นิพนธ์ต้นฉบับ • Original Article

ความชุกของภาวะโลหิตจาง ในผู้ป่วยเบาหวานประเภทที่ 2 ที่ไม่ได้ถูกวินิจฉัยว่ามีโรคหลอดเลือดหัวใจหรือโรคไตเรื้อรังร่วมด้วย

พัชราภรณ์ สุดชาฎา[1], ภิวดี ขุนมธุรส[2], รวิสุดิ เดียวอิสเรส[3]
[1]หน่วยวิจัยการบริบาลทางเภสัชกรรม ภาคเภสัชกรรมปฏิบัติ คณะเภสัชศาสตร์ มหาวิทยาลัยนเรศวร
[2]ฝ่ายเภสัชกรรม และ [3]ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยนเรศวร

Prevalence of Anemia in Thai Type 2 Diabetic Patients with No Diagnosis of Associated Cardiovascular or Chronic Kidney Diseases

Patcharaporn Sudchada[1], Piwadee Kunmaturos[2], Rawisut Deoisares[3]
[1]Pharmaceutical Care research Unit, Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok, Thailand
[2]Department of Pharmacy and [3]Department of General Medicine, Faculty of Medicine, Naresuan University, Phitsanulok, Thailand

หลักการและวัตถุประสงค์: ภาวะโลหิตจางในผู้ป่วยเบาหวานประเภทที่ 2 อาจเป็นปัญหาที่ถูกมองข้าม เนื่องจากการศึกษาส่วนใหญ่มุ่งเน้นไปที่การศึกษาถึงปัจจัยเสี่ยงต่อโรคหลอดเลือดและหัวใจอย่างอื่น การศึกษานี้มีวัตถุประสงค์เพื่อหาความชุกของการมีภาวะโลหิตจางในผู้ป่วยเหวานประเภทที่ 2 ที่ไม่ได้รับการวินิจฉัยว่ามีโรคหลอดเลือดหัวใจ หรือ โรคไตเรื้อรังร่วมด้วย

วิธีการศึกษา: การศึกษานี้เป็นการศึกษาเชิงสำรวจ และผู้ป่วยเบาหวานประเภทที่ 2 ทั้งหมด 1,876 ราย ถูกคัดกรองและมีผู้ป่วยทั้งหมด 714 รายที่ไม่ได้รับการวินิจฉัยว่ามีโรคทางหลอดเลือดและหัวใจ หรือ โรคไตเรื้อรังร่วมด้วย และมี 247 ราย (ชาย 106 ราย; หญิง 141 ราย) ที่ถูกนำเข้าร่วมการศึกษาเนื่องจากมีค่าการตรวจครีเอตินีน และฮีโมโกลบินในช่วงที่ทำการศึกษาข้อมูลถูกเก็บแบบย้อนหลังจากเวชระเบียนผู้ป่วยนอก และ ฐานข้อมูลอิเลคโทรนิกส์ ของโรงพยาบาลที่ทำการศึกษา 1 แห่ง ในช่วงปี พ.ศ. 2553 ค่าผลตรวจทางห้องปฏิบัติการครั้งล่าสุดถูกนำใช้ในการวิเคราะห์ข้อมูล

ผลการศึกษา: จากผู้เข้าร่วมการศึกษาทั้งหมด 247 ราย มี ผู้ป่วยจำนวน 122 ราย (ร้อยละ 49.4, 95% CI 43-55%)

Background and Objectives: Anemia in type 2 diabetes may be unrecognized since most studies have been interested in other risk factors for cardiovascular (CVD). The objective of this study was to investigate the prevalence of anemia in type 2 diabetes patients who has no diagnosis of associated CVD or chronic kidney diseases (CKD).

Methods: This is a survey study in the type 2 diabetic individuals. All of 1878 patients were screened and 714 had no diagnosis of CVD or CKD. Only 247 individuals (Males: 106; females: 141) with completion of creatinine and hemoglobin values were enrolled into the study. The data were collected retrospectively from out-patient medical records and the electronic data bases for the patients who were followed up at a university hospital during 2010. The latest laboratory values of all patient visits were used in the analysis.

