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Original Article

Biochemistry Section

Diabetes Mellitus in Thalassaemia Major Patients: A Report from the Southeast of Iran

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ABSTRACT

Introduction: Diabetes Mellitus (DM) represents a major concern in Thalassaemia Major (TM) patients.

Aim: The present study was conducted to evaluate the frequency of Impaired Fasting Glucose (IFG) and DM in TM patients in Southeast of Iran.

Materials and Methods: Fasting Blood Glucose (FBS) was determined using fasting blood samples in 148 TM patients. Demographical data was collected by a questionnaire. Clinical and laboratory variables including cell blood counts, pre-transfusion Haemoglobin (Hb) level, and five-year ferritin were extracted from medical records. Statistical analysis was performed in SPSS19.0 software using chi-square, student t-test and logistic regression.

Results: Females and males comprised 83 (56.1%) and 65 (43.9%) subjects respectively. The mean age and mean five-year ferritin were 17.3±6.1 year-old and 5060.6±2395 ng/ml respectively. Overall, 39 (26.4%) patients had IFG, while 13 (8.8%) were diagnosed with DM. Significant differences were identified in the mean age, volume of transfused blood per occasion, and mean five-years ferritin between the patients with IFG or DM and the patients with normal fasting glucose level. Patients with age >25-year-old had an increased risk of both IFG (OR=4.7,95% CI: 1.3-17, p=0.01) and DM (OR= 7.1, 95% CI: 1-49.2, p=0.04). In addition, splenectomized patients showed a higher risk for IFG (OR=4.3, 95% CI: 1.5-12.1, p=0.005), and ferritin value >6000 ng/ml were associated with an elevated risk of DM (OR=7, 95% CI: 0.8-60.1, p=0.07).

Conclusion: Our results indicated that higher age, mean five-years ferritin, volume of blood transfused per occasion, as well as splenectomy were risk factors of IFG and DM in TM patients.

Keywords: Endocrinopathy, Impaired fasting glucose, Thalassaemia complications

INTRODUCTION

Thalassaemia results from defects in normal haemoglobin production, and represents the most common inherited anaemia worldwide. Patients with severe form of thalassaemia (TM or transfusion dependent thalassaemia) require regular blood transfusions in order to maintain an appropriate haemoglobin level. Although, life expectancy of TM patients has improved substantially by regular blood transfusions, secondary haemosiderosis and organ dysfunctions including cardiomyopathies, endocrinopathies, gonadal insufficiency and osteoporosis are yet among the most debating conundrums in TM [1,2].

DM represents a common endocrine complication in TM with occurrence of 20-30% [3]. Background pathophysiologic mechanism leading to DM in TM is unclear; some regard the iron induced pancreas cytotoxicity as the most significant contributor. While this was a traditional idea, a new hypothesis suggests the exhaustion of beta pancreatic cells subsequent to a chronic period of hyperinsulinemia to be involved in development of DM in TM [4]. The later notion is further supported by studies reported a higher fasting insulin level and beta cell functionality in TM patients [5,6]. Thalassaemia associated DM has been reported to be specially more frequent in older patients, and has been considered to be responsible for high rate of morbidities [4]. DM has been associated with higher incidence of cardiac complications and heart failure in TM [7]. In fact, DM may lead to an ongoing organ deterioration despite using chelation therapies in TM patients [8]. Regarding prevalence and comorbidities associated with DM, understanding of risk factors associated with the thalassaemia related DM is crucial.

DM is also a relatively common endocrinopathy among Iranian TM patients accounting for 11-13% of hospitalization cases [9,10]. Previous studies have demonstrated a prevalence of 5-7% of DM in Iranian TM patients [11,12]. In our region, Sistan and Baluchestan province, there are more than 2000 registered TM patients in which 10% of them reside in Sistan area. However, there was no previous study on prevalence of DM and IFG in TM patients in our region. In present study, we evaluated frequency of IFG, DM and their associated factors in patients receiving care in Imam Khomeini hospital of Zabol (major city of Sistan).

MATERIALS AND METHODS

Present study was conducted in a care center for specialized patients at Imam Khomeini hospital of Zabol city in southeast of Iran within February 2015 to July 2015. There were 207 TM patients receiving clinical care in our center. All the patients registered at our center were included in the study, with those who were <10-year-old and received less than eight units of blood transfusion excluded [13]. A total number of 148 patients were included into our study. An informed consent was acquired from the patients or their parents, and our method was in agreement with Ethical Standards of the Declaration of Helsinki (October 2008 revision).

