Detection of Iron in Liver and Myocardial by Magnetic Resonance Imaging

Bassam Abuarquob
Department of Medical Imaging, Faculty of Health Professions; Al Quds University /Jerusalem
Bassamabu@paluniv.edu.ps

Hjouj MOHAMMAD*
Associate Professor Of Medical Imaging, Faculty Of Health Professions; Al Quds University/Jerusalem,
mhjouj@Staff.Alquds.Edu
mhjouj@Hotmail.Com

ABSTRACT

Background: Magnetic Resonance Imaging (MRI) is a non-invasive modality used to detect the iron overload in the liver and myocardial . The aim of the current study was to assess both Liver Iron Concentration (LIC) and Myocardium Iron Concentration (MIC) for thalassemia major patients using MRI.

Methods and sample: The current study dealt with 70 thalassemia patients aged 11-31y. 20 of them, do not suffer from heart disease and do not have a satisfactory history of blood transfusion. cardiac and liver T2* MRI and Serum Ferritin estimation was done for all subjects. Measurements were obtained using (a 1.5T MRI Philips Ingenia), at the Radiology Department in Hebron Governmental Hospital.

Results: The mean Serum Ferritin (SF) among participants was 2150 ng/ml (SD 2179ng/ml). Significant correlation was found in participants between LIC, mean 15mg/g, (dry weight), and SF levels ($r = 0.522$; $p < 0.001$), and also significant but weaker correlation was found in patients between MIC, mean 1.3mg/g. (dry weight), and SF levels ($r=0.483$; $p<0.001$). Seventeen participants (34%) had a SF of <1000 ng/ml. Of them, 11 and 3 participants respectively had LIC and MIC more than normal range.

Conclusions: The relaxation rates R2 (1/T2) and R2* (1/T2*) measured by MRI is a valuable non-invasive tool for quantification of liver and myocardium iron deposition in patients with thalassemia major

CCS CONCEPTS

• **MRI**; • **Iron**; • **thalassemia**;

KEYWORDS

Myocardium Iron Concentration, T2* MRI, liver iron overload,

ACM Reference Format:
Bassam Abuarquob and Hjouj MOHAMMAD*. 2022. Detection of Iron in Liver and Myocardial by Magnetic Resonance Imaging. In *2022 5th International Conference on Digital Medicine and Image Processing (DMIP 2022), November 10–13, 2022, Kyoto, Japan.* ACM, New York, NY, USA, 5 pages. https://doi.org/10.1145/3576938.3576945

DMIP 2022, November 10–13, 2022, Kyoto, Japan

ACM ISBN 978-1-4503-9764-3/22/11.
https://doi.org/10.1145/3576938.3576945

1 INTRODUCTION

Magnetic Resonance Imaging (MRI) is a non-invasive medical imaging modality that produces detailed three dimensional anatomical and functional images. It utilizes a combination of a strong magnetic field and radio waves with a sophisticated technology that excites and detects the change in the direction of the rotational axis of protons in water that makes up living tissues. High-resolution MRI play a great role in the diagnoses, treatment design and monitoring the minimally invasive ablation procedures such as Non-Thermal Irreversible Electroporation (NTIRE) technology to carry out the treatment with high accuracy and effectiveness [1, 2].

In the literature, the reconstruction problem- in general- is the determination of some property of an internal structure of an object without having to damage the object. In doing so, different probes have been used such as visible light, sound waves ray, Gamma ray, nuclear magnetic resonance signals, and many others. A large variety of objects can be studied whose size ranges, from measurements used by astronomer to microscopes. Among these, of course, is the human body. In 1917 J. Radon, [3], showed that it is possible to reconstruct a suitably regular real valued function f from the set of all projections for angles of projections. Radon's work found application in the field of Computed Tomography [4-8]. In this context, the function f of study corresponds to the density of tissue at a point (x,y) in some plane slice through a human body and the Radon Transform is a measure of the logarithm of the absorption of an x-ray beam that passes through the body along the lines (rays).

It is impressive to observe that the one unifying Mathematical tool for this technology is the Radon Transform. This Technology is applied not only in medicine, but recent success in many other fields, such as Seismology, Geophysics, Digital Rock Physics, and others [9-11]. In addition, image registration techniques utilize the Integral Transforms approach including the Radon, Fourier, Hough, Trace Transform, and many others. Different approaches are proposed to recover spatial transformations relating two images using their Radon transforms another major approach related to Radon transform uses invariant pattern recognition using the theory of moments [12-16].

