Pituitary iron and volume predict hypogonadism in transfusional iron overload

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Hypogonadism is the most common morbidity in patients with transfusion-dependent anemias such as thalassemia major. We used magnetic resonance imaging (MRI) to measure pituitary *R*2 (iron) and volume to determine at what age these patients develop pituitary iron overload and volume loss. We recruited 56 patients (47 with thalassemia major, five with chronically transfused thalassemia intermedia and four with Blackfan-Diamond syndrome) to have pituitary MRIs to measure pituitary *R*2 and volume. Hypogonadism was defined clinically based on the timing of secondary sexual characteristics or the need for sex hormone replacement therapy. Patients with transfusional iron overload begin to develop pituitary iron overload in the first decade of life; however, clinically significant volume loss was not observed until the second decade of life. Severe pituitary iron deposition ($Z > 5$) and volume loss ($Z < -2.5$) were independently predictive of hypogonadism. Pituitary *R*2 correlated significantly with serum ferritin as well as liver, pancreatic, and cardiac iron deposition by MRI. Log pancreas *R*2* was the best single predictor for pituitary iron, with an area under the receiving operator characteristic curve of 0.88, but log cardiac *R*2* and ferritin were retained on multivariate regression with a combined r^2 of 0.71. Pituitary iron overload and volume loss were independently predictive of hypogonadism. Many patients with moderate-to-severe pituitary iron overload retained normal gland volume and function, representing a potential therapeutic window. The subset of hypogonadal patients having preserved gland volumes may also explain improvements in pituitary function observed following intensive chelation therapy. Am. J. Hematol. 00:000–000, 2011. © 2011 Wiley Periodicals, Inc.

Introduction

Iron overload is common for patients with thalassemia major and other transfusion-dependent anemias. The toxic effects of iron include heart failure, diabetes, and hypogonadism. Hypogonadism is the most common endocrinopathy in thalassemia major, with a prevalence rate of over 50% in multicenter studies [1,2]. Early recognition of pituitary iron loading is imperative because hypogonadism is only partially reversible by intensive chelation [3]. Hypogonadism can result from impairment of the gonad (primary), pituitary gland (secondary), and hypothalamus (tertiary). Secondary hypogonadism, often referred to as hypogonadal hypogonadism, is the most cause of hypogonadism in thalassemia major [4,5]. Unfortunately, pituitary dysfunction is difficult to detect before puberty because of immaturity of the hypothalamic-pituitary-gonadal (HPG) axis. Magnetic resonance imaging (MRI) has become quite successful at quantifying preclinical iron deposition in the liver, heart, and pancreas [6–8]. Prior work using pituitary *R*2 as a surrogate for pituitary iron, and pituitary height as a surrogate for gland volume are promising techniques for stratifying hypogonadism risk, but further work is necessary to identify risk thresholds [9–14].

Thus, the purpose of this study was (1) to determine at what age pituitary iron deposition and volume loss occur, (2) to stratify the risk of clinical hypogonadism based on pituitary *R*2 and pituitary volume, and (3) to determine predictors of pituitary iron deposition based upon other surrogates of iron overload. Reference data for pituitary *R*2 and volume were derived from 100 normal subjects and have been presented elsewhere [15].

Methods

We recruited 56 patients (47 with thalassemia major, five with chronically transfused thalassemia intermedia (25.8 ± 13.3 years of transfusion), and four with Blackfan-Diamond syndrome) to have a brain MRI to measure pituitary iron and volume. Patients as young as 4-year old were examined by adding the 15 min brain MRI to their clinically indicated heart and abdomen MRI with anesthesia. MRI assessments of liver *R*2 and *R*2*, cardiac *R*2*, and pancreas *R*2* were done as previously described [16]. This study was approved by the Committee of Clinical Investigation at Children's Hospital Los Angeles (CCI #08-00143 and 09-00065). Informed consent was obtained for all patients.

Diagnosis of hypogonadism was determined by either lack of secondary pubertal characteristics by age 13 years for females or age 14 years for males, by primary or secondary amenorrhea in females ages 16 years or older, or by the need for testosterone administration in males. The use of brief testosterone treatment to initiate puberty was not considered evidence of hypogonadism. Females <13-year old and males <14-year old with no signs of puberty were considered prepubertal [17]. This information was obtained by reviewing clinical notes.

