RESEARCH ARTICLE

The Correlation between Glycemic Characteristic and Erythrocyte Indices in Obesity

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Abstract

BACKGROUND: Elevated blood glucose level is a major factor in development of diabetic complications due to unfavorable hyperglycemic induced biochemical as well as hematological indices changes. The aim of this study was to evaluate the correlation between glycemic characteristic and erythrocyte indices in obese subjects with different glycemic status.

METHODS: Cross cross-sectional study was designed, and 80 obese subjects were enrolled. The correlations between glycemic characteristic (fasting plasma glucose (FPG), postprandial plasma glucose (PPG), hemoglobin A1c (HbA1c) and homeostasis model assessment of insulin resistance (HOMA-IR)) and erythrocyte indices (Hb, red blood count (RBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC)) were evaluated.

RESULTS: Of 80 obese subjects with different glycemic status, there were 48 patients with only obesity (HbA1c <5.7%), 19 patients with pre-diabetes (HbA1c 5.7-6.4%) and 13 patients with diabetes (HbA1c >6.4%). Glycemic characteristic and profile lipid (high-density lipoprotein cholesterol (HDL-C), triglycerides (TG)) were differ significantly in the different HbA1c level. Erythrocyte indices were not differ significantly in the different HbA1c level. Partial Spearman's correlation analysis showed that only MCV was significantly correlated with glycemic characteristic of FPG, PPG, HbA1c and HOMA-IR (r=-0.36, p=0.001; r=-0.29, p=0.007; r=-0.27, p=0.014 and r=-0.236, p=0.035; respectively).

CONCLUSION: MCV was significantly correlated with glycemic characteristic (FPG, PPG, HbA1C and HOMA-IR). Further investigations are recommended.

KEYWORDS: MCV, glycemic-characteristic, HbA1c, erythrocyte indices

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Introduction

Hemorheological inflammatory parameters in diabetes mellitus are often disturbed. Red cells of patients with type 2 diabetes are known to aggregate more readily than those of normal subjects, with excessive aggregation of red cells considered one of the most prominent features in diabetes patients with poor glycemic control. Erythrocyte aggregation directly affects the viscosity of whole blood.(1) The major determinants of erythrocyte deformability include cell shape (*i.e.,* the surface-to-volume ratio); the mechanical properties of the cell membrane and its cytoskeleton; and intracellular viscosity, which are related to mean cell hemoglobin concentration.(2)

Study has been reported that blood viscosity is significantly increased in 64 patients suffering from long-

standing diabetes compared to non-diabetic control.(3) This increase was most pronounced in the proliferative retinopathy or nephropathy, and low in myocardial ischemia, or peripheral artery disease (PAD). Erythrocyte deformability was lower in the 14 diabetic patients with the most extensive microangiopathy than in the 22 diabetes patients with slight or no complications and in controls. These findings suggest that hyper viscosity and reduce the deformability of erythrocytes may be an important factor and can potentially be treated in the etiology or microcirculatory disease in diabetes. Hemorheological disorders may promote stagnation of blood flow in the capillaries and post-capillary venules of diabetes patients. Circulatory stagnation is thought to play an etiological role in capillary non-perfusion, acting as a stimulus for new vessel formation. The latter is regarded as a major cause of blindness in diabetes patients.(4) Independently, high values of HbA1c are associated deformability of erythrocytes.(5)

Glycosylated hemoglobin A1c (HbA1c) is an important biomarker, which represents the average of fasting or prandial blood glucose during the previous 2-3 months.(6) HbA1c is regarded as an important tool in diabetes diagnosis and management.(7) Elevated HbA1c levels are indicative of long-term insulin resistance, which may accompany hyperglycemia, dyslipidemia, hypercoagulability, and systemic inflammatory responses.(8)

The study shows a significant increase in all erythrocyte indices in diabetic patients as compared to control group. Significant increase was also observed in red blood cell (RBC), hemoglobin, hematocrit (HCT), mean corpuscular hemoglobin concentration (MCHC) and red cell distribution width (RDW) in both males and females patients when compared to controls.(9,10)

The aim of the present study was to evaluate the correlation between glycemic characteristic and erythrocyte indices in obese with the different glycemic status.