The success of computerized Tomography (CT),[6] motivated researchers for different reconstruction methods to serve other medical modalities such as Emission CT, Ultrasound CT, Magnetic Resonance, and others.

Thalassemia is one of the most common blood diseases, where the efficiency of red blood cell production is low. Thalassemia patients who receive blood transfusion continuously accumulate an amount of iron in the body's cells. The accumulation of iron amounts leads to a fatal iron overload (IO) [17]. Serum ferritin (SF)

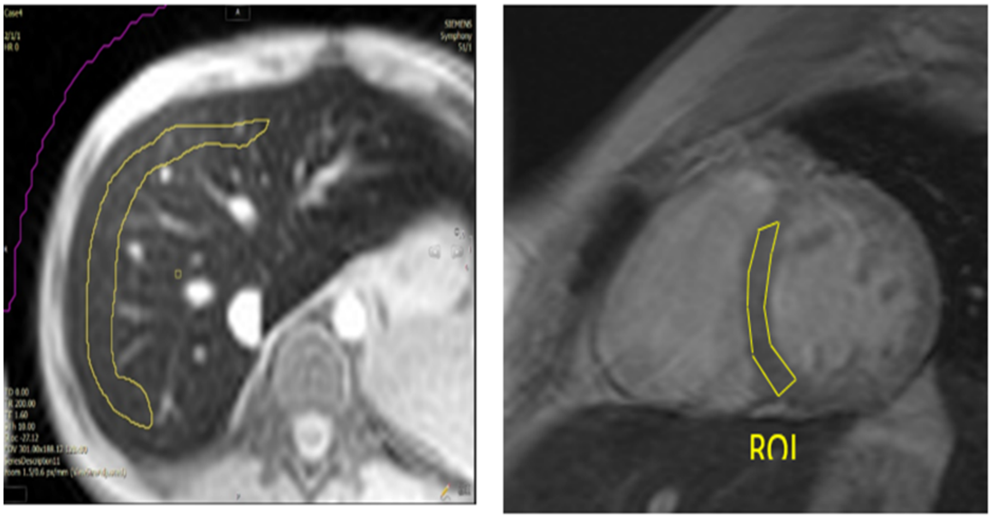

Figure 1: Liver and Myocardium muscle ROI.

test determines the level of iron in the blood. However, SF results cannot be completely trusted in determining the amount of iron stored in the liver or myocardium. Recently, studies have reported the ability of MRI to detect the presence of amounts of iron in the myocardium and liver [18-22].

Previous studies have shown that MRI is better than the SF test in detecting the amount of iron in the liver than in the myocardium. SF and T2* MRI myocardium results in thalassemia patients were weak while the difference was significant [23-26]. Therefore, the current study assesses iron levels in both myocardium and liver using MRI of thalassemia patients.

Serum markers such as serum iron, transferrin, and ferritin can be assessed through blood serology, and provide the simplest and least expensive method to assess body iron stores. While they show some correlation with quantitative Liver Iron Concentration (LIC), serum iron markers are often inaccurate and, because they are acute phase reactants, can be confounded by systemic conditions such as malignancy or inflammatory states. Although these limitations are widely recognized, serum markers remain the primary means of diagnosis, and are often used to initiate and modify chelation therapy.

The current study aims to validate MRI in determining the amount of iron in both myocardium and liver and to use T2*MRI to estimate IO in thalassemia patients in Palestine.

2 METHODOLOGY AND MATERIALS

Liver and myocardium MRI used to estimate the amount of iron in tissues. Procedure was performed using a body coil on a 1.5T (PHILIPS-INGENIA). Multiple recombined gradient echo (MERGE) T2* images were applied.

A dedicated protocol was applied to capture multiple images during a single breath hold with 12 echoes, first echo time (TE) 0.8 ms, ΔTE = 1.3 ms, and TR 200 ms. Each sequence time equals seven minutes. To measure the intensity of the TE signal, a region of interest (ROI) was determined for the 1.2-1.4 cm^2. The liver and myocardium ROIs were determined by plotting it in the right lobe that does not contain any blood vessels or bile ducts as shown in (Fig. 1); [27, 28]. T2* value or the reciprocal R2* (=1/T2*) is calculated by using a gradient echo sequence. However, the signal loss in this sequence is very fast due to the strong local variations in the magnetic field known as the susceptibility effect e.g. the iron oxide. For MIC, the gradient echoes of T2* at the breath-hold and ECG gates which were used with varying TEs. The triggering technique was used in conjunction with the heart cycle. Multi-localizer sequences were obtained followed by a 2-chamber, 4-chamber, and a Short-axis localizer.