Pituitary imaging was performed using an eight element head coil on a 1.5 Tesla Philips Achieva system running system 2.5 [18]. Following standard localizers, a coronal 3D fast spoiled gradient echo image was performed using 1-mm isotropic voxels, slab thickness of 12–16 cm and a field of view of 20–24 cm. Images were two-fold Fourier interpolated in-plane for reconstructed voxel sizes of 0.5 mm by 0.5 mm by 1 mm. Repetition time was 7 msec, echo time 3.2 msec, flip angle was 8°, and bandwidth was 241 Hz/pixel. Pituitary *R*2 was measured using

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TABLE I. Demographics of the Study Population

Age, years	20.4 ± 12.1 [17.5, 4.1–58.3]
Sex	25F; 31M
Age onset of Transfusion, years	3.4 ± 5.9 [1.0, 0.0–29.7]
Years of Transfusion	17.7 ± 10.1 [15.9, 2–44.3]
Chelator	44 DFX; 7 DFO; 2 DFX + DFO; 2 DFP; 1 DFP + DFX *
HIC by MRI, mg/g	9.2 ± 10.7 [4.5, 1.0–49.3]
Cardiac *R2*[a], Hz	51.0 ± 51.3 [33.6, 22.6–338.0]
Pancreas *R2*[a], Hz	169.6 ± 182.7 [103.0, 17.0–715.0]
Ferritin, ng/mL	1543.3 ± 2095.9 [949, 100–10300]
Pituitary *R2 Z*-score	4.5 ± 4.2 [3.4, −2.1 to 17.5]
Anterior pituitary volume *Z*-score	−0.9 ± 1.3 [−0.9, −4.2 to 2.3]

[a] DFX, deferasirox; DFO, deferoxamine; DFP, deferiprone. Results reported as mean ± standard deviation [median, range].

a multiple-echo spin echo images collected in a single midline sagittal plane. Imaging parameters were a TR of 500 msec, flip angle's 90-180-180. . ., TE of 15, 30, 45, 60, 75, 90, 105, and 120 msec, 1-mm inplane isotropic resolution and 3-mm slice thickness.

Pituitary volumes, both anterior and posterior, were manually planimetered on the Synapse imaging PACS (Fuji Medical Systems). Individual cross-sectional areas were multiplied by the slice thickness and summed across the gland to calculate gland volume. A single board-certified neuroradiologist (AP) confirmed all anatomic boundaries.

Pituitary *R2* was calculated on a pixel-wise basis from the multi-echo spin echo images. Each pixel was fit to a simple monoexponential across all echoes creating a *R2* map; no offset correction was needed. The entire visible anterior pituitary gland was traced in the *R2* map, yielding a distribution of *R2* values, from which mean and median values were retained for statistical considerations. We chose to use the sagittal *R2* images for statistical analysis because the sagittal plane has been used in prior studies.

Z-scores for pituitary volume and *R2* were calculated from regression equations and residual errors derived from a normal cohort of 100 controls [15]. From this normal cohort, we showed that females have larger pituitary glands than males. Therefore, separate equations were used for pituitary volume *Z* estimates. We used anterior pituitary measurements (rather than total pituitary volume) for both *R2* and volume analysis because iron is not significantly deposited in the posterior pituitary gland, and the posterior pituitary is not thought to play a role in puberty.

Logistic regression and receiver operator characteristic curves were used to obtain optimal discriminating thresholds between pituitary iron, pituitary volume, and hypogonadism. Univariate and multivariate linear regression was used to determine relationships between pituitary iron and metrics of iron overload [serum ferritin, liver iron concentration (LIC), pancreas and cardiac *R2**]. All statistics were performed in JMP 5.1(SAS, Cary, NC).

Results

Demographics for the population are summarized in Table I. Sixteen of the 41 patients old enough to attain puberty were diagnosed with clinical hypogonadism, including one of the DBA patients. Patients were 20.4 ± 12.1 years old and well distributed by sex (31 males, 25 females). All subjects received blood transfusions every 2–4 weeks and were on appropriate chelation therapy as indicated by their physician. 44/56 patients were on Deferasirox (DFX) monotherapy; other patients were on either Deferoxamine (DFO), Deferiprone (DFP), or on combination therapy with DFX + DFO or DFX + DFP. This cohort had started transfusions at an average age of 3.4 years, and was moderately iron overloaded: mean ferritin was 1543.3 ng/mL, LIC was 9.2 mg/g, cardiac *R2** was 51.0 Hz, and pancreas *R2** was 169.6 Hz. Mean pituitary *R2 Z* was 4.5 and mean anterior pituitary volume *Z* was −0.9. No sex differences were observed with respect to any of these variables. Females had larger absolute anterior and total pituitary volumes, but this systematic bias was corrected using *Z*-scores derived from a prior control cohort [15].

