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Original Article

Abnormal glucose homeostasis in patients of HbEβ-thalassemia: Prevalence and possible pathogenesis using the Oxford HOMA model

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ABSTRACT

Objectives: Eβ-thalassemia, the most serious form of HbE syndromes, may develop pre-diabetes (PD) and diabetes mellitus (DM), together constituting abnormal glucose homeostasis (AGH) as an endocrinopathy. This study aims to assess AGH prevalence and pathogenesis in this thalassemia subtype.

Material and Methods: A cross-sectional study was conducted at a tertiary care hospital from February 2017 to December 2018 (1.9 years). One hundred and four HbEβ-thalassemia patients were randomly selected aged ≥5 years, irrespective of transfusion requirement. AGH was diagnosed by the American Diabetes Association criteria. The patient's history, relevant examination details, and parameters related to glucose homeostasis were studied. The homeostasis assessment (HOMA) model of Oxford University was used, and formulae were applied to calculate HOMA-insulin resistance (IR) or HOMA-β (β-cell function).

Results: The status of glucose homeostasis was as follows: Normal glucose homeostasis tolerance 83/104(79.8%), PD 20/104(19.2%), and DM one(1%). The patient's age, age of starting transfusions, and HOMA-IR were significantly related to AGH. AGH was inversely associated with the age of starting chelation, though not significant ($P = 0.07$). There was no statistical significance of AGH development, with transfusion dependence ($P = 0.63$), family history of DM ($P = 0.42$), hepatitis C ($P = 0.36$), and higher ferritin levels (800/1000/1500/1700 ng/ml) ($P > 0.5$)/HOMA-β ($P > 0.5$).

Conclusion: HbEβ-thalassemia patients are prone to develop AGH including overt diabetes. It is related to the patient's age, age of initiation, and duration of transfusion therapy. The likely mechanism of pathogenesis is IR, though pancreatic β-cell destruction may also be contributory.

Keywords: HbEβ-thalassemia, Abnormal glucose homeostasis, Diabetes mellitus, Pre-diabetes, Prevalence, Homeostasis assessment model

INTRODUCTION

Eβ-thalassemia, the most serious form of HbE syndromes, affects nearly half of all patients with severe β-thalassemia worldwide and incidence in East India ranges between 0.42 and 1.16%.[1-3] Nearly 50% of HbEβ-thalassemia patients are non-transfusion dependent (NTDT), defined as patients not requiring regular transfusions for survival, and the rest who require regular transfusions for growth and survival are transfusion dependent (TDT).[4,5]

Pre-diabetes (PD) (impaired fasting glucose [IFG] and/or impaired glucose tolerance [IGT]), and diabetes mellitus (DM) together constituting abnormal glucose homeostasis (AGH), is one of the most common endocrinopathies in thalassemia.[6] Worldwide, the prevalence of AGH in β-thalassemia patients varies in different studies as follows: DM (5.4–30%), IFG (25%), and IGT (8.5–12.2%).[7-9] Among a few Indian studies on β-thalassemia, the reported case of AGH was IFG (11.9%), IGT (10.4%), and DM (1.4%).[10,11] There are very few studies available evaluating AGH among HbEβ-thalassemia patients. The pathogenesis of DM in thalassemia syndromes is unclear. There are two schools of thought: One claims that iron-induced pancreatic toxicity is the contributory factor and the other claims that prolonged hyperinsulinemia due to insulin resistance (IR) ultimately leads to exhaustion of pancreatic β-cells.[12] To date, many studies highlight the association of β-thalassemia with AGH; however, not much is known regarding HbEβ-thalassemia and AGH. A unique model, the homeostasis assessment (HOMA) model of Oxford University, was chosen as a screening tool for AGH in the HbEβ-thalassemic population.[13]

This study was done in the HbEβ-thalassemia population, to assess the pathogenesis and patterns of AGH in this population. Early diagnosis can aid in prevention.

Subjects

This is a cross-sectional study conducted in the department of hematology, at a tertiary care public hospital in East India to assess the prevalence and pathogenesis of AGH in HbEβ-thalassemia patients and the relation with associated factors. HbEβ-thalassemia patients irrespective of transfusion dependence were included in the study after obtaining written consent from the patient or legal guardian as applicable following ethical approval (vide order No./NMC/961, dated February 23, 2017) from February 2017 to December 2018. TDT and NTDT were considered as patients receiving ≥1 PRBC every 2 months or lesser, respectively.

