# A T2* magnetic resonance imaging study of pancreatic iron overload in thalassemia major

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## ABSTRACT

We studied the utility of pancreatic magnetic resonance imaging (MRI) in 72 thalassemia major patients (21 diabetic, 51 normoglycemic). Diabetic patients were significantly older ($p<0.0001$) and had smaller pancreas volume ($p<0.0001$). The two groups were comparable for ferritin and MRI-T2* heart, liver and pancreas. Pancreatic T2* signals were abnormal in 80% of both groups, and correlated with heart T2*. In normoglycemic patients, cardiac T2* and log-pancreatic T2* values correlated with homeostatic model assessments HOMA-B (β cell reserve), HOMA-IR (insulin resistance) and fasting insulin/C-peptide levels. This suggested that improved chelation may improve β cell reserve and prevent pancreatic atrophy.

Key words: magnetic resonance, thalassemia

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## Introduction

Thalassemia major patients require life-long transfusion chelation to avoid premature death due to organ damage by hemosiderosis. The leading cause of death is cardiac failure, but many patients also suffer from endocrine damage such as pituitary failure, hypogonadism, diabetes mellitus, and hypothyroid and hypoparathyroidism.

Even aggressive deferoxamine chelation, does not provide complete cardiac and endocrine protection. The availability of new oral iron chelating agents[1,2] and cardiac T2* magnetic resonance imaging (MRI) has revolutionized thalassemia management.[3] There are still few reports, however, on the use of MRI to study iron deposits in the endocrine organs. Pancreatic hemosiderosis can cause insulin dependent diabetes mellitus.

This can be rapid in onset and is largely irreversible. The incidence of impaired glucose tolerance and diabetes in thalassemia major patients varied from 9% to 15%, depending on the age of assessment, the intensity of chelation and transfusion and related patient compliance.[4,5] It is uncertain whether early assessment and tailored chelation can prevent diabetes and preserve pancreatic reserve. The current study explores the utility of pancreatic MRI in thalassemia major cases.

## Design and Methods

All MRI examinations were performed with a 1.5T scanner (Sonata, Siemens Medical, Erlanger, Germany). T2* myocardium was assessed by a cardiac gated single breath hold 8-echo sequence (field of view: 400 mm, slice thickness 10 mm; time of repetition: 160 ms; Time to echo: 2.6 ms, 4.6 ms, 6.6 ms, 8.7 ms, 10.7 ms, 12.7 ms, 14.7 ms and 16.7 ms; resolution: 256 x 256, flip angle: 20; number of average: 1).[6] Cardiac gated breath hold cine true FISP sequence was performed and ejection fraction (EF) was analyzed using Argus software (Siemens Medical Systems, Erlangen, Germany). Analysis of the T2* values and T2 value of the myocardium were performed with a dedicated software (CMRtools; Cardiovascular Imaging Solutions, London, UK). A true FISP breath hold sequence (field of view: 350 mm, TR/TE=280.5/1.22 ms, flip angle: 65$^0$; number of excitation+1, slice thickness of 6 mm with gap of 1.5 mm) was used to cover the whole abdomen, including the liver and pancreas. Analysis was performed on raw values and after logarithmic transformation of T2* values of liver and pancreas. The area of the pancreas was outlined by electronic caliper and the volume was calculated by multiplying the total area by 7.5mm. The normal MRI T2* values of pancreas were determined from 20 local age and sex