Figure 1 shows the pituitary *R2* values for this population as a function of age; lines reflect Zs from −2 to +2 [15]. In our patient cohort, 26.8% of patients were pre-pubertal, 28.6% of patients had been diagnosed with hypogonadism,

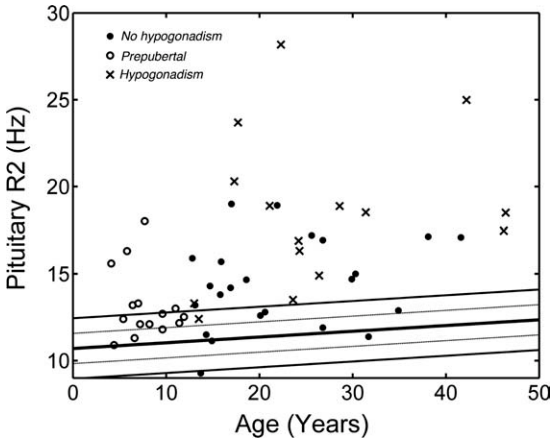

Figure 1. Pituitary R2 as a function of age. Trend lines represent mean and standard deviations (from $Z = +2$ to -2) of the control population. Chronically transfused patients are represented by the symbols: pre-pubertal patients by the open circles, post-pubertal patients without hypogonadism by the filled circles, and hypogonadism patients by the ×.

and 44.6% were normal post-pubertal. Pituitary iron was detected (*R2* $Z > 2$) in two-thirds of patients. *R2* rose sharply during the teenage years, plateauing during adulthood. During the first decade of life, 7/12 children had normal pituitary *R2*, with 2/12 just outside the normal range. However, 3/12 had markedly increased iron, including two children who were 4.1- and 5.8-year old, respectively. In contrast, patients older than 21 years of age had a mean pituitary *R2 Z* of 5.8, and only 3/17 patients had normal *R2*.

Figure 2 demonstrates anterior pituitary growth curves for males and females. Patients trended along a *Z* of −1 throughout childhood and adolescence. Nine patients had decreased anterior pituitary volume ($Z < -2$); eight of these nine had hypogonadism. The youngest patient with decreased pituitary volume was 14 years of age, but pituitary volume loss was most evident during the 3rd decade of life.

Pituitary iron was increased in all patient groups relative to normal controls ($Z > 0$, $P < 0.001$). Patients who were diagnosed with hypogonadism had significantly higher pituitary *R2 Z*-scores than post-pubertal patients without hypogonadism or pre-pubertal patients ($P < 0.0001$, Fig. 3, left). Anterior pituitary volumes from pre-pubertal patients (Fig. 3, right) were lower than from the control population ($Z = -0.76 \pm 0.21$, $P = 0.002$); this disparity lessened for post-pubertal patients with normal gonadal function ($Z = -0.55 \pm 0.26$, $P = 0.06$). However, patients with hypogonadism had significantly lower anterior pituitary volumes than controls, post-pubertal patients without hypogonadism, or the pre-pubertal group ($P < 0.0001$, $P = 0.03$ and $P = 0.002$, respectively).

The interaction between pituitary iron and pituitary volume is demonstrated in Figure 4. Only patients old enough to have undergone puberty are displayed to clarify predictors of hypogonadism. There was a weak negative correlation between pituitary *R2 Z* and anterior pituitary volume *Z* ($r^2 = 0.08$, $P = 0.05$). The green zone indicates patients with normal pituitary volume and pituitary *R2*; none of these patients had hypogonadism. Red zone depicts optimal discriminators of hypogonadism for volumetric and *R2* measurements ($Z < -2.5$ and $Z > 5$, respectively, determined by ROC analysis). Volume loss was highly specific for hypogonadism; seven of eight patients with volume $Z < -2.5$ had hypogonadism. Heavy pituitary siderosis (*R2* $Z > 5$) was sensitive, but less specific, with 11 of 18 patients having hypogonadism. Yellow zone depicts intermediate regions where the volumetric and iron measurements were abnormal, but no hypogonadism was detected, representing preclinical pituitary iron deposition.

