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Assessment of Pancreatic Iron Overload in Transfusion Dependent Thalassemic Patients

Mozhgan Hashemieh MD[1,*]

1. Imam Hossein Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
*Corresponding author: Dr Mozhgan Hashemieh, Pediatric hematologist and oncologist, Imam Hossein Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. E-mail: m.hashemieh@sbmu.ac.ir. ORCID ID: 0000-0003-1109-7285

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Abstract
Advances in the management of transfusion dependent thalassemic patients have improved the survival of these patients. The most important consequence of repeated and frequent transfusions is iron accumulation in vital organs. The magnetic resonance imaging (MRI) is a non-invasive and valid technique for the estimation of iron stores. Despite multiple studies about cardiac and liver MRI T2*, there is limited experience about pancreatic MRI. Although there is a weak correlation between hepatic and pancreatic siderosis, MRI assessment of iron deposition in the pancreas can reduce cardiac morbidity. Pancreatic siderosis may be a predictor for the development of glucose dysregulation. Pancreatic R2* > 100 Hz is a risk factor for glucose intolerance or even overt diabetes. Splenectomy can accentuate the pancreatic iron overload. Early intensive chelation therapy in thalassemia patients can reverse glucose metabolism impairment. In this review, the MRI assessment of pancreatic iron overload in transfusion dependent thalassemia, the correlation between pancreas with liver and myocardial hemosiderosis and the importance of pancreatic iron overload in pathogenesis of diabetes mellitus in these patients were discussed.
Key words: Iron overload, Magnetic Resonance Imaging, Pancreas, Thalassemia

Introduction

Thalassemia syndromes are the most prevalent hereditary hemoglobinopathy in the world. On the other hand, our country, Iran, is located on thalassemia belt (1). Reduction or absence of β chain synthesis is the hallmark of β -thalassemia, resulting in excess of alpha chains which are unstable and precipitate in erythroid cells. This precipitation leads to accelerated apoptosis of red blood cells and hemolysis (2). Clinical manifestation appears in young infancy and major thalassemic patients, while some of its intermediate forms became transfusion dependent. The consequence of these regular and repeated transfusions is iron deposition in multiple organs of these patients. The severity of transfusional hemosiderosis depends on the frequency, volume, and duration of blood transfusion therapy (3). Iron can accumulate in heart, liver, pancreas, spleen, thyroid, parathyroid, gonads, and adrenal. Therefore, transfusion dependent thalassemic (TDT) patients need iron chelator drugs in order to improve their survival. In absence of effective chelation therapy, the main cause of death among thalassemia patients is cardiomyopathy due to iron overload. Liver fibrosis, cirrhosis, diabetes mellitus, hypogonadism, hypothyroidism, hypoparathyroidism, and adrenal insufficiency are the other complications of iron accumulation (4). Therefore, methods to estimate total body iron stores are definitely required, especially in the tailoring of chelation protocols. Serum ferritin level is a convenient, non-expensive, and available marker for the evaluation of iron stores in body, but it cannot predict cardiac siderosis properly (5). Clinical situations, such as inflammation, infection, liver disease,

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hepatitis, and vitamin C deficiency can affect the ferritin level. However, ferritin trends are unable to predict liver iron concentration (LIC) in thalassemic patients (6).

The most accurate method for the assessment of tissue iron stores in body is the biopsy of organ, but its implementation is limited because of its invasive nature (7). Reliable assessment of cardiac iron stores is a remarkable factor in predicting the survival of thalassemic patients (8). Recent advances have promoted the use of T2* magnetic resonance imaging (MRI) in the non-invasive detection of iron overload in various organs for thalassemia major and intermedia (9). This method allows for the early diagnosis of liver (10,11) and cardiac hemosiderosis (12,13). Despite numerous studies about MRI T2* of liver and heart in TDT, there are only a few published data on the pancreatic MRI T2*. In recent years, some authors have studied the correlation between hemosiderosis of myocardium, liver, and pancreas among TDT patients by means of MRI T2* (14-17). Azarkeivan et al., reported a poor correlation between liver and heart, as well as a weak to moderate correlation between pancreas and liver T2* (14). Similarly, Assis et al., reported that siderosis in other organs did not correlate significantly
with pancreatic hemosiderosis (16), while Noetzli et al., reported that pancreatic iron overload might be used as a predictor of cardiac iron overload (15).