Inclusion criteria

The following criteria were included in the study:

i. HbEβ-thalassemia patients, detected by HPLC or mutation study, attending our thalassemia clinic
ii. Age ≥5 years.

Exclusion criteria

The following criteria were excluded from the study:

i. Patients with other hemoglobinopathies
ii. Pregnancy
iii. On medications known to cause hyperglycemia.

MATERIAL AND METHODS

Relevant history and clinical examination of all patients with HbEβ-thalassemia were done as per Thalassemia International Federation guidelines, and a standard protocol for PRBC transfusion support and oral iron chelation with deferasirox was done in patients, as necessary.[5,14,15]

The investigations performed at baseline were serum ferritin, fasting plasma glucose (FPG), postprandial plasma glucose (PPPG), fasting plasma insulin (FPI), fasting C-peptide (FC), and anti-hepatitis c virus antibody (anti-HCV). FPG was measured after 8 h of fasting and PPPG after 2 h of glucose ingestion at 1.75 g/kg body weight (maximum up to 75 g). Patients were divided into normal glucose homeostasis (NGH), PD, and DM (together AGH) as per the American Diabetes Association (ADA) criteria.[6] DM was defined as FPG ≥126 mg/dl and/or 2 h PPPG ≥200 mg/dl (after oral glucose tolerance test/OGTT), while IFG and IGT, which together constitute PD, were defined as FPG 100–125 mg/dl and 2 h PPPG 140–199 mg/dl (after OGTT), respectively.[6] Plasma glucose was measured by the Glucose oxidase-Peroxidase method in XL-600 Erba Mannheim automated clinical chemistry analyzer. Serum ferritin was measured by chemiluminescence immunoassay in the Beckman Coulter Access 2 Immunoassay system in ng/ml. HbA1c was not considered for diagnosing PD/DM as the estimation of HbA1c is misleading in hemoglobinopathies.[16] Anti-HCV was measured by the enzyme-linked immunosorbent assay (ELISA) method.

FPI in micro-International Unit/milliliter (μIU/mL) was assessed by the Enzyme Immunoassay test kit from Bios, based on the solid-phase ELISA technique on a blood sample collected after 8 h of fasting.[17] The FC levels in ng/mL were evaluated by direct immunoenzymatic assay using the C-peptide ELISA kit from DiaMetra.[18] The reference range of insulin in children <12 years and adults is <10 microIU/ml and <25 μIU/mL, respectively, and the normal FC range is 0.3–0.6 nmol/l, increasing to 1–3 nmol/l in the postprandial state.[19,20]

The HOMA model is a method to assess pancreatic β-cell function (βf) and IR, using FPG and FPI/FC parameters.[21] HOMA is the simplest method widely used as a surrogate marker for IR assessment.[21] The model is derived from a mathematical computation of the interaction between the function of β-cell and IR in an ideal model that is then used to compute steady-state insulin and glucose concentrations. The output of the model is calibrated to give a normal βf of 100% and normal IR of 1.[21] Estimation of the HOMA model requires only a single-point measurement of basal insulin and glucose.[22]

The different formulae used in the HOMA model for the estimation of AGH are as follows:

HOMA-IR[23] = (*FPI in μIU/ml* × *FPG in mmol/l*)/22.5

HOMA-β (*using FPI*)[21,23] = *20* × *Insulin levels* (*μIU/mL*)/{*Glucose* (*mmol/L*)-3.5}

HOMA-β (*using FC*)[21,23] = *20* × *C-peptide levels* (*ng/mL*)/{*Glucose* (*mmol/L*)-3.5}

HOMA-S[21] = (*1/HOMA-IR*) × *100*

HOMA-IR is used to measure IR.[23] There is no established cutoff of HOMA-IR for diagnosing AGH, and for this study, the cutoff taken was 1.5, after analyzing existing published literature.[8] HOMA-β estimated by either FC/FPI values was used to assess the pancreatic βf.[21,23] C-peptide values seem more appropriate for HOMA-β calculation, as it leads to accurate estimation of endogenous insulin.[21] There is no fixed cutoff for HOMA-β and the median values vary among different study populations.[22] Values were calculated as percentages of a normal reference population. Insulin sensitivity (S) was assessed using HOMA-S, as percentages of a normal reference population.[21] Insulin secretion and insulin sensitivity are reciprocally related.[24]

