Glycemic Status of Transfusion Dependent B Thalassemia Patients

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Impaired glucose tolerance and diabetes are well known complications in multitransfused thalassemia patients due to iron overload. This study was a cross-sectional descriptive type of study, conducted at Paediatric department of Rajshahi Medical College from January 2013 to December 2014. Eighty transfusion dependent thalassemia major patients were enrolled by purposive sampling. The aim of this study was assessment of glycemic status in transfusion dependent thalassemia major patient. Medical history, physical findings were noted and OGTT and serum ferritin level was estimated in all patients. Evidence of diabetes was based on WHO criteria. This study has shown that abnormal glucose tolerance developed in 22.5% (18 patients) among which IGT in 17.5% (14 patients), and DM in 5% (4 patients). Serum ferritin (mean 4036.27±2013.35) was very high in all patients. Frequently transfused older patient with poor compliance and delay in starting iron chelation therapy has increased risk of development of abnormal glucose tolerance. Early starting and regular chelation therapy might prevent such complication.

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Key words: Thalassemia major, Serum ferritin, OGTT, Iron overload, Diabetes

Introduction

β-thalassemia major is more prevalent in the Mediterranean basin, the Middle East, Southern and Eastern Asia, the South Pacific and South China. Recent data indicate that about 7% of the world's population is a carrier of a haemoglobin disorder, and that 300,000-500,000 children are born each year with the severe homozygous states of this diseases.[1] The diagnosis is usually made within the first year of life. Regular blood transfusion is the mainstay of therapy but results in increases iron store to many times the normal unless chelation therapy is given[2]. The chronic anemia produces an increase in iron absorption from the gastrointestinal tract. However, despite chelation therapy, excess iron is deposited, in various endocrine organs especially in the beta cells of the pancreas leads to diabetes mellitus.[3,4,5.] Adolescent and young adult patients are at increased risk and frequently developed IDDM.[6,7] The severity and type of glucose disturbances vary greatly in different studies. In addition, controversy about the etiology of this glycemic abnormality still exists.[7, 8,9,10]

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Diabetes mellitus in thalassemia has been attributed to impaired secretion of insulin secondary to chronic pancreatic iron overload,[11] and to insulin resistance[12] as a consequence of iron deposition within liver or skeletal muscle. Diabetes has also been linked temporarily to episodes of acute viral hepatitis in some patients.[13] Prevalence has been reported to range from 2.3 to 24%, [14] and risk factors for diabetes in patients with β-thalassemia major have been suggested to include age, increased amount of blood transfusion, serum ferritin level, compliance with iron-chelation therapy, family history of diabetes, hepatitis viruses, and pubertal status.[9,15,16,17] In a study performed on 384 thalassemia major patients that referring to Ali Asghar Hospital, Iran, with age range of 10-30 years, prevalence of diabetes was 15.1% (58 patients) that 37.9% were women and 62.1% were men. [18] So this study has been undertaken to see the glycemic status of transfusion dependent β-thalassemia patients and how many patients have developed diabetes and impaired glucose tolerance.

Aims and objective

General objective - The aim of this study was the assessment of glycemic status in transfusion dependent β-thalassemia patients.
Specific objective -

1. To find out the frequency of IGT and DM in β-thalassemia patients.
2. To determine the relation of IGT and DM with age of patients with β-thalassemia.
3. To estimate the relation of IGT and DM with S. ferritin level with β-thalassemia.

Methods

*Type of Study***:** The study was hospital based a cross-sectional descriptive one.

Place of Study: The study was conducted in the Department of Paediatrics and Department of Pathology of Rajshahi Medical College and Hospital.

Study population: All the β-thalassemia patients those were fulfilled the selection criteria.

Period of Study: January 2013 to December 2014.

*Sample size***:** Total number of sample was 80.

Sample size determination technique:

$n_0 = \frac{Z^2 pq}{d^2}$ n_0 = Sample Size

= 73 p = prevalence rate of the disease (5%) = 0.05

q =1-p=1-0.05 = 0.95

d = acceptable slandered error (5%) = .05

z = 1.96 at 95% Confidence limit

There was chance of dropout about 10% (7); therefore estimated total sample size was 73+7= 80.

Sampling methods: Purposive sampling.