One of the most debilitating complications of thalassemia major is glucose intolerance and diabetes mellitus. The incidence of impaired glucose tolerance test and diabetes mellitus varies from 9% to 24%. The exact etiology of diabetes mellitus in TDT patients is unclear; however, the most published data is based on increased peripheral resistance to insulin and direct toxic effect of iron deposition in pancreatic acinar and beta cells (16). Unlike the heart, the link between MRI -detectable iron and pancreatic beta cell dysfunction is not well characterized (18). Overt diabetes is rarely irreversible but in asymptomatic patients who manifest biochemical diabetes, clinical diabetes can be prevented or sometimes reversed (19). Some authors have shown that impaired glucose tolerance can be reversed by using iron chelators (20, 21). Iron accumulation in pancreas due to repeated transfusion in thalassemic patients often shows hypointensity on the T2 MRI images (22).

Cut off of pancreatic hemosiderosis in MRI study

In MRI imaging, different siderotic tissues darken extensively. The "half life" of this phenomenon is used to estimate the iron content. The results are then shown in milliseconds (ms) of T2* relaxation time. Iron overload tissues have shorter T2* relaxation times. T2* is transformed into reciprocal R2* as follows: R2 [Hz] =1000/T2 [ms] (16). Therefore R2 and R2* are directly proportional to tissue, while T2 and T2* are inversely proportional (23). The technique for measurement of pancreatic R2* and liver R2* is identical (24). In healthy individuals, pancreas R2 is less than 30 Hz, and the values of 30 – 100 Hz, 100-400 Hz, and > 400 Hz means mild, moderate, and severe pancreatic hemosiderosis, respectively (25).

Fatty infiltration of pancreas gland in older thalassemic patients can lead to many difficulties in the measurement of pancreas R2*, so the identification of pancreas R2* is much easier in children and young adults (23). In addition, the measurement of pancreatic R2* is more difficult in splenectomized patients since the splenic artery is a useful landmark (25).

In T2* measurement, the lowest threshold of normal T2* value was 26 ms (26).

Correlation between pancreas and liver hemosiderosis

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Many authors in several studies have shown that different tissues in body have various iron deposition kinetics (13, 27, 28). Therefore, every physician in the field of thalassemia must have enough information about iron overload in various organs, such as liver, myocardium, pancreas, kidneys, and hypophyseal gland. Assis et al., performed a retrospective study on pancreatic MRI in beta thalassemic patients. They had 289 MRI studies from 115 patients. These authors described a weak correlation between liver iron concentration (LIC) and cardiac as well as pancreatic R2* (16). In addition, in another study in Brazil, the authors found no correlation between pancreas and liver hemosiderosis (29). Kosariyan et al., revealed a weak correlation between liver and pancreas T2* values (30). Azarkeivan et al., found a weak to moderate correlation between T2*of pancreas and liver in 164 major thalassemic Iranian patient (14). Noetzli et al., demonstrated a weakly association between pancreas R2* and LIC due to difference in iron uptake between the liver and endocrine glands (15). Papakonstantinou et al., yielded that hepatic siderosis could not predict pancreatic siderosis. In other words, they concluded that measurement of hepatic iron concentration is a weak predictor for pancreatic or myocardial hemosiderosis (31).

Correlation between pancreas and myocardial siderosis measured by MRI

Despite a very weak correlation between hepatic and pancreatic hemosiderosis in MRI images, some authors reported a more significant correlation between cardiac and pancreatic siderosis, so pancreatic iron overload might predict cardiac hemosiderosis (15).In a retrospective study in 2012 on 115 patients with beta thalassemia, Assis et al., found a weak correlation between cardiac and pancreatic R2*(16). In a review article in 2015, Wood suggested that iron deposition in the pancreas occurred earlier than heart and non transferrin bound iron (NTBI) accumulating in both organs (23). In a prospective study on 131 thalassemia major patients between 2004 and 2007, Noetzli et al., found a relatively strong relationship between cardiac and pancreatic R2* (15). They observed that patients with myocardial siderosis had elevated pancreatic R2* (15). They found that a pancreas R2* cut off of 100 Hz had a positive predictive value of 61.5% and a false negative rate of only 3%., but they noted that the relatively weak positive predictive value made this test only suitable as a screening tool (15). Meloni et al., in a prospective study on 147 thalassemia major patients in 2015, observed a positive correlation between pancreatic hemosiderosis and cardiac iron overload. These authors noted that pancreas R2* could predict left ventricular function (32). In many studies, the positive correlation between pancreatic hemosiderosis and cardiac iron accumulation were suggested to be due to the same L-type calcium iron channels in heart and pancreas. Therefore, it was concluded that these two organs took up NTBI (33). This strong correlation between cardiac and pancreatic hemosiderosis shows that chelation protocols which fail to prevent cardiac siderosis may also fail to stop pancreas siderosis (34).