Methods

Study Population

Cross cross-sectional study was designed, and 80 obese subjects were enrolled. Obese was defined as body mass index (BMI) ≥25 kg/m^2.(10) Furthermore, the patients were subdivided according to the glycemic control state into a good glycemic control group (HbA1c <5.7), fair glycemic control group (HbA1c ≥5.7-6.4) and poor glycemic control group (HbA1c ≥6.5).(11) Subjects with secondary obese due to, for example, endocrine disease was excluded, as were subjects taking steroids, and those with infectious, hepatic, renal, or hematologic diseases. The study protocol was approved by The Health Research Ethical Committee Faculty of Medicine, University of Sumatera Utara/H. Adam Malik General Hospital (No.53/KOMET/FK USU/2015).

Laboratory Assays

Venous blood samples were collected from subjects in the morning after a 10-12 hour fast, into plain, ethylenediaminetetraacetate (EDTA)-containing and heparin-containing vacutainers. Plain and EDTA-containing vacutainers were centrifuged. HbA1c was measured in EDTA-containing serum. Fasting plasma glucose (FPG), plasma high-density lipoprotein-cholesterol (HDL-C) and low-density lipoprotein-cholesterol (LDL-C) were measured by Architect Ci 8200 (Abbot, Illinois, USA) and triglycerides (TG) by GPO-PAP method. High sensitivity C-reactive protein (hs-CRP) was measured by an immunoturbidimetric assay (Siemens Diagnostics, Los Angeles, USA), insulin (Siemens Diagnostic, Los Angeles, USA) and adiponectin were measured by Elisa (Daiichi, Tokyo, Japan). Homeostasis model assessment of insulin resistance (HOMA-IR) were calculated from fasting glucose and insulin concentrations by formula of Matthews.(12)

Statistical Analysis

All statistical analysis using SPSS Statistics V22.0. Data were expressed as mean±standard deviation and comparison of data using one-way ANOVA. The correlation between glycemic characteristic and erythrocyte indices were determined by Spearman's correlation analysis. *p*-value <0.05 was considered as statistically significant.

Results

A total of 80 subjects was enrolled in this study. There were 48 subjects with HbA1c <5.7%, 19 subjects with HbA1c 5.7-6.4% and 13 subjects with HbA1c >6.4%. The average glycemic characteristic (FPG, postprandial plasma glucose

(PPG), fasting insulin, HOMA-IR and HbA1C) were 95.70±36.00 mg/dL; 94.83±21.55 mg/dL; 8.991±7.93µIU/mL; 2.37±3.02 and 5.94±1.30; respectively, the average erythrocyte indices (Hb, RBC, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and MCHC) were 13.62±1.35; 4.77±0.41; 86.15±6.81; 28.66±2.65; and 33.23±1.29; respectively.

General characteristics and laboratory data of groups (lipid profile, hs-CRP and adiponectine) enrolled in the study are shown in Table 1. One-way ANOVA test showed that glycemic indices (FPG, PPG, fasting insulin and HOMA-IR) were differ significantly in the different HbA1c level. Otherwise, erythrocyte indices (Hb, RBC, MCV, MCH and MCHC) were not differ significantly but having trend toward to decline. Lipid profile (LDL-C, HDL-C and TG) and inflammatory characteristic (hs-CRP and adiponectin) were not differ significantly (Table 2). Meanwhile, the result of Partial Spearman's correlation analysis showed that only MCV was significantly correlated with all glycemic characteristic: FPG, PPG, HbA1c and HOMA-IR (r=-0.36, p=0.001; r=-0.29, p=0.007; r=-0.27, p=0.014 and r=-0.236, p=0.035; respectively), but MCH and MCHC were not significantly correlated with all glycemic characteristic (Table 3).

Table 1. Clinical and biochemical characteristics of obese subjects.

Characteristic	Total (mean±SD)
n	80
Age (year)	38.95±8.14
BMI (kg/m^2)	31.74±5.21
WC (cm)	91.95±9.59
FPG (mg/dL)	95.70±36.00
PPG (mg/dL)	94.83±21.55
Fasting insulin (µIU/mL)	8.991±7.93
HOMA-IR	2.37±3.02
HbA1c (%)	5.94±1.30
LDL-C (mg/dL)	138.12±32.40
HDL-C (mg/dL)	53.72±16.73
TG (mg/dL)	131.30±75.92
hs-CRP (mg/dL)	4.24±3.86
Adiponectin (µg/dL)	4.42±2.40
WBC (10^3/µL)	7.76±1.62
Thrombocytes (10^3/µL)	307.22±70.09
Hb (g/dL)	13.62±1.35
RBC (M/mm^3)	4.77±0.41
MCV (fL)	86.15±6.81
MCH (pg)	28.66±2.65
MCHC (g/dL)	33.23±1.29

WC: waist circumference; CRP: C-reactive protein; MPV: mean platelet volume; WBC: white blood cell.