Statistical analysis

Data were digitized in Microsoft Excel; analyzed using Epi-Info-7 and R 3.5.1 software. Discrete variables were summarized using proportions or percentages and the odds ratio was also calculated. Measures such as mean, median, standard deviation, and range were calculated for continuous variables. The difference in proportion for discrete independent variables among those with AGH and those with NGH was analyzed using the Chi-square test with or without Yates correction (cell values <10). For continuous variables, an unpaired *t*-test was used to assess statistical significance. $P < 0.05$ was considered statistically significant. Receiver operating characteristic curves were drawn to review the area under the curve and identify optimal cutoff points for various laboratory parameters to differentiate between abnormal and normal glucose homeostasis.

RESULTS

Out of a total 104 HbEβ-thalassemia patients, included in this cross-sectional study to assess the prevalence of AGH, 79.8% (n = 83) had normal glucose tolerance (NGH) and 20.2% (n = 21) had AGH (19.2%, n = 20 PD and 1%, n = 1 DM) [Figure 1a]. The mean age of the total population was 19.7 years (range 5–50 years). The mean age of patients with NGH (16.78 ± 7.08 years) was significantly lower (P = 0.003) than patients with AGH (22.5 ± 10.5 years) [Table 1]. Majority of patients were in their second decade in the total (n = 59, 56.7%) as well as in the AGH population (n = 10, 45.45%) [Figure 1b]. Growth retardation and delayed puberty are present in patients with both AGH and NGH. In the AGH group, 14 patients and, in the NGH group, 46 patients were diagnosed with growth retardation. Although, the proportion of cases of growth retardation was higher in the AGH group (odds ratio 0.62), this was not statistically significant (P = 0.46) [Table 1]. Sexual maturity by Tanner staging was assessed in patients >12 years of age (n = 63). In the AGH population, 11 patients had delayed puberty, and in the NGH population, 32 patients had delayed puberty. Although, the proportion of cases with delayed puberty was higher in the AGH group (odds ratio 0.51), this too was not statistically significant (P = 0.5) [Table 1].

Although in the total population, 59 (56.7%) patients were TDT and the rest NTDT, 85 patients had received transfusions at some point in life. The mean age of starting transfusions was lower (4.5 ± 4 years) in the NGH group compared to the AGH group (7.9 ± 7.7 years) and the difference was statistically significant (P = 0.015) [Table 1]. In the AGH group, 17/21 (81%) and the NGH group, 59/83 (71.1%) patients had TDT without a statistically significant difference (P = 0.5) two groups [Table 1]. Ferritin levels were known in 87 patients. The mean ferritin level in the NGH group was lower (2035.1 ± 1748 ng/ml) compared to the AGH group (2265.8 ± 1629 ng/ml) without a statistically significant difference (P = 0.6) [Table 1]. Although a receptor operator characteristic (ROC) curve revealed the optimum cutoff ferritin level of 1644 ng/ml with a sensitivity of 65% for identifying AGH, different ferritin cutoff levels

