Original Paper

Medical Principles and Practice

Med Princ Pract 2014;23:421–425
DOI: 10.1159/000363603

Received: October 23, 2013
Accepted: May 11, 2014
Published online: July 3, 2014

Is β-Thalassaemia Minor Associated with Metabolic Disorder?

Sinan Kırım Şakir Özgür Keşkek Ali Turhan Tayyibe Saler

Department of Internal Medicine, Numune Education and Research Hospital, Adana, Turkey

Key Words

β-Thalassaemia minor · Metabolic syndrome · Metabolic syndrome components · Insulin resistance

Abstract

Objective: To investigate the frequency of metabolic syndrome and its components in subjects with β-thalassaemia minor. ***Subjects and Methods:*** A total of 194 subjects, i.e. 92 subjects with β-thalassaemia minor (study group) and 102 subjects without β-thalassaemia minor (control group), were enrolled into this case-control study. Haemoglobin electrophoresis was performed on all patients. The waist circumference and systolic and diastolic blood pressure of the subjects were recorded. Fasting blood glucose and serum lipid levels were measured. ***Results:*** Both groups were similar in terms of age and sex ($p > 0.05$ for each). The percentages of haemoglobin A_2 (4.3 ± 0.4 vs. 2.0 ± 0.3) and haemoglobin F (3.38 ± 1.4 vs. 0.26 ± 0.4) and the mean corpuscular volumes (64 ± 4.7 vs. 81.5 ± 9.3) of the groups were statistically different ($p < 0.001$ for each). The frequency of metabolic syndrome and its components was similar in both groups ($p > 0.05$ for each). According to correlation analyses, the percentage of haemoglobin A_2 correlated with fasting insulin, fasting glucose, systolic blood pressure, high-density lipoprotein, and low-density lipoprotein levels ($p < 0.05$). ***Conclusions:*** No association was found between β-thalassaemia minor and metabolic syndrome despite insulin resistance, which was shown in subjects with β-thalassaemia minor.

Introduction

Metabolic syndrome (MS) is a common chronic metabolic diseases complex that affects several people worldwide [1, 2]. It is a cluster of metabolic abnormalities that includes abdominal obesity, hypertriglyceridaemia, low levels of high-density lipoprotein (HDL) cholesterol, hypertension, and hyperglycaemia. MS and its components are major risk factors for the development of cardiovascular diseases [2, 3]. Insulin resistance, physical inactivity, and hormonal imbalance are common underlying risk factors for MS [1–4].

Thalassaemias are hereditary diseases caused by a defect in α- or β-globin synthesis. β-Thalassaemia is due to an impaired production of β-globin chains. β-Thalassaemia minor (βTM) is the term applied to heterozygotes who have inherited a single gene leading to a reduced β-globin production. As a common and mostly symptomless disease, βTM is most prevalent in Mediterranean countries such as Turkey. Although βTM is usually discovered when a blood count is obtained for other reasons, it has been reported to be associated with certain diseases such as diabetes mellitus and depression [5–9].

Insulin resistance has been reported to be strongly associated with MS and it has also been shown in subjects with βTM [2, 7, 8]. Subjects with βTM and MS may have an increased risk of cardiovascular diseases due to insulin resistance. In this study, we aimed to investigate the frequency of MS and its components in subjects with βTM. We also investigated the association between βTM and MS.

KARGER

E-Mail karger@karger.com
www.karger.com/mpp

1011–7571/14/0235–0421$39.50/0

Dr. Şakir Özgür Keşkek
Department of Internal Medicine
Numune Education and Research Hospital
TR–01240 Adana (Turkey)
E-Mail drkeskek@yahoo.com

Subjects and Methods

This case-control study was carried out at the Internal Medicine Outpatient Clinic of Adana Numune Training and Research Hospital from August 15, 2012, to May 15, 2013. This institute is one of the largest tertiary hospitals in the south of Turkey. The Institutional Review Board approved this study, and informed consent was obtained from all subjects. All procedures were conducted in accordance with the ethical standards of the responsible committee for human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

A total of 194 subjects were enrolled into this study. The study group was comprised of 92 subjects with βTM, and the control group included 102 subjects without βTM. All subjects (including patients and controls) were from the same population of Adana, in the south of Turkey, and were chosen from among individuals who were admitted to the Internal Medicine Outpatient Clinics of the institute. Although the subjects in the control group had no known health complaints, they were admitted for check-ups only. Both the study group and the control group were age and sex matched. Finally, 69 of the 92 patients in the study group were women and 23 were men. In the control group, 87 patients were women and 15 were men. Patients with a history of acute or chronic disease other than MS or its components, malignancy, and mental disorders were excluded.

