**Introduction**

In patients with β-thalassemia major (BTM), hyper-transfusion therapy has dramatically increased the duration and quality of life but has been associated with chronic iron overload, and frequently complicated by the development of diabetes mellitus (DM) or impaired glucose tolerance in adolescents with BTM, which could affect their growth and development. To the best of our knowledge, this is the first study that uses continuous glucose monitoring (CGM) to detect glycemic abnormalities in adolescents with BTM. The purpose of this study is to compare the oral glucose tolerance test (OGTT) and CGM in the assessment of glycemic control in adolescents with BTM receiving regular blood transfusions and iron-chelation therapy since early childhood.

**Background:** Both insulin deficiency and resistance are reported in patients with β-thalassemia major (BTM). The use of continuous blood glucose monitoring (CGM), among the different methods for early detection of glycemic abnormalities, has not been studied thoroughly in these adolescents. **Materials and Methods:** To assess the oral glucose tolerance (OGT) and 72-h continuous glucose concentration by the continuous glucose monitoring system (CGMS) and calculate homeostatic model assessment (HOMA), and the quantitative insulin sensitivity check index (QUICKI) was conducted in 16 adolescents with BTM who were receiving regular blood transfusions every 2-4 weeks and iron-chelation therapy since early childhood. **Results:** Sixteen adolescents with BTM (age: 19.75 ± 3 years) were investigated. Using OGTT, 25% had impaired fasting blood glucose (BG) concentration (BG) (>5.6 mmol/L), 2 hours after the glucose load, one of them had BG = 16.2 mmol/L (diabetic) and two had impaired glucose tolerance (IGT) (BG > 7.8 and <11.1 mmol/L). Monitoring the maximum (postprandial) BG using CGMS, 4 adolescents were diagnosed with diabetes (25%) (BG >11.1 mmol/L) and 9 with IGT (56%). HOMA and QUICKI revealed levels <2.6 (1.6 ± 0.8) and >0.33 (0.36 ± 0.03), respectively, ruling out significant insulin resistance in these adolescents. There was a significant negative correlation between the β-cell function (B%) on one hand and the fasting and the 2-h BG (r=−0.6, and − 0.48, P < 0.01, respectively) on the other hand. Neither fasting serum insulin nor c-peptide concentrations were correlated with fasting BG or ferritin levels. The average and maximum blood glucose levels during CGM were significantly correlated with the fasting BG (r = 0.68 and 0.39, respectively, with P < 0.01) and with the BG at 2-hour after oral glucose intake (r = 0.87 and 0.86 respectively, with P < 0.001). Ferritin concentrations were correlated with the fasting BG and the 2-h blood glucose levels in the OGTT (r = 0.52, and r = 0.43, respectively, P < 0.01) as well as with the average BG recorded by CGM (r = 0.75, P < 0.01). **Conclusion:** CGM has proven to be superior to OGTT for the diagnosis of glycemic abnormalities in adolescents with BTM. Defective β-cell function rather than insulin resistance appeared to be the cause for these abnormalities.

**Key words:** β-Thalassemia major, continuous glucose monitoring, diabetes mellitus, impaired fasting glucose, impaired glucose tolerance, oral glucose tolerance
tolerance (IGT). DM is still responsible for significant morbidity and mortality in thalassemic patients. Prevalence has been reported to range from 2.3% to 24%.[14]

Increased intestinal iron absorption appears to increase the iron load in these patients. In β-thalassemia, iron absorption is regulated by tissue hypoxia, erythropoietin excretion and ineffective erythropoiesis of an enormously expanded and active bone marrow. The latter leads to over expression of growth differentiation factor (GDF15), which inhibits hepcidin in synthesis, increasing the rate of iron absorption even in the presence of iron overload. Bone marrow erythroid activity (BMA) and ineffective erythropoiesis further disturb iron homeostasis by increasing plasma iron turnover, outpouring catabolic iron (NTBI) which exceeds the iron-carrying capacity of transferrin and circulates in plasma in high levels. Plasma iron turnover is increased many folds releasing considerable amounts of NTBI.[5-7]

The etiology of DM in BTM is suggested to be due to the effect of iron overload on the different tissues controlling the carbohydrate homeostatic mechanisms; including the pancreas and liver. However, controversy about the etiology of this glycemia abnormality still exists. Both insulin deficiency and insulin resistance are reported in patients with BTM. Suggested risk factors for development of DM in patients with BTM include old age, increased amount of blood transfusion, high serum ferritin level, family history of DM, hepatic impairment, and genetic modifiers of iron overload.[8-13]

