Thailand Diabetes Registry Project: Prevalence of Vascular Complications in Long-standing Type 2 Diabetes

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Objective: *To explore the nature of diabetic complications in type 2 diabetic patients who had had diabetes for longer than 15 years (long-DM), compared to those with duration of less than 15 years (short-DM).*
Material and Method: *Patients studied were adult type 2 diabetic patients registered to the Diabetes Registry Project, a nationwide cross-sectional study of diabetes mellitus in Thailand. Information collected included demographic data, age at diagnosis of diabetes, blood pressure, body mass index, fasting plasma glucose, HbA_{1c}, serum creatinine, and major diabetic vascular complications, including diabetic retinopathy (DR), albuminuria or renal insufficiency (diabetic nephropathy; DN), myocardial infarction (MI), stroke, peripheral arterial disease (PAD), foot ulcer and amputation.*
Results: *There were 9284 patients, consisting of 2244 (24.17%) subjects with long-DM (mean $\pm$ SD, mean duration of DM 21.3 $\pm$ 5.8 years), and 7040 subjects with short-DM (mean duration 7.0 $\pm$ 3.9 years). The long-DM group was older than the short-DM group (65.5 $\pm$ 10.3 vs 58.2 $\pm$ 12.6 year-old, p less than 0.0001), and had higher HbA_{1c} (8.5 vs 8.0%, p = 0.009). The prevalence of diabetic complications in the long-DM group was higher than that in the short-DM group (DN 49.4% vs 33.9%, DR 54.3% vs 22.8%; MI 9.4% vs 3.5%, PAD 17.3% vs 5.5%, foot ulcer 13.4% vs 5.3%,, stroke 9.4% vs 7.0% and amputation 5.5% vs 2.0%; all p values less than 0.01). The duration of DM significantly affected the risk of diabetic complications after adjustment for age, hypertension, and levels of glycemic control.*
Conclusion: *Diabetic duration was independently associated with increased risk of having diabetes-related complications without threshold. Monitoring of complications in patients having long-standing diabetes is warranted in order to provide appropriate management.*

Keywords: *Vascular complications, Long-standing diabetes*

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With modern technology, people live longer and diabetic survival is better. The combination of higher incidence of diabetes and lower mortality, contribute to the epidemic of diabetes worldwide[1,2]. Thailand is in a transitional period, changing from an agricultural society to an industrial society, together with having better health technology and health care policy. These changes result in increased life-expectancy for Thais[3] as well as increased prevalence of obesity among Thai children and adolescents[4]. Mo-suwan et al have showed that Thai children were getting more obese at a dangerous rate, from 12.2% in 1990 to 15.6% in 1992. It is unlikely among this group of obese children to succeed in controlling their body weight[5]. In 1999, Thai females had a life expectancy of 75 years while the life expectancy of Thai males was 70 years[3]. From these data, it is predictable that there will be more young type 2 diabetes patients, and with better health care, the life expectancy of patients with diabetes is expected to be longer. However, there is limited information on patients with long-standing diabetes. Their proportion will be significant in the near future. Available data indicate that duration of diabetes is a significant risk factor for diabetic complications. However, only two studies (the KIDS[6] and Pima Indian[9],) have clearly shown the impact of having diabetes for longer than two decades while other studies[7,8,10-12] only indicated an impact of diabetic duration on the risk of diabetic complications, but provided limited information for this group of patients. The major limitation of the KIDS study was that they did not adjust for a hypertensive state on the risk of complications. In addition, it may not be possible to apply the outcomes of those studies to Thai diabetic population due to certain societal or population differences such as race, glycemic control, lifestyle, lipid profile or obesity among Thais, Caucasians or other ethnic groups. This may affect the risk of diabetic complications. The authors have to be concerned about the differences in race in existing studies, since it is well recognized that insulin resistance varies according to race[13]. Asians have higher insulin resistance despite lower body mass index[14]. This remarkable high insulin resistance in Asians is associated with a higher prevalence of diabetes and may be related to the higher percentage of body fat[15] than Caucasians with a comparable BMI[16]. Another reason why the authors need information on diabetic complications is for health economic analyses. It could guide health care practice and management, especially with regard to the complication surveillance required in this group.

The objective of the present study was to study how the duration of diabetes affects the vascular complications among Thai type 2 diabetic patients.