Table 2. Comparison of hematological indices and various parameters in the different HbA1c level.

Characteristic	HbA1c levels			*p* value
	HbA1c <5.7 (mean±SD)	HbA1c 5.7-6.4 (mean±SD)	HbA1c >6.4 (mean±SD)	
n	48	19	13	
BMI (kg/m^2)	31.17±4.91	31.97±3.88	33.50±7.57	0.356
WC (cm)	90.45±8.49	92.10±7.48	97.27±14.13	0.074
FPG (mg/dL)	81.94±9.57	97.63±34.12	143.69±56.28	0.000*
PPG (mg/dL)	94.83±21.55	48.50±11.13	97.97±27.17	0.000*
Fasting insulin (µIU/mL)	7.06±6.12	12.24±11.39	11.38±5.89	0.025*
HOMA-IR	1.53±1.23	3.51±5.35	3.81±1.96	0.008*
LDL-C (mg/dL)	136.39±32.93	136.89±32.39	146.30±31.67	0.614
HDL-C (mg/dL)	57.56±18.55	49.00±12.18	46.46±11.01	0.037*
TG (mg/dL)	112.70±47.931	154.73±61.20	165.69±140.71	0.023*
hs-CRP (mg/dL)	4.34±4.26	3.40±2.30	5.06±4.07	0.471
Adiponectin (µg/dL)	4.67±2.39	3.83±1.82	4.32±3.12	0.433
WBC (10^3/µL)	7.80±1.63	7.46±1.65	8.07±1.58	0.574
Thrombocytes (10^3/µL)	306.25±75.83	295.84±55.99	327.46±66.82	0.456
Hb (g/dL)	13.73±1.33	13.58±0.95	13.30±1.90	0.606
RBC (M/mm3)	4.71±0.33	4.83±0.46	4.88±0.55	0.291
MCV (fL)	87.43±6.09	85.14±5.96	82.92±9.34	0.079
MCH (pg)	29.18±2.36	28.25±2.29	27.33±3.63	0.061
MCHC (g/dL)	33.34±1.26	33.16±1.04	32.89±1.72	0.525

p-value between HbA1c (One-way ANOVA test), *$p<0.05$.

Table 3. Correlation between glycemic characteristic and hematological.

Characteristic	FPG value		PPG value		HbA1c value		HOMA-IR value	
	r	p	r	p	r	p	r	p
WBC (10^3/µL)	0.5	0.1	0.3	0.1	0.1	0.6	0.3	0.008*
Thrombocytes (10^3/µL)	0.18	0.098	0.61	0.056	0.07	0.507	0.33	0.003*
Hb (g/dL)	-0.52	0.072	-0.25	0.129	-0.1	0.377	0.08	0.483
RBC (M/mm3)	0.3	0.116	0.67	0.047*	0.04	0.69	0.21	0.064
MCV (fL)	-0.36	0.001*	-0.29	0.007*	-0.27	0.014*	-0.24	0.035*
MCH (pg)	-0.3	0.006*	-0.2	0.1	-0.2	0.047*	-0.2	0.1
MCHC (g/dL)	0.1	0.3	0.4	0.1	-0.3	0.004*	0.0	0.7

*$p<0.05$.

Discussion

Variable or persistent hyperglycemia induces changes in the erythrocyte membrane and its cytoplasm, leading to modifications in erythrocyte deformability.(13,14) Elevated glucose concentration is a major factor affecting erythrocyte morphology.(15) As diabetic conditions are prolonged, the deformability of erythrocytes is further reduced, while their aggregation increases, making whole blood more viscous and possibly obscuring the flow of red cells in micro vessels.(16)

Several pathophysiological disorders, including rheological disorders of RBCs and decreased RBC deformability, were found to be involved in the development of diabetic microangiopathy.(13,14) Impaired erythrocyte deformability has been attributed to alterations in membrane structure, including alterations in the ratio of cholesterol to phospholipids in the lipid membrane core and amplified peroxidation.

In the previous study, prior exposure of the erythrocytes to carbon monoxide (known to inhibit heme-protein degradation) prevented almost completely the loss in deformability caused by hydrogen peroxide to the extent of malonyldialdehyde (an indicator of lipid peroxidation) and alanine production (an indicator of protein degradation).(16) The study was carried out to evaluate the influence of dyslipidemia in patients with stable angina on some rheological properties of the erythrocytes. This study revealed that atherogenic lipids increased erythrocyte's aggregation, but not erythrocyte deformability.(17) The increase in MCV was significant in diabetic males and insignificant in diabetic females (9) and there was correlation between HbA1c and MCHC in diabetic subjects (18). In the present study, we found that only MCV was correlated significantly with FPG, PPG, HbA1c and HOMA-IR. The results were different with other previous studies because in this study enrolled obesity subjects with different glycemic control.