Inclusion criteria

1. Thalassemia major.
2. Age: 5 -15 years.

Exclusion criteria

1. Age <5 and >15 years.
2. New case of β-thalassemia.
3. Thalassemia minor.

Study Procedure

For face to face formal interview, an interviewer administered questionnaire used to collect data from the study subjects. All patients were interviewed and filled out partially standard questionnaires and physical findings were noted. This information included followings: age, sex, age at first blood transfusion, frequency of blood transfusion, total number of transfusions, about chelation therapy, serum ferritin and family history of diabetes. All the patients were divided into two age group, 5-10yrs, and >10 yrs. For OGTT child were advised to kept overnight fast for 8-12 hours. With all aseptic precaution fasting venous blood sample taken for FBS, Hb%. Then 1.75gm/kg glucose was given by mouth and two hours later second blood sample taken for 2hABG level. Serum ferritin level was estimated from first sample if it was not done within last 6 (six) months of examination. All the findings and investigation reports were recorded and analyzed.

Result

Primary analysis of clinical data from 80 β-thalassemia major patients, of which males were 49 (61.3%) and females were 31 (38.8%). The age range of all patients was from 5 to 16 years (mean 10.19±2.52) (table-1). All patients showed high serum ferritin ranges from 1580-9700ng/ml (mean 4036.27±2013.35ng/ml). Chelation therapy was received 30 (37.5%) patients but regular only 9 (11.2%) patients.

Table I: Demographic characteristics of patients

Sl. no	Patients characteristics	Mean	Range
1.	Age	10.19±2.25	5.50-15.5
2.	Sex		
	Male	49(61.2%)	
	Female	31(38.8%)	
3.	Weight (kg)	25.75±7.33	12-48
4.	Height (cm)	126±12.30	105-161
5.	Age at first BT (months)	13.10±6.03	4-30
6.	Duration of BT (years)	8.71±2.47	4-14.5
7.	Age of start chelation	8.81±1.97	5-13
8.	Serum ferritin	4036.27±2013.35	1580-9700
9.	Fasting blood sugar	5.31±1.57	2.3-14.44
10.	Blood sugar 2h after glucose	6.47±2.49	3.8-21.38

This table shows that most of study patients were in lower age group and male were more in number. They started 1st blood transfusion around one year of age. There were delay in starting chelation therapy (mean age 8.81±1.97 years).