The relationship between glucose concentrations in interstitial fluid (ISF) and blood has generated great interest due to its importance in minimally invasive and non-invasive techniques for measuring blood glucose. The relationship between glucose levels in dermal ISF, and glucose levels in capillary and venous blood measured simultaneously was studied. Glucose levels in the three compartments exhibited high correlations both when individual subjects were considered separately and when data from all subjects were combined. No significant time lag during glucose excursions was observed among the ISF, and capillary and venous glucose levels.[14] Therefore, it has been demonstrated recently that the continuous glucose monitoring system (CGMS) is a useful and valid tool in defining glucose metabolism affected by secondary forms of glucose derangements. The advantages of CGMS are that it can help to identify fluctuations and trends that would otherwise go unnoticed with other standard methods and that these measurements are during real life of the subject.[15,16]

Rimondi et al., used CGMS in a small number (n = 6) of thalassemic patients with abnormal glucose homeostasis after an oral glucose tolerance test (OGTT). In five patients, the CGMS confirmed the IGT. This study suggested that the use of CGMS is a useful method to detect the variability of glucose fluctuations and offers the opportunity for better assessment of glucose homeostasis in TM patients.[17]

The aim of the work was to assess oral glucose tolerance (OGT) and the 72-h continuous blood glucose concentrations during normal (usual) life-style (natural and various carbohydrate loads) and in adolescents with BTM, measure their fasting insulin secretion and calculate their HOMA and QUIKI indices and correlate these findings with serum ferritin concentration and hepatic functions in adolescents with BMT.

**Materials and Methods**

Sixteen adolescents (age between 14 and 22 years) with BTM on regular blood transfusion and iron chelation therapy attending the BTM were randomly recruited (randomly including every third patient with TM attending the clinic) from the Paediatric and Endocrinology and Haematology outpatient clinics in Hamad Medical Center (HMC) and Al Amal Hospitals. Thalassemic patients with hepatic impairment, or history of other systemic or endocrine abnormalities were excluded.

The study has been approved by the ethical committee of Hamad medical center (HMC) and informed consents obtained from all the patients and their parents before including in the study. Patients with hepatic impairment, family history of DM, or other systemic illness were excluded from the study.

All adolescents were assessed clinically and the following lab investigations performed in a fasting venous sample at 8 AM: Serum insulin, C-peptide, and ferritin and plasma glucose levels. A standard OGTT was performed [0 and 2 h BG using 1.75 g of glucose/kg (max 75 g)]. Every patient was supplied with a glucometer (one touch ultra-machine, which uses the glucose oxidase principle for measuring capillary BG) and asked to measure BG before meals and snacks and record the values in the CGMS for better calibration. Meanwhile, a CGMS (Medtronic type) (which continuously measures glucose in the ISF every 5 minutes) was inserted. These glucose concentrations (by CGMS and glucometer) were downloaded after 3 days and interpreted using Medtronic software. The diagnosis of glycemia status whether normal, diabetic, IFG, IGT was done according to American diabetes association criteria.[18] As plasma, serum and IF glucose levels exhibit high correlations and
in the absence of published criteria for diagnosing glycemic abnormalities by CGMS, the same criteria were applied for both the OGTT results as well as the CGMS data.[18,38]

Serum insulin levels were measured by a chemi-luminescent immunoassay method on ADVIA Centaur analyser using a commercial kit (ADVIA Centaur IRI). Lower and upper detection limits were 0.5 and 300 μIU/ml (3-1800 pmol/l), respectively. The intra-and inter-assay CV ranges were 3.3-4.6% and 2.6-5.9%, respectively. C-peptide concentrations were measured using (C-peptide ELISA kit) in the fasting state. The DAI C-PEPTIDE is a quantitative solid phase ELISA. (Cortez Diagnostics, Inc., USA).

Homeostatic model assessment (HOMA) is a widely validated clinical and epidemiological tool for estimating insulin resistance and beta cell function. It is derived from mathematical assessment of balance between hepatic glucose output and insulin secretion from fasting levels of glucose and insulin. The HOMA-IR index the HOMA of insulin resistance and is the product of basal glucose and insulin levels divided by 22.5 and is regarded as a simple, inexpensive and reliable surrogate measure of insulin resistance. The HOMA-B index is the HOMA of B cell function computed as the product of 20 and basal insulin levels divided by the value of basal glucose concentrations minus 3.5, this has been proposed to be a good measure of B cell function.[19] Quantitative insulin sensitivity check index (QUICKI) correlates well with glucose clamp studies (r = 0.78), and is useful for measuring insulin sensitivity (IS), which is the inverse of insulin resistance (IR).[20] Percent beta cell function was calculated.[21]

Statistical analysis
Data are expressed as means ± SD. To explore the factors predicting the presence of glucose values above 200 mg/dl, a logistic regression analysis was performed with the presence/absence of glucose values above 200 mg/dl at follow-up as the dependent variable. Linear regression equations were used to investigate correlations between the different variables including: Age, BMI, insulin, C-peptide, and glucose data measured by the two methods (OGTT and CGMS). Data were presented as mean ± SD and significance was accepted at P < 0.05. Excel version 2007 was used for all analysis

RESULTS

Sixteen adolescents and young adults with BTM (age 19.75 ± 3 years, 12 males and 4 females) were investigated. They were 10 males and 6 females, with mean height (157.5 ± 8.7 cm) and weight (51.4 ± 10.3 kg). Their height SDS (HtSDS) = −2.2 ± 0.9 and BMI = 20.6 ± 3. Seven out of the 14 patients were short (HtSDS < −2) and 6 were very short (HtSDS < −3). One patient had low BMI (13.2 kg/m²).