Results: Of all 247 individulas, it was found that 122 patients (49.4 %, 95% CI 43-55%) of these individuals had anemia (haemoglobin<12 g/dl for women and <13 g/dl for men). A general linear model showed that gender, renal function and weight were significantly correlated

**Corresponding Author: PatcharapornSudchada, Pharmaceutical Care research Unit,Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok, 65000, Thailand Tel: +66 55 961-830 Fax: +66 55 963-731 E-mail: patcharaporns2000@yahoo.com, psudchada@gmail.com*

มีภาวะโลหิตจาง (ฮีโมโกลบิน < 12 กรัม/เดซิลิตร ในเพศหญิง, ฮีโมโกลบิน < 13 กรัม/เดซิลิตร ในเพศชาย) จากการวิเคราะห์โดย ใช้ general linear model พบว่า เพศ การทำงานของไต และน้ำหนัก มีความสัมพันธ์กันอย่างมีนัยสำคัญทางสถิติกับระดับฮีโมโกลบิน (p< 0.001) เพศชายมีระดับ ฮีโมโกลบิน สูงกว่าหญิงตามที่คาดการณ์ จากจำนวนผู้ป่วยทั้งหมด 122 ราย ที่มีภาวะโลหิตจางพบว่า ร้อยละ 45.9 มีค่าการทำงานของไต (eGFR) 60-89 มิลลิลิตร/นาที/ตารางเมตร และผู้ป่วยร้อยละ 37.7 มี ค่าการทำงานของไต น้อยกว่า 30 มิลลิลิตร/นาที/ตารางเมตร

สรุป: การศึกษานี้แสดงให้เห็นว่าภาวะโลหิตจาง เป็นภาวะที่พบบ่อยในผู้ป่วยเบาหวานที่ไม่ได้รับการวินิจฉัยว่ามีโรคหลอดเลือดหัวใจ หรือ โรคไตเรื้อรังร่วมด้วย ปัจจัยหนึ่งที่สำคัญและสัมพันธ์กับการเกิดภาวะโลหิตจางในผู้ป่วยกลุ่มนี้คือการทำงานของไตบกพร่อง การระบุการมีภาวะโลหิตจางและการมีโรคไตเรื้อรัง อย่างรวดเร็วเป็นสิ่งจำเป็นเพื่อป้องกันการดำเนินไปของภาวะดังกล่าว และ ผลแทรกซ้อนที่รุนแรงตามมาในประชากรกลุ่มนี้

คำสำคัญ: เบาหวาน, ภาวะโลหิตจาง

with haemoglobin levels (p< 0.001). Males had higher haemoglobin levels than females as expected. Of all 122 anemia patients, it was observed that 45.9% had eGFR 60-89 ml/min/m^2 and 37.7% had eGFR less than 30 ml/min/m^2.

Conclusion: The study indicated that anemia occurs commonly in diabetic patients who have no diagnosis of CVD and CKD. One of crucial factors associated with anemia in the population was renal impairment. Early identification of anemia and CKD is warrant in order to preventprogression of anemia and consequent severe complications in this population.

Keywords: Diabetes, anemia

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Introduction

In diabetes, hypertension and dyslipidemia are well-known cardiovascular risk factors[1, 2]. Beside these risk factors, anemia and renal impairment are also important in preventing cardiovascular complications in these patients. In these patients, chronic kidney disease (CKD) is one of the most common complications in diabetes causing anemia[3, 4]. Anemia potentially affects mortality, morbidity as well as quality of life[3, 5-7]. In addition, anemia in patient with diabetes mostly develops in relation to progression of CKD and is more severe than those who have no diabetes[5, 6, 8-10].

It has been reported that hemoglobin levels is associated with the risk of quality of life, cardiovascular events, morbidity as well as mortality[10-12]. In some populations, it has been reported that there are about 20% of diabetes patients who have anemia and the majority of these patients have glomerular filtration rate of 30-60 mL/min[6, 13, 14].