Blood analyses were performed and the waist circumference and blood pressure were measured. A venous blood sample was collected in the morning after overnight fasting. A complete blood count and peripheral blood samples were evaluated in all subjects. Haemoglobin electrophoreses [Primus Ultra2 (USA) with high-performance liquid chromatography] of all subjects were analysed. Complete blood counts were measured with the Sysmex XE 2100i (Japan) by fluorescence flow cytometry. Fasting glucose, triglyceride, and HDL levels were analysed with a Roche C-501 (Tokyo, Japan) using the hexokinase method (glucose) and a homogeneous colourimetric enzyme test (triglycerides and HDL). Insulin levels were measured using the Abbott Architect i2000SR analyser system (USA). Ferritin, vitamin B_{12}, and folate levels were measured with the Roche C-601 analyser system (Japan) using an electrochemiluminescence immunoassay. The waist circumference was measured on the plane between the anterior superior iliac spines and between the lower costal margins at the narrowest part of the waistline. Blood pressure was measured using a mercury sphygmomanometer, and 3 separate readings at 5-min intervals were taken.

A diagnosis of βTM was made based on haemoglobin A_2 levels (HbA_2) ≥3.5%, mean corpuscular volumes <80 fl, and haemoglobin F levels between 2 and 10%. MS was defined according to National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines [10].

The components of MS included: waist circumference >102 cm in men or >88 cm in women, triglycerides ≥150 mg/dl, HDL <40 mg/dl in men or <50 mg/dl in women, blood pressure ≥130/85 mm Hg, and fasting glucose ≥110 mg/dl. MS was defined as having at least 3 of the 5 components [10].

Statistical Analysis

MedCalc 12.7 software (MedCalc, Turkey) was used. Categorical measurements were reported as numbers and percentages. Quantitative measurements were reported as means ± SD.

Table 1. Comparison of the two groups according to biochemical parameters and demographical properties

	Study group (n = 92)	Control group (n = 102)	p
Age, years	42.2±13.1	38.8±12.2	0.602
Females, n (%)	69 (75)	87 (85.3)	0.104
BMI	25.1±3.7	24.6±3.5	0,364
RBC, $\times10^{12}$/l	5.65±0.66	4.79±0.55	<0.001
Haemoglobin, g/dl	11.4±1.4	12.6±1.8	<0.001
Haematocrit, %	36.1±4.0	38.9±4.3	<0.001
White blood cells, $\times10^9$/l	7.2±2.0	7.5±1.8	0.316
Platelets, $\times10^3$/μl	289.4±81.8	295.5±82.2	0.606
HbA_2, %	4.3±0.4	2.0±0.3	<0.001
Haemoglobin F, %	3.38±1.4	0.26±0.4	<0.001
Corpuscular volume, fl	64±4.7	81.5±9.3	<0.001
Vitamin B_{12}, pg/ml	308±105	316±111	0.664
Folate, ng/ml	9.1±3.1	8.6±3.1	0.213
Ferritin, ng/ml	52.5±56.7	48.8±33.2	0.563

Quantitative measurements are presented as means ± SD.

The Kolmogorov-Smirnov test was used to show the normal distribution of quantitative measurements. The χ^2 test was used to compare categorical measures and the frequency of MS and its components between the groups. A t test or Mann-Whitney U tests were used to compare quantitative measurements between the two groups. A correlation coefficient was used to analyse the degree of association between two variables [Pearson's correlation coefficient (r) with a p value and a 95% CI for r). A log transformation was used for variables that were not normally distributed. A multiple linear regression test (backward method) was used to analyse the relationship between a dependent variable (HbA_2) and one or more independent variables (predictor variables or explanatory variables). $p < 0.05$ was considered statistically significant.