Twelve out of the 16 patients started transfusion at age of 2 years while the remaining 4 started at the age of one and half years. One patient was on packed cell transfusion (PCTx) every 5 weeks, 7 patients were receiving every 3 weeks, 1 patient every 2 weeks, and the remaining 7 were on PCT every 4 weeks. Fourteen patients were on hyper transfusion regimen (i.e., pre transfusion Hb > 9.5 g/dl and post transfusion Hb not exceeding 14 g/dl). Two patients were on medium transfusion regimen (pre transfusion Hb not less than 8.5 g/dl). Fourteen patients were on oral deferasirox, one on deferoxamine subcutaneous therapy and one patient was receiving sequential therapy deferoxamine plus deferiprone. Neither of our patients was splenectomized nor did they have hepatitis C, B or HIV.

Using OGTT, 4 patients had impaired fasting BG > 5.6 mmol/L. One of them had BG = 16.2 mmol/L after 2 h (diabetic) and two patients had IGT (BG > 7.8 and < 11.1 mmol/L). Using CGMS in addition to the glucose data measured by glucometer (3-5 times/day), the maximum (postprandial) BG recorded exceeded 11.1 mmol/L in 4 patients (25%) (diabetics) and was > 7.8 but < 11.1 mmol/L in 9 cases (56%) (IGT). HOMA and QUICKI revealed levels < 2.6 and > 0.33, respectively, in most of the patients (13/16) [mean ± SD = (1.38 ± 0.8) and (0.37 ± 0.04), respectively] ruling out significant insulin resistance in these adolescents [Table 1].

There was a significant negative correlation between the β-cell function (B%) on the one hand and the fasting and the 2-h blood glucose levels during OGTT (r = −0.6 and −0.48, P < 0.01) on the other hand [Table 2].

During continuous glucose monitoring (CGM), the average and maximum (postprandial) BG were positively correlated with the fasting BG (r = 0.69 and 0.6, respectively, with P < 0.01) and with the 2-hour glucose level of the OGTT (r = 0.87 and 0.86 respectively, with P < 0.01). Fasting serum insulin and c-peptide concentrations did not reveal significant insulin resistance.

| Table 1: Glycemic abnormalities diagnosed by OGTT versus CGMS in thalassemia patients |
|-----------------|--------|--------|--------|-------------------|
| Method         | Patient # | IFG (%) | IGT (%) | DM (%) | Glycemic abnormalities (%) |
| OGTT           | 16      | 4 (25)  | 2 (12.5)| 1 (6.25) | 5 (31.25) |
| CGMS           | 16      | 6 (37.5)* | 9 (56.25)* | 4 (25)* | 12 (75)* |

*P < 0.01 CGMS versus OGTT, IFG: Impaired fasting glucose, IGT: Impaired glucose tolerance, DM: Diabetes mellitus, OGTT: Oral glucose tolerance test, CGMS: Continuous glucose monitoring system
not correlate with fasting BG or ferritin levels [Table 2]. The statistical power of diagnosing glycemic abnormalities using CGMS versus OGTT = 100% at a confidence level of 0.05.

Serum ferritin concentrations were positively correlated with the fasting and 2-h BG in the OGTT ($r = 0.69, 0.43$, respectively, $P < 0.01$) as well as with the average and the maximum BG recorded by the CGMS ($r = 0.75, 0.64$, respectively, with $P < 0.01$). Ferritin concentrations were negatively correlated with the β-cell function ($r = -0.41, P < 0.01$) [Figure 1].

**DISCUSSION**

Worldwide, DM and IGT are still prevalent complications in patients with BTM with hyper-transfusion therapy. DM is responsible for significant morbidity and mortality in these patients. $^{[22-25]}$ CGMS is an FDA-approved device that records blood sugar levels throughout the day and night. It has the advantage of measuring glucose concentrations under the usual (day-to-day) real-life conditions of the patient. This CGM can help identify fluctuations and trends that would otherwise go unnoticed with standard OGTT, intermittent finger stick and HbA1c measurements.