A section was taken during the contraction of the ventricles by using the same parameter. The sequence performed during a single breath-hold as follows: TR = 200 ms, 10 echoes, TE1 = 2 ms, and longest TE2 of 20. To measure the signal intensity of the TE in the period of ventricles constriction, the ROI was drawn with a 1.0−1.3cm2 as shown in (Fig.1).

A consultant hematologist selected patients for MRI scan and provided baseline clinical data (hematocrit, SF levels, age, sex, disease type, chelation system, and hemoglobin). The schedule of procedures was arranged in agreement with the MRI department at Hebron Governmental Hospital.

Interpretation and reporting performed locally in the MRI unit, and results were submitted to the referring physician for further patient management.

2.1 Research setting

The study focused on Palestinian patients with thalassemia major, whose ages ranged between 11 and 31 years. Patients were sampled and their SF examined. At the same time, iron levels in the myocardium and liver were measured by T2*MRI and then the results were compared.

2.2 Sample and population

The study population consisted of all thalassemia patients who underwent blood transfusions several times in Hebron Governmental Hospital - Palestine. A total of 70 subjects participated in this study, 50 patients with thalassemia major, and 20 healthy subjects as a control group. Patients were selected based on the evaluation of a consultant hematologists/pediatricians. All participants underwent an MRI procedure from December 2018 to March 2019, and a printed or online report of the procedure including liver and myocardium IO assessment provided to the participant within 15 days of examination. Participants clinical record including (age, gender, diagnosis, transfusion history, chelation, doses, hemoglobin level, ferritin level, history of hepatitis C and splenectomy) were collected from the Hospital Information System (HIS) at Hebron General Hospital.

2.3 Inclusion criteria

All Palestinian thalassemia patients with chronic regular blood transfusions or with an abnormal level of SF in Hebron General Hospital, who were referred to clinical MRI and aged ≥ 11 years were included.

2.4 Exclusion criteria

Patients with contra-indications for MRI, such as permanent pacemakers or Cochlear implants, cerebral aneurysm clips, etc. or <11 years old were excluded.

2.5 Research design

The researchers adopted a prospective case study design utilizing files in HIS at Hebron Governmental Hospital, comparing thalassemia patients MRI and SF results to a control group results.

2.6 Statistical analysis

Statistical analysis in this study was based on SPSS software version 16. The Mean values of SF, LIC, and MIC were calculated. In addition, the correction coefficient was calculated for MIC, LIC, T2*, and SF levels. T-test was used for the comparison of means. The value p< 0.05 was considered as significant change. The various variables were analyzed by Pearson correlation coefficient. Coefficient of determination (R2) for curve fitting was calculated from the preprogrammed excel sheet. Results are expressed as mean ±SD.

3 RESULTS

50 patients with thalassemia major, referred for liver and myocardium iron detection were enrolled in the study. The age range of the participants was 11–31 y (mean 20.6 ± 6.18 SD, median of 21), of which 38 (76%) were males and 12 (24%) were females. 20 participants as controls with age range of 11to 31 y (mean 21.6± 5.64 SD, median of 21Y), of which 12 males were (60%) and 8 females were (40%). The weight range of the participants was 33–83 kg (mean 67 ± 13.364 SD) and of controls was 42–86 kg (mean 67 ± 12.0265 SD).

The height range of participants was 122-164 cm (mean 144.62 ± 13.06 SD) and controls were 126-175 cm (mean 154.7 ± 12.95 SD). The participants' AST range was 15-143 U/L (mean 53.20 ± 27.750 SD) and of the controls was 14-30 U/L (mean 21.50 ± 4.628 SD), the difference was statistically significant (p < 0.001) . The participants' ALT range was 13-137 U/L (mean 68.12 ± 36.136 SD) and it was 20-35 U/L (mean 27.50 ± 4.490 SD), the difference was statistically significant (p < 0.001).