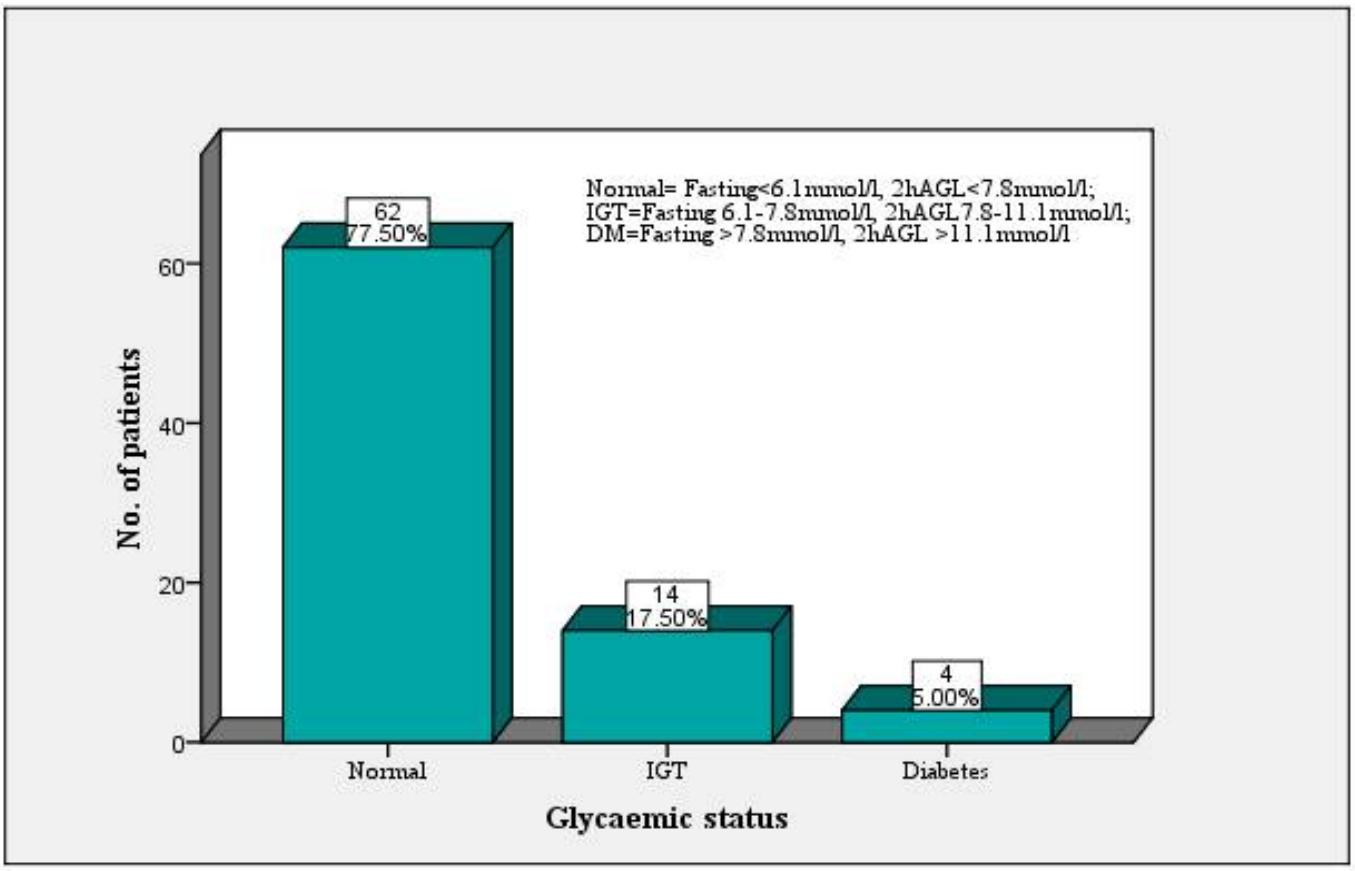

Figure 1. Frequency distribution of glycemic status of TM patients.

Of 80 patients 62 (77.5%) had normal glucose tolerance, 14 (17.5%) had IGT and 4 (5%) had diabetes. All patients with IGT and DM were diagnosed on the basis of OGTT results except 1 DM patient was diagnosed previously. Mean age at diagnosis of IGT and DM was 12.07±2.65 and 11.5±6.4 years respectively. Three IGT and 2 DM patients were diagnosed before 10 years of age. There was significant association (p value <0.018) with age of the TM patients.

The compliance of chelation therapy was very poor in all patients; only 5 IGT patients were on irregular oral chelation therapy and DM patient not at all. Mean age at start of chelation therapy in both group were nearly similar (11.6±1.14 and 11 years). The serum ferritin concentration at the time of diagnosis among IGT and DM group was 6319.28±1105.61ng/ml (ranges from 4502 to 8084ng/ml) and 7701.25±1366.79ng/ml (ranges from 6270 to 9320ng/ml) respectively. Minimum level at which IGT diagnosed was 4922ng/ml and above 6000ng/ml most had abnormal glucose tolerance test result. Age at start of chelation, and serum ferritin level were closely associated with abnormal glucose tolerance (p value .000).

Table II: Relation of glycemic status with age of thalassemia patients

Age				Total
	Normal	IGT	Diabetes	
<10 years	41 (51.2%)	1 (1.3%)	2(2.5%)	44(55%)
>10years	21 (26.3%)	13 (16.2%)	2(2.5%)	36 (45%)
Total	62 (77.5%)	14 (17.5%)	4 (5%)	80 (100%)

χ^2= 7.980 df = 2 p= .018

Above result shows that IGT 1(1.3%) and diabetes 2(2.5%) were less common below 10 years of age. Those who were above 10 years, 13(16.2%) patients had IGT and 2(2.5%) patients had DM. There was significant association of glycemic status with age of the patients (p< .05).

Table III: Relation of glycemic status with serum ferritin level

Glycaemic status	Serum Ferritin level group			Total
	<3000	3000-6000	>6000	
Normal	32(40%)	27(33.75%)	3(3.75%)	62(77.5%)
IGT	0	7(8.75%)	7(8.75%)	14(17.5%)
Diabetes	0	0	4(5%)	4(5%)
Total	32(40%)	34(42.5%)	14(17.5%)	80(100%)

χ^2=40.878 df=4 p=.000

This table shows that serum ferritin level <3000ng/ml had showed no abnormal OGTT result. Between 3000-6000ng/ml there were 7(8.75%) patients had developed IGT and above 6000ng/ml IGT and diabetes developed among 7(8.75%) and 4(5%) patients respectively. Serum ferritin >3000ng/ml was a risk for development of abnormal result. P <.001.

