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Cardiac Hemosiderosis in Transfusion Dependent Thalassemia: A Mini-Review

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Abstract
Iron toxicity within cardiomyocytes is considered as the main pathogenesis of cardiac dysfunction in transfusion dependent thalassemia (TDT). Various methods such as measuring serum ferritin, evaluating cardiac functional and structural parameters by either cardiac magnetic resonance imaging (CMRI) or echocardiography, and monitoring the heart rate variability (HRV) have been proposed to monitor cardiac iron content in patients. High inconsistency is present regarding predictability of various parameters derived by each of these methods in order to predict the cardiac iron overload. The aim of present review was to grasp the most appropriate parameters predicting cardiac hemosiderosis in TDT. Predicating values for cardiac iron deposition of the most in-use indicators such as ferritin, cardiac T2* relaxation time, left ventricular ejection fraction (LVEF), and HRV were discussed. In addition, a description on the most effective preventive measures for cardiac hemosiderosis was provided.
Keywords: Cardiomyopathy, Heart, Hemosiderosis, Thalassemia, Magnetic resonance imaging.

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Introduction

Transfusion dependent thalassemia (TDT) is the most frequent hereditary anemia caused by mutations in alpha or beta globin genes.[1] Although TDT patients benefit from the effects of blood transfusions, this therapeutic strategy is associated with a wide spectrum of secondary organ deficiencies due to transfusion related iron overload. Employment of effective iron chelators has resulted in outstanding improvements in both organ functions and life-expectancy in TDT patients. Nevertheless, these patients are still endangered with various morbidities and organ insufficiencies.[2,3]
Cardiac abnormalities are among the most problematic transfusion related complications in TDT patients.[4] These complications are responsible for a substantial rate of mortalities with cardiac failure, being the most common cause of death in TDT.[5] Clinical picture of cardiac dysfunction in TDT can vary from arrhythmia to pericarditis, and from heart failure to death.[6,7] TDT patients with an iron loaded heart may represent a lower heart rate, lower left ventricular ejection fraction (LVEF), and higher rates of left ventricular diastolic dysfunction.[8] Assessment of cardiac function in TDT must be routinely performed to early diagnose various functional abnormalities, and to consider required therapeutic measures.

Risk Factors of Cardiac Disease in Transfusion Dependent Thalassemia

Excess iron is considered as the main pathogenesis of heart disease in TDT. Cardiac iron overload has been associated with decreased cardiac ejection fraction in TDT.[9] Homogenous iron deposition in various heart compartments conferred the highest risk of abnormalities in ventricular dysfunction and heart failure.[10] Oxidative stress caused by excess iron within cardiomyocytes may interfere with the entrance of essential ions such as Ca^{2+} into the cells hampering the heart regular contraction patterns.[3] Iron toxicity also seems to be the main culprit in the development of cardiac fibrosis in TDT.[11] Although a relatively uncommon phenomenon, myocardial fibrosis has been reported in as high as 15%-21% of TDT patients in some studies.[12,13] Hepatitis

C infection has been noted as a factor accelerating cardiac fibrosis in TDT patients that may be promoted both directly through toxic effects of hepatitis C infection on cardiomyocytes and indirectly via developing other predisposing factors such as diabetes or hepatic disorders.[12]
Presence of other transfusion related comorbidities such as diabetes, hepatic disease, and other endocrinopathies such as thyroid disease may pave the way to the heart disease in TDT.[14] In particular, TDT patients affected with diabetes mellitus (DM) showed significantly higher possibilities for developing heart failure, arrhythmia, and cardiac fibrosis.[15] TDT patients with DM also had significantly lower cardiac T2* value respective to those without this condition indicating a heavier iron load of the heart in presence of DM.[16] These potential relationships are to be more explored in future reports.
In addition to acquired factors, genetic variations may also be of importance in iron accumulation within the heart. Among these, genetic polymorphism of glutathione S-transferase gene has been associated with reduced activity of the respective enzyme, and has acted as an independent predictor of cardiac iron overload in TDT patients.[17] Role of genetic determinants in clinical course of TDT has been neglected in the literature, and it is highly recommended to be dissected in future studies.

Cardiac Function Monitoring

Because of poor prognosis of patients diagnosed with symptomatic heart conditions, it is essential to detect high-risk patients before development of advanced clinical stages of heart disease. In-time diagnosis of a dysfunctional heart can reduce occurrence of sudden death in TDT patients. Unfortunately, concomitant presentations of the clinical, and the echocardiographic signs of heart disease confine the capability of the diagnostic methods for early detection of high-risk subjects. Nevertheless, a body of efforts have been made to present a reliable risk indicator. However, there is still no consistency on an early indicator of cardiac involvement in TDT.