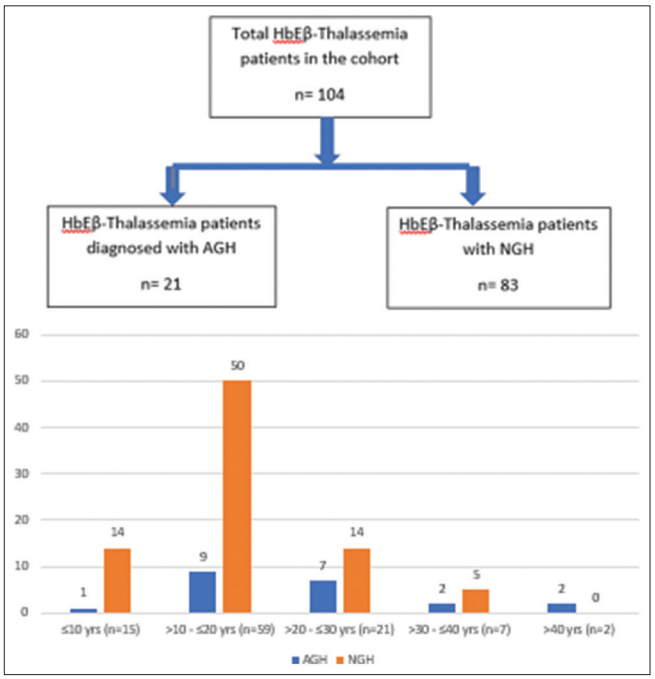

Figure 1: Distribution of patients. (a) Distribution of patients in the cohort (n = 104). (b) Distribution of patients with AGH (n = 21) and NGH (n = 83) according to age. AGH: Abnormal glucose homeostasis, NGH: Normal glucose homeostasis, and yrs: Years.

Table 1: Relation of different parameters with the development of AGH.

Parameters assessed (*n*)	AGH Mean±SD (range) (*n*)	NGH Mean±SD (range) (*n*)	*P*-value	Significance (Y/N)
Age (years) (*n*=104)	22.54±10.4 (9–50) (*n*=21)	16.78±7.08 (5–38) (*n*=83)	0.003	Y
Sex (F: M) (*n*=104)	14:7	42:41	0.2	N
TDT: nTDT (*n*=104)	17:4	59:24	0.52	N
Growth retardation Y: N (*n*=104)	14:7	46:37	0.46	N
Delayed puberty Y: N (*n*=63)	11:3	32:17	0.51	N
Age at 1st transfusion (years) (*n*=85)	7.89±7.73 (0.6–30) (*n*=18)	4.54±4.09 (0.1–22) (*n*=67)	0.015	Y
Ferritin level (ng/ml) (*n*=87)	2265.8±1629 (611–6359) (*n*=17)	2035.07±1748 (50–10,001) (*n*=70)	0.62	N
Ferritin 800 ng/ml Y: N (*n*=87)	14:3	56:14	0.99	N
Ferritin 1000 ng/ml Y: N (*n*=87)	12:5	51:19	0.99	N
Ferritin 1500 ng/ml Y: N (*n*=87)	11:6	42:28	0.92	N
Ferritin 1700 ng/ml Y: N (*n*=87)	10:7	35:35	0.7	N
Chelation Y: N (*n*=104)	16:5	59:24	0.8	N
Age at 1st chelation (years) (*n*=75)	17.47±11.4 (2–41) (*n*=16)	12.79±8.01 (2–37) (*n*=59)	0.064	N
Duration of chelation (years) (*n*=73)	4.86±5.3 (0.5–22) (*n*=14)	4.23±4.4 (0.5–27) (*n*=59)	0.65	N
FH positive: negative (*n*=56)	4:10	6:36	0.24	N
Hydroxyurea use Y: N (*n*=104)	14:7	49:34	0.69	N
HCV R: NR (*n*=89)	4:13	28:44	0.27	N
FPG (mg/dl)	109.9±20.6 (72–186) (*n*=21)	86.5±8.1 (54–99) (*n*=83)	<0.00	Y
PPPG (mg/dl)	127.8±23.4 (96–182) (*n*=21)	102.9±14.9 (49–134) (*n*=83)	<0.00	Y
FPI (mIU/l)	6.7±5 (0.7–18.5) (*n*=21)	4.6±5.3 (0.4–30.3) (*n*=83)	0.1	N
FC (ng/ml)	3.1±2.8 (0.1–11.4) (*n*=21)	3.42±3.3 (0.1–20.9) (*n*=83)	0.6	N
HOMA-IR (*n*=104)	1.8±1.4 (0.2–5.6) (*n*=21)	0.95±1.1 (0.1–5.9) (*n*=83)	0.003	Y
HOMA-β (FPI) (*n*=104)	63.4±60.9 (4–248) (*n*=21)	57.9±188.1 (5.57–746.6) (*n*=83)	0.8	N
HOMA-β (FC) (*n*=104)	30±35.3 (1.1–153.6) (*n*=21)	41.1±138.1 (0.66–726.6) (*n*=83)	0.7	N
HOMA-S (*n*=104)	110±120 (20–500) (*n*=21)	230±210 (0–1250) (*n*=83)	0.02	Y