Results

The mean age of the study and control groups was 42.2 ± 13.1 and 38.8 ± 12.2 years, respectively. The characteristics of the groups are shown in table 1. The mean HbA_2 and haemoglobin F percentages were 4.3 ± 0.4 and 3.38 ± 1.4 in subjects with βTM, while the corresponding percentages were 2.0 ± 0.3 and 0.26 ± 0.4 in the control subjects. The differences were statistically significant ($p < 0.001$ for each). The mean corpuscular volume in the study group with βTM was 64 ± 4.7 fl, while it was 81.5 ± 9.3 fl in the control subjects; the difference was statistically significant ($p < 0.001$). The haemoglobin and haematocrit levels were low ($p < 0.001$) and the RBC

Table 2. Metabolic parameters, blood pressure, and waist circumference of the groups

	Study group (n = 92)	Control group (n = 102)	p
Waist circumference, cm	95.8±15.8	94.6±15.2	0.601
Fasting glucose, mg/dl	103.3±32.9	99.6±34.9	0.012
Fasting insulin, μU/ml	14.2±8.5	13.6±11.6	0.027
Systolic blood pressure, mm Hg	117.1±14.9	121.3±14.4	0.041
Diastolic blood pressure, mm Hg	76.7±8.8	75.1±8.9	0.274
HDL, mg/dl	49.0±11.8	44.0±9.3	0.023
LDL, mg/dl	99.6±29.3	108.3±30.8	0.046
Triglycerides, mg/dl	147.9±60.4	137.5±64.7	0.035

Quantitative measurements are presented as means ± SD.

Table 3. Frequency of the MS and its components in the study and control groups

	Study group (n = 92)	Control group (n = 102)	p
Abdominal obesity (waist circumference >102 cm in men or >88 cm in women)	44 (47.8)	39 (38.2)	0.228
Hyperglycaemia (fasting glucose >110 mg/dl)	8 (8.6)	15 (14.7)	0.274
Hypertension (blood pressure >130/85 mm Hg)	8 (8.6)	9 (8.8)	0.837
Low HDL (<40 mg/dl in men or <50 mg/dl in women)	54 (58.6)	57 (55.8)	0.804
High triglycerides (>150 mg/dl)	25 (27.1)	31 (30.3)	0.739
MS	26 (28.3)	25 (24.7)	0.662

Values are presented as numbers (%).

Table 4. Frequency of the MS and its components in the study group according to gender

	Females (n = 69)	Males (n = 23)	p
Abdominal obesity (waist circumference >102 cm in men or >88 cm in women)	31 (44.9)	13 (56.5)	0.469
Hyperglycaemia (fasting glucose >110 mg/dl)	7 (10.1)	1 (4.3)	0.668
Hypertension (blood pressure >130/85 mm Hg)	5 (7.2)	3 (13.0)	0.407
Low HDL (<40 mg/dl in men or <50 mg/dl in women)	39 (56.5)	15 (65.2)	0.624
High triglycerides (>150 mg/dl)	20 (28.9)	5 (21.7)	0.687
MS	21 (30.4)	5 (21.7)	0.592

Values are presented as numbers (%).

Table 5. Correlation of HbA_2 with metabolic parameters, blood pressure, and waist circumference in subjects with βTM

	HbA_2	
	r	p
Fasting insulin	0.248	0.016
Fasting glucose	0.240	0.020
Waist circumference	–0.145	0.166
Systolic blood pressure	–0.219	0.035
Diastolic blood pressure	–0.08	0.401
Triglycerides	–0.061	0.559
HDL	0.280	0.006
LDL	–0.206	0.048

A log transformation was used for fasting insulin, fasting glucose, HbA_2, systolic blood pressure, diastolic blood pressure, and triglycerides.

count was high ($p < 0.001$) in subjects with BTM. There were no statistically significant differences between the platelet, white blood cell, ferritin, vitamin B_{12}, and folate levels of the groups ($p > 0.05$ for each; table 1).

The waist circumference and diastolic blood pressure of the groups were comparable ($p = 0.601$ and $p = 0.274$, respectively). The fasting glucose, fasting insulin, HDL, and triglyceride levels were higher in the study group ($p = 0.012$, $p = 0.027$, $p = 0.023$, and $p = 0.035$, respectively). The systolic blood pressure and serum low-density lipoprotein (LDL) levels were lower in the study group ($p = 0.041$ and $p = 0.046$, respectively; table 2).

The frequencies of abdominal obesity, hyperglycaemia, hypertension, low HDL, and high triglycerides in the study group were 47.8, 8.6, 8.6, 54.3, and 27.1%, respectively, while the corresponding percentages in the control group were 38.2, 14.7, 8.8, 50, and 30.3%. The differences were not statistically significant ($p = 0.228$, $p = 0.274$, $p = 0.837$, $p = 0.207$, and $p = 0.739$, respectively). The frequencies of MS were comparable between the study and control groups ($p = 0.662$; table 3).