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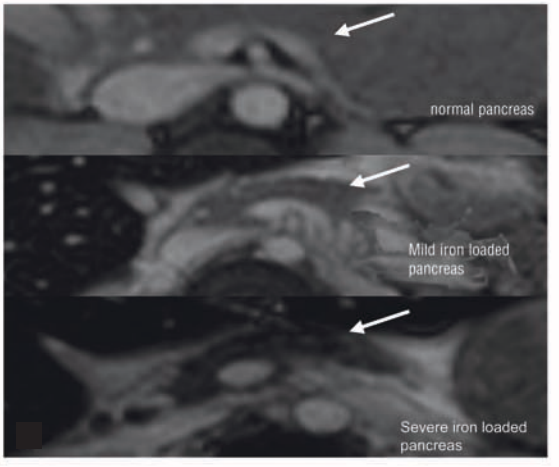
matched controls. For patients not on exogenous insulin, fasting glucose, C-peptide and insulin levels were assessed, and homeostatic model assessment (HOMA) indices for β-cell function (HOMA-B: Insulin x 20/Glucose - 3.5, normal 130-400) and insulin resistance (HOMA-IR: Insulin x Glucose/22.5, normal 0.8-1.6) were calculated. Statistical analysis was performed using SPSS 13.0 (Chicago, IL, USA)

## Results and Discussion

A total of 72 thalassemia major patients (median age: 27, range 12-47, 31 males and 41 females) were recruited. Their clinical details have been previously reported and are representative of the local cohort.[5,7] The median ferritin level was 6,259 pmol/L (range 605-14,380). Subcutaneous deferoxamine was used for life-long chelation in all cases, but compliance was poor, with only 22% of cases maintaining ferritin below 3,000 pmol/L. Short-term (3-6 months) free trial of deferiprone (n=18) and deferasirox (n=16) was used in some cases. The mean number of units of red cell transfused per month was 3.3 (range 2-5) and the incidence of heart failure (EF<55%) and hypogonadism on hormonal replacement were 20% and 62% respectively. A total of 21 patients (29%) were already on insulin replacement. Patients with diabetes were significantly older (32 *vs.* 24.4 years old, $p<0.0001$) and had lower pancreatic volumes ($p<0.0001$, Table 1, *online supplement*) than patients without diabetes. Receiver operating characteristic (ROC) analysis showed < 3,705 $mm^3$ was predictive of diabetes in the cohort ($p=0.0001$) with a sensitivity of 80% (95% confidence interval (CI): 52-95%) and a specificity of 92% (95% CI: 78-98%). The median pancreas T2* was 12.2 ms (range 1.3-61.9), significantly lower than 20 normal controls (median 37.5 ms, range 21.3-53 ms, $p<0.0001$). The incidence of abnormal T2* (taken as <21 ms) was 81% among both diabetic and non-diabetic cases ($p=0.9$, Wilcoxon test). The two groups were also comparable for T2* of the heart ($p=0.24$) and liver ($p=0.11$), median ferritin level ($p=0.16$) and median monthly volume transfused red cells ($p=0.22$). The pancreatic T2* values increase with age (r=0.27, $p=0.028$) and showed correlation with cardiac T2* ($p=0.008$) and EF ($p=0.024$), but only a trend with liver T2* ($p=0.09$). It did not relate to pancreatic volume ($p=0.29$) or ferritin levels ($p=0.45$). The correlations were stronger after logarithmic transformation of pancreatic T2* (Table 1) and applied in both diabetic and non-diabetic cases. Biochemical tests for sub-clinical pancreatic insufficiency were further analyzed in 51 patients not on exogenous insulin supplement. Although the fasting glucose, insulin and C-peptide levels were mostly within normal range, abnormal HOMA-B and HOMA-IR was found in 90% and 33% of patients. The reduction in pancreatic β cell reserve (HOMA-B) was predicted by abnormal T2* in the pancreas, liver (after log transformation) and especially abnormal T2* of the heart, but not by pancreatic volume (Table 2, *online supplement*). The T2* of heart and log T2* of pancreas also showed significant correlation with reduced fasting insulin