The diagnosis of CKD may be under documented and under diagnosed in Thailand. Therefore, anemia and CKD problems may not be brought to attention of healthcare providers and policy makers. Besides, anemia problem in Thai diabetes individuals may be unrecognized since most studies have been interested in diabetes and other common cardiovascular risk factors including hypertension and dyslipidemia[15-21]. Current Thai diabetes management guideline has launched in 2008 which was established by a cooperation of Diabetes Association of Thailand, the Endocrine Society of Thailand and National Health Security of Thailand[22]. However,the management of anemia in diabetes patients has not been warranted in the guideline. Limited evidence is available about the prevalence of anemia in Thai diabetes patients with no diagnosis of cardiovascular complications in association with CKD. This study was, therefore, aimed to survey the prevalence of anemia in the Thai type 2 diabetes particularly in patients with no diagnosis of CVD or CKD. We hope

that this information will be useful in developing the strategies of anemia management as one of primary prevention for cardiovascular complications in diabetes individuals in our country.

Methods

Subjects and Methods

This study was a retrospective cross-sectional survey study. The study was approved by the Ethics Committee of Naresuan University. Of 1876 Thai type 2 diabetes who were followed up at a university hospital during 2010, the patients were excluded if they were having long-term follow-up at other hospitals, only coming for emergency treatments or health checking visits, receiving insulin therapy, being diagnosed of micro- and macro-vascular complications as reported in the electronic hospital data base, having cancer or other serious chronic diseases other than hypertension and dyslipidemia. After initial screening, a total of 714 individuals were identified to have no diagnosis of CVD and CKD.

The data were collected from out patient medical records and an electronic hospital database. Patient demographics including age, gender, weight, medical history and medication used were collected. However, the information of height was not available since it was not recorded in the out patient medical records, therefore, the body mass index could not be calculated. Levels of glycosylated haemoglobin (HbA1c), fasting blood sugar (FBS), lipid profiles, albumin, serum creatinine and hemoglobin were collected for each individual. The presence of anemia was defined by a haemoglobin < 13 g/dL in men and <12 g/dL in women as described by World Health Organization (WHO) (23). Renal function was assessed by calculating estimated glumerular filtration rate using the 4- variable Modification of Diet in Renal Disease (MDRD) formula (24): eGFR = $175[(\text{creatinine}- 3.08)/(1.004 \times 88.4)]^{-1.154} \times \text{age}^{-0.203}$ (x 0.742 if female, x 1.21 if black). Stages of CKD are defined as CKD stage 1 is eGFR greater than 90 mL/min/1.73 m^2, with some sign of kidney damage on other tests (if all the other kidney tests are normal, there is no CKD). CKD stage 2 is eGFR 60-90 mL/min/1.73m^2 with some sign of kidney damage (if all the kidney tests are normal, there is no CKD). CKD stage 3 is eGFR 30-59 mL/min/1.73 m^2, a moderate reduction in kidney function. CKD stage 4 is eGFR 15-29 mL/min/1.73 m^2, a severe reduction in kidney function and CKD stage 5 is e GFR less than 15 mL/min/1.73 m^2, established kidney failure, when dialysis or a kidney transplant may be needed.

Statistical analysis

The statistical package for Social Science version 17.0 (SPSS Inc, Chicago, IL, USA) was utilized for the analysis. Data are presented as mean and standard deviation (SD), range, or percentage. The χ 2 test was used to compare the distributions of between groups. Student t's test and analysis of variance (ANOVA) were used to compare means of values among groups. Spearman correlation coefficients were utilized to determine the correlation of anemia and other variants. A p-value < 0.05 was considered significant. In order to determine the correlation of hemoglobin and eGFR, linear regression models and diagnostic plots were utilized.

Results

All of 1,876 patients with type 2 diabetes were screened. Of these, a total of 714 (325 males; 388 females) patients were type 2 diabetes with no cardiovascular complications and only 661 patients (303 males; 358 females) were able to calculated estimated glomerular filtration rate (eGFR). Of these, only 247 subjects (106 males; 141 females) were measured haemoglobin at least 1 times during the study period and included in the analysis (Figure 1).

