Assis et al. 2012 (13)	Retrospective cross-sectional	Moderate	Moderate	Low	Moderate	Moderate	Moderate
Casale et al. 2014 (18)	Retrospective multicenter	Moderate	Moderate	Moderate	Moderate	Low	Moderate
De Sanctis et al. 2016 (4)	Consensus guideline	Moderate	—	—	Low	Low	Moderate
Poggi et al. 2016 (19)	Retrospective longitudinal	Moderate	Low	Moderate	Moderate	Low	Moderate
Kosaryan et al. 2017 (14)	Case-control	Moderate	Moderate	Moderate	Low	Moderate	Moderate
Shur et al. 2020 (10)	Retrospective cross-sectional	Moderate	Moderate	Low	Moderate	Low	Moderate
De Sanctis et al. 2021 (16)	Retrospective cohort	Moderate	Moderate	Moderate	Low	Low	Moderate
Meloni et al. 2021 (12)	Multicenter cross-sectional	Low	Low	Low	Low	Low	Low
Pistoia et al. 2022 (15)	Multicenter cross-sectional	Low	Low	Low	Low	Low	Low
De Sanctis et al. 2023 (17)	Retrospective cohort	Moderate	Moderate	Moderate	Low	Low	Moderate

Legend: Selection Bias: representativeness of the study population and recruitment method; Comparability: adequacy of adjustment for key confounders (age, chelation regimen, HCV status, splenectomy); MRI Standardization: use of validated T2*/R2* protocols with defined organ-specific thresholds; Glucose Assessment: use of standard OGTT with ADA-based classification vs. fasting glucose alone; Outcome Reporting: completeness of reported outcomes and absence of selective reporting. *Abbreviations:* Low = low risk of bias; Moderate = moderate/ unclear risk; High = high risk; — = domain not applicable; *Review articles assessed for reporting quality only. RoB = Risk of Bias.

patients with initially normal fasting glucose developed glucose dysregulation in the second–third decade of life. This validates the ICET-A recommendation for annual OGTT starting from the age of 10 years (4). The 2-hour OGTT (4 points) with extended insulin response profiling enables detection of early secretory insufficiency that is missed by standard 2-hour protocols (17). Surrogate indices of insulin secretion and sensitivity/resistance integrate glucose-stimulated insulin secretion and reflect the progressive depletion of functional β-cell mass by iron-catalyzed oxidative damage (5). Both vitro and mechanistic studies support this pathway, demonstrating dose-dependent reactive oxygen species accumulation in iron-exposed β-cells, with one experimental study reporting up to a 64% reduction in glucose-stimulated insulin secretion following high iron exposure, while broader mechanistic reviews confirm iron-induced mitochondrial dysfunction and oxidative β-cell injury (6, 24). The principal finding of this systematic review is that pancreatic T2*/R2* MRI is the single most powerful noninvasive predictor of glucose dysregulation across all major iron overload disorders. However, the relationship between pancreatic iron and glucose dysregulation is not uniform across iron overload conditions. In β-TDT, ineffective erythropoiesis combined with chronic transfusion produces persistent, high-level NTBI exposure that loads both parenchymal and endocrine organs symmetrically (2, 3). In SCD, hemosiderosis occurs primarily in the liver and reticuloendothelial system. Pistoia et al. (15) and other researchers (25-27) confirmed that while SCD patients with pancreatic siderosis are at 8-fold increased risk of metabolic alterations, the absolute prevalence of both pancreatic iron and DM is substantially lower than in β-TTD patients. The diagnostic performance of pancreatic T2* for detecting glucose dysregulation has been most rigorously characterized by the E-MIOT network, which enrolled 1,079 β-TDT patients by 11 MRI sites and across 66 Italian thalassemia centers using standardized MRI protocols. The T2* threshold of 13.07 ms identified by Pepe et al. (2) achieves an AUC of 0.79 with 100% NPV for glucose dysregulation, representing a clinically meaningful benchmark. The threshold of 17.9 ms in β -NTDT patients reflects the generally milder iron loading in β-NTDT patients relative to β -TDT patients, suggesting disease-specific thresholds are needed (12). A lower threshold of 5.6 ms was reported by Kosaryan et al. (14) in 51 Iranian patients (26 with diabetes, 8 with IGT or pre-diabetes and 17 without dysglycemia) . These differences underscore the need for threshold calibration and diagnostic definitions in different patient populations. Pancreatic iron overload shows also a close link with cardiac iron accumulation (12). The pancreas-heart co-loading relationship — whereby a normal pancreatic T2* demonstrates 100% NPV for significant cardiac iron — is among the most clinically actionable observations in this field (2, 12). The temporal sequence observed in Coates et al. (25) analysis of chronically transfused SCD patients — pancreatic iron reaching glucose-intolerance-associated levels approximately 2 years before cardiac T2* deteriorated — underscores that pancreatic MRI provides the earliest warning signal of systemic iron toxicity (25, 26). A critical source of controversy in the literature is the finding by Shur et al. (10) that pancreatic fat fraction, rather than R2*, was the independent predictor of glucose dysregulation when both parameters were simultaneously quantified. This finding highlights the importance of co-occurring pancreatic steatosis and mandates that all future pancreatic MRI protocols acquire both multi-echo gradient-echo R2* maps and PDFF maps to disentangle the independent contributions of iron and fat to pancreatic metabolic dysfunction (10). Due to the promising results of using iron chelators both individually and combined for the treatment of iron overload, iron chelators have become increasingly important in medicine over recent years. The oral options of iron chelators are associated with improved adherence. Additionally, the usage of combination and consecutive chelating agents can enhance efficiency and decrease the incidence of adverse events (29). However, it has been reported that is difficult to remove the iron from the pancreas (30), and higher improvements were detected in patients who were more heavily loaded at the pancreatic level (31). Notably, in a study of Meloni et al. (30) iron chelators in monotherapy (DFO, DFP and DFX) were equivalent in the reduction of pancreatic iron and Ricchi et al. (31), documented that in transfusion-dependent patients who started regular transfusions in early