FC: Fasting C-peptide, FPI: Fasting plasma insulin, TDT: Transfusion dependent, and comparison of the different variables associated with HOMA model with the development of AGH. AGH: Abnormal glucose homeostasis, NGH: Normal glucose homeostasis, FH: Family history, TDT: Transfusion-dependent thalassemia, NTDT: Non-transfusion-dependent thalassemia, Y: Yes, N: No, HCV: Hepatitis C virus, R: Reactive, NR: Non-reactive, HOMA model: Homeostasis assessment model of Oxford University, SD: Standard deviation, FPG: Fasting plasma glucose in mg/dl, PPPG: Postprandial plasma glucose in mg/dl, IR: Insulin resistance, FPI: Fasting plasma insulin mIU/l, FC: Fasting C-peptide in ng/ml, and S: Sensitivity

(800/1000/1500/1700 ng/ml) could not differentiate AGH and NGH groups with statistical significance [Figure 2 and Table 1]. In the AGH group, 16/21 (76.2%), and in the NGH group, 59/83 (71.1%) patients were receiving chelation with a total number of 75 on chelation. There was no statistically significant difference in the chelated population in both the AGH and NGH groups ($P = 0.84$) [Table 1]. The mean age of starting chelation was higher (17.4 ± 11.4) in the AGH group compared to the NGH group (12.8 ± 8). However, there was no statistically significant difference in the age of starting ($P = 0.06$) or duration of chelation ($P = 0.6$) in the AGH and NGH populations [Table 1]. In the AGH population, 14/21 (66.7%) patients, and in the NGH population, 49/83 (59%) patients were receiving hydroxyurea (HU). There was no statistically significant difference in patients receiving HU in the AGH and NGH groups ($P = 0.84$) [Table 1].

Family history of DM in first-degree relatives was collected from a total of 56 patients. Of them, 14 (66.7%) patients were in the AGH population and 42 (50.6%) patients were in the NGH population. 4/14 (28.6%) patients in the AGH group and 6/42 (14.3%) patients in the NGH group had a positive family history, but the difference was not statistically significant ($P = 0.2$) [Table 1]. The HCV status was known in 89 patients. 4/17 (23.5%) patients had HCV reactivity in the AGH compared to 28/72 (38.9%) patients in the NGH group. However, HCV reactivity is not statistically significant with the development of AGH ($P = 0.27$) [Table 1].

There is a significant relationship between FPG and PPPG ($P < 0.05$), and HOMA-IR ($P = 0.003$), with the development of AGH [Table 1]. There is no significant relation between HOMA-β (both FPI and FC) and AGH ($P = 0.8$ and $P = 0.7$, respectively). However, HOMA-β is lower in the AGH group compared to the NGH group. HOMA-S is significantly associated with the development of IR ($P = 0.02$). HOMA-β values (FC/FPI) were reduced among known AGH patients, signifying reduced βf [Table 1].

[Figure 3] depicts the utility of the HOMA model to detect patients with AGH in the patient cohort. The ADA criteria

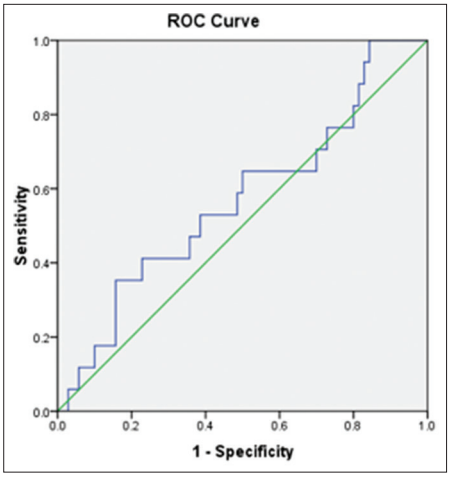

Figure 2: ROC curve depicting the relationship of development of AGH with the level of ferritin: Total cases=87, AGH=17, NGH=70, fitted ROC area=0.59, sensitivity 65%, and specificity 50%. ROC: Receptor operator characteristic, AGH: Abnormal glucose homeostasis, and NGH: Normal glucose homeostasis.