Methods of Estimating Cardiac Iron Overload

Various methods have been proposed for evaluating cardiac function in TDT. The most common in-use procedures include cardiac magnetic resonance imaging (CMRI),[18-20] and echocardiography.[19,21] In fact, CMRI procedure could be a reliable method based on the chelation therapeutic strategy.[22] However, CMRI as the gold standard method for cardiac iron assessment is not available in many care centers especially in third world nations such as Iran.[8] Besides, due to late appearance of the sings of cardiac involvement in echocardiograms and electrocardiograms, using these two methods may not retrieve favorable results for detection of initial phases of cardiac iron deposition.[23]

When to Initiate Cardiac Functional Assessment

Assigning a critical age in which TDT patients should undergo tests related to cardiac iron status evaluation is unclear. In a recent study on 102 TDT patients, none of the <5 years old patients showed echocardiography evidences of cardiac iron overload. On the other hand, 15.7% of the TDT patients <7 years old showed a moderate cardiac iron overload (deduced by a T2* value <20 ms). Moderate and severe (T2*<10 ms) cardiac iron loading were identified in 42.2% and 21.6% of TDT patients older than 7 years old, respectively.[24] In another study by Borgna-Pignatti et al, a T2* <20 ms was detected in a 6-year-old TDT patient.[25] In this regard, it may be a good practice to perform heart examinations in as early as childhood period in TDT.

Cardiac Iron Overload Indicators

Heavy cardiac hemosiderosis has been described in 8%-37% of TDT patients.[16,26-28] Different indicators have been suggested as predicting factors for the rate of iron deposits within cardiomyocytes in TDT. In following sections, some of the commonly used indicators have been reviewed.

Ferritin Levels

Traditional indicator of iron status, serum ferritin level, has been repeatedly encountered as an unreliable index for organ iron load. Nonetheless, Casale et al have recently reported that a serum ferritin level >2000 ng/mL can serve as an appropriate estimate of iron deposition within the heart.[13] Furthermore, the mean ferritin level obtained by intermittent measures over the past 12 months has also been proposed as a reliable index for forecasting the cardiac iron overload.[29]

Cardiac T2* Relaxation Time

T2* MRI relaxation time has been noted as the most weighted parameter that can be exploited to monitor cardiac iron overload in TDT.[19] T2* value of ≤20 ms is consistently considered as a measure of cardiac iron overload.[5,8,19] Based on this index, TDT patients can be categorized into three risk groups including high-risk patients (T2*<10 ms), intermediate-risk patients (T2*: 10-20 ms), and low-risk patients (T2*>20 ms).[30,31] In line with this, TDT patients with T2* value <20 ms have had 4.6 times higher risk of arrhythmia compared to those who had T2*>20 ms.[32] According to a recent statement by the American Heart Association, the T2* value <10 ms may be considered as the most prominent predictive factor for heavy iron loading of the heart in TDT.[33] Despite this, some inconsistencies between T2* values and other iron estimators have been noted in various reports.
T2* relaxation times have not been correlated with ferritin level in multiple occasions.[9,17,30] On the other hand, some authors have described a negative correlation between T2* values and ferritin.[34-36] In another study, ferritin was poorly correlated with the cardiac T2* value in TDT patients.[37] Both ferritin and liver iron concentration have been associated with cardiac derived T2* values and LVEF.[27] To resolve these discrepancies, a proposition has been made noting

that ferritin may be an acceptable predictive factor of cardiac iron overload wherein at least some extent of iron deposition within the heart is noticed (e.g. in patients with T2*<20 ms).[7] This may be logically a plausible explanation for ferritin as a representing factor for iron storages within the tissues. However, a validated approach to interpolate the universally available ferritin assessment with the T2* values needs to be implemented.

As noted earlier, cardiac fibrosis represents a prominent risk for cardiac failure in TDT. Performing CMRI using gadolinium approach is commonly used for detection of cardiac fibrosis in TDT.[13] Cardiac fibrosis has been associated with lower cardiac T2* value corresponding with greater iron content.[13] However, association of cardiac fibrosis with T2* value may not be always reproducible.[38] Kirk et al has reported cases of patients with cardiac fibrosis who had T2* value >20 ms. This is in contrast to the suggested independent role of hemosiderosis in development of cardiac fibrosis in TDT.

Cardiac T2* value has been correlated with EF of both left and right ventricles, but not with mass indexes of the ventricular compartments.[39,40] T2* values have also been correlated with levels of pancreases derived digestive enzymes.[16] This observation may indicate a parallel iron deposition patterns for the heart and pancreas. In fact, there may be a possibility for using T2* values of either pancreas or liver to predict the pace of iron loading in the heart.[41] Such correlations between T2* values of the heart and of the liver has also been reported by Chen et al.[24]

Left Ventricular Ejection Fraction

Relying on LVEF for identifying TDT patients at risk of cardiac failure is highly discouraged. This is because of the adaptation of cardiac function in TDT patients in response to chronic anemia which may overestimate LVEF and therefore neglect an underlying cardiac disorder.[33] There has been a suggestion that falling more than 7% of LVEF in course of the disease may be considered as the most predictive factor for upcoming cardiac failure.[42] In echocardiographic studies, early signs of cardiac abnormalities with preserved LVEF may be presented with increased index of left ventricular mass, higher left atrium volume, and right ventricular diameter.[43] Association of T2* MRI with cardiac function is controversial. Some researchers have reported an association between the T2* value and LVEF.[39,40] In another study, T2* was not correlated with LVEF.[26] Furthermore, LVEF was of no predictive value for either estimation of heart iron content or occurrence of clinical symptoms such as arrhythmia.[7] Conclusively, LVEF may not be a true representative of cardiac iron in TDT.

