

ปัจจัยทางด้านฮีโมโกลบินผิดปกติ ชนิดอี
ที่มีผลต่อการวัดระดับน้ำตาลสะสมในผู้ป่วยเบาหวาน
**Effect of Hemoglobin E disorder on Hemoglobin A_{1c}
in Diabetic patients**

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ABSTRACT

- Objective** : This research aims to study effect of hemoglobin E disorder on hemoglobin A_{1c} (HbA_{1c}) level of diabetic patients in Surin hospital.
- Methods** : A retrospective study was conducted from 2006 to 2007. Patient's profile, blood glucose and HbA_{1c} level were collected and divided in hemoglobin E disorder group and control group. Each sample arm was classified into seven subgroups according to blood glucose level to compare HbA_{1c} level in each subgroup.
- Results** : During 2006-2007, 28 diabetic patients with hemoglobin E disorder were found from overall 910 diabetic patients. There is no difference of sex, average age and blood glucose between hemoglobin E disorder and control group. Patients with hemoglobin E disorder had lower HbA_{1c} level than those of control group ($P < 0.001$).
- Conclusion** : Since HbA_{1c} levels is presently the best indicator of long term glycemic control. With similar fasting glucose, hemoglobin E disorder is associated with lower HbA_{1c} level.
- Key words** : Diabetes mellitus, Hemoglobinopathy, Hemoglobin A_{1c} (HbA_{1c})

บทคัดย่อ

บทนำ

: จุดมุ่งหมายของการศึกษาเพื่อทำการศึกษาลักษณะของฮีโมโกลบินผิดปกติ ชนิดอีต่อการแปลผลระดับน้ำตาลสะสมในผู้ป่วยเบาหวานในโรงพยาบาลสุรินทร์

วิธีการศึกษา

: ผู้วิจัยศึกษาโดยการเก็บรวบรวมผลการตรวจเลือดจากผู้ป่วยเบาหวานซึ่งได้รับการตรวจเลือดตั้งแต่ปี พ.ศ. 2549-2550 เปรียบเทียบระหว่างผู้ป่วยที่มีฮีโมโกลบินผิดปกติชนิดอีกับผู้ป่วยเบาหวานอื่น ๆ แยกเป็น 7 กลุ่ม ตามระดับน้ำตาลในเลือด; ควบคุมน้ำตาลได้ดี 3 กลุ่ม (ระดับน้ำตาลน้อยกว่า 99, 100-109, 110-126 มิลลิกรัม/เดซิลิตร) ; ควบคุมน้ำตาลได้ปานกลาง 1 กลุ่ม (ระดับน้ำตาล 127-139 มิลลิกรัม/เดซิลิตร) ; หรือควบคุมน้ำตาลได้ไม่ดี 3 กลุ่ม (ระดับน้ำตาล 140-199, 200-239, > 240 มิลลิกรัม/เดซิลิตร) โดยเปรียบเทียบกับระดับน้ำตาลสะสมในแต่ละกลุ่ม

ผลการศึกษา

: ในช่วงระหว่าง ปี พ.ศ. 2549-2550 ผู้ป่วยเบาหวาน 910 ราย อายุ 11-93 ปี มีผู้ป่วยเบาหวานที่มีฮีโมโกลบินผิดปกติ ชนิดอี 28 ราย เจาะเลือด 44 ครั้ง เปรียบเทียบกับกลุ่มควบคุม 882 ราย เจาะเลือด 958 ครั้ง ทั้งสองกลุ่มไม่มีความแตกต่างกันในค่าเฉลี่ยของอายุ เพศ และระดับน้ำตาลในเลือด แต่ระดับน้ำตาลสะสมในผู้ป่วยที่มีฮีโมโกลบินผิดปกติ ชนิดอีต่ำกว่าผู้ป่วยเบาหวานทั่วไปอย่างมีนัยสำคัญทางสถิติ ($P < 0.001$)

สรุป

: ปัจจุบันระดับน้ำตาลสะสมสามารถบ่งบอกประสิทธิภาพการควบคุมระดับน้ำตาลในเลือด การแปลผลระดับน้ำตาลสะสมในผู้ป่วยเบาหวานทั่วไปและผู้ป่วยที่มีฮีโมโกลบินผิดปกติ ชนิดอี ที่ระดับน้ำตาลเท่ากัน ผู้ป่วยที่มีฮีโมโกลบินผิดปกติ ชนิดอี จะมีระดับน้ำตาลสะสมน้อยกว่า

คำสำคัญ

: โรคเบาหวาน, ฮีโมโกลบินผิดปกติ, ฮีโมโกลบินสะสม (HbA_{1c})



The most important factor that determines hemoglobin (Hb) A_{1c} concentration is the blood glucose level^{1,2}. This feature makes HbA_{1c} the standard for monitoring long-term glycemia and estimating the probability of complications in diabetes^{1,2}. However, alterations of HbA_{1c} in diabetes mellitus (DM) due to factors that affect hemoglobin levels have not been extensively investigated.