have been taken as the gold standard for detecting AGH. 9/21 (42.9%) patients in the AGH cohort (detected by ADA) and 12/83 (14.5%) patients in the NGH cohort (detected by ADA) were found to have AGH when HOMA criteria were applied with a cutoff of HOMA-IR >1.5 [Figure 3ai]. The sensitivity was 45.5% and the specificity was 85.5%. As there is no established cutoff using the HOMA criteria among HbEβ-thalassemia patients, a ROC assessment was done to find a suitable cutoff value of HOMA-IR. An optimum cutoff of 0.96 was analyzed, having a sensitivity of 72.7% and specificity of 70% [Figure 3b]. Using the cutoff of HOMA-IR >0.96, 16/21 (76.2%) patients in the AGH cohort (detected by ADA) and 24/83 (28.9%) patients in the NGH cohort (detected by ADA) were found to have AGH [Figure 3aii]. Although a greater number of patients with AGH were detected by the HOMA method, among the NGH cohort (detected by ADA), few patients of AGH (detected by ADA) could not be assessed by the HOMA method. No significant cutoff levels for HOMA-β could be detected.

DISCUSSION

This is the first-ever dedicated study to assess the status of glucose homeostasis in HbEβ-thalassemia patients in India. In our patient population, the prevalence of AGH is 20.2% (PD 19.2% and DM 1%), the mean age of patients being 19.7 years (range 5–50 years), with the majority of patients in the second decade. In the general population of India, the percentage of AGH (PD and DM) varies from 7.7% to 9.01% in the ≥20 years age group.[25,26] Hence, a higher percentage of thalassemia patients are more prone to develop AGH at a younger age than the general population. Mahapatra *et al.* and Dandona have shown the prevalence of PD and DM in West Bengal, as 27.8% and 10.41%, respectively, with an increased incidence of obesity and family history, the mean age being 42.4 years, much higher than our study population.[25,26]

Different studies in patients with β-thalassemia major showed the prevalence of glycemic abnormalities varying from 0 to 26.4% and DM up to 8.8%.[8,12,15,27] Of the few studies available from India, one reported IFG (11.9%), IGT (10.4%), and DM (1.4%) in β-thalassemia major patients, with a mean age of 7.43 ± 4.48 years.[11] Very few studies have been conducted in HbEβ-thalassemia patients. Wankanit *et al.* showed a 14% prevalence of abnormal OGTT in HbEβ-thalassemia patients.[28] The prevalence of AGH in both β-thalassemia major and HbEβ-thalassemia patients is seen to have an earlier onset than in the age-matched general population.

PD and DM type 2 were seen in 19.2% and 3.9%, respectively, of non-thalassemia children from Southeast Asia.[29] These children were mostly overweight and had a positive family history of diabetes, unlike our study population. This indicates that AGH in most HbEβ-thalassemia patients occurs in an earlier age group irrespective of conventional risk factors.[30] In another study, all patients of HbEβ-thalassemia were underweight, similar to our study with an AGH prevalence of 14%.[28] From our observations, we can suggest another etiology for increased AGH in HbEβ-thalassemia patients. These patients, including children, who stay away from an active lifestyle because of their disease and the sedentary lifestyle, may be contributory to IR.

In our study, the mean age of patients with AGH (22.5 years, range 9–50 years) was higher than that of NGH (16.8 years, range 5–38 years) and this was statistically significant (P = 0.003). The mean age at diagnosis of DM was 18.2 ± 3.6 years in thalassemia major patients.[31] Many authors have shown that the incidence of DM in thalassemia increases with age, similar to the finding in our study.[12,32] In our study population, the AGH population (20.2%) was higher compared to a similar study by Wankanit *et al.* (14%).[28]

The mean age of initiation of transfusions among our HbEβ-thalassemia population was 3.79 years, later than the age of onset β-thalassemia patients (5.75 months) in established studies.[33] In our findings, the mean age of initiation of transfusions in the AGH population (7.9 years) was significantly higher (P = 0.015) compared to the NGH population (4.5 years).