Material and Method

A cross-sectional, multi-center, hospital-based diabetes registration was carried out from April 2003 to December 2003. The authors registered diabetic patients from diabetes clinics of 11 tertiary centers in Thailand. The study was approved by the Ethics Committee of each participating hospital. Signed informed consent was obtained from all participants. The method of registration and data collection was described in a previous section[22]. Only adults aged 15 years or older with type 2 diabetes were included in this study. Patient information was retrieved through medical records in addition to an interview by individual site investigators using a structured questionnaire. The patient's weight was measured in kilograms using a balance beam scale with the patient wearing only light clothes. Height in centimeters was measured by a wall-mounted scale, with the patient shoeless. Blood pressure was measured at least twice, at least 1 minute between measurements, by an automatic digital sphygmomanometer (Omron T4), with the patient having been at rest for at least 5 minutes. Mean values of both systolic and diastolic blood pressure were used to define blood pressure levels. Patients had peripheral pulses palpated at all 4 extremities.

Laboratory studies consisted of fasting plasma glucose (FPG), serum creatinine (Cr), total cholesterol, HDL- cholesterol, triglyceride, calculated LDL-cholesterol, and urinary albumin excretion (calculated as albumin/creatinine ratio) collected from first-void morning urine sample.

Diabetic complications consisted of diabetic retinopathy (DR), diabetic nephropathy (DN), coronary artery disease, cerebrovascular disease, and peripheral arterial disease. DR included either proliferative or background diabetic retinopathy diagnosed by an ophthalmologist. DN was defined as serum creatinine greater than 2 mg/dl, or proteinuria greater than 1+ by dip stick test on at least two separate occasions without other etiology, or the presence of random microalbuminuria/creatinine ratio greater than 30 mg/gram at least twice in a 6-month period. For the definite diagnosis of coronary artery diseases (CAD), the patients must have had at least 2 of 3 clinical criteria of acute myocardial infarction, a proven coronary angiogram, or have had a coronary artery bypass graft or coronary intervention. Patients were defined as having probable

CAD if they were diagnosed as such by a cardiologist without previous criteria. The diagnosis of cerebrovascular disease was made by documentation of sudden neurological deficit supported by the results of appropriate imaging techniques. The definition of peripheral arterial disease (PAD) was the absence of dorsalis pedis artery and posterior tibialis artery pulses in the same foot. Lower limb amputations were recorded. There were some limitations in defining the cause of amputation, that is, whether it was resulted from infection or PAD, thus in the present study, having an amputation was not defined as a PAD complication.

Microalbumin uria (MAU) in this study was assessed with immunoturbidimetry technique (Hitachi 717, Roche) or Micral test. HbA_{1c} was measured by immunoturbidimetry technique (Hitachi 717, Roche).

Statistical analysis

Data were expressed as mean $\pm$ SD. Statistical analyses were performed using STATA version 8.0 (STATA Corporation, College Station TX, US). For group comparisons, t-test was used where appropriate, and Chi-square or Fishers' Exact test was used to determine the likelihood of having a diabetic complication. To explore the effect of duration of diabetes, logistic regression was used. Statistical significance was considered when p-value was less than 0.05.

Results

There were 9,284 registered adult patients with type 2 diabetes. Duration of DM ranged from 0.0 to 46.5 yrs. The present study revealed 2,244 patients with duration of diabetes of more than 15 years (long-DM) and 7,040 patients with duration of diabetes of less than 15 years (short-DM). The long-DM group had a mean duration of DM of 21.3 $\pm$ 5.8 years, while the duration of DM in the short-DM group was 7.0 $\pm$ 3.9 years. The characteristics of these two groups of patients were presented in Table 1.

The mean age of long-DM group was 65.5 $\pm$ 10.3 years and of the short-DM was 58.2 $\pm$ 12.6 years. The first group had prevalence of hypertensive of 85% whereas that of short-DM was 80%. The mean HbA_{1c} of the first group was 8.5% and of the latter was 8.0%.

Table 1. Characteristics of long-DM and short-DM patients

Characteristic	Long-DM (N = 2244)	Short-DM (N = 7040)	p value
Sex (M/F)	728/1516	2424/4616	0.083
Age (yr)	65.5±10.3	58.2±12.6	<0.0001
Type of DM (type1/type 2)	81.0±2156	248.0±6724	0.096
Hypertension (%)	85	80	<0.0001
HbA1c(%)	8.5±1.8	8.0±1.8	0.009
BMI (kg/m2)	25.0±4.2	25.7±4.3	<0.0001
HDL-C (mg/dl)	54.3±15.5	53.5±15.0	0.047
LDL-C (mg/dl)	110.3±36.1	115.0±36.6	<0.0001
TG (mg/dl)	142.9±88.6	154.1±110.1	<0.0001
Cr (mg/dl)	1.30±0.93	1.13±0.87	<0.0001