Of all 247 subjects who had haemoglobin levels available, the prevalence of anemia was 49.4% (95% CI 43-55%). Table 1 showed the differences in parameters among patients with and without anemia. These subjects were not diagnosed to have CKD, anemia or any of cardiovascular complications based on the ICD-10 diagnosis system in the electronic data-based

of the hospital. The mean age of individuals with and without anemia were 63.2 and 58.2 (p > 0.05) years, respectively. Patients with anemia had significantly lower mean of eGFR compared with the patient without anemia (p = 0.04). The mean of other variants were not different between groups. However, the correlation tests revealed that haemoglobin levels were negatively correlated with age (r = 0.31, p = 0.000). In addition, haemoglobin levels were also have positively correlated with weight (r = 0.369, p =0.000), diastolic blood pressure (r = 0.204, p = 0.000), and eGFR (r = 0.223, p = 0.000). Progression of CKD was correlated with anemia (r = 0.183, p = 0.004) and haemoglobin levels (r = 0.250, p =0.000). Moreover, regression analysis showed significant correlations between haemoglobin levels and eGFR (p= 0.002) and anemia and eGFR (p = 0.019). Figure 2 illustrates the relationship of haemoglobin and estimated glomerular filtration rate (eGFR) by gender. An increase of severity of CKD (GFR falling) was observed with a decrease of mean of haemoglobin in both males and females. Hence, females had significantly more anemia than males (56.0% vs. 40.6%, p = 0.016). A mean of hemoglobins in females and males were 11.8 ± 1.4 and 13.1 ± 1.8 (p =0.002).

Figure 3 shows the proportion of type 2 diabetes patients, by CKD category who were anemic and without anemic. The proportion of patients with anemia has increased enormously when the patient is in stage 3 or more advanced CKD. Table 2 illustrates patients' characteristics by stages of CKD. More numbers of anemic patients with CKD stage 3 were higher than patients with CKD stage 1 or 2 (67.6% vs. 41.5% vs. 45.5%, p =0.008). Hence, of all 122 anemia patients, it was observed that 45.9% had eGFR 60-89 ml/min/m^2 and 37.7% had eGFR less than 30 ml/min/m^2. Moreover, there were 38.7% of anemia individuals were ACEIs or ARBs users, and correlation tests showed that the use of ACEI or ARBs and the presence of hypertension were not correlated with haemoglobin levels or anemia.