The frequency of MS, hyperglycaemia, and high triglycerides was high in females, while the frequency of abdominal obesity, low HDL, and hypertension was

Table 6. Multiple linear regression analysis (backward method) with HbA_2 as the dependent variable and age, gender, fasting glucose, fasting insulin, systolic blood pressure, diastolic blood pressure, HDL, triglycerides, BMI, and waist circumference as independent variables

Independent variables	Coef.	SE	$r_{partial}$	p
Constant	4.2736			
Fasting insulin	0.01739	0.004511	0.3800	0.0002
Systolic blood pressure	–0.006259	0.002539	–0.2541	0.0157
HDL	0.01204	0.003254	0.3668	0.0004

Coef. = Coefficient; SE = standard error.

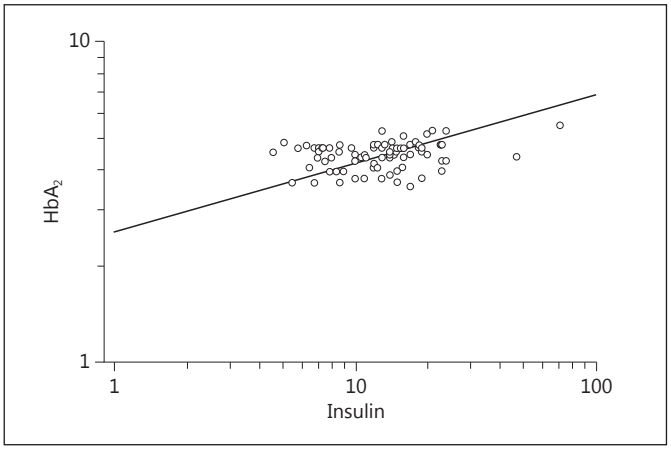

Fig. 1. Scatter diagram of the correlation between HbA_2 and insulin.

high in the males in the study group. However, these results did not reach statistical significance ($p > 0.05$ for each; table 4).

Fasting glucose, fasting insulin, and HDL levels positively correlated with the HbA_2 percentage ($p = 0.020$, $r = 0.240$; $p = 0.016$, $r = 0.248$, and $p = 0.006$, $r = 0.280$, respectively). The correlation between HbA_2 and insulin is shown in figure 1. Systolic blood pressure and LDL were inversely correlated with the HbA_2 percentage ($p = 0.035$, $r = –0.219$, and $p = 0.048$, $r = –0.206$, respectively). Waist circumference and diastolic blood pressure did not correlate with HbA_2 ($p > 0.05$ for each; table 5).

Multiple regression analyses (backward method) performed with HbA_2 as a dependent variable showed that a significant correlation persisted between HbA_2 and fasting insulin ($p = 0.0002$), between HbA_2 and systolic blood pressure ($p = 0.015$), and between HbA_2 and HDL ($p = 0.0004$; table 6).

Discussion

This study showed that the frequency of MS was comparable in subjects with or without βTM. Fasting insulin and glucose levels, which are strongly associated with MS, were high in subjects with βTM in our study. Furthermore, fasting insulin and glucose levels were positively correlated with the percentage of HbA_2.

Our finding that insulin resistance plays an important role in the development of MS in subjects with βTM confirmed reports in previous studies [7, 8]. Bahar et al. [7] reported that the development of diabetes mellitus and insulin resistance in subjects with βTM was more frequent than in the general population due to liver inflammation and increased oxidative stress secondary to microcytic erythrocytes haemolysis [7], while Tong et al. [8] showed high fasting insulin levels and insulin resistance in βTM subjects with normal glucose tolerance.

Although hypertension is known to be associated with diabetes and obesity, which are strongly related to insulin resistance [11], in this study, the systolic blood pressure of the subjects with βTM was low despite high insulin levels. A probable explanation could be the haemodynamic variations seen in anaemia, such as arterial dilatation and a decreased blood viscosity. Arterial dilatation leads to a decrease in vascular resistance and a decreased blood viscosity that could improve the circulation, as reported previously. [12–14]. Further reinforcing this link, in a study by Vyssoulis et al. [15], hypertensive patients with βTM presented a better 24-hour blood pressure profile compared to patients without βTM.

