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Renal Function Changes Between Anemic and Clinical Silent Hemoglobin E Disorder, Diabetic Patients in Surin Hospital, Thailand

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ABSTRACT

Background: *Diabetes is now the common cause of end-stage renal disease (ESRD). This research aims to study the rate of decline in estimated glomerular filtration rate (eGFR) in hemoglobin E disorder diabetic patients in Surin hospital.*

Methods: *This case control cohort study was conducted from 2009 to 2018. Patient's general clinical information, fasting plasma glucose (FPG), HbA1c levels, hematocrit (Hct) and eGFR were collected and divided into two groups, anemic hemoglobin E homozygote group (anemic group) and clinical silent hemoglobin E homozygote group (control group).Subjects were confirmed diabetics who already had been treated either with insulin, oral hypoglycemic drugs or a physician-prescribed diet. Target of diabetic control follow standard treatment, not try to intensive control. The endpoint was rate of decline of eGFR per year. The hypothesis was that the cumulative average duration of disease was equally, the renal complication between two groups was not different.*

Results: *From 2009 to 2018, 195 diabetic patients with hemoglobin E homozygote, 72 anemic hemoglobin E homozygote group (anemic group) and 123 clinical silent hemoglobin E homozygote group (control group). There were no significant differences in regard to fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), triglyceride (TG) and low-density lipoprotein (LDL) among the groups. The hematocrit (Hct), diastolic blood pressure (DBP), high-density lipoprotein (HDL), eGFR was significantly lower in anemic group. The age, cholesterol (CHO), systolic blood pressure (SBP), serum creatinine (Cr) and duration of disease was significant high in anemic group. The rate of decline in eGFR were significant much slower in control group 0.74 ml/min/year and 1.41 ml/min/year in anemic group ($P<0.001$), after adjusted confounding factors.*

Conclusion: *With long term cohort study, anemic hemoglobin E homozygote group have artificial lower HbA1c. Diabetic patients with clinical silent hemoglobin E homozygote group should be monitored using HbA1c level as an indicator for long-term glycemic control. But in anemic hemoglobin E homozygote group should be use self-monitoring blood sugar level.*

Keywords

Diabetes mellitus, Hemoglobinopathy, Hemoglobin E disorder, Diabetic nephropathy, Surin hospital.

Background

Diabetic is now the common cause of end-stage renal disease (ESRD). In addition to the excess morbidity, premature mortality and reduced quality of life experienced by diabetic people with renal failure. Previous large prospective research trials in patients with diabetes mellitus have demonstrated the strong relationship between intensive glucose lowering and microvascular outcomes has long been known [1-3]. The most important factor that determines hemoglobin A1c (HbA1c) concentration is long-term blood glucose level witch, makes HbA1c the standard for monitoring long-term glycemic control in diabetics [4-6]. The data from some researches have shown that too intensive glucose control can lead to increased hypoglycemic attacks in diabetic patients [7]. In patients with diabetes having normal hemoglobin,

HbA1c values strongly correlate with blood glucose level. However, many studies have shown that decreased erythrocyte life-span such as observed in hemolytic anemia, is associated with lower concentration of HbA1c [8-14]. This has been suggested to be because HbA1c is correlated with the developmental stage of erythrocytes. The concentration of minor hemoglobins in young erythrocytes was found to be lower than that in the older erythrocytes. Therefore, HbA1c concentration has been proposed as a diagnostic parameter in anemia associated with short erythrocyte life-spans [15-16]. More than 700 forms of hemoglobinopathy or abnormal hemoglobin variants have been reported [21-26]. Hemoglobin E disorder is the most prevalent hemoglobinopathy in Surin, Thailand. Therefore, patients with diabetes who have concomitant hemoglobin E disorder is also frequently encountered [27]. There were many reported cases for low HbA1c levels in a poorly controlled diabetic [17-20]. However, the decline in kidney function between anemic and clinical silent hemoglobin E disorder, diabetic patients have not been clearly identified. This research aims to study the rate of decline in glomerular filtration rate (eGFR) between anemic and clinical silent hemoglobin E disorder, diabetic patients in Surin hospital, Thailand.