childhood, combined DFP+DFO was significantly more effective in reducing pancreatic iron than was either DFP or DFX. Deferasirox is the only iron chelator that is specifically approved by the FDA and EMA as a first-line iron chelator in patients with NTDT who are aged ≥10 years, based on data from the THALASSA trial. Experience with other iron chelators, such as deferoxamine and deferiprone, is limited. Liver iron concentration (LIC) ≥5 mg/g/d.w., measured by MRI, and ferritin level > 300 ng/mL were suggested as indicators to start iron chelation therapy (32). In HH, early phlebotomy before fibrosis offers the greatest opportunity to prevent β-cell failure (1). These disease-specific patterns mandate individualized monitoring strategies. The findings of this review should be interpreted in light of the methodological limitations summarized in Table 5. Most included studies were retrospective or cross-sectional, limiting temporal assessment of whether pancreatic iron deposition directly precedes progressive β-cell failure and dysglycemia. Earlier studies also demonstrated variability in MRI acquisition protocols and pancreatic iron quantification methods, which likely contributed to differences in reported thresholds for diabetes risk. In contrast, more recent multicenter studies, particularly from the MIOT Network and ongoing E-MIOT prospective follow-up cohorts, have strengthened the evidence base through improved imaging standardization and more robust metabolic assessment. Supporting this trend, a recent 2025 systematic review of quantitative MRI beyond the liver and heart in β-thalassemia confirmed significant correlations between T2*/R2* measurements and endocrine dysfunction across multiple organs, while emphasizing that diagnostic performance in extrahepatic tissues remains only fair to good because of persistent methodological heterogeneity. Collectively, these findings highlight the urgent need for standardized multi-organ MRI protocols and larger prospective longitudinal studies. Several clinically actionable implications emerge from this synthesis. Firstly, annual OGTT should be supplemented — not replaced — by pancreatic T2* MRI in all transfusion-dependent thalassemia patients from age 10 years and specially during the pubertal age (4). Secondly, a pancreatic T2* in the abnormal range should trigger immediate revision of chelation therapy and endocrinology specialist assessment. Thirdly, in β-TDT, the absence of pancreatic iron on MRI provides high clinical reassurance that the detected cardiac iron may be mild or absent. Fourthly, in HH, initiation of systematic phlebotomy before cirrhosis may preserve β-cell function. Finally, in centers where quantitative MRI is unavailable, OGTT associated to biochemical surrogates' indices of insulin secretion and sensitivity/resistance may serve as metabolic alerting tools to prompt endocrinology specialist referral (28).

Conclusion

This systematic review demonstrates that quantitative MRI, principally pancreatic T2*/R2* relaxometry, provides the most validated, non-invasive, and clinically actionable biomarker of β-cell vulnerability across all major iron overload disorders. The inverse association between pancreatic iron and β-cell functional reserve is consistent across disease entities, MRI platforms, and study designs, with a normal pancreatic T2* yielding complete reassurance against concurrent glucose dysregulation and significant cardiac iron accumulation. Simultaneous assessment of pancreatic proton density fat fraction (PDFF) is increasingly important to distinguish true iron-related signal changes from potential confounding caused by coexisting pancreatic steatosis. Imaging-guided chelation intensification, particularly with monotherapy or associated oral iron chelator regimens—represents an evidence-supported strategy to reduce iron-mediated β-cell injury before progression to irreversible failure, while also underscoring the need for serial pancreatic MRI assessments, as chelation adherence and iron burden often fluctuate over time. However, major barriers to implementation remain. Collaborative multicenter prospective studies are urgently needed to establish field-strength–specific, fat-corrected, and disease-specific T2* thresholds that can be applied consistently across diverse healthcare settings (10,12). Access to pancreatic MRI remains largely limited to specialized centers with expertise in quantitative iron imaging, and its additional cost represents a significant challenge—particularly in low- and middle-income countries where thalassemia prevalence is highest (3,9).

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Ethical statement: This study was a systematic review based exclusively on previously published PubMed-indexed data and did not involve direct patient recruitment, intervention, or access to identifiable personal data; therefore, institutional review board approval and informed consent were not required.

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