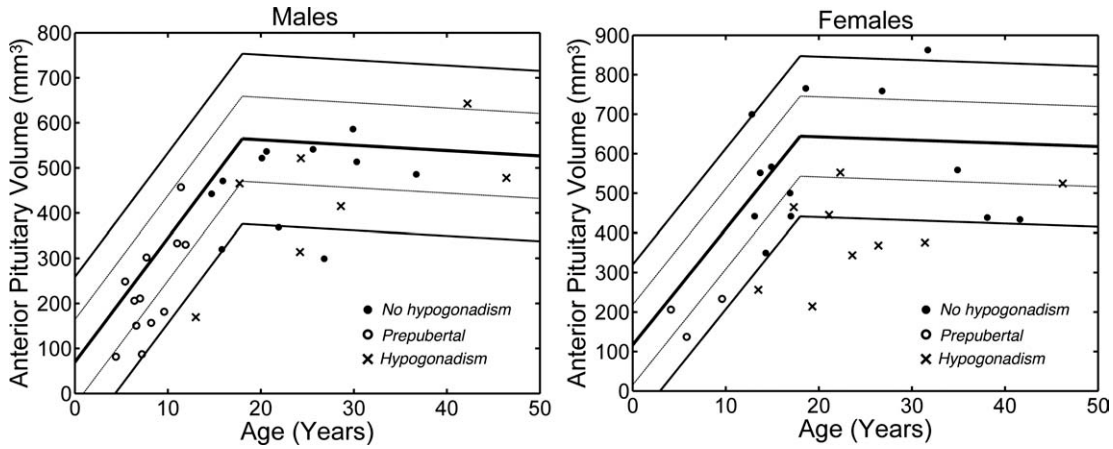

Figure 2. Anterior pituitary volume as a function of age. Males are shown on the left and females on the right. Trend lines represent mean and standard deviations (from $Z = +2$ to -2) of the control population. Symbols as in Fig. 1.

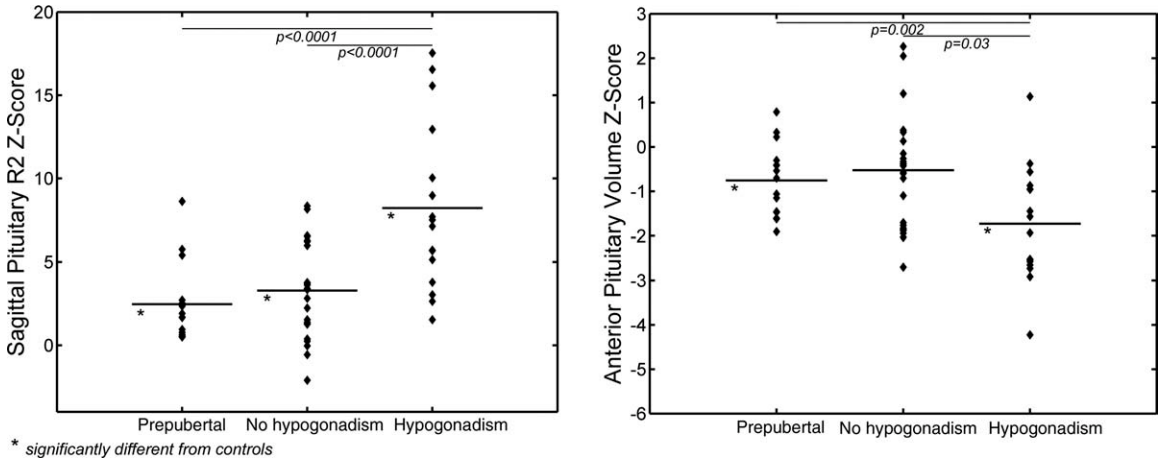

Figure 3. Pituitary *R2* *Z*-scores are on the left and anterior pituitary volume *Z*-scores on the right. Individual values are shown for pre-pubertal, post-pubertal without hypogonadism, and hypogonadism patients separately, as indicated by the diamond markers. Group means are shown by the horizontal lines through the points. *P*-values at the top of the graphs represent significant difference between groups. Significant difference from the control population is indicated by the *.