Although the mean ferritin level was higher among the AGH group, this difference was not statistically significant. Hence,

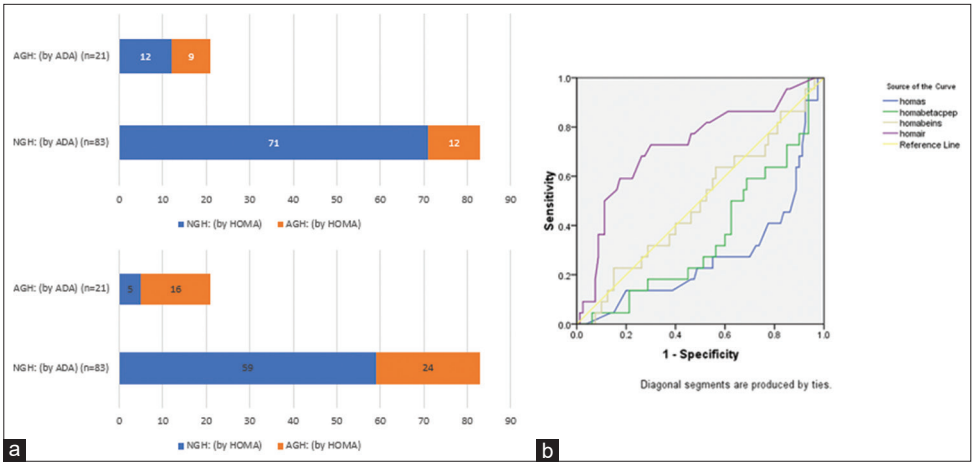

Figure 3: Use of HOMA criteria as a screening tool to detect AGH and NGH among our study population (n = 104). The ADA criteria had been taken as the gold standard to detect patients with AGH. (ai): Detection of AGH using the HOMA method with a cutoff >1.5. Sensitivity: 45.5%, specificity: 85.5%, PPV: 47.6%, and NPV: 86.6%; (aii): Detection of AGH using the HOMA method with a cutoff >0.96. Sensitivity: 72.7%, specificity: 70%. (b) ROC curve: Cutoff for HOMA IR: 0.96, optimum sensitivity: 72.7%, and specificity: 70%. HOMA model: Homeostasis assessment model of Oxford University, AGH: Abnormal glucose homeostasis, NGH: Normal glucose homeostasis, ROC: Receptor operator characteristic, and ADA: American Diabetes Association.

in this study, ferritin level was not found to be an associated factor with AGH. Although different studies performed in patients with β-thalassemia major have shown that higher ferritin levels are established risk factors of AGH, other studies have found no relationship between serum ferritin levels and the development of DM.[12,30,32,34]

Nearly 76.2% of patients in the AGH group and 71.1% in the NGH group were receiving chelation in our study, but this difference was not statistically significant (P = 0.84). Contrary to published literature, our study did not show any correlation between chelation and the occurrence of AGH.[12] Although published studies have shown that delay in initiation of chelation was associated with AGH, in our study, delay in initiation of chelation in AGH (mean age 16.04 years) was not statistically higher (P = 0.07), compared to the NGH population (mean age 11.46 years).[12]

Although different studies have shown a correlation between HCV and AGH, our findings did not find any correlation between HCV with AGH. Although there was a high prevalence of 36% (32/89) of HCV positivity in our patient population, the presence of HCV positivity between the AGH and NGH groups was not significant. HCV prevalence among β-thalassemia major patients is 13.6%, and these thalassemia patients infected with HCV are diabetic more often than those without HCV infection (P < 0.001).[35,36]

Even though, the pathogenesis of DM in thalassemia major has been discussed in various studies; it is still unclear, and the two hypotheses for DM were cytotoxicity of pancreatic cells and exhaustion of the pancreatic β-cells.[33] Not many studies have been conducted on HbEβ-thalassemia patients to study the pathogenesis of AGH. In NTDT patients, there is an iron excess, which may contribute to both impaired β-cell function and/or IR.[37]