Discussion

Effective management of thalassemia major patients had leaded to improved life expectancy and decrease endocrine complications like diabetes.[19] But unlike hemochromatosis where incidence of diabetes is as high as 80% ,[20] the incidence is lower in thalassemia due to better diagnosis and treatment of the condition.[21]

The primary purpose of this study was to explore the relationship between serum ferritin and blood glucose status in transfusion dependent thalassemia patients. To this date numerous report have been published and the reported incidence are 0-26%. Various risk factors for development of abnormal glucose tolerance have been suggested which includes age, increase amount of BT, serum ferritin level, compliance with chelation, family H/O of DM, hepatitis and pubertal status. [7, 9,17,22,23.]

In my study the frequency of DM was 5% and IGT was 17.5% which is comparable to 74 Greek cases of TM where the prevalence of DM was 5.4% and that of IGT was 12.4%.[24] Very similar results found among 437 TM patients at Ali Asghar Children Hospital Tehran Iran where prevalence of DM was 5.4%, but they found no relation with serum ferritin and age of the patients.[25] This result

also similar to the result of Italian working group (1995); they demonstrate DM in 4.9% patients. Poor compliance with chelation and disturbed insulin secretion due to iron overload were the risk factors[17]. An international multicenter Study in a large series of children in 29 centers showed IGT 6.5% and IDDM 3.2% and serum ferritin, liver damage, F/H of DM identified as risk factors.[26]

Similar result was found in a study among 115 TM patients in the thalassemia center of Indonesia Jakarta where 14.8% of the patients had IGT but DM diagnosed in 2.6 % patients. They found no correlation between ferritin and glucose levels but beta cells damage and cirrhosis of liver were found as risk.[27]

One study in India the reported prevalence of DM and IGT was 12.1% and 14% respectively.[28] In another study the prevalence of diabetes was 10.4% (5 of 48) and IGT was 14.6% (7 of 48) and chronic hepatitis C was an important risk factor.[9,29] Diabetic incidence was higher in these studies but IGT was slightly lower than my result.

In Iraq showed prevalence of IGT was 24.1% [30] which was similar to the result of Saudy children where IGT was 24%[7] among 50 TM patients aged <15 years which was significantly higher than my result. They concluded that despite iron chelation disturbed insulin secretion and liver damage were the risk factors. Higher incidence of DM and IGT (16% and 28.6%) has been reported by Hashemi.[31]

A long prospective study at Ferrara Italy among 29 TM patients developed IGT and DM was 37.9% and 20.6% respectively. The mean age of these patients was 20±4.[29] Incidence of Diabetes mellitus in patients with Beta thalassemia major increases with age.[17] Several studies revealed that diabetes mellitus is more common in patients in second decade of life. In our study the youngest patients who showed abnormal glucose tolerance was aged 9 years and received 106 unit blood that was comparable to a result where youngest patient age was 10 years.[32]

The mean age at which IGT diagnosed in my study was 12.07±2.65 years and DM was 11.5±2.64 years, it was comparable to study at Iraq by Saleem where mean age was 13±1.5 years [33] but it was much lower than the mean age of study by Shamshirsaz where it was 15±3 years [34]. It seems that our diabetic patients were of younger ages at the time of diagnosis in comparison to other studies. This may be due to the fact that the age range of my study patients was limited to <16 years.

The serum ferritin concentration in this study was high, mean value among IGT and DM group was 6319.28±1105.61ng/ml and 7701.25±1366.79 ng/ml respectively. Nearly similar result (7627ng/ml) [22] and (6127ng/ml)[33] also found other studies. Other study found very high level ferritin in IGT and DM patients and mean ferritin was significantly higher than the mean level of patients with normal glucose tolerance.[26,31] In this study ferritin was a risk factor which is similar to above but dissimilar to Najafipour.[35]

Compliance with Chelation therapy was very poor in the study patients. Those who were on chelation received very irregularly. Mean age of starting chelation in our study was (8.81±1.97 years) higher.[33,34] Those who started chelation after 10 years of age; 100% of them had abnormal glucose tolerance which is similar to one result.[6]

Early identification of thalassemic patients with impaired glucose tolerance has decreased presentations with diabetic ketoacidosis. So, glucose tolerance test should be an integral

part of the long term follow up of children and adolescents with β-thalassemia major. Serum ferritin level should be done regularly and Early and regular iron chelation therapy should be advised for all patients to improve or maintain glycemic status.