Correlation between diabetes mellitus and pancreatic iron overload

Several studies have reported that pancreatic iron overload occurs in 75%-100% of thalassemic patients (14, 17, 31). The overall incidence of diabetes and impaired glucose tolerance test varies from 9% to 15% in different studies (35, 36). In a study by Inati et al. in 2015, the prevalence of diabetes and glucose intolerance was 9.9% and 7.1% in β-

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thalassemia major and 2% and 24% in thalassemia intermedia (37). The incidence of diabetes and impaired glucose tolerance increases among older patients due to the increase in pancreatic hemosiderosis.

Papakonstantinou et al., revealed that the problems in the regulation of glucose metabolism usually occurred after the second decade of life (31). One of the most important factors in the pathogenesis of diabetes mellitus in thalassemic patients is pancreatic iron overload leading to impairment in insulin excretion. However, pancreatic hemosiderosis is not the sole etiology of diabetes among thalassemic patients. With advancing age, peripheral insulin resistance occurs. Liver dysfunction due to chronic iron overload is responsible for increased insulin resistance. Pancreatic autoimmunity is another factor that can affect the pancreatic function. This immune damage can be demonstrated by auto antibodies against islet cells in pancreas (38). Pfeifer et al., demonstrated that fatty transformation of pancreas might be a risk factor for impaired glucose metabolism (39).

The relationship between pancreatic hemosiderosis measured by MRI and diabetes mellitus or impaired glucose tolerance in different published studies is controversial. Matter et al., (2010) found iron deposition in pancreas of young thalassemic patients and reported a relationship between pancreatic siderosis and diabetes in these patients (17). Youssef et al., also found an association between pancreatic hemosiderosis and diabetes (P<001)(40). Noetzeli et al., showed that pancreas R2 reading was a relatively reliable predictor for glucose metabolism impairment ($r^2 = 0.28$, $P<0.001$). Although cardiac R2* was less sensitive ($r^2 = 0.23$, $P<0.001$), it was a more specific predictor because it implied increased pancreatic iron for a longer duration. Additionally, an association between insulin resistance and LIC ($r^2 = 0.19$, $P<0.001$) as well as insulin resistance and ferritin levels ($r^2 = 0.20$, $P<0.001$) was reported (18). De Sanctis et al., reported a correlation between diabetes mellitus and pancreatic iron using imaging technique (36). Assis et al., found that pancreatic and cardiac R2* had a predictive power ($p<0.0001$) for identifying diabetes (16) .In contrast to above mentioned studies, no significant correlation between pancreatic MRI reading and diabetes mellitus in thalassemic patients was in other studies. Hashemieh et al., studied 130 Iranian thalassemic patients (26 diabetic and 104 non diabetic) and did not find a significant difference between diabetic and normoglycemic thalassemia patients regarding pancreas T2* relaxation times ($P=0.202$) (41). Li et al. did not find a statically significant relation between pancreatic iron overload and diabetes mellitus, either. However, they found that patients with diabetes mellitus had a significantly lower pancreatic volume when compared with those without diabetes ($p< 0.001$) (19). It was shown that intensive combination chelation therapy with deferoxamine and deferiprone might partially reverse the course of diabetes mellitus among thalassemia patients .The level of pancreatic hemosiderosis should be considered in all patients with thalassemia major, since the early detection of pancreatic iron overload and its control in young patients can delay the onset of overt diabetes or totally prevent it in adulthood(42).

Conclusion

Estimation of pancreatic iron content by MRI study is a valid and non invasive method. Despite the weak correlation between liver and pancreas hemosiderosis, research has shown that MRI assessment of iron deposition in the pancreas can predict cardiac function. Additionally, in some studies, pancreatic siderosis was introduced as a predictor for glucose dysregulation or overt diabetes. However, in some other studies, no correlation between pancreatic iron overload and diabetes mellitus was reported. However,

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review of literature has shown that early iron chelation in patients with pancreatic iron overload can partially reverse glucose intolerance.

Conflicts of interest

There are no conflicts of interest.

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