Methods

Subject

This cases control cohort study was approved by the institutional review board and conducted in the diabetes clinic at Surin Hospital from January 2009 to December 2018. Informed consent was obtained from all subjects. The sample size was calculated from the average and variance obtained from a previous study in 2006. The number in each group was calculated to be representative of the population at 95% confidence. Subjects were confirmed diabetics who already had been treated either with insulin, oral hypoglycemic drugs or a physician-prescribed diet. Target of diabetic control follow standard treatment, not try to intensive control. For analysis measurements from 2 data sets were used. Exclusion criteria included hemoglobin H disease and hemoglobin E heterozygote.

Measurement

For the laboratory measurements, a blood sample was taken in the morning after an overnight fast and tested for fasting plasma glucose, lipid profile, complete blood count, blood urea nitrogen, creatinine, and HbA1c. Subjects were classified into one of 2 groups: anemic hemoglobin E homozygote group (anemic group) and clinical silent hemoglobin E homozygote group (control group). Anemic group defined as hematocrit (Hct) <32% and control group defined as Hct ≥ 32%. Serum creatinine levels were measured annually throughout the course of the study. The estimated glomerular filtration rate (eGFR) was estimated with the use of the Chronic Kidney Disease Epidemiology Collaboration formula. Baseline characteristrics, FPG, HbA1c, lipid profile, complete blood count including hematocrit, creatinine, systolic blood pressure and diastolic blood pressure were collected from the first visit of year 2009, retrospective to year at diagnosis and once time per year until 2018 or loss follow up or dead.HbA1c was measured using the turbidimetric inhibition immunoassay (TINIA) for hemolyzed whole blood (Cobas®, Roche Diagnostics, USA). The endpoint was that of rate of decline of eGFR per year. The hypothesis was that the cumulative average duration of disease was equal, the renal complication between two groups was not different.

Statistical analysis

Statistical analysis was carried out using STATA14. Descriptive parameters are presented as means with standard deviations or percent. The general data were compared between the anemic hemoglobin E homozygote group (anemic group) and clinical silent hemoglobin E homozygote group (control group).by Fisher's exact tests or unpair t-test. Gaussian regression analysis was performed to identify rate of decline of eGFR per year between two groups. Two-sided $P<0.05$ was considered significant.

Results

A total of 195 hemoglobin E homozygote diabetic patients treated at the diabetes clinic at Surin hospital were studied from January 2009 to December 2018. Among these, 72 patients were anemic group and 123 patients were in the control group. A total of, 1516 blood tests were done with 900 in control group and 616 in anemic group.

Demographic characteristics

Table 1 describes the list of the demographic characteristics of the patients. There were no significant differences in regard to fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), triglyceride (TG) and low-density lipoprotein (LDL) among the groups. The hematocrit (Hct), diastolic blood pressure (DBP), high-density lipoprotein (HDL), eGFR was significantly lower in anemic group. The age, cholesterol (CHO), systolic blood pressure (SBP), serum creatinine (Cr) and duration of disease was significant high in anemic group. Table 1 describes patient characteristics and results of laboratory blood tests.

Variable	Anemic group	% or SD	Control group	% or SD	P-Value
N	616		900		
Age	65.8	0.42	59.6	0.36	<0.001
Sex M/F	106/510	17.2%	300/600	33.3%	<0.001
Duration	8.8	0.26	6.7	0.17	<0.001
SBP	130.8	0.73	128.9	0.49	0.024
DBP	73.7	0.43	75.4	0.37	0.002
FPG	154.4	2.5	155.5	2.08	0.736
HbA1c	7.08	0.1	7.4	0.18	0.213
CHO	188.7	1.86	184.2	1.31	0.042
TG	155.7	3.7	165.9	4.83	0.124
HDL	47.4	0.51	49.5	0.43	0.002
LDL	116.3	1.41	111.9	1.72	0.057
Cr	1.13	0.02	0.93	0.01	<0.001
eGFR	67.2	0.96	78.3	0.79	<0.001

Table 1: Baseline characteristics by anemic group and control group.