Electrocardiogram

Studies assessing role of electrocardiogram (ECG) in predicting cardiac iron overload are limited. However, a specific ECG feature known as Fragmented QRS characterized with additional R waves along with abnormal wave morphology may be an early sign of cardiac iron overload in ECG.[11] This phenomenon has been correlated with abnormal indices of diastolic and systolic assessments in echocardiography.[11]

Heart Rate Variability

Recording the heart rate variability (HRV) by 24-hour Holter monitoring device has recently been noted as a potential method for assessment of cardiac siderosis in TDT.[44] A recent report showed that reduced HRV may hint the cardiac iron deposition in very early stage before being detectable by T2* MRI.[23,45,46] In assistance, HRV has also been correlated with ferritin level.[29,46] HRV is hindered by important confounding factor of anemia, and therefore may not represent true cardiac function. In fact, after correction for anemia, neither ferritin level nor not-transferrin bound iron (NTBI) did not correlate with HRV in TDT.[29] Higher numbers of premature ventricular contractions (PVCs) in a 24-hour Holter monitoring result has been noted as a sensitive and specific indicator of iron deposition in the heart.[8] T2* index can be used for predicting HRV in TDT.[29] In HRV analysis by 24-hour Holter monitoring system, R-R intervals of 5-minute segments may also be used as a predictor of T2*<20 ms in CMRI.[29] Potential of HRV analysis for monitoring the iron overload within the heart is needed to be more explored in future studies.

Preventive Measures

Iron chelator therapy is the most efficient protective measure against iron induced heart toxicity.[47] Choosing an efficient chelation strategy can dramatically reduce the risk of death because of cardiac complications in TDT. Accordingly, appropriate modifications in iron chelation regimes respective to CMRI results has been shown to lower the risk of heart failure in TDT.[18,30] In fact, using long-term continuous chelation therapy has improved T2* relaxation time even in patients with severely loaded cardiac tissue.[31] However, selecting an effective chelation strategy may be a challenging matter in TDT.

Randomized control trials on assessing the effects of different iron chelators on cardiac siderosis are limited. In one of the earliest studies in 2006, Pennell et al showed the beneficiary effects of combinational deferiprone (DFP) and deferoxamine (DFO) over monotherapy with DFO.[48] Later on in 2013, these researchers showed advantages of oral DFP monotherapy over DFO monotherapy,[33] and recently they have mentioned equal effects of DFO or deferasirox (DFX) monotherapies on the improvement of cardiac siderosis.[49] In line with these trials, TDT patients treated with combination of DFO and DFP showed significantly lower risk of heart failure than the patients who were chelated with DFO alone.[50-52] Using combinational chelation therapy of DFP and DFO resulted in better LVEF compared to DFO monotherapy.[53] Nevertheless, less willingness of TDT patients toward using DFP is its higher rate of adverse effects.[53] According to the American Heart Association guideline for management of cardiac function in TDT, it is suggested to administer combina-

tional DFP and DFX as the most effective chelator regime for removing the iron from cardiomyocytes.[33] In another study, using DFX resulted in normalization of T2* values in all patients who had T2*<20 ms after a 5-year follow-up.[54] There is a notion that iron chelation regimes are more effective in improving cardiac iron overload in more heavily iron loaded patients than those with lower content of cardiac iron overload.[28]

Poor compliance to chelation regimes is a significant factor leading to higher cardiac iron load in TDT patients.[13] Independence of chelation regime, adherence to either of these regimens (DFO, DFX, combined DFO and DFP or DFP alone) when implemented in a proper dose can result in significant improvement in T2* value of the heart.[55]

Future Perspectives

Promising ideas are emerging regarding pathophysiology of iron-loaded heart functionality in TDT. Instead of focusing on iron chelation from intracellular space, it is more intriguing to block iron entry into cardiac cells. This necessitates understanding of iron entry route into cardiomyocytes. Some candidate pathways have been proposed to participate in this process including L-type Ca^{2+} channels.[56] A recent study has divulged a potential role for calcium channel inhibitors in alleviating iron deposition within cardiomyocytes.[57] In this regard, a clinical trial is ongoing by Shakoor et al in Pakistan to explore the potential role of amlodipine (an inhibitor of the Ca^{2+} channels) in protection of cardiomyocytes from iron accumulation.[58] This is of great interest as it may introduce a new generation of therapeutic strategies in management of heart function in iron overload conditions.

Conclusion

Although ferritin may be still a useful parameter for assessment of iron loading of the heart in TDT, it renders somehow inconsistent and unreliable results. Applying more sensitive approaches that represent structural and functional status of the heart, such as CMRI, and echocardiography is recommended for identifying patients at early stages of cardiac hemosiderosis. Patients detected with cardiac iron overload should be proceeded with more intense (and optimally combined) chelation therapy for prevention of cardiac damage.

Ethical Approval

Not applicable.

Competing Interest

None.

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