Pituitary *R2* correlated with LIC, ferritin, cardiac *R2** and pancreas *R2** ($r^2 = 0.43$, 0.35, 0.49, and 0.52, respectively, $P < 0.0003$, Fig. 5). Pituitary *R2* had a curvilinear relationship with both pancreatic and cardiac *R2**, presumably because pituitary iron loading occurred earlier than the other two organs. On multivariate regression, log (pancreas *R2**), ferritin, and log (cardiac *R2**) were retained with a combined r^2 of 0.71. The presence of MRI-detectable cardiac iron (*R2** $>$ 50 Hz) was specific for pituitary iron overload. Pituitary *R2* *Z* was 9.2 ± 4.8 when cardiac iron was present versus 3.1 ± 2.7 when it was not ($P = 0.0005$). In addition, the prevalence of hypogonadism in subjects with cardiac iron was 75% versus 21% in patients lacking cardiac iron ($P < 0.001$). Using logistic regression, however, pancreas *R2** was the best overall predictor of pituitary iron overload with an area under the receiver operator characteristic curve (AUROC) of 0.88 compared with 0.62, 0.55, and 0.69 for LIC, ferritin, and cardiac *R2**, respectively. A pancreas *R2** of 88 Hz was the optimal cutoff for predicting elevated pituitary *R2*. Pituitary *R2* *Z* was 1.9 ± 1.9 in patients having pancreatic *R2** $<$ 88 versus 6.9 ± 4.3 in patients whose pancreas *R2** was $>$ 88 Hz ($P < 0.0001$).

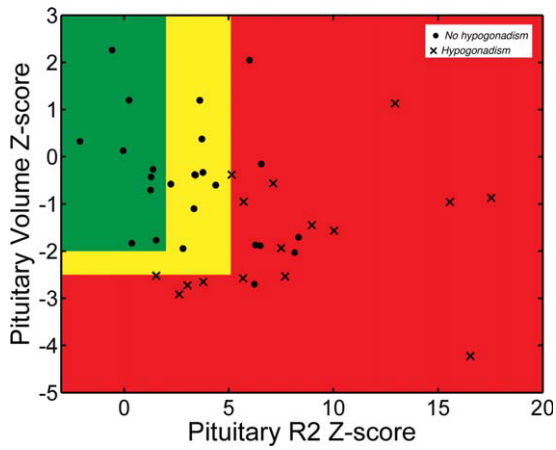

Figure 4. The relationship between pituitary *R2* *Z* (*x*-axis) and anterior pituitary volume *Z* (*y*-axis) is shown for all post-pubertal patients. The green zone represents normal pituitary *R2* and volume *Z*-scores. The red zone represents significant risk for hypogonadism, as determined by ROC analysis; cutoffs are at a pituitary *R2* *Z* of 5.1 and a pituitary volume *Z* of −2.5. The yellow zone represents the intermediate area in which patients have elevated iron but are at lower risk for developing hypogonadism.

Discussion

Our first study objective was to determine at what age pituitary iron deposition and volume loss occur. These observations are important to the timing of MRI surveillance. We found that severe pituitary iron deposition occurred in the first decade of life in 25% of patients. These data are the first to demonstrate that pituitary iron overload occurs in early childhood and suggest that an initial scan at 7 years