Conclusion

Glucose intolerance was not uncommon in multiple transfused TM patients. This present study concluded that abnormal glucose tolerance related with age of the patients, serum ferritin level. All the patients in this study had very high serum ferritin level, 4(5%) patients had DM and 14(17.5%) patients had IGT. The lowest ferritin level in IGT and DM were 4502ng/ml and 6270ng/ml (mean 6319±1105.1ng/ml and 7701.25±1366.79ng/ml) respectively. Abnormal glucose tolerance might happen before 10 years of age. The risk factors for development of abnormal glucose tolerance were age, serum ferritin level and delay in start of chelation therapy ($p<.001$).

References

1. Guidelines for the clinical management in thalassemia. Eleftheriou, A. 2nd ed. Thalassemia International Federation, 2008;11.
3. Nasef A, Helmy F, Kamal I and Awady EIS. C-Peptide in Thalassemic Patients. Sci.Med. J. ESCME, April 2,2004;16:2.
4. Jensen, Tuck, Agnew, Koneru, Morris, Yardumian, Prescott, Hoffbrand, and Wonke, High prevalence of low bone mass in thalassaemia major. British Journal of Haematology, 1998;103(4):911-915.
5. Quirolo K and Vichinsky E; Hemoglobin Disorders. In: Kliegman RM,Behrman RE, Jenson HB, Stanton BF, Nelson Textbook of Pediatrics. 19th ed. London: Elsevier Health Sciences, 2011;151-153.
6. Chern J, Lin K, Lu M, Lin D, Lin K, Chen J and Fu C; Abnormal Glucose Tolerance in Transfusion-Dependent β-Thalassemic Patients. Diabetes Care, 2001;24(5):850-854.
7. Hazmi EM, Swailem AI, Fawaz AI, Warsey A; Diabetes Mellitus in Children Suffering from Â -Thalassaemia. Journal of Tropical Pediatrics, 1994;40(5):261-266.
8. Gamberini M, Fortini M, Gilli G, Testa M and Sanctis D. Epidemiology and chelation therapy effects on glucose homeostasis in thalassemia patients. J Pediatr Endocrinol Metab,1988;11 (Suppl.3):867- 869.
9. Khalifa A, Salem M, Mounir E, Tawil EM, Sawy EM. and Aziz AAM. Abnormal glucose tolerance in Egyptian beta-thalassemic patients: possible association with genotyping. Pediatric Diabetes, 2004;5(3):126-132.
10. Toumba M, Sergis A, Kanaris C and Skordis N. Endocrine complications in patients with Thalassaemia Major. Pediatr Endocrinol Rev., 2007;5:642-648.
11. McIntosh, N. Endocrinopathy in thalassaemia major. Archives of Disease in Childhood, 1976;51(3):195-201.
12. Olivieri N, Silva DS, Premawardena A, Sharma S, Viens A, Taylor C, Brittenham G and Weatherall D. Iron Overload and Iron-Chelating Therapy in Hemoglobin E-β Thalassemia. Journal of Pediatric Hematology/Oncology,2000;22(6):593-597.
13. Awai M, Yamanoi Y, Kuwashima J and Seno S. Induction mechanism of diabetes by ferric nitriloacetate injection. in Saltman P, Hegenauer J (eds): The Biochemistry and Physiology of Iron, Amsterdam, The Netherlands, Elsevier/North, 1943;543.
14. Arrigo T, Crisafulli G and Meo A. Glucose tolerance, insulin secretion and peripheral sensitivity in thalassaemia major. Journal of Pediatric Endocrinology Metabolism 1988;11(Suppl. 3):863-866.