Previous studies have shown that a decreased life-span of erythrocytes, as observed in hemolytic anemias, is associated with lower concentration of glycated Hb^{3,4,5,6}. Fitzgibbons et al³. have demonstrated that the glycated Hb concentration is correlated with the developmental stage of erythrocytes. In this study, the concentration of minor hemoglobins in young erythrocytes was found to be lower than that in the older erythrocytes. Therefore, the glycated Hb concentration was proposed as a diagnostic parameter in anemias associated with short erythrocyte life-spans.

The most common cause of anemia in endemic area of hemoglobinopathy is hemoglobin E disorder. Therefore, the possibility of the coexistence of DM and hemoglobin E disorder is higher than any other type of anemia in Surin, Thailand⁷. Consequently, the clinical implications of any correlation between FPG and glycated Hb will affect many patients with DM and hemoglobin E disorder. Any cause of shortened erythrocyte survival will reduce

exposure of erythrocytes to glucose with a consequent decrease in HbA_{1c} values even though the time-averaged blood glucose level may be elevated^{8,9,10}, the relationship between hemoglobin E disorder and glycated Hb in DM has not been previously studied. We aimed to investigate this issue in a retrospective study.

Methods

1. Research design and methods

1.1 Study subjects

Study subjects were apparently diabetes patients in diabetes clinic. Among them, 910 had the blood laboratory tests, 882 in control group and 28 in hemoglobin E disorder. Subjects who already had been treated for diabetes (on insulin, oral hypoglycemic drugs or a physician-prescribed diet) and HbA_{1c} were measured. We used HbA_{1c} and capillary whole blood glucose concentrations from 2 data sets.

1.2 Measurement of glucose and glycosylated hemoglobin

For the laboratory measurements of capillary whole blood glucose and HbA_{1c}, a blood sample was taken in the morning after an overnight fast. For each data set, we classified into 7 intervals according to their baseline blood glucose level : good control, < 99 mg/dl (< 5.55 mmol/l), 100-109 mg/dl (5.55-6.09 mmol/l), 110-126 mg/dl (6.10-6.99 mmol/l); moderate control, 127-139 mg/dl (7.00-7.8 mmol/l); or poor control, 140-199 mg/dl (7.8-11.0 mmol/l), 200-239

mg/dl (11.1-13.3 mmol/l), > 240 mg/dl (> 13.3 mmol/l), in combination with HbA_{1c} level was compared between groups.

The HbA_{1c} levels were measured using the turbidimetric inhibition immunoassay (TINIA) for hemolyzed whole blood (Cobas®, Roche Diagnostics, USA). The normal range for HbA_{1c} in our laboratory was 6-16% and the coefficient of variation in repeated tests was less than 0.1. In the study, HbA_{1c} in each group was compared with fasting plasma glucose measured before breakfast. In patients with hemoglobinopathy hemoglobin typing was compared with liquid chromatography.

1.3 Statistical analysis

Statistical analysis were carried out. Descriptive parameters are presented as means with standard deviations, or as percentiles. Analysis of variance were used to compare the mean values among the various groups defined by different levels of blood glucose and HbA_{1c}. Unpaired T- test analysis was used to compare the mean values among the group defined by different levels of blood glucose and HbA_{1c}. A p-value < 0.001 was considered statistically significant.

Results

Of 910 patients with DM have the laboratory measurements of capillary whole blood glucose and HbA_{1c}, a blood sample was taken in the morning after an overnight fast, 882 cases, 958 blood sample were unknown Hb typing and 28 cases, 44 blood sample were hemoglobin disorder. 8 of the 28 patients have hemoglobin E heterozygote [EA] with DM and 20 have hemoglobin E homozygote [EE] with DM. The two groups were not significantly different from each other with respect to age or sex, the mean age 56.7 years in control group versus 55 years in hemoglobinopathy group (P > 0.001). The mean hemoglobin E was 63.8 percent in studied group.