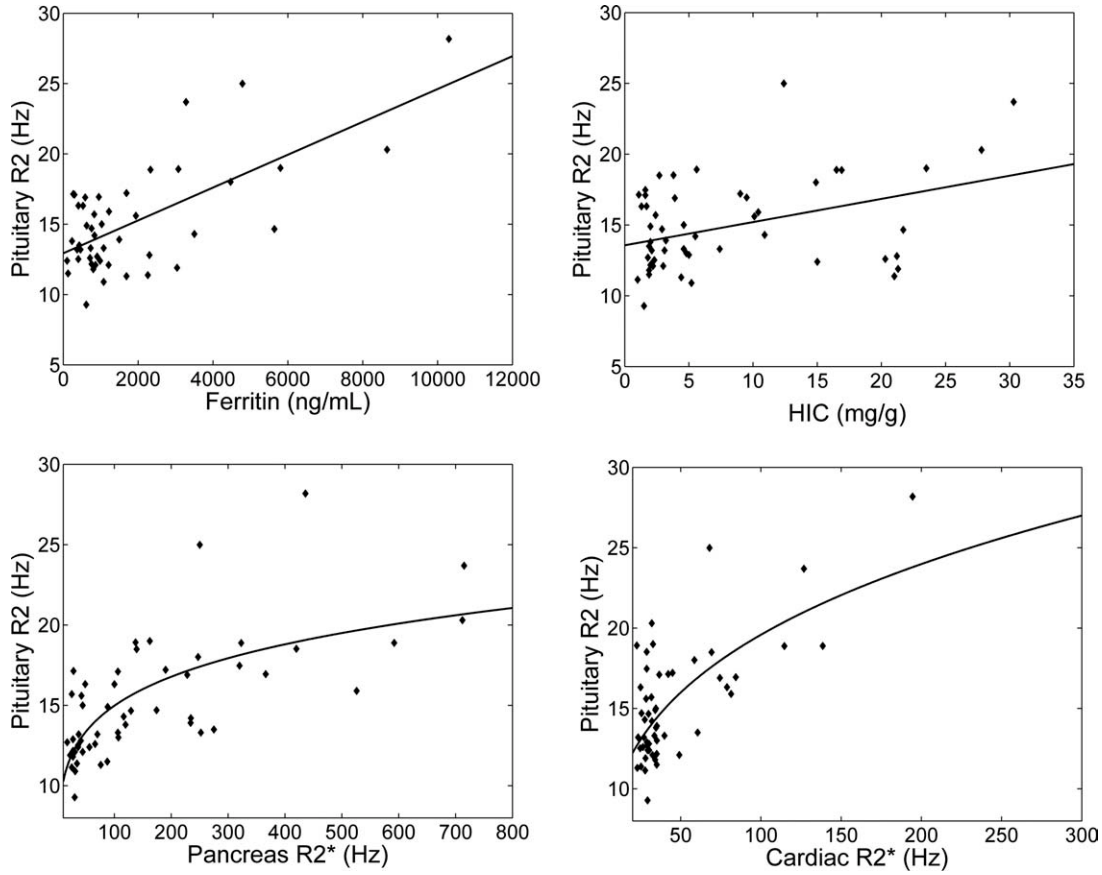

Figure 5. The relationships between pituitary iron and other markers of iron overload are shown. Pituitary *R*2 correlated with ferritin, LIC, pancreas *R*2*, and cardiac *R*2* (r^2 = 0.43, 0.35, 0.49 and 0.52, respectively, $P < 0.0003$, Fig. 5). Pituitary *R*2 had a logarithmic relationship with pancreatic and cardiac *R*2* values.

of age would be prudent to pick up early accumulation. However, the most critical time for surveillance is the second decade of life where many patients rapidly accumulate pituitary iron and pituitary volume loss first becomes evident. We postulate that serial *R*2 and volumetric observations will offer greater sensitivity for recognition of pituitary toxicity than single measurements, similar to patient trends on standard growth charts. However, longitudinal studies will be required to test this hypothesis.

Our second study objective was to stratify the risk of clinical hypogonadism based on pituitary *R*2 and pituitary volume *Z*-scores. Loss of pituitary volume and excess pituitary iron were independently associated with hypogonadism. Decreased pituitary volume could represent either volume loss through apoptosis, or failure to grow properly; we cannot distinguish between these two mechanisms on a cross-sectional study. Furthermore, the role of pituitary iron in causing volume loss cannot be inferred using a single observation. There is evidence that other factors besides pituitary iron may be limiting pituitary size. One patient with severe pituitary volume loss and hypogonadism had no detectable pituitary iron. Three other patients with volume loss and hypogonadism had only modest pituitary iron overload ($Z < 4$). We cannot exclude the possibility that chronic anemia, increased metabolic demand, or other physiologic stressors may contribute to decreased pituitary volume in TM patients; these factors could influence hypothalamic function, for example, by suppressing leptin levels [19–22]. Alternatively, these patients may have had severe pituitary iron overload in the past, suffered irreversible damage, and were subsequently chelated to a normal or less severe pituitary iron levels. Regardless of the mechanism, however, a volumetric *Z*-score lower than -2.5 was highly specific for hypogonadism. These findings are concordant with the observations of Argyropoulou et al., who demonstrated that a pituitary height <4.4 mm strongly predicted hypogonadism [9]. Given the limited distribution of pituitary volumes in our study, further work will be necessary to stratify risk for volumetric *Z*-scores between -2 and -2.5.