15. Pignatti BC, Rugolotto S, Stefano DP, Zhao H, Cappellini M and Vecchio DG. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologica, 2004;89:1187-1193.
16. Fung E, Harmatz P, Lee P, Milet M, Bellevue R, Jeng M, Kalinyak K, Hudes M, Bhatia S and Vichinsky E. Increased prevalence of iron-overload associated endocrinopathy in thalassaemia versus sickle-cell disease. British Journal of Haematology, 2006;135(4):574-582.
17. Multicentre study on prevalence of endocrine complications in thalassaemia major. Clinical Endocrinology, 1995;42(6):581-586.
18. Jahantigh M, Naderi M, Dorgalaleh A and Tabibian S. Prevalence of diabetes and impaired glucose tolerance test in Thalassemia major patients. Zahedan J Res Med Sci (ZJRMS), 2013;15:29-31.
19. Karahanyan E, Stoyanova A, Moumdzhiev I and Ivanov I. secondary diabetes in children with thalassemia major'. Folia Medica 1994;XXXVI, (1):29-34.
20. Finch S and Finch C. Idiopathic hemochromatosis, An Iron Storage Disease. Medicine, 1995;34(4):381-430.
21. Tiosano D and Hochberg Z. Endocrine complications of thalassemia. Journal of Endocrinological Investigation, 2001;24:716-723.
22. Suvarna J, Ingle H and Deshmukh C. Insulin Resistance and Beta Cell Function in Chronically Transfused Patients of Thalassemia Major. Ind. Pediatr.,2006;43:3.
23. Shams S, Ashtiani M, Monajemzadeh M, Koochakzadeh L, Irani H, Jafari F and Mohseni A. Evaluation of Serum Insulin, Glucose, Lipid Profile, and Liver Function in Â -Thalassemia Major Patients and Their Correlation With Iron Overload. Laboratory Medicine, 2010;41(8):486-489.
24. Christoforidis A, Perifanis V, Tsatra I, Vlachaki E and Athanassiou-Metaxa, M. Glucose metabolism in conventionally treated patients with β-thalassaemia major assessed with oral glucose tolerance test. Arch Med Sci, 2008;4(2):191-196.
25. Mehrvar A, Azarkeivan A, Nejad J, Faranoush M and Mehrvar N. Prevalence of diabetes mellitus in patients with transfusion dependent β-talassemia.Iranian Journal of Blood Cancer, 2008;1(1 October):23-27.
26. DeSanctis V, Eleftheriou A and Malaventura C. Prevalence of endocrine complications and short stature in patients with thalassemia major: a multicenter study by the Thalassemia International Federation (TIF). Pediatr Endocrinol Rev., 2004;2(Suppl 2):249-55.
27. Wirawan R, Setiawan S, Kusnandar S and Munthe B. Diabetes mellitus in β-thalassemia major patients. Med J Indones,2003;87.
28. Ramachandran A, Snehalatha C, Kapur A, Vijay V, Mohan V, Das A, Rao P, Yajnik C, Prasanna K and Nair J. High prevalence of diabetes and impaired glucose tolerance in India: National Urban Diabetes Survey. Diabetologia,2001;44(9):1094-1101.
29. Sanctis V, Zurlo M, Boffa C, Cavallo L and Gregorio F. Insulin dependent diabetes in thalassemia. Archieves of Disese in Childhood,1988;63:58-62.
30. Hafez M, Youssry I, Hamed EF and Ibrahim A. Abnormal Glucose Tolerance in β-Thalassemia: Assessment of Risk Factors. Hemoglobin, 2009;33(2):101-108.
31. Hashemi A, Hashmain Z, Ordooei M, Amanat M and Purshamsi F. Endocrine dysfunctions in iron overload in patients with major thalassemia. Iranian Journal of

Pediatric Hematology Oncology, 2012;2(2):60-66.
32. Flynn D, Fairney A, Jackson D and Clayton B. Hormonal changes in thalassaemia major. Archives of Disease in Childhood,1976;51(11):828-836.
33. Saleem L. Impaired Glucose Tolerance Test among B Thalassemia Patients in Hawler province , Iraq. Middle East Journal of Internal Medicine, 2013;6(3):14-20.
34. Shamshirsaz A, Bekheirnia M, Kamgar M, Pourzahedgilani N, Bouzari N and Habibzadeh M. Metabolic and endocrinologic complications in beta-thalassemia major. A multicenter study in Tehran. BMC Endocrine Disorders, 2003;l(3):4.
35. Najafipour F, Aliasgarzadeh A, Aghamohamadzadeh N, Bahrami A, Mobasri M, Niafar M and Khoshbaten M. A cross-sectional study of metabolic and endocrine complications in beta-thalassemia major. Ann Saudi Med, 2008;28(5):361.
36. Mowla A, Karimi M, Afrasiabi A and Sanctis V. Prevalence of diabetes mellitus and impaired glucose tolerance in beta thalassemia patients with and without hepatitis C virus infection. Pediatr Endocrinol Rev,,2004;Dec;2 (Suppl 2):282-4.
37. Saudek C, Hemm R and Peterson C. Abnormal glucose tolerance in β-thalassemia major. Metabolism, 1977;26(1):43-52.