The range of hemoglobin of the participants was 6.2–10.5 g% (mean 7.4 ± 1.214 SD) and of controls was 10.2–13.4 g% (mean 11.79 ± 0.941 SD), the difference being statistically significant (p < 0.001).

Among 50 participants, 14 had previous splenectomy. No statistically significant variant was seen in the mean SF levels, liver T2*, LIC, heart T2* and MIC values in patients with and without splenectomy. Participants mean SF was 1505.882 ng/ml (SD 2843.9 range: 76–12,800, median: 481.5). While controls mean SF was 98.7 ng/ml (SD 25.03, range: 72–142, median: 89.5).

Mean liver T2*, R2*, LIC in participants with normal and abnormal SF levels are depicted in Table 1. Statistically significant variation (p < 0.001) was seen in mean LIC between group of participants having normal and abnormal SF. Mean heart T2*, R2*, MIC among participants with abnormal and normal SF levels are shown in Table 2. There was a statistically significant difference found in mean MIC (p < 0.001) between groups of participants with normal and abnormal SF levels. Among the 50 patients, 39 (78%) had a blood transfusion every 2 weeks, while 11 (22%) had a blood transfusion every 3 weeks. No statistically significant variation in mean SF, T2*, LIC, cardiac T2*, and MIC values was observed between patients on 2-week and -3-weekly transfusion therapy.

Participants LIC mean was 5.696 mg/g (SD 8.879, range: 0.48–35.6, median: 2...39) and mean LIC in controls was 0.73 mg/g (SD 0.5293, range: 0.1–1.5, median: 0.5146). There were 41 patients with abnormal LIC and 9 patients with abnormal LIC values. Among the 50 patients, 9 (18%) patients had normal (degree one) LIC, 10 (20%) patients had degree 2 (moderate) LIC, 13 (26%) patients had degree 3 (light) LIC, and 18 (36%) patients had degree four (severe) LIC. Participants with a normal LIC also had a normal MIC, 30 patients had a normal MIC and 11 had an abnormal MIC out of the 41 patients with an abnormal LIC.

The distribution of patients with normal and abnormal LIC and MIC is shown in Table 1. The mean SF levels in participants with normal LIC was 385 mg/g (SD 319) and variance was seen between mean SF levels in normal vs. abnormal LIC (p < 0.001). Participants mean MIC was 1.5 mg/g (SD 1.3, range: 0.42–4.77, median: 0.81) and mean MIC in between controls was 0.58 mg/g (SD 0.1, range: 0.4–1, median: 0.61).

Among the 50 patients, 5 (10%) patients had grade 4 (severe) MIC, 4 (8%) patients had grade 3 (moderate) MIC, 3 (6%) patients had grade 2 (light) MIC, and 38 (67%) patients had normal (grade 1) MIC. Amongst the 34 participants with normal MIC, 15 had normal LIC and 23 had abnormal LIC. All the 12 participants with abnormal MIC also had abnormal LIC.

Among the participants with normal MIC the mean SF was 1498.5 mg/g, and in participants with abnormal MIC SF levels was 3357.8 mg/g.

Statistically, a significant difference was seen between the mean SF levels in group of participants with normal vs. abnormal MIC (p 0.01). Liver T2* had significant weak negative correlation with SF levels (r = -0.327, p 0.011). Heart T2* had moderate negative correlation with SF levels (r = -0.4750, p 0.002).

Table 1: Mean Liver T2*, R2*, LIC and Heart T2*, R2* MIC among participants with normal and abnormal SF

Parameters	Liver T2*Mean (SD)	Liver R2*Mean (SD)	LICMean (SD)	Heart T2*Mean (SD)	Heart R2*Mean (SD)	MIC Mean (SD)
Normal SF	19.115 (13)	84.4 (76.7)	1.8(2.14)	36.49(7.47)	29 (7.6)	0.61 (0.19)
Abnormal SF	3.5 (3.9)	512.7 (241.)	16 (07.8)	22.7 (10.4)	53.4 (35.2)	1.5 (1.3)

LIC Liver iron concentration; MIC Myocardial iron concentration; SF serum ferritin

Table 2: Distribution of participants with normal and abnormal LIC and MIC

	Normal MIC (%)	Abnormal MIC (%)	Total (%)
Normal LIC	9 (100)	0 (0)	9 (18)
Abnormal LIC	30 (60)	18 (36)	41 (82)
Total	39 (78)	18 (36)	50 (100)

Liver T2* had weak positive correlation with heart T2* ($r = 0.339$, p 0.01).