SD: Standard deviation, M: Male, F: Female, SBP: Systolic blood pressure; DBP: Diastolic blood pressure, FPG: Fasting plasma glucose; HbA1c: Hemoglobin A1c, Hct.: Hematocrit, CHO: Cholesteral, TG: Triglyceride, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, Cr: Creatinine, CI: Confidence interval, eGFR: Estimated glomerular filtration rate.

P<0.05 for the comparison between anemic group and control group with the use of the unpair t test or Fisher's exact test.

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The relation of HbA1c and duration of disease are given in figure 1control group have higher level of HbA1c during follow-up (Figure 1). The relation of serum creatinine and duration of disease are given in figure 2, the anemic group have higher level of serum creatinine during follow-up (Figure 2).

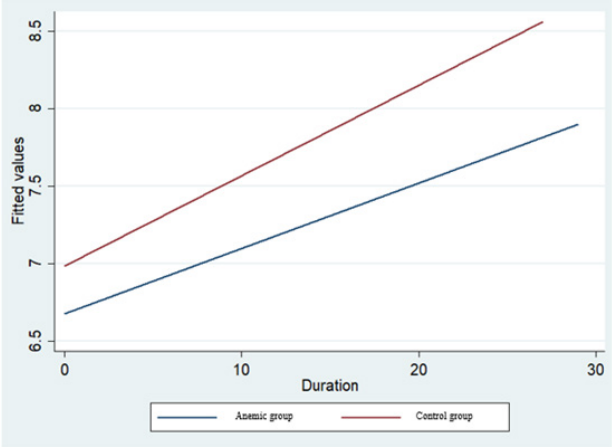

Figure 1: HbA1c level during follow up between anemic group and control group.

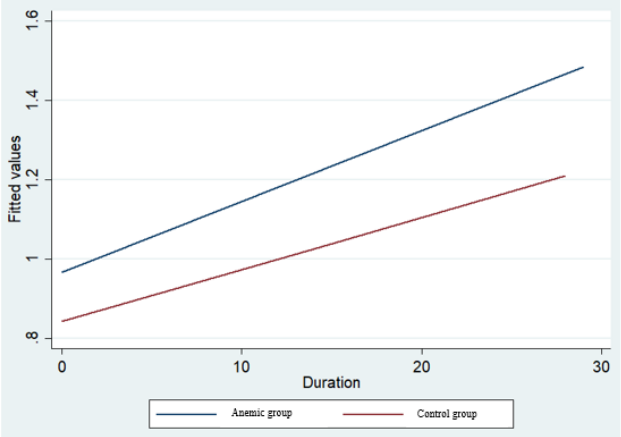

Figure 2: Creatinine level during follow up between anemic group and control group.

Table 2 and Table 3 show when compared with controls, the rate of decline in eGFR were significant much slower in control group 0.66 ml/min/year and 1.32 ml/min/year in control group (P<0.001), and 0.74 ml/min/year and 1.41 ml/min/year in control group (P<0.001) after adjusted confounding factors, SBP, DBP, CHO, TG, HDL and LDL. The relation of eGFR and duration of disease are given in figure 3, the anemic group have lower level of eGFR during follow-up (Figure 3).

eGFR	Coef.	95% CI		P-value
Anemic group	-1.32	-1.54	-1.10	<0.001
Control group	-0.66	-0.92	-0.40	<0.001

Table 2: Effects of anemic group compared with control groupon eGFR by univariable analysis.

CI: Confidence interval, eGFR: Estimated glomerular filtration rate.

P<0.05 for the comparison between anemic group and control group with the use of Gaussian regression analysis.

eGFR	Coef.	95% CI		P-value
Anemic group	-1.41	-1.66	-1.15	<0.001
Control group	-0.74	-1.01	-0.46	<0.001
SBP	-0.21	-0.29	-0.12	<0.001
DBP	0.31	0.19	0.44	<0.001
CHO	0.01	-0.04	0.05	0.781
HDL	0.05	-0.05	0.16	0.316
LDL	0.04	0.00	0.07	0.052

Table 3: Effects of anemic group compared with control groupon eGFR by multivariable analysis.