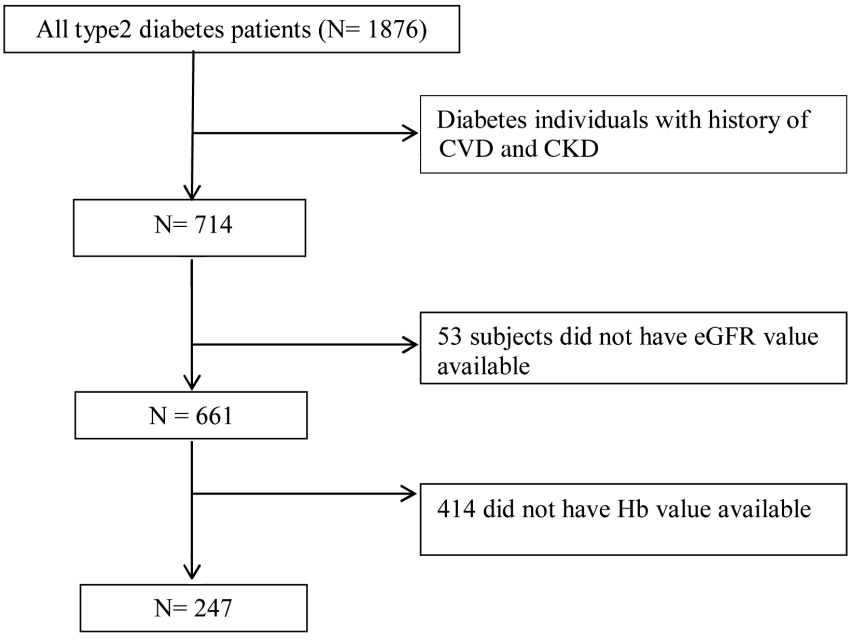

Figure 1 Flow diagram of subject enrollment

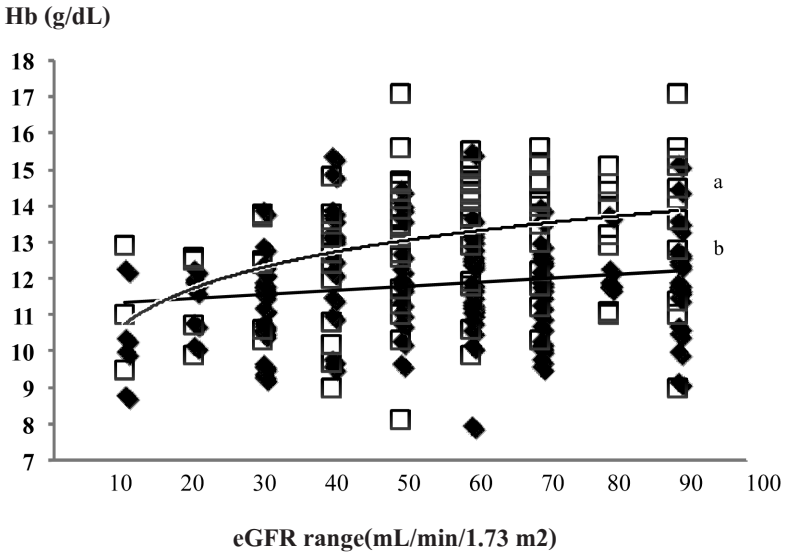

Figure 2 The relation of haemoglobin (Hb) to estimated glomerular filtration rate (eGFR) by gender (a, males; b, females). The squares indicate haemoglobin levels of males and the black diamonds indicate haemoglobin levels of females.

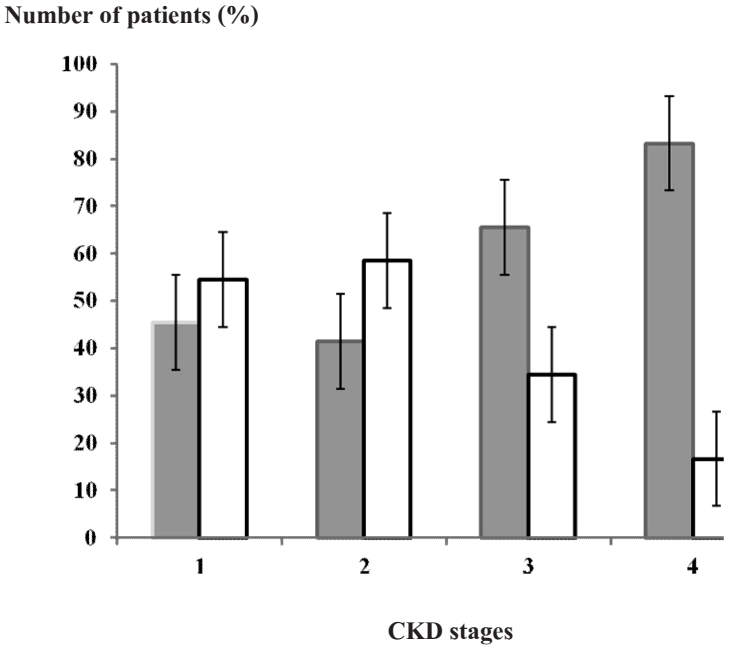

Figure 3 Proportion (with 95% confidence intervals) of type 2 diabetes patients, by chronic kidney disease (CKD) category who have subnormal haemoglobin or are anemic determined by the WHO definition stating in the method section. eGFR, estimated glomerular filtration rate. Black bars indicate the percentage of the number of patients with anemia. White bars indicate the percentage of the number of patients without anemia.