LIC had moderate positive correlation with SF ($r = 0.546$, $p < 0.001$). MIC had moderate positive correlation with SF ($r = 0.454$, $p < 0.001$). There was also a significant positive correlation found between LIC and MIC ($r = 0.437$, p 0.001).

4 CONCLUSION

An MRI can be used to estimate the amount of iron in the liver and myocardium. Most previous studies recommended the use of T2*MRI for iron detection. In addition, both liver and myocardial iron concentrations are obtained from the T2*GRE sequence can be repeated several times for aquirate iron quantification. There are limitations to the accuracy of the MRI method in hematology and hepatology. but, relaxation rates measured by MRI are a valuable non-invasive tool for estimating iron deposition in the liver and myocardium in patients with thalassemia major, and it is expected that they will be used frequently in the near future for this purpose.

REFERENCES

[1] Hjouj, Mohammad; Lavee, Jacob; Last, David; Guez, David; Daniels, Dianne; Sharabi, Shirley; Rubinsky, Boris; Mardor, Yael. “The Effect of Blood Flow on Magnetic Resonance Imaging of Non Thermal Irreversible Electroporation” Nature – Scientific Reports Volume: 3 Article Number: 3088 DOI: 10.1038/srep03088 Published: OCT 30 2013

[2] Osama Makhamrah, Muntaser S. Ahmad, Mohammad Hjouj “Evaluation of Liver Phantom for Testing of the Detectability Multimodal for Hepatocellular Carcinoma” DMIP2019. ACM (ISBN: 978-1-4503-7698-3),”

[3] J. Radon, "On the determination of functions from their integral values along certain manifolds," in IEEE Transactions on Medical Imaging, vol. 5, no. 4, pp. 170-176, Dec. 1986, doi: 10.1109/TMI.1986.4307775.

[4] Hounsfield GN. “Computerized transverse axial scanning (tomography). 1. Description of system”, Br J Radiol. Dec;46(552):1016-22, 1973, doi: 10.1259/0007-1285-46-552-1016.

[5] F. Hjouj, “Towards tomography with random orientation”, ACM International Conference Proceeding Series, pp. 49–53, 2019, https://doi.org/10.1145/3379299.3379309

[6] Deans S.R, “The Radon Transform and Some of Its applications”, New York, USA: John Wiley& Sons, Inc,1983

[7] H. Arjah, M. Hjouj, F. Hjouj, “Low dose brain CT, comparative study with brain post processing algorithm,” 2nd International Conference on Digital Medicine and Image Processing, DMIP 2019. pp.1-7, 2019, https://doi.org/10.1145/3379299.3379308

[8] Hansen, Per Christian, Jakob Jørgensen, and William RB Lionheart, eds. “Computed Tomography: Algorithms, Insight, and Just Enough Theory”, Society for Industrial and Applied Mathematics, 2021.

[9] M. S. Jouini, F. Bouchaala, M. K. Riahi, M. Sassi, H. Abderrahmane and F. Hjouj, "Multifractal Analysis of Reservoir Rock Samples using 3D X-ray Micro Computed Tomography Images," in IEEE Access, 2022, doi: 10.1109/ACCESS.2022.3186476

[10] M.S. Jouini, F. Bouchaala1, E. Ibrahim, F. Hjouj, " Permeability and Porosity Upscaling Method Using Machine Learning and Digital Rock Physics," Conference Proceedings, 83rd EAGE Annual Conference & Exhibition, vol. 2022, pp.1 – 5, 2022, DOI: https://doi.org/10.3997/2214-4609.202210016

[11] Tembely, M., AlSumaiti, A., Jouini, M. S and Rahimov, K. (2017). The Effect of Heat Transfer and Polymer Concentration on Non-Newtonian Fluid from Pore-Scale Simulation of Rock X-ray Micro-CT. Polymers, 9(10), 509.