The Hb level has been maintained above 10 g/dl, and rarely dropped as low as 7 g/dl mainly due to tardiness of the patients to meet the schedule. The patients were from two main ethnic groups residing in our region including Sistani and Baluchestani. Our patients have been transfused at two to four weeks' intervals; however, shorter periods have generally been assigned to the patients with splenomegaly.

A comprehensive questionnaire was used for obtaining demographical data such as age, sex, blood group, chelation therapy, and history of splenomegaly, splenectomy or hepatomegaly. Further, we studied the clinical records thoroughly for history of hepatitis C and hepatitis B infections, pre-transfusion Hb and cell blood counts, as

well as hepatic enzymes; Aspartate Aminotransferase (AST), and Alanine Aminotransferase (ALT). These measures all were calculated based on values of the three last blood receiving occasions. Mean transfused blood per occasion was calculated based on data of the recent year of blood receiving records. Also, ferritin was calculated as a mean value of the past five-years.

FBS was determined using fasting blood samples. The patients who had FBS level of ≥126 mg/dl or the patients with history of receiving insulin therapy were considered as DM. The FBS level of 100-125 mg/dl was regarded as IFG, and normal level of FBS was regarded as <100 mg/dl [4].

STATISTICAL ANALYSIS

We used SPSS version 19.0 software. Descriptive and inferential analyses were done on the studied variables. Independent sample t-test was used for detecting significant differences of means of quantitative variables between diabetic versus non diabetic patients. Chi-square test was performed to detect any significant association between categorical variables and either DM or IFG. Logistic regression was applied for identifying variables predicting the risk of DM or IFG. Statistical significant level was considered at two-tailed p<0.05.

RESULTS

Regarding glucose metabolism, 96 (64.9%) patients showed normal fasting glucose level. Besides, 39 (26.4%) had IFG, and 13 (8.8%) were diagnosed with DM. Mean age of the patients was 17.3±6.1-year-old (range of 10-40 year-old). Demographical, therapeutic, clinical and laboratory characteristics of the patients have been presented in [Table/Fig-1]. Also, [Table/Fig-2] shows these features among groups of normal FBS, IFG, and DM.

There was a significant association between glucose metabolism and age, therapeutic strategy, and spleen status [Table/Fig-2]. Accordingly, the patients with IFG and DM showed significantly higher mean ages (19.2±5.7 and 19.7±5.9 year-old respectively) than the patients without these conditions (16.3±6.1 year-old, p=0.01). Also, the patients with normal glucose metabolism have been transfused with lower blood volume per occasion (445.4±116.1 ml) in comparison with the patients with IFG (493.7±104.2 ml) or DM (508±74.8 ml, p=0.01).The patients with either IFG or DM also revealed significantly higher mean levels of five-years ferritin (respective values of 5550.7±2513.2 ng/ml and 6975.7±2546.3 ng/ml) than the patients with normal FBS (4652.4±2180 ng/ml, p=0.002). [Table/Fig-3] demonstrates laboratory features of the patients with DM, IFG and normal glucose metabolism.

In logistic regression analysis, the most significant risk factor of abnormal fasting glucose was age >25 year-old (OR=4.7 for IFG, p= 0.01, and OR=7.1 for DM, p= 0.04). Furthermore, Splencetomy was found to significantly increase the risk of IFG (OR=4.3, p=0.05). Other factors that may contribute to the risk of IFG or DM in patients with TM were monotherapy chelation regime, hepatomegaly, and mean five-years ferritin >6000 ng/ml. [Table/Fig-4] shows results of regression analysis for the studied variables.

DISCUSSION

In present study, we assessed frequency and risk factors associated with IFG and DM in TM patients. Overall, IFG and DM were identified in 26.4% and 8.8% of our patients respectively. In other studies, DM has been reported with frequency of 5%-15% in Iranian TM patients [12,14]. However, in one study on the Iranian patients with similar ages of our patients (10-22 year-old), the prevalence of DM was 7.3% which is close to our results [11]. DM has also been reported with frequencies of 10.5% in United Arab Emirates [15], 6% in Saudi Arabia [16], 9.4% in Brazil [17], 18.6% in United States of America [13], and 41% in United Kingdom [18].