In this study, we demonstrated high prevalence of glycemic abnormalities in adolescents with BTM that differ by the different methods used. CGMS diagnosed glycemic abnormalities in 75% of our adolescents with BTM, whereas OGTT diagnosed 25% only. DM was diagnosed in 25% of our patients during CGMS whereas only one diabetic patient was diagnosed using OGTT. CGMS appears to be more sensitive and superior to the conventional OGTT or HbA1c concentrations. In support to this view, CGMS has proved to be superior to the conventional methods of glucose monitoring in diabetic and non-diabetic patients. $^{[26-28]}$

Decreased insulin secretion in response to iron overload has been supported by animal experiments. The effect of iron overload on function of pancreatic islet cells was studied in four groups in Wistar rats. Group A received repeated intraperitoneal (i.p.) injections of ferric nitroltriacetic acid (FeNTA); group B received the equivalent dose of Na2 NTA; Group C received i.p. injection of diethylenetriaminepentaacetic acid in addition to FeNTA; and Group D rats were untreated controls. Glucose tolerance tests were performed at the beginning, 5th week, and 10th week. At the 10th week, the levels of plasma

### Table 2: Correlation analysis between variables

| Variables | Age | C-peptide | F-insulin | FBG | QUICKI | % B | HOMA-IR | OGTT |
|-----------|-----|-----------|-----------|-----|--------|-----|---------|------|
| Age       | 1   | 1         | 1         |     |        |     |         |      |
| C peptide | 0.09| 1         | 1         |     |        |     |         |      |
| Fasting insulin | -0.14| 0.52 | 1 |     |        |     |         |      |
| Fasting BG | 0.01| 0.18 | -0.02 | 1 |        |     |         |      |
| QUICKI    | 0.4 | -0.75 | -0.82 | -0.36 | 1 |      |         |      |
| % B       | -0.23| 0.75 | 0.52 | -0.36 | -0.68 | 1 |         |      |
| HOMA-IR   | -0.15| 0.53 | 1 | 0.01 | -0.31 | 0.51 | 1      |      |
| 0-OGTT    | 0.07| 0.06 | -0.11 | 0.55 | -0.24 | -0.42 | -0.66 | 1     |
| 2-h OGTT  | 0.20| -0.08 | -0.24 | 0.67 | 0.06 | -0.48 | -0.72 | 0.71  |
| Average BG-CGMS | 0.17| 0.08 | -0.19 | 0.68 | -0.06 | -0.39 | -0.16 | 0.69  |
| Maximum BG-CGMS | 0.36| -0.18 | -0.35 | 0.39 | 0.22 | -0.44 | -0.34 | 0.49  |
| Ferritin  | 0.21| 0.31 | 0.08 | 0.52 | -0.29 | -0.37 | 0.11 | 0.39  |

FBG: Fasting blood glucose, OGTT: Oral glucose tolerance test, % B: % beta cell function, F: Fasting, 0: Basal, 2 h: 2 h after oral glucose intake, CGMS: Continuous glucose monitoring system, QUICKI: Quantitative insulin sensitivity check index.
Glucose at 2 hours after glucose load in groups A and C were higher than those in groups B and D ($P = 0.043$); the granules of insulin in $\beta$-cells of group A were decreased obviously, the area of islets of group A was smaller than those of other groups ($P = 0.000$). Iron overload might influence glycometabolism. The $\beta$-cells’ capability to secrete insulin was obviously decreased.\[31\] A longitudinal study in thalassemic children showed progressive decrease in the beta cell function with age.\[32\]

However, three of our adolescents with BTM showed insulin resistance state (HOMA and QUIKI), one of them had DM, one had IGT during CGM and the third did not have any glycemic abnormality during CGM or OGTT. Other authors suggested that insulin resistance precedes the glycemic abnormalities. This state of insulin resistance may overwork the beta cell function and in addition to iron toxicity, lead to IGT and DM later.\[14-16\]

Three of our patients with BTM and increased insulin resistance had hepatomegaly, with ultrasonographic evidence of iron overload and high serum ferritin concentrations denoting a chronic form of liver siderosis. During a study of pathogenetic mechanisms in the hepatic cirrhosis of thalassemia major, 16 liver biopsies were examined by electron microscopy. Ultrastructural studies of liver cells during iron overload have shown electron-dense iron as lysosomal hemosiderin, and as lysosomal and cell-sap ferritin. Ferritin molecules have been shown within lysosomes in a specific pattern in relationship with regularly arranged lamellae. Increased insulin resistance is frequently associated with chronic liver disease and is a pathophysiological feature of hepatogenous diabetes.\[33,34\]

CGM discloses early and frequent hyperglycemia in non-diabetic patients with BTM. Intensive glucose monitoring during the late childhood and adolescence appears to be an efficient method in screening for hyperglycemia and could be a valuable guide to initiating insulin therapy and to further investigate outcomes in BTM.

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