and C-peptides, as well as insulin resistance, as reflected by HOMA-IR. None of the biochemical measurements showed significant correlation with age. On multivariate analysis, only T2* of the heart (but not log-liver T2* or log-pancreas T2*) showed significant correlation with HOMA-B ($p<0.001$) and HOMA-IR ($p=0.009$). It is known that pancreatic hemosiderosis results in abnormal MRI signal intensity, and there is iron overload in the pancreas in up to 75-100% of thalassemia major cases.[7-9] The signal intensity ratio results showed correlation with ferritin levels[9] and also related to iron load in other organs.[7] They also correlated with exocrine pancreatic secretion function[9] and endocrine function as assessed by oral glucose tolerance test (OGTT).[8] Pancreatic abnormalities in thalassemia major patients can also be defined by other imaging modalities such as ultrasound echogenicity.[10] However, MRI has become an integral part of iron assessment in thalassemia, so new pancreatic MRI studies using other signal algorithms are urgently needed. In the current study, the single breath T2* assessment was also preferred for its short scanning time. Similarly, a fasting blood sample was chosen over OGTT (or the gold standard of euglycemic clamp)[11] due to patient preference. Both insulin secretion capacity (HOMA-B) and insulin sensitivity (HOMA-IR) are known to be impaired in thalassemia major, even in apparently normoglycemic cases.[12] It is important, therefore, to correlate these pre-diabetic biochemical abnormalities with MRI studies. Our results showed that hemosiderosis of the pancreas, as measured by MRI T2*, could not be predicted by age or ferritin levels. This matches the low predictive value of most forms of ferritin measurements.[13] We also confirmed that pancreatic hemosiderosis did not correlate with liver hemosiderosis.[8] However, there was strong correlation between hemosiderosis of the pancreas and heart. This may be due to the same L-type calcium iron channels in the two organs.[14] This is of clinical importance. Firstly, chelation regimens that fail to prevent cardiac siderosis may also fail in the pancreas, and vice versa. Secondly, without pancreatic MRI, cardiac MRI T2* becomes a surrogate assessment for pancreatic hemosiderosis. This is particularly relevant since we showed that cardiac T2* correlated strongly with sub-clinical pancreatic impairment and insulin resistance, in fact, even more so than pancreatic T2*. Thirdly, in areas where even cardiac T2* is unavailable, biochemical measurements of HOMA-B may be used for surrogate assessment of cardiac risk. Our study showed that pancreatic atrophy (volume) was a better predictor of diabetic status than pancreatic hemosiderosis (T2*). In other studies, MRI documented pancreatic fatty replacement has also been shown to predict diabetes[8] Pancreatic damage represents an irreversible, cumulative destruction of β cells[15] and pancreatic atrophy is a common finding in all diabetes patients irrespective of etiology.[16] Unlike the heart or liver, the pancreas may not regenerate or remodel even with reduction in hemosiderosis. Furthermore, there are other causative factors for diabetes such as genetic pre-