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, CHO: Cholesteral, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, eGFR: Estimated glomerular filtration rate, CI: Confidence interval.

P<0.05 for the comparison betaween anemic group and control group with the use of Gaussian regression analysis.

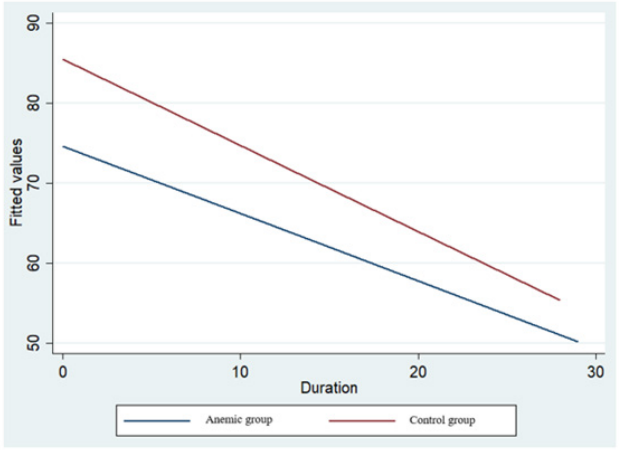

Figure 3: eGFR level during follow up between anemic group and control group.

Discussion

Thalassaemia and haemoglobinopathy are the most common inherited disorders among humans, and they represent a major public health problem in many areas of the world, including south-east Asia [22]. The most important disorders are alpha-thalassaemia and beta-thalassaemia. Among the structural haemoglobin (Hb) variants, Hb E (a2b226glu-lys) is the most common, especially in the north-eastern part of Thailand, and in Cambodia and Laos [23-26]. The World Health Organization (WHO) estimates that in Thailand at least 10,000 new cases of Hb E Beta-thalassemia are

expected in the next few decades. High estimates are predicted for India, Sri Lanka, Malaysia and southern China. The prevalence of Hb E in California parallels the rise in Asian births [22].

A high incidence of Hb E has been reported in many groups with Surin province [26,27]. In these areas, the prime targets of prevention and control of severe thalassaemia are homozygous alpha-thalassaemia, homozygous b-thalassaemia and b-thalassaemia–Hb E disease. The aim of screening for thalassaemia and Hb disorders is to offer carrier testing to every member of the population, ideally before they have children, in order to identify carrier couples and inform them of the risk and their options. The people targeted by screening are therefore carriers of alpha-thalassaemia, beta-thalassaemia and Hb E. As a general guideline, primary screening for all forms of thalassaemia involves using an electronic blood-cell counter to provide accurate erythrocyte indices. Individuals who have hypochromic microcytosis with mean corpuscular volume (MCV) below 80 fl or mean corpuscular Hb (MCH) below 27 pg. should be investigated further using Hb electrophoresis or high-performance liquid chromatography (HPLC). This, however, can be problematic in rural areas in south-east Asia where the expense usually precludes the possibility of electronic blood-cell counting. A cheaper alternative screening method be used a modified dichlorophenolindophenol (DCIP) precipitation test. This method could be used in any primary health care setting where a program of prevention and control is needed.