Table 1 Patients' characteristics among individuals with and without anemia

Patient characteristics	With anemia		Without anemia		*p-value	Mean ± SD
	N	Mean ± SD	N	Mean ± SD		(all patients)
Age (Years)	122	63.2 ± 10.3	125	58.2 ± 9.2	> 0.05	60.7 ± 10.0
Weight (kg)	107	62.4 ± 11.7	121	69.2 ± 12.4	> 0.05	66.0 ± 12.5
SBP(mmHg)	114	137.0 ± 18.9	123	138.9 ± 21.8	> 0.05	138.0 ± 20.4
DBP (mmHg)	114	73.6 ± 11.6	123	78.7 ± 11.7	> 0.05	76.3 ± 11.9
LDL-C (mg/dl)	99	96.3 ± 33.6	112	116.2 ± 47.0	> 0.05	106.8 ± 42.3
HDL-C (mg/dl)	99	46.8 ± 11.8	112	46.3 ± 13.8	> 0.05	46.5 ± 12.9
TG (mg/dl)	101	152.5 ± 79.1	114	176.2 ± 119.5	> 0.05	165.1 ± 103.0
TC (mg/dl)	100	171.7 ± 39.2	112	193.7 ± 45.0	> 0.05	183.3 ± 43.7
Non HDL-C (mg/dl)	99	126.6 ± 34.8	112	147.4 ± 43.5	> 0.05	137.7 ± 40.9
% HbA1C	91	7.1 ± 1.6	85	7.2 ± 1.4	> 0.05	7.1± 1.5
FBS (mg/dl)	119	135.0 ± 52.3	120	142.3 ± 48.4	> 0.05	138.6 ± 50.4
eGFR (mL/min/1.73 m2)	122	69.2 ± 29.8	125	77.4 ± 24.4	0.04	87.7 ± 35.5
Hb (g/dL)	122	11.0 ± 1.0	125	13.7 ± 1.1	> 0.05	12.4 ± 1.7

* p-value of student't-test between mean of variants of patient with anemia and patient without anemia For abbreviations, please see table 1.

Table 2 Patient characteristics by stages of chronic kidney disease

CKD category (n = 661)	Stage 1 or no CKD (eGFR≥90)	Stage 2 (eGFR 60-89)	Stage 3 (eGFR 30-59)	Stage 4 (eGFR 15-29)	Stage 5 (eGFR< 15)	p value
Mean Hb	12.8 + 1.8	12.6 + 1.7	11.7 + 1.5	10.9 + 1.5	9.5	0.000
(N valid)	(44)	(135)	(61)	(6)	(1)	
Range of Hb	9.0-17.1	8.0-17.1	9.0-15.4	8.8-12.9	-	-
Subnormal Hb (%)	20 (45.5)	56 (41.5)	40 (65.5)	5 (83.3)	1 (100)	0.008

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; S.D., standard deviation; Hb, haemoglobin; HbA1c, glycatedhaemoglobin; FBS, fasting blood sugar. N valid, the number of patients that were included in the analysis.

Discussion

This present study is the first study to determine the prevalence of anemia in type 2 diabetes in Thai subjects with never been diagnosed for CKD or anemia or other cardiovascular complication in the electronic database of the hospital using ICD-10 system. This indicates that the patients may be under optimal care by the inefficient system. We observed that the prevalence of haemoglobin level measurement in this population was low. Of 661 subjects who were able to calculated eGFR, only 37.4 % were measured for haemoglobin level at least 1 time/ years.

Several studies have reported about 10-23 % of diabetes patients had anemia in various population[6, 10, 14, 25-28]. Our study demonstrates that anemia is a common complication in diabetic patients supported by previous findings[5, 6, 10, 25]. There were 49.4% of these type 2 diabetic patients who were anemic as define by WHO definitions[23]. In addition, there were about 21.9% with haemoglobin levels less than 11 g/dL which indicated for anemia correction recommended by National Kidney foundation: KDOQI clinical practice guideline for anemia of CKD[29]. It has been reported that anemia is common in type 2 diabetes

individuals with elevated albuminuria, established renal impairment, macrovascular disease or advanced age, especially, impaired renal function and albuminuria are the predominant risk factors for anemia[5,6,10,14,25,30]. In agreement with previous findings, we found that anemia in diabetes patients strongly correlated with progression of CKD. A low haemoglobin level has significantly correlated with a decrease of renal function and the increased prevalence of anemia was noted when eGFR was below 60 mL/min/1.73 m^2.