Adiponectin, synthesized in the adipose tissue, appears to play an important role in hyperglycemia and dyslipidemia, as well as in inflammatory mechanisms, which lead to a markedly increased atherosclerotic risk in diabetic subjects. Previous study supports the hypothesis that increased adiponectin levels might be associated with better glycemic control, better lipid profile, and reduced inflammation in diabetic subjects.(20) In this study, we found that hs-CRP and adiponectin was not correlated significantly with glycemic control. The results were different with other previous studies because in this study enrolled obesity subjects with different glycemic control.

There are several potential limitations of this study. The limited sample size and the cross-sectional study design involving single measurement of erythrocyte indices which may not demonstrate a temporal relationship with glycemic characteristic.

Conclusion

In this study, we found that there were negative correlations between MCV and FPG, PPG, HbA1c and HOMA-IR, suggesting that MCV may be a potential indicator in finding the risk of developing micro- and macro-vascular complications in diabetic patients.

References

1. Cho YI, Mooney MP, Cho DJ. Hemorheological disorders in diabetes mellitus. J Diabetes Sci Technol. 2008; 2: 1130-8.
2. Stoltz JF, Singh M, Riha P. Hemorheology in Practice. Amsterdam: IOS Press; 1999.
3. Barnes AJ, Locke P, Scudder PR, Dormandy TL, Dormandy JA, Slack J. Is hyperviscosity a treatable component of diabetic microcirculatory disease? Lancet. 1977; 2: 789-91.
4. Peduzzi M, Melli M, Fonda S, Codeluppi L, Guerrieri F. Comparative evaluation of blood viscosity in diabetic retinopathy. Int Ophthalmol. 1984; 7: 15-9.
5. Bauersachs RM, Wenby RB, Meiselman HJ. Determination of specific red blood cell aggregation indexes via an automated system. Clin Hemorheol. 1989; 9: 1-25.
6. Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, Kirkman MS, *et al*. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Diabetes Care. 2011; 34: e61-99.
7. Gorus F, Mathieu C, Gerlo E. How should HbA1c measurements be reported? Diabetologia. 2006; 49: 7-10.
8. Selvin E, Steffes MW, Gregg E, Brancati FL, Coresh J. Performance of A1C for the classification and prediction of diabetes. Diabetes Care. 2011; 34: 84-9.
9. Jabeen F, Rizvi HA, Subhan A. Effect of hyperglycemia on superoxide dismutase defense system and erythrocyte indices in diabetic patients. Pak J Biochem Mol Biol. 2012; 45: 85-9.
10. WHO/IASO/IOTF. The Asia-Pacific Perspective: Redefining Obesity and its Treatment. Melbourne: Health Communications Australia Pty Ltd; 2000.

11. WHO. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus: Abbreviated Report of a WHO Consultation. Geneva: WHO; 2011.
12. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985; 28: 412-9.
13. Hoare EM, Barnes AJ, Dormandy JA. Abnormal blood viscosity in diabetes mellitus and retinopathy. Biorheology. 1976; 13: 21-5.
14. Schwartz RS, Madsen JW, Rybicki AC, Nagel RL. Oxidation of spectrin and deformability defects in diabetic erythrocytes. Diabetes. 1991; 40: 701-8.
15. Singh M, Shin S. Changes in erythrocyte aggregation and deformability in diabetes mellitus: a brief review. Indian J Exp Biol. 2009; 47: 7-15.
16. Srour MA, Bilto YY, Juma M, Irhimeh MR. Exposure of human erythrocytes to oxygen radicals causes loss of deformability, increased osmotic fragility, lipid peroxidation and protein degradation. Clin Hemorheol Microcir 2000: 23: 13-21
17. Katiukhin LN. Rheological properties of erythrocytes and lipid profiles of blood plasma. JMED Research 2015; 2015: 1-5.
18. Jabeen F, Rizvi HA, Aziz F, Wasti AZ. Hyperglycemic induced variations in hematological indices in type 2 diabetics. IJAR. 2013; 1: 322-34.
19. Schulze MB, Rimm EB, Shai I, Rifai N, Hu FB. Relationship between adiponectin and glycemic control, blood lipids, and inflammatory markers in men with type 2 diabetes. Diabetes Care. 2004; 27: 1680-7.