Surin Province is located in the northeast of Thailand, the boundaries between Thailand and Cambodia. There is a prevalence of Thalassemia and hemoglobin E disorder higher than other areas of the world, as well as in patients with diabetes who have hemoglobin E disorder very high as well, approximately 30-50% of all diabetes population which is a problem in the care of these patients [27]. In Surin hospital, Thailand, hemoglobinopathies is routinely performed as part of diabetes patients screening programs in diabetic clinic, screening method be used a modified dichlorophenolindophenol (DCIP) precipitation test before further using Hb electrophoresis. Clinically silent hemoglobinopathies may affect HbA1c results more often than currently recognized, particularly in Surin with type 2 diabetes,because of the high prevalence of both diseases and hemoglobin E disorder in this population. If hemoglobinopathy is suspected, hemoglobin electrophoresis should be performed for confirmation and identification of the hemoglobin variant. Because of some evidence that questions the reliability of in patients with hemoglobinopathies. Knowledge and awareness of hemoglobin variants affecting HbA1c measurements is essential, especially in areas with a high prevalence of hemoglobinopathy, in order to avoid mismanagement of diabetic patients. Alternative non-hemoglobin methods of measuring glycemic control such as self-monitoring of blood glucose may be more appropriate than HbA1c in patients with hemoglobin variants and should be considered. Lowering HbA1c to below or around 7% has been shown to reduce microvascular and neuropathic complications of type1 and type2 diabetes. Therefore, for microvascular disease prevention, the HbA1c goal for non-pregnant adults in general is <7% [4]. HbA1c represents the main fraction of hemoglobin bound to glucose and is normally present at low levels in red blood cells. In patients with diabetes having normal hemoglobin, HbA1c values strongly correlate with blood glucose level. Because the HbA1c test is based on normal hemoglobin, hemoglobinopathies can affect the reliability of the test in three ways, altering the normal process of glycation of HbA to HbA1c , causing an abnormal peak on chromatography, making estimation of HbA1c unreliable and making the red blood cell more prone to hemolysis, thereby decreasing the time for glycosylation to occur and producing a falsely low HbA1c result. Because HbA1c is based on normal hemoglobin, qualitative or quantitative differences in hemoglobin can affect HbA1c values. Further, it has been suggested that the abnormal hemoglobin found in those with HbE may also make red blood cells more vulnerable to hemolysis, thereby decreasing red blood cell lifespan. In selecting glycemic goals, the benefits on long-term health outcomes of achieving a lower HbA1c must be weighed against the unique risks of hypoglycemia and the difficulties achieving near-normoglycemia in hemoglobin E disorder. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was specifically designed to determine whether a therapeutic strategy targeting normal glycated hemoglobin levels (i.e., below 6.0%) would reduce the rate of cardiovascular events, as compared with a strategy targeting glycated hemoglobin levels from 7.0 to 7.9% in middle-aged and older people with type 2 diabetes mellitus and either established cardiovascular disease or additional cardiovascular risk factors. The finding of higher mortality in the intensive-therapy group led to a decision to terminate the intensive regimen in February 2008, 17 months before the scheduled end of the study [7].

In this study, all physicians were following the ADA recommended glycemic goals for non-pregnant individuals are based on data of HbA1c. The listed blood glucose goals are levels that appear to correlate with achievement of HbA1c of <7%. During follow up, anemic group have higher level of FPG and very low in HbA1c. Because the physician was not trying to intensive control when FPG were still high with low HbA1c. The patients in anemic group have higher rate of decline in eGFR. That should be the artificial low of HbA1c.

The decline in glomerular filtration rate is highly variable, ranging from 2-20 ml/min/year, with a median of 12 ml/min/year [28]. In this data show very low rate of decline in eGFR 0.74 ml/min/year (0.46-1.01, 95% confidence interval). Lower than lower range from previous study. The natural history of no risk factor Caucasians is median decline of GFR 0.4 ml/min/year [29]. Data from this study evaluated the rate of decline in eGFR were significant slower in control group, but higher 1.9 times and 3.5 times in anemic group, if compared with normal population.

Several limitations are worth mentioning in this study. First, patients with hemoglobin E heterozygote and hemoglobin H were excluded. Second, there are some missed data in antihypertensive drugs that may be effect in renal function. Last, many clinical endpoints were not completed evaluated, all caused mortality, macro-

vascular complication and other micro-vascular complication. In hemoglobin E disorder, there are high clinical variant. The patients with beta thalassemia/HbE were not excluded. Therefore, FPG is likely not appropriate for monitoring in HbEE patients and instead, HbA1c should be used in clinical silent hemoglobin E homozygote patients' population.

Conclusion

With long term cohort study, anemic hemoglobin E homozygote group have artificial lower HbA1c. Diabetic patients with clinical silent hemoglobin E homozygote group should be monitored using HbA1c level as an indicator for long-term glycemic control. But in anemic hemoglobin E homozygote group should be use self-monitoring blood sugar level.

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