Besides, we could not determine the association of albuminuria because there was no data available due to the screening for albuminuria in these patients not routinely performed. Even though we did not look into levels of albuniuria and erythropoietin levels, our findings were similar to other reports that the prevalence of anemia increased when renal function declined[5, 6, 10, 25]. The use of ACEIs may contribute to anemia in patients with diabetes[31, 32] but we did not found the association between the use of ACEIs or ARBs and anemia which was supported by Hayashi et al[33]. On the other hand, this was opposed to the finding by Bonakdaran et al.[25] but after adjustment for CrCL, this association was not significant.

Considering other variants correlated with anemia in diabetic patients, similar trend with previous reported[5, 10] we found that females had higher prevalence of anemia than males. Advanced age and lower weight were expected variants to be correlated with occurring of anemia. Interestingly, we observed that low diastolic blood pressures not systolic blood pressures were correlated with low haemoglobin levels which may suggest possible diastolic dysfunction impaired in diabetes patients with anemia which similar to previous study[34].

Anemia is one of cardiovascular risk factors which can be modified and anemic patients have higher risk for morbidity and mortality[3, 5-7]. Occurring of left ventricular hypertrophy, heart failure, and reduction in both physical capacity and quality of life in patients with reduced kidney function may be mediated through anemia[35-38]. In addition, normalization of haemoglobin may prevent progressive left ventricular dilatation in patients with normal left ventricular volumes[39]. Therefore, correction of anemia may be enormous benefits in these patients. However, this present study shows that there were under diagnosis of CKD and therefore less attention paid to management of anemia in these type 2 diabetic patients. The explanation to this occurring may be due to these patients were followed by general practice or by other specialized physicians but not endocrine physicians. In addition, the current Thai guideline for management of diabetes[22] has not mentioned about anemia care.

A study by New et al.[6] observed that haemoglobin starting to fall downward when eGFR was below 83 mL/min/1.73 m^2 suggesting that erythropoietin deficiency begins to cause anemia with an average a fall of 0.1 g/dL in haemoglobin for every 2.5 mL/min/1.73m^2 loss of eGFR. In addition, it suggested the optimal cut-off level of eGFR for further investigation of anaemia would be 66 mL/min/1.73 m^2 [6]. This was supported by the current practice guideline of CKD which suggests that patients with eGFR< 60 mL/min/1.73 m^2 should receive a routinely screening for anemia[29]. Anemia is occurred in diabetic patient both with and without nephropathy and iron stores is one of potential causes[10]. Besides, survey studies reported that the risk of anemia in patients with diabetes is approximately two to three times that of a general population with the same level of GFR and similar iron stores[5,10]. It is noted that iron deficiency is one of causes for anemia in diabetic individuals[5, 8, 25]. Therefore, adequate iron store is important in anemia management of diabetic patients. However, the levels of iron store were not available. Since Iron indices are not routinely laboratory measurements in general medicine out-patient-clinic. Therefore, screening for anemia as well as iron status should be integrated into the guideline of diabetic management. Regular screening of haemoglobin levels on annual or biannual basis would facilitate the early detection of individuals with anemia[30].

However, there were some limitations of the present study. Because this is retrospective cross-sectional study and no intervention was given, therefore, not all patients could have all values of all laboratory tests

that were interested in the study. Since more than 95% of the patients were not measured for albumin and microalbumin and all of these patients were not measured for iron indices, we could not be able to determine the association between haemoglobin levels and these laboratory values. In addition, there was no information relating to other potential non-renal-causes of anemia. Our diabetic patients were not entirely typical of general diabetic population in Thailand. However, the strong association of anemia with progression of nephropathy should be in awareness of health care providers and policy makers. Finally, the number of the patients included in the analysis was only based on the availability of interested laboratory values and was not all of the patients who were identified of having no diagnosis of CVD or CKD. Therefore, the information should be interpreted and utilized in caution and a large epidemiology study is needed to confirm the results.

This study highlights the awareness of unrecognized anemia, particularly, in Thai diabetes individuals who have no diagnosis of CVD or CKD. Incorporating of routinely anemia screening and making diagnosis of anemia or CKD would help to bring up awareness in diabetes care and finally benefit in improving quality of life as well as reducing anemia related morbidity and mortality in diabetic patients. However, these can be accomplished by cooperating of all clinicians and policy makers.

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