While pituitary volume loss was specific for hypogonadism, it lacked sensitivity. In patients with normal pituitary volume, a pituitary *R*2 $Z > 5$ also predicted hypogonadism, with a positive predictive value of $>50\%$. Our observations parallel those of Argyroupolou et al., who observed a pituitary *R*2 of 24 ± 6 Hz in TM patients with hypogonadism compared with 17 ± 4 Hz in asymptomatic TM patients and 11 ± 1 Hz in age-matched control subjects [10]. Using a combination of pituitary volume and pituitary *R*2 *Z*-scores, we identify a logical three-tiered grading system similar to the "stoplight" scheme used for cardiac *T*2* analysis [23]. Large, long-term observational studies will be required to quantify the prospective risk of developing hypogonadism in currently asymptomatic patients with pituitary iron, as was recently accomplished with cardiac *T*2* [8]. However, clinical prudence suggests that therapy escalation may be warranted for patients in the "red" zone and careful observation for patients having intermediate iron deposition and volume loss.

Our third study objective was to determine predictors of pituitary iron deposition based upon other surrogates of iron overload. Pituitary *R*2 exhibited a generally linear relationship with LIC and ferritin but curvilinear relationships with pancreatic and cardiac iron. This suggests that the kinetics of pituitary iron loading are likely intermediate between the liver and the pancreas [24,25]. Cardiac iron,

having the slowest response time to iron chelation, was therefore a strong positive predictor of pituitary iron. However, this result is not particularly useful because most clinicians escalate chelation therapy in response to an abnormal cardiac *T*2*. The relatively strong logistic relationship (AUROC of 0.88) between increased pituitary *R*2 and pancreas *R*2* suggests that trends in pancreas iron burden may be a more valuable surrogate marker for pituitary *R*2. However, trends in serum ferritin and LIC are also likely to correlate with changes in pituitary *R*2 during serial evaluation; this requires further investigation.

This study was limited by its cross-sectional nature and incomplete access to clinical data. Characterization of gonadatropin and steroid hormone levels at the time of hypogonadism diagnosis was too spotty to draw meaningful conclusions. The relative efficacy of different iron chelators on pituitary iron overload cannot be inferred from cross-sectional data. We are currently evaluating a cohort of children and young adults (<25 years of age) on defersirox monotherapy to determine the trajectory of pituitary iron and growth over time. We postulate that the sensitivity and specificity of pituitary *R*2 and volume will improve with longitudinal assessment. Nonetheless, cardiac *T*2* risk stratification was originally based upon cross-sectional observations [26], yet proved clinically useful for nearly a decade before longitudinal validation was completed [8].

A second limitation is that the data were collected on a single MRI scanner. Further work will be necessary to demonstrate inter-machine and inter-institution transferability of pituitary *R*2 measurements. However, the changes in pituitary *R*2 are so large compared with intersubject variability (threshold *Z* of 5) that small measurement biases are likely to be unimportant. The concordance of our results with pituitary *R*2 estimates by Argyropoulou is reassuring that these techniques will transfer well across platforms [10]. Pituitary volumetric analysis has not been previously performed in iron overloaded subjects, however, data from our control subjects agreed very closely with previously published work [27,28].

A third limitation is that our study cannot localize the anatomic level of HPG axis dysfunction. However, prior work suggests that primary gonadal dysfunction is a late finding, when irreversible damage to the HPG axis has already occurred [4,29]. While the strong association between pituitary *R*2 and pituitary volume with clinical disease suggests that secondary hypogonadism is the dominant etiology, we cannot exclude tertiary hypogonadism. Further, targeted studies are needed to address these questions.

Finally, risk thresholds might be different had we used a biochemical definition of hypogonadism rather than a clinical definition. For example, it is likely that some of the patients with heavy pituitary iron burdens and no clinical evidence of hypogonadism would have exhibited impaired pituitary response to GnRH stimulation or abnormal GnRH pulsatility profile on ultradan monitoring [30]. Thus the cutoffs proposed in this paper probably underestimate the disease burden and should be utilized accordingly. However, this study clearly demonstrates the ability of MRI to stratify hypogonadal risk and suggests clear targets for chelation therapy.

In summary, pituitary iron deposition occurs in the first decade of life but accelerates dramatically in adolescence. Pituitary iron deposition and volume loss are independently associated with hypogonadism, with demarcated thresholds, leading to satisfactory risk stratification. Pituitary *R*2 correlates with all metrics of iron overload, but is most strongly associated with pancreas *R*2*. Multicenter, longitudinal studies are necessary to further refine the relationship between pituitary *R*2 and hypogonadism.

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