The mean HbA_{1c} concentration in hemoglobin E group was lower than control diabetic group [6.4 ± 1.6 SD and 8.0 ± 1.94 SD], as expected (P < 0.001). [Table 1]

Table 1 Combination of blood glucose and HbA_{1c} in hemoglobin E and control group

Blood glucose	HbA _{1c}		P value
	Hb E	Control group	
< 99 mg/dl (< 5.5 mmol/l)	5.3 ± 1.27 SD	6.6 ± 0.79 SD	< 0.001
100-109 mg/dl (5.5-5.9 mmol/l)	5.8 ± 0.9 SD	7.2 ± 1.48 SD	< 0.001
110-126 mg/dl (6.0-6.9 mmol/l)	6.0 ± 1.1 SD	7.3 ± 1.57 SD	< 0.001
127-139 mg/dl (7.0-7.8 mmol/l)	6.2 ± 0.41 SD	7.4 ± 1.38 SD	< 0.001
140-199 mg/dl (7.8-11.0 mmol/l)	6.4 ± 1.34 SD	8.2 ± 1.53 SD	< 0.001
200-239 mg/dl (11.1-13.3 mmol/l)	8.2 ± 0.14 SD	9.3 ± 1.46 SD	< 0.001
> 240 mg/dl (> 13.3 mmol/l)	8.5 ± 2.26 SD	11.4 ± 3.45 SD	< 0.001
Total	6.4 ± 1.6 SD	8.0 ± 1.94 SD	< 0.001

Similarly, the mean HbA_{1c} concentration in 7 intervals was lower than control group, as presented in table 1.

There was no significant difference in the mean blood glucose concentration of the patients in both groups ($P > 0.001$) 142 ± 52.7 SD and 145 ± 52.34 SD. In addition, the mean HbA_{1c} concentration in hemoglobin E disorder group (6.4 ± 1.94 SD) was significantly lower than control group (8.0 ± 1.94 SD)

Discussion

Diabetes mellitus is a frequent disorder affecting individuals of all ages¹¹. Glycohemoglobin has a key role in the assessment of glycemic control in diabetic patients¹². Several studies have clearly shown that improved glycemic control is strongly associated with decreased development and progression of diabetic complications in both type 1 and 2 DM¹². Therefore, accurate

determination of glycohemoglobin concentration is an important issue for clinical laboratories.

HbA_{1c} is the result of an irreversible non-enzymatic glycation of the beta chain of hemoglobin A¹³. HbA_{1c} is routinely used to assess long term glycemic control in patients with DM¹³. It is normally present in circulating red cells because of the glycosylation reaction between hemoglobin and circulating glucose¹⁴. In the presence of excessive plasma glucose, the hemoglobin beta-chain becomes increasingly glycosylated, making the HbA_{1c} a useful index of glycemic control¹⁴.

These results clearly demonstrate that there is a relationship between the hemoglobinopathy and HbA_{1c} in adult patients with type 1 and type 2 DM. Although this correlation had been previously reported, we have demonstrated it in diabetes patients in a clinical data. Our data are in accordance with the findings that the concentration of minor hemoglobins in young erythrocytes was found to be lower than that in the older erythrocytes. HbA_{1c} concentrations in diabetic patients with hemoglobin E disorder were found lower than control group when compared to similar glycemic control level.

Several limitations are worth mentioning in this study. First, information on type hemoglobin in control group was not obtained. By incidence of hemoglobinopathy in Surin⁷, there are some hemoglobinopathies in control group, we should undergo measurement. Second, in this study group, there are high concentrations of hemoglobin E, most of subjects are homozygote E. That may have more effect to HbA_{1c} level than dose of heterozygote. This association must be investigated in a large patient group, where the level of glycemic control can be further stratified and the correlation of HbA_{1c} with hemoglobin status can be determined. Finally, diabetic complication and duration of disease were not assessed. Further study is needed to confirm that long term glycemic control in hemoglobin E DM patient should be lower than 5.3% as standard recommend.

We conclude that HbA_{1c} concentrations in diabetic patients with hemoglobin E should be interpreted with caution. This can be the problem in the endemic areas of these hemoglobinopathies. This association must be investigated in a larger patient group.

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