We noticed that mean ages of the patients with DM (19.7±5.9-year-old) and IFG (19.2±5.7 year-old) were significantly higher than mean

Parameters	Minimum Maximum	Mean (SD)	N=148 n (%)
Age (years)	10-40	17.3 (6.1)	
Weight (kg)	15-65	36.4 (10.9)	
Total blood volume (ml)	1920-14180	7917.3 (2245)	
Mean blood volume (ml)	159- 685	463.4 (112.2)	
WBC (*10^3/µl)	2.6- 51.4	11.3 (7.7)	
Haemoglobin (g/dl)	5.4-11.9	9.1 (0.9)	
Platelet (*10^3/µl)	80-1213	348 (187.9)	
AST (IU/l)	10-256	52.3 (35.8)	
ALT (IU/l)	6-333	58 (55.5)	
Five-years mean ferritin (ng//ml)	721- 11997	5060.6 (2395)	
Five-years maximum ferritin (ng/ml)	800- 21605	7904 (4047)	
Age categories	<15		52 (35.2)
	15-25		77 (52)
	>25		19 (12.8)
Chelation drug	Osveral*		65 (43.9)
	Deferoxamine and Deferiprone		49 (33.1)
	Deferoxamine and Osveral		15(10.2)
	Deferoxamine		19 (12.8)
Five-years mean ferritin (ng/ml)	<3000		30 (20.3)
	3000-6000		65 (43.9)
	>6000		53 (35.8)
Five-years maximum ferritin (ng/ml)	<5000		35 (23.7)
	5000-8000		44 (29.7)
	>8000		69 (46.6)

[Table/Fig-1]: Demographic and laboratory characteristics of thalassaemia major patients.
*; Iranian synthetic Deferasirox
Abbreviations; WBC: White Blood Cell count, AST; Aspartate Transaminase, ALT; Alanine Transaminase

Parameters		Normal FBS N=96	IFG N=39	DM N=13	p
Sex	Male	42	19	4	0.4
	Female	54	20	9	
Age (years)	<15	43	7	2	0.01
	15-25	44	25	8	
	>25	9	7	3	
Five-years mean ferritin (ng/ml)	<3000	22	7	1	0.04
	3000-6000	46	16	3	
	>6000	28	16	9	
Five-years maximum ferritin (ng/ml)	<5000	27	8	0	0.04
	5000-8000	32	8	4	
	>8000	37	23	9	
Therapeutic strategy	Mono therapy	58	17	12	0.005
	Combinational therapy	38	22	1	
Spleen	Normal	36	6	2	0.03
	Splenomegaly	31	12	4	
	Splenectomy	29	21	7	
Liver	Normal	73	33	7	0.08
	Hepatomegaly	23	6	6	
WBC	Normal	61	24	6	0.4
	Leukocytosis*	31	14	7	
	Leukopenia*	4	1	0	
Platelet count	Normal	61	24	11	0.4
	Thrombocytosis*	31	12	2	
	Thrombocytopenia*	4	3	0	
HCV Ab	Negative	82	34	12	0.9
	Positive	14	5	1	
HBs Ag	Negative	95	36	13	0.08
	Positive	1	3	0	

[Table/Fig-2]: Demographical, clinical and laboratory features of thalassaemia major patients with normal fasting glucose, impaired fasting glucose and diabetes mellitus.
* Stable high or low cell counts for at least six successive occasions.
IFG; Impaired Fasting Glucose, DM; Diabetes Mellitus, WBC; White Blood Cell Count.

Parameters		Minimum	Maximum	Mean±SD	p
Age (years)	Normal	10	40	16.3±6.1	0.01
	IFG	10	32	19.2±5.7	
	DM	10	31	19.7±5.9	
Total blood volume per year (ml)	Normal	2550	14200	7867.7±2327.2	0.3
	IFG	2520	11400	8299.2±1973.6	
	DM	1920	10800	7336.2±2405.6	
Mean blood volume per occasion (ml)	Normal	159	600	445.3±116.1	0.01
	IFG	229	685	493.7±104.2	
	DM	314	600	508±74.8	
Weight (Kg)	Normal	15	65	34.8±11.2	0.03
	IFG	17	54	39±10.2	
	DM	23	53	40.1±8	
WBC (*10^3/µl)	Normal	2.7	51.4	10.8±7.8	0.3
	IFG	2.6	38.5	11.4±7.5	
	DM	4.9	35.2	14.3±8.4	
Hb (g/dl)	Normal	5.7	11.5	9±0.9	0.2
	IFG	5.4	11.9	9.3±1	
	DM	7.3	10.5	8.9±0.9	
Plt (*10^3/µl)	Normal	80	1213	369.3±196	0.1
	IFG	102	714	317.1±171.7	
	DM	93	666	278.7±159.7	
AST (IU/l)	Normal	10	159	47.3±27	0.03
	IFG	19	256	57.8±49.9	
	DM	32	170	72.7±36.9	
ALT (IU/l)	Normal	6	333	55.6±54.1	0.5
	IFG	9	263	61.1±62.5	
	DM	25	165	66.8±45.9	
Five-years mean ferritin (ng/ml)	Normal	1027	10500	4652.4±2180	0.002
	IFG	721	12000	5550.7±2513.2	
	DM	2455	10800	6975.7±2546.3	
Five-years maximum ferritin (ng/ml)	Normal	1475	18700	7228.8±2601.1	0.002
	IFG	800	21600	8603.6±4330	
	DM	5815	20400	11147±4846.9	