Table 2. Prevalence of diabetic complications in long-DM and short-DM patients

	Long-DM (N = 2244)	Short-DM (N = 7040)	p-value
Diabetic retinopathy	50.3%	24.2%	<0.001
Diabetic nephropathy	62.9%	45.7%	<0.001
History of foot ulcer	9.9%	4.7%	<0.001
Amputation	3.5%	0.9%	<0.001
PAD	7.4%	2.8%	<0.001
CAD	14.5%	6.2%	<0.001
Stroke	6.4%	3.8%	<0.001

PAD, peripheral arterial disease; CAD, coronary artery disease

Table 3. The effects of duration of diabetes on complications

Complication \ Diabetic duration (yrs)	Odds ratio (95%CI)*				
	<5	5-9.99	10-14.99	15-19.99	>20
CAD	1	1.11 (0.85-1.44)	1.10 (0.84-1.44)	1.64 (1.23-2.18)	2.22 (1.69-2.91)
DN	1	1.16 (0.99-1.36)	1.50 (1.26-1.78)	1.93 (1.58-2.36)	2.12 (1.73-2.60)
DR	1	1.54 (1.28-1.83)	2.45 (2.05-2.93)	3.99 (3.27-4.87)	5.89 (4.79-7.23)
CVA	1	0.98 (0.71-1.36)	1.12 (0.79-1.56)	1.44 (1.00-2.06)	1.50 (1.05-2.16)

* Adjusted for age, HbA1c, LDL, and the presence of hypertension
DN, diabetic nephropathy; DR, diabetic retinopathy; PAD, peripheral arterial disease; CAD, coronary artery disease

The long-DM patients had mean BMI of 25.0 kg/m^2 which was significantly smaller than the short-DM patients whose mean BMI was 25.7 kg/m^2. The long-DM group had LDL-C, HDL-C and TG levels of 110.3 $\pm$ 36.1 mg/dl, 54.3 $\pm$ 15.0 mg/dl and 142.9 $\pm$ 88.6 mg/dl respectively and those of short-DM group were 115.0 $\pm$ 36.6 mg/dl, 53.5 $\pm$ 15.0 mg/dl and 154.1 $\pm$ 110.1 mg/dl respectively.

The prevalence of diabetic complications was shown in Table 2. Sixty-two percent of long-DM patients had DN, 50.3% had DR and 14.5% had CAD. The prevalence of DN, DR and CAD among short-DM were 45.7%, 24.2% and 6.2% respectively, all of those were significantly lower in short-DM group ($p < 0.001$). Table 3 showed the effect of duration of diabetes on the risk of diabetic complications after adjusted for age, HbA_{1c}, LDL-C levels and hypertension. The risk of CAD among patients having diabetes for longer than 20 years was 2.2 folds higher than patients having diabetes for less than 5 years. The odds ratios of microvascular complication risk of patients with diabetes longer than 20 years were 5.89 for DR and 2.1 for DN.

Discussion

The current paradigm of treating diabetic patients is focused on the patient's state of health, including longevity and quality of life. This present study showed that 24.2% of adult diabetic patients had duration of diabetes of longer than 15 years. The long-DM group had some better as well as some worse risk factors. For the better risk factors, the long-DM had BMI of 25.0 kg/m^2 compared with short-DM of 25.7 kg/m^2 and also had better lipid profiles (LDL-C 110.3 vs 115.0 mg/dl, HDL 54.3 vs 53.5 mg/dl and TG 142.9 vs 154.1 mg/dl). On the other hand, the long-DM had poorer glycemic control (HbA_{1c} 8.5% vs 8.0%), more hypertensive (85 vs 80%) and were older than the short-DM group (65.5 vs 58.2 years old).

The prevalence of diabetic complications in the present study was very high, especially the microvascular complications in both long-DM and short-DM groups, [DR 50.3%, DN 62.9%] [DR 24.2%, DN 45.7%] respectively. DN is one of the major causes of death among Thai diabetics[17]. This finding should raise concern among health care policy makers. Early detection of DR and DN should be encouraged because these complications can be attenuated with appropriate medication and glycemic control.

The long-DM group had prevalence of CAD, PAD and stroke of 14.5%, 7.4% and 6.4% respectively all were significantly higher than those of short-DM group, those were 6.2%, 2.8% and 3.8% respectively.