[12] F. Hjouj and MS. Jouini, “On the Radon transform and linear transformations of images”, ACM International Conference Proceeding Series, pp. 26–31, 2019, https://doi.org/10.1145/3379299.3379306

[13] F. Hjouj and MS. Jouini, “On Image Registration using The Radon Transform": Review-and-Improvement", DMIP ’21: 2021 4th International Conference on Digital Medicine and Image Processing, pp. 17–23, 2021, https://doi.org/10.1145/3506651.3506654

[14] F.Hjouj, M.S Jouini, “On Orthogonal Polynomials and Finite Moment Problem ”, Open Chemical Engineering Journal, to appear

[15] G. Chen, S. Coulombe, “A new image registration method robust to noise, Multidimen”, Syst. Signal Process. 25 (3) , 601–609.2014

[16] Hjouj, F. Jouini, M.S. Review and improvement of the finite moment problem. Open Chemical Engineering Journal, 14, pp. 17–24, 2020, DOI:10.2174/1874123102014010017

[17] Aessopos, A., Fragodimitri, C., Karabatsos, F., Hatziliami, A., Yousef, J., Giakoumis, A., . . . Karagiorga, M. (2007). Cardiac magnetic resonance imaging R2* assessments and analysis of historical parameters in patients with transfusion-dependent thalassemia. Haematologica, 131-132.

[18] Anderson, L., Holden, S., Davis, B., Prescott, E., Charrier, C., Bunce, N., . . . Pennell, D. (2001). Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. European Heart Journal, 2171-2179.

[19] Ballas, K. S., Kesen, R. M., Goldberg, F. M., Lutty, A. G., Dampier, C., Osunkwo, I., . . . Malik, P. (2012). Beyond the Definitions of the Phenotypic Complications of Sickle Cell Disease: An Update on Management. Hindawi, 1-56.

[20] Carpenter, J.-P., He, T., Kirk, P., Roughton, M., Anderson, J. L., Noronha, V. S., . . . Pennell, J. D. (2011). On T2* Magnetic Resonance and Cardiac Iron. Circulation, 1519-1528.

[21] Castiella, A., Alustiza, M. J., Emparanza, I. J., Zapata, M. E., Costero, B., & Diez, I. M. (2011). Liver iron concentration quantification by MRI: are recommended protocols accurate enough for clinical practice? Europian Radiology, 137-141.

[22] Chandarana, H., Lim, P. R., Jensen, H. J., Hajdu, H. C., Losada, M., Babb, S. J., . . . Taouli, B. (2009). Hepatic Iron Deposition in Patients With Liver Disease: Preliminary Experience With Breath-Hold Multiecho T2*-Weighted Sequence. American Journal of Roentgenology, 1261-1267.

[23] Douskou, M., Terpos, E., Papassotiriou, L., Stamoulakatou, A., Ourailidis, A., Loutradi, A., & Loukopoulos, D. (2004). Magnetic resonance imaging in the evaluation of iron overload in patients with beta thalassaemia and sickle cell disease. British Journal of Haematology, 736-742.

[24] Engelfriet, C., Harmatz, P., Butenski, E., & Quirolo, K. (2003). Severity of Iron Overload in Patients with Sickle Cell Disease Receiving Chronic Red Blood Cell Transfusion Therapy. VoxSanguinis, 265-265.

[25] Ghugre, R. N., Enriquez, M. C., Gonzalez, I., Nelson Jr, D. M., Coates, D. T., & Wood, C. J. (2006). MRI detects myocardial iron in the human heart. Magnetic Resonance in Medicine, 681-686

[26] Zamani, F., Razmjou, S., Akhlaghpoor, S., Eslami, S.-M., Azarkeivan, A., & Amiri, A. (2011). T2* magnetic resonance imaging of the liver in thalassemic patients in Iran. World Journal of Gastroenterology, 522-525.
[27] Kirk, P., He, T., Anderson, J. L., Roughton, M., Tanner, A. M., Lam, W. W., . . . Pennel, J. D. (2010). International reproducibility of single breathhold T2* MR for cardiac and liver iron assessment among five thalassemia centers. JMRI, 315-319.
[28] Kolnagou, A., Natsiopoulos, K., Kleanthous, M., Loannou, A., & Kontoghiorghes, J. G. (2013). Liver iron and serum ferritin levels are misleading for estimating cardiac, pancreatic, splenic and total body iron load in thalassemia patients: factors influencing the heterogenic distribution of excess storage iron in organs as identified by MRI T2*. Toxicology Mechanisms and Methods, 48-56.
[29] Abdelghaffar, H., Kamel, S., and Duquenoy, P. (2010). "Studying E-Government Trust in Developing Nations: Case of University and Colleges Admissions and Services in Egypt". Proceedings of the International Information Management Association Conference, Utrecht, The Netherlands.

,