[Table/Fig-3]: Comparison between mean values of selected parameters between thalassaemia major patients with DM or IFG and the patients without these conditions.
Abbreviations: IFG; Impaired Fasting Glucose, DM; Diabetes Mellitus, WBC; White Blood Cell Count, Hb; Haemoglobin, Plt; Platelet Count, AST; Aspartate Transaminase, ALT; Alanine Transaminase

Parameters		IFG			DM		
		OR	95% CI	p	OR	95% CI	p
Age (years)	<15	Reference			Reference		
	15-25	3.4	1.3-8.9	0.009	3.9	0.7-19.4	0.09
	>25	4.7	1.3-17	0.01	7.1	1-49.2	0.04
Chelation therapy	Combinational therapy	Reference			Reference		
	Monotherapy	0.5	0.2-1	0.07	7.8	0.9-62.9	0.05
Spleen	Normal	Reference			Reference		
	Splenomegaly	2.3	0.7-6.9	0.1	2.3	0.3-13.5	0.3
	Splenectomy	4.3	1.5-12.1	0.005	4.3	0.8-22.5	0.08
Liver	Normal	Reference			Reference		
	Hepatomegaly	0.5	0.2-1.6	0.3	2.7	0.8-8.9	0.09
HCV Ab	Negative	Reference			Reference		
	Positive	0.8	0.2-2.5	0.7	0.4	0.05-4	0.5
Five-years mean ferritin (ng/ml)	<3000	Reference			Reference		
	3000-6000	1	0.3-3	0.8	1.4	0.1-14.5	0.7
	>6000	1.7	0.6-5.1	0.2	7	0.8-60.1	0.07

[Table/Fig-4]: Parameters associated with risk of impaired fasting glucose and diabetes mellitus in thalassaemia major patients.
HCV Ab: Hepatitis C virus antibody

age of the patients with normal fasting glucose (16.3±6.1 year-old). The mean age of Iranian TM patients who were diagnosed with DM has been reported 13.9±2.8 year-old by Karamifar H et al., [11]. Despite, the mean age was higher in a previous study conducted in our province; 19.6±4.4 year-old [19]. Most significantly, age was found to be a substantial contributor to the risk of either IFG or DM in our study. We observed that age >25 year-old was associated with an OR=4.7 (95% CI: 1.3-17, p=0.01) for IFG, and an OR=7.1 (95% CI: 1-49.2, p=0.04) for DM. In accordance with our findings, DM has also been associated with older patients in precedent reports [5,18,20].

To explain this, relatively long lag phase for DM development in TM can partly be attributable to the pattern of iron loading following intermittent transfusions. Initially, excess iron is absorbed by splenic macrophages known as Reticulo-Endothelial System (RES). Following saturation of transferrin capacity for up taking Non-Transferrin–Bind Iron (NTBI), as well as releasing of transferrin-bound iron from RES cells, iron initiates to precipitate in hepatocytes. With ongoing entrance of iron to the body from transfusions, NTBI gradually affects myocardium and other parenchymal cells including endocrine glands [21]. This time course is usually reached in third or fourth decades giving that patients effectively used iron chelation drugs, otherwise one can expect the organ complications including DM in younger ages.