In our study, the mean HOMA-IR value was 1.8 in the group with AGH and 0.95 in the group with NGH with a significant difference between the two groups (P = 0.003). Thus, in our findings, IR is an important risk factor for AGH in patients with HbEβ-thalassemia. We also found that the population of HbEβ-thalassemia patients with NGH had lower HOMA-IR and HOMA-β values. A high value of HOMA-IR and low HOMA-β were independently and consistently associated with an increased risk of diabetes.[22,38] Arrigo *et al.* have also demonstrated a decreased IR and βf (by HOMA model) in non-diabetic thalassemia major adults.[10,39] Wankanit *et al.* have compared pre- and post-transfusion effects on glucose metabolism in 50 children and adolescents with β-thalassemia/HbE disease and concluded that increased blood transfusions and increased ferritin levels led to an increased IR. In their study, HOMA-IR values ranged between 0.68 and 0.91.[28] Various studies were conducted on β-thalassemia patients and showed that HOMA-IR values ranged between >1.55 and >3.8, with a mean of 2.31 ± 0.66.[8]

Due to the dearth of studies on AGH in HbEβ-thalassemia patients, the prevalence of AGH patients was calculated using the HOMA-IR cutoff of 1.5.[8] However, using the ROC analysis, a lower cutoff of 0.96 had been calculated for HOMA-IR among our patients, which led to a greater number of patients being

screened for AGH. However, the number of patients detected as AGH by the gold standard ADA criteria was not the same as those detected by the HOMA method. This lowers the utility of HOMA-IR as a screening tool. The cutoff of 0.96 was found to have optimum sensitivity and specificity (sensitivity 72.7% and specificity 70%), and though, some cases of AGH were missed, the overall number of cases being detected was much more. It can be concluded that the use of the HOMA model as a screening tool for AGH though not 100% effective at detecting AGH patients may be indicated as a screening test to detect hitherto undetected patients with IR (among patients who were not detected by the ADA criteria).

In our study, no significant difference in HOMA-β was detected between the two groups of patients with/without AGH. There was, however, a difference in HOMA-β values among the two study groups (using both FPI and FC levels). This implied that there was some component of pancreatic β-cell destruction along with IR as the mechanism of DM pathogenesis in HbEβ-thalassemia. There was also a significant reduction in HOMA-S values in the group with AGH pointing to the fact that there was indeed a component of β-cell destruction due to direct iron damage to the pancreatic cells. No significant cutoff for HOMA-β could be obtained from our ROC curve analysis, and further, longitudinal studies on a larger number of patients may be useful. HOMA-β indicates the pancreatic βf and most studies have found that HOMA-β is lower in individuals who go on to develop AGH. These findings were concluded from studies in non-thalassemic individuals.[40] HOMA-β was lower and FPI was higher in patients with β-thalassemia having IGT/DM, along with a higher HOMA-IR and lower HOMA-S.[41] A study on healthy non-thalassemic individuals showed that those who developed diabetes tended to have higher HOMA-β in contrast to the other studies.[40]

Further, a comparison with age-matched controls from the general population in the same geographical area would accurately assert the difference in AGH prevalence in the HbEβ-thalassemia patients and the general population. Furthermore, due to a lack of a normal control population in our study, it cannot be said with certainty that the association of AGH in HbEβ-thalassemia was indeed IR.

CONCLUSION

HbEβ-thalassemia patients are at lifelong risk of AGH, with a possibility of progression to overt DM. Hence, there arises the need to closely observe the patients for timely intervention and prevention of AGH. The age of the patient and the age of initiation of transfusion are related to the development of AGH in HbEβ-thalassemia. The utility of using the HOMA model to establish the prevalence of AGH among HbEβ-thalassemia patients is because it is inexpensive, reliable, less invasive, and less laborious than other methods to estimate IR and βf in patients with AGH. IR was the predominant cause of developing AGH in HbEβ-thalassemia patients. Significant reduction in the HOMA-S values, along with the fact that there were reduced HOMA-β levels in the AGH population, led to the conclusion that pancreatic β-cell dysfunction may also be a contributory factor in the development of AGH. Our study has found that lowering the HOMA-IR cutoff to 0.96 in HbEβ-thalassemia patients may be more suitable as a screening method, rather than the cutoff of 1.5, which has been tested in β-thalassemia patients.

A prospective study and a comparison with a healthy population may be able to better understand glucose homeostasis in HbEβ-thalassemia. The early detection of PD will help to prevent DM through close monitoring and lifestyle modifications.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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