There are well documented risk factors for diabetic complications such as age, hypertension, glycemic control and lipid profile[19]. To study the impact of duration of diabetes, adjustment for age, hypertensive state, HbA_{1c} and LDL-C were done and the impact of duration of diabetes on the risk of micro- and macrovascular complications remained, with the highest odds ratio in patients having diabetes for longer than 20 years comparing to patients having diabetes for less than 5 years, with odds ratios of 2.1, 5.9, 2.2 and 1.5 for DN, DR, CAD and stroke respectively. Moreover, the impact of diabetes duration on risk of having complications continued without plateau (Table 3).

The present study was in accordance with others that diabetic duration has a significant effect on the risk of vascular complications[6-12]. The prevalence of micro-vascular complication in patients having diabetes for 20 years in this study were very similar to that of Haupt et al[6], 50% for both DN and DR, as well as to those of Krakoff et al[9]. However, there were some differences in the prevalence of micro-vascular complications between the present study and others. The short-DM group in the present study had the prevalence of DN of 45.7% while the numbers from Haupt

et al[6], Krakoff et al[9] were approximately 20%.

There is an effect of race on the risk of DN. Earle and colleagues found that the Indo-Asians had more rapid diabetic nephropathy progression than Africans or whites[18].

There are some limitations in the present study. There was a significant number of patients who did not have complete evaluation of microvascular complications, especially, on DN. Therefore, the prevalence of DN should be higher than the present figure. In addition, the present results might have been confounded by other unexplored factors such as genetics, medications, or lifestyle[20;21].

In conclusion, a significant number of diabetic patients have lived with diabetes for a long time. They have high risk of micro- and macrovascular complications independent of glycemic control, blood pressure status, age, or lipids levels. The risk of diabetic complications increased the duration of diabetes.

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โครงการลงทะเบียนผู้ป่วยเบาหวานในประเทศไทย: ความชุกของโรคแทรกซ้อนจากเบาหวานในผู้ที่มีระยะเวลาของการเป็นเบาหวานนาน

รัตนา ลีลาวัฒนา, ธงชัย ประฏิภาณวัตร, พงศ์อมร บุนนาค, ณัฐพงศ์ โฆษชุณหนันท์, สมพงษ์ สุวรรณวลัยกร, สิริเนตร กฤติยาวงศ์, ธัญญา เชฏฐากุล, ณัฐเชษฐ์ เปล่งวิทยา, ยุพิน เบ็ญจสุรัตน์วงศ์, ชัยชาญ ดีโรจนวงศ์, สิริมา มงคลสัมฤทธิ์, ฉัตรประอร งามอุโฆษ, เพชร รอดอารีย์

วัตถุประสงค์*: เพื่อศึกษาผลของระยะเวลาของการเป็นเบาหวานต่อการเกิดภาวะแทรกซ้อนในผู้ป่วยเบาหวาน*

วัสดุและวิธีการ*: การศึกษานี้เป็นการศึกษาภาคตัดขวางในคลินิกเบาหวานของโรงพยาบาลตติยภูมิ 11 แห่ง การเก็บข้อมูลประกอบด้วยข้อมูลพื้นฐาน ได้แก่ อายุที่ได้รับการวินิจฉัย, ความดันโลหิต, ดัชนีมวลกาย, ระดับน้ำตาลในเลือด HbA1c, ซีรัม creatinine, และภาวะแทรกซ้อนทางตา, ทางไต, การเกิดกล้ามเนื้อหัวใจตาย, โรคหลอดเลือดสมอง, การมี แผลเรื้อรังที่ขาหรือการถูกตัดขา ซึ่งนำมาใช้ในการวิเคราะห์ผลของระยะเวลาที่เป็นเบาหวานต่อการเกิดภาวะแทรกซ้อน*

ผลการศึกษา*: ผู้ป่วยกลุ่มที่มีระยะเวลาของการเป็นเบาหวานนานกว่า 15 ปีมีความชุกของโรคแทรกซ้อนไม่ว่าด้าน microvascular หรือ macrovascular complications บ่อยกว่า แม้ว่าจะปรับแก้กับภาวะอื่น ๆ ได้แก่ อายุ ภาวะความดันโลหิตสูง ระดับ HbA1c ระดับ LDL แล้วก็ตาม ยังพบว่า ระยะเวลาที่เป็นเบาหวานมีผลต่อความชุกของการพบภาวะแทรกซ้อนจากเบาหวาน*

สรุป*: ระยะเวลาของการเป็นโรคเบาหวานที่เพิ่มขึ้นทำให้เกิดภาวะแทรกซ้อนต่าง ๆ มากขึ้น ดังนั้นจึงควรมีการเฝ้าระวัง และติดตามผู้ป่วยเหล่านี้ เพื่อให้ได้รับการดูแลรักษาที่เหมาะสม*