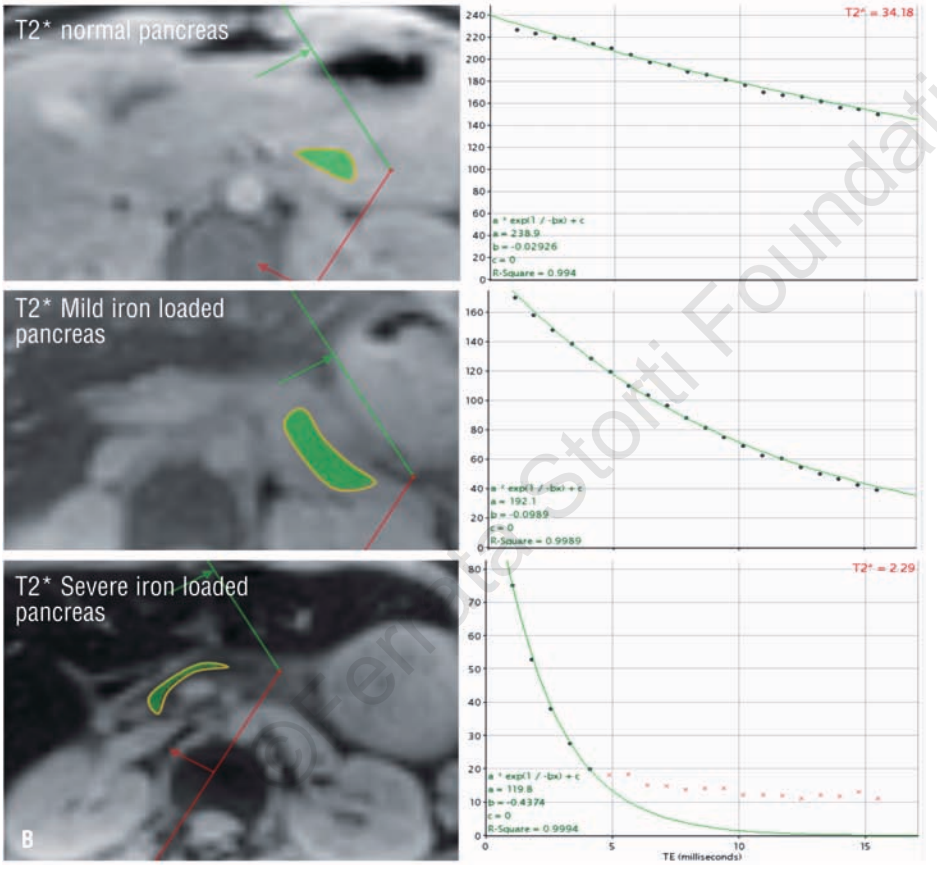




**Figure 1A and B. Composite MRI images showing mild, moderate to severe iron deposition in the pancreas at the level of the inferior vena cava, and corresponding differences in rate of signal decay resulting in different pancreatic T2* values in patients with mild, moderate and severe pancreatic iron overload.**

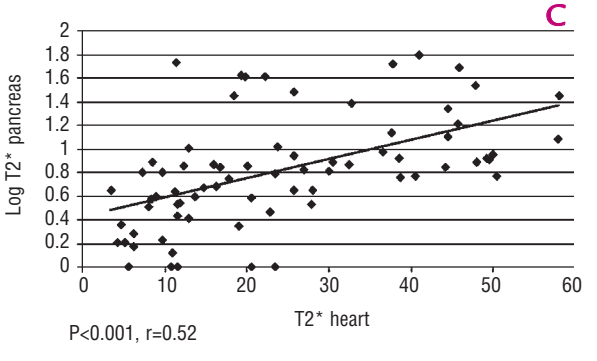



**Figure 1C. Correlation between pancreatic T2* log with Heart MRI T2*.**

disposition and immune damage which are unlikely to be reflected by MRI T2* results.[17] Thus, established diabetic thalassemic patients seldom recover normal glucose tolerance.[18] On the other hand, in normoglycemic patients, pancreatic hemosiderosis may affect β cell reserve and insulin resistance. The latter was notably unrelated to liver hemosiderosis, and it is unclear whether insulin resistance in thalassemics is related to iron in the fat or skeletal muscles. Irrespective of the mechanism, these parameters are known to improve with intense chelation, especially in patients with impaired glucose tolerance.[19] It is likely, therefore, that advancement in iron assessment and chelation will not only reduce cardiac morbidity but will impact on future diabetic

risks. Study limitations included the lack of biopsy data to verify the pancreatic MRI T* signal, and the over-representation of poorly chelated patients. It is also possible that, as in MRI assessment of liver iron load, other algorithms and reading transformation may yield better correlations.[20] Hopefully, these questions will be addressed by future studies.

## Authorship and Disclosures

WYA: conceived study, analyzed data, wrote paper; WL, WC: performed MRI, analyzed data, approved paper; ST, WKW: performed biochemical analysis, approved paper; RL, SYH: provided patients, approved paper.

The authors reported no potential conflicts of interest.

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