The high plasma concentrations of triglycerides and HDL and the low LDL concentrations in this study have previously been reported in patients with βTM [16]. The hypocholesterolaemia in βTM could be due to accelerated erythropoiesis and an increased LDL uptake by macrophages of the reticuloendothelial system [16, 17]. Furthermore, the high triglyceride levels in the subjects with βTM in our study could be dependent on insulin resistance and high glucose levels as reported by Hashemieh et al. [17]. Further reinforcing this link, high triglyceride levels in patients with diabetes mellitus were reported by Keşkek et al. [18].

Carriers of thalassaemia minor are usually clinically asymptomatic but sometimes have a mild anaemia. They are associated with microcytic anaemia with an associated increase in RBC number and a minimal decrement in the haemoglobin concentration [19, 20]. The subjects with βTM in this study apparently had such a link.

The limitations of this study were: first, the lack of genetic analyses both for MS and for βTM, and second, that free cell haemoglobin, LDH, and high-sensitivity CRP were not measured to show any association with liver inflammation and haemolysis.

Conclusion

βTM was not associated with MS despite insulin resistance, which was well demonstrated in subjects with βTM. A low systolic blood pressure due to haemodynamic variations such as arterial dilatation and a decreased blood viscosity and an abnormal lipid profile might be the factors that prevent the development of MS in subjects with βTM.

References

1 Church TS: Metabolic syndrome and diabetes, alone and in combination, predictors of cardiovascular disease mortality among men. Diabetes Care 2009;32:1289–1294.
2 Grundy SM, Cleeman JI, Daniels SR, et al: Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735–2752.
3 Dagogo-Jack S: Metabolomic prediction of diabetes and cardiovascular risk. Med Princ Pract 2012;21:401–403.
4 Groop L: Genetics of the metabolic syndrome. Br J Nutr 2000;83:39–48.
5 Damon LE, Andreadis C, Linker CA: Blood Disorders; in Papadakis MA, McPhee SJ (eds): Current Medical Diagnosis and Treatment. New York, McGraw-Hill, 2013, vol 52, pp 494–496.
6 Benz EJ: Disorders of Hemoglobin; in Longo DL, Fauci AS, Kasper DL, et al (eds): Harrison's Principles of Internal Medicine. New York, McGraw-Hill, 2012, vol 18, pp 858–861.
7 Bahar A, Kashi Z, Sohrab M, et al: Relationship between beta-globin gene carrier state and insulin resistance. J Diabetes Metab Disord 2012;19;11:22.
8 Tong PC, Ng MC, Ho CS, et al: C-reactive protein and insulin resistance in subjects with thalassemia minor and a family history of diabetes. Diabetes Care 2002;25:1480–1481.
9 Keşkek SO, Kırım S, Turhan A, et al: Depression in subjects with beta-thalassemia minor. Ann Hematol 2013;92:1611–1615.
10 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–2497.
11 Elkhalifa AM, Kinsara AJ, Almadani DA: Prevalence of hypertension in a population of healthy individuals. Med Princ Pract 2011;20:152–155.
12 Karimi M, Marvasti VE, Motazedian S, et al: Is beta-thalassemia trait a protective factor against hypertension in young adults? Ann Hematol 2006;85:29–31.
13 Cavelaars M, Tulen JH, van Bemmel JH, et al: Reproducibility of intra-arterial ambulatory blood pressure: effects of physical activity and posture. J Hypertens 2004;22:1105–1112.
14 Vyssoulis G, Karpanou E, Kyvelou SM, et al: Ambulatory blood pressure profile in anemic hypertensive patients. Int J Cardiol 2010;145:301–302.
15 Vyssoulis G, Karpanou E, Kyvelou SM, et al: Ambulatory blood pressure profile in hypertensive patients with β-thalassemia minor. Hypertens Res 2011;34:253–256.
16 Maioli M, Pettinato S, Cherchi GM, et al: Plasma lipids in beta-thalassemia minor. Atherosclerosis 1989;75:245–248.
17 Hashemieh M, Javadzadeh M, Shirkavand A, et al: Lipid profile in minor thalassemic patients: a historical cohort study. Bangladesh Med Res Counc Bull 2011;37:24–27.
18 Keşkek SO, Kirim S, Karaca A, et al: Low serum magnesium levels and diabetic foot ulcers. Pak J Med Sci 2013;29:1329–1333.
19 Galanello R, Origa R: Beta-thalassemia. Orphanet J Rare Dis 2010;5:11.
20 Clarke GM, Higgins TN: Laboratory investigation of hemoglobinopathies and thalassemias: review and update. Clin Chem 2000;46:1284–1290.