We observed a significant relationship between therapeutic strategy (monotherapy or combinational therapy) with DM. In fact, a considerable number of our diabetic patients (12/13) exploited a monotherapeutic strategy. Besides, 11 out of 13 patients who had DM showed poor compliance with chelation therapy. In parallel, the poor compliance and late initiation of chelation therapy have also been associated with abnormal glucose metabolism in TM patients [18,20]. In addition, Egyptian patients who received no chelation or had irregular chelation regimens were reported to have higher fasting glucose level [22]. A median time of six years of deferasirox chelation therapy was shown to effectively control the progression of endocrine complications in TM [23].

We also observed that patients with either IFG or DM received significantly higher mean blood volume per transfusion compared to the patients with normal FBS. In accordance, there has also been a relationship between impaired pancreatic function and the number of transfused blood units in TM patients [5]. In a study conducted by Mehrvar A et al., TM patients with DM have been transfused with higher mean volume of blood per occasion (1.8 blood units) than non diabetic patients (1.6 blood units) [12]. An appropriate chelation therapy is suggested to prevent impaired glucose metabolism and DM in TM patients.

Furthermore, we observed a significant difference for mean five-years ferritin level between the patients with either DM or IFG and the patient with normal fasting glucose in present study. In comparison, serum ferritin has been described as a risk factor for DM in TM patients in previous reports [4,5,20]. An average of ten-years ferritin levels of >1500 ug/l and >1250 ug/l were described to increase the risk of TM related DM 3.4 and 4.9 times respectively [21]. Likewise, ferritin level of 3000 ng/ml has been associated with development of DM and other endocrinopathies in TM [20]. This is also in line with our finding that showed 12 out of 13 patients with DM had mean five-years ferritin level of >3000 ng/ml. In addition, our results revealed a seven times higher risk of DM in the patients with mean five-years ferritin of >6000 ng/ml.

Regarding that patients with TM are at risk of being affected with various organ disabilities, it is highly desirable to provide an organ specific predictor of iron load in these patients. Multiple reports are now available arguing the efficiency and predictability of ferritin level in anticipating organ iron load and toxicity [4]. Iron toxicity is a factor of time exposure to reactive iron species, as well as genetic and environmental factors. A highly variable interaction of these factors is supposed to determine the net organ toxicity [24]. Today, T2 Magnetic Resonance Imaging (MRI) provides a sensitive and non invasive method for assessment of iron content of different organs. In fact, T2 MRI value of pancreas was reported to be inversely associated with FBS level in TM patients [4]. Nevertheless, ferritin provides an inexpensive and easily available indicator of iron loading, and it is still generally acceptable predictor of iron toxicity especially in less developed societies.

A multifactorial approach has been suggested in development of deranged glucose metabolism in TM. Insulin insufficiency due to iron cytotoxicity to the pancreatic β-cells has been proposed as a contributing factor. Regarding that excess iron in pancreatic β-cells can perturb normal signaling and energy resources, regulated iron metabolism is essential for normal secretion of insulin [25]. Genetic susceptibility, liver dysfunction, cirrhosis, liver fibrosis, and viral infections have also been suggested as potential contributing factors to DM in TM [3,4,18,26,27]. Similarly, it was stated that prevalence of DM was significantly higher in TM patients who were seropositive for anti-HCV antibodies [4,28]. In addition to these, cardiac dysfunction has been noted in association with DM in TM [18,21]. Nevertheless, we found a higher risk of IFG and DM in the patients who had either splenomegaly or splenectomy. The patients with IFG also had higher levels of AST hepatic enzyme, which is suggestive for a role of liver abnormalities in predisposing to abnormal glucose metabolism in TM.

LIMITATION

Our study may have shortcoming using single test of FBS for detecting DM and IFG, while Oral Glucose Tolerance Test (OGTT) could provide diagnosis of these conditions, as well as revealing cases with glucose intolerance. Although, OGTT is used as a common test for diagnosis of DM and glucose dysregulation, and for confirming results of FBS [29], however, based on American Diabetes Association criteria all the OGTT, FBS or HbA1c can be used independently for diagnosis of DM, and IFG [5]. There are also previous studies who diagnosed these situations only based on the FBS results [4]. However, it is clear that an OGTT test should be considered when evaluating impaired glucose tolerance.

CONCLUSION

A higher risk of abnormal glucose metabolism was found in older splenectomized TM patients in current study. It is critical to monitor TM patients on a routine basis in order to identify patients with IFG and DM. This is of vital importance because of the possibility of prevention the clinical diabetes by administrating regular chelation therapy at earlier phases. Moreover, management of diabetes in preclinical phases may also be accomplished by appropriate nutritional diets.

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