RESEARCH NOTE

FACTORS INFLUENCING CHRONIC DIABETIC COMPLICATIONS IN TYPE 1 DIABETES

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Abstract. Although type 1 diabetes mellitus (T1DM) usually begins in childhood or adolescence, the prevalence of complications increases in adulthood. The objective of this study was to determine the complications of T1DM and the factors that influence them. This retrospective study of 43 patients with T1DM was carried out during 2006-2007. We collected and analyzed demographic data, the clinical status of their diabetes, the complications and treatment. The subjects consisted of 16 males (37.2%) and 27 females (62.8%) with a mean age of 17.8 ± 7.1 years (range 4.1 - 37.5), a mean age at onset of T1DM of 11.3 ± 5.9 years (range 0.9 - 28.1) and a mean duration of T1DM of 6.8 ± 4.3 years (range 1.1 - 19.0). The mean HbA1c of the most recent visit of 9.6 ± 3.1% (range 5.2-17.6). Self - monitoring of blood glucose (SMBG) was performed by 21 patients (48.8%). Acute complications (diabetic ketoacidosis and hypoglycemia) had occurred in 29 patients (67.4%); chronic (microvascular and macrovascular) complications were documented in 13 patients (30.2%). Older age of onset and longer disease duration were factors associated with chronic diabetic complications (p=0.004 and 0.006, respectively). There were no significant differences in HbA1c level, frequency of daily insulin injections, and presence of SMBG between patients with and without complications. Our results suggest patients with T1DM who had older age at onset or longer disease duration are at higher risk for complications.

Keywords*:* type 1 diabetes, chronic complications, factors

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a form of diabetes mellitus characterized by severe insulinopenia and dependence on exogenous insulin to prevent ketoacidosis, hyperosmolar coma and to preserve life. Despite great advances in diabetes care, including better treatment of complications and better glycemic controls, T1DM is still associated with considerable premature mortality resulting from both

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acute and chronic complications of diabetes (EDIC, 2003). Acute complications include ketoacidosis, hyperosmolar coma and hypoglycemia and chronic complications comprised of microvascular, macrovascular and miscellaneous complications (DCCT, 1993; EDIC, 2003). Microvascular complications include retinopathy, nephropathy and neuropathy whereas macrovascular complications include cardiac, cerebrovascular, and peripheral vascular disease. Miscellaneous chronic complications, such as hyperlipidemia, can contribute to coronary atherosclerosis and cardiac complications (Larsen *et al*, 2002).

The reported annual incidence of T1DM varies from <1 per 100,000 in China, Peru and Pakistan to >30 per 100,000 in Finland and Sweden. Thailand has a low incidence of T1DM (Panamonta *et al*, 2011), with an incidence of 0.3:100,000 in northeastern Thailand during 1991-1995 (Panamonta *et al*, 2000) incidence to 0.6:100,000 during 1996-2005 (Panamonta *et al*, 2011). This increasing incidence of T1DM in northeastern Thailand is similar to the rising incidence of T1DM in countries with a high incidence of T1DM. This increasing incidence of T1DM may be associated with an increasing prevalence of chronic complications. The risk factors known to be associated with chronic complications in countries with a high incidence of T1DM are long-term poor glycemic control, longer duration of diabetes, older age at onset and puberty (Krolewski *et al*, 1985). Since there is scarce data regarding the factors influencing chronic complications in patients with T1DM in areas of the world with a low incidence of T1DM, we conducted a retrospective study of T1DM patients at Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand to determine the factors influencing chronic diabetic complications in these patients.

MATERIALS AND METHODS

We retrospectively reviewed the charts of all T1DM patients who presented to Srinagarind Hospital, Khon Kaen University (KKU) during 2006-2007. We recorded their demographic data (age and sex), clinical status, age at onset of T1DM, duration of diabetes, type of insulin used, lipid lowering agents, antihypertensive drugs, self-monitoring of blood glucose (SMBG), mean hemoglobin A1c and chronic complications during the study period.

T1DM was defined as a patient who had acute onset of diabetic symptoms or diabetic ketoacidosis below age 40 years, a BMI < the 85th percentile for age and sex, a fasting plasma glucose > 126 mg/dl, and the need to inject insulin to control their plasma glucose levels. All patients with a first diagnosis of T1DM at Srinagarind Hospital had low insulin or c-peptide levels. Microvascular complications recorded included retinopathy, nephropathy and neuropathy. Macrovascular complications recorded included cardiovascular, cerebrovascular, and peripheral vascular disease. Retinopathy was detected by the regular dilated eye examinations by ophthalmologist yearly or every second year. Nephropathy was defined as persistent proteinuria greater than 500 mg/24 hours or microalbuminuria greater than 30 mg/24 hours confirmed on at least 2 occasions 3-6 months apart, a continuous decline in glomerular filtration rate and an elevated arterial blood pressure (Mogensen *et al*, 1995). Hypertension was defined as a blood pressure ≥ 130/80 mmHg or ≥ 90th percentile for age, sex and height

Table 1
Characteristics and treatment of 43 patients with type 1 diabetes.

	Number of patients	Percentage
Sex		
Male	16	37.2
Female	27	62.8
Age at onset		
< 15 years	33	76.7
≥ 15 years	10	23.3
Disease duration		
≤ 5 years	18	41.9
> 5-10 years	15	34.8
> 10 years	10	23.3
First diagnosed at our hospital	25	58.1
First diagnosed at another hospital	18	41.9
Insulin treatment		
Premix twice daily injection	35	81.4
Multiple daily injections	8	18.6
Oral drugs		
Antihypertensive drugs	5	11.6
Lipid lowering agents	14	32.6
The mean HbA1c		
5-7%	6	14.0
7-10%	17	39.5
> 10%	20	46.5
Self-monitoring of blood glucose	21	48.8

in patients under 15 years old. Dyslipidemia was defined as an LDL cholesterol ≥ 100 mg/dl, a triglyceride level ≥ 150 mg/dl or an HDL cholesterol < 40 mg/dl in males and < 50 mg/dl in females.

We used numbers and percentages for the demographic data, number of patients with complications, and mean ±SD for serum lipid and HbA1c levels. We used a 2-tailed *t*-test to compare data between patients with and without complications and $p < 0.05$ was considered statistically significant. The Khon Kaen University Human Investigation Committee approved the study.

RESULTS

Forty-three T1DM patients, 16 (37.2%) males and 27 (62.8%) females, age between 4.1 and 37.5 years (mean± SD: 17.8 ± 7.1) were enrolled in the study. The age range for onset of diabetes was 0.9 years (11 months) to 28.1 years (11.3 ± 5.9). Thirty-three patients (76.7%) were diagnosed with T1DM below age 15 years and 10 patients (23.3%) at ≥ 15 years. Eighteen patients (41.9%) were referred to our hospital from primary and secondary hospitals by general practitioners. The duration of having T1DM ranged from 1.1 to 19.0 years (6.8±4.3). The body mass indicies (BMI)

Table 2
Chronic complications among 13 patients with type 1 diabetes.

Chronic complications	Number of patients (%)
Nephropathy	8 (18.6)
Retinopathy	7 (16.3)
Hypertension	5 (11.6)
Neuropathy	4 (9.3)
Ischemic stroke	1 (2.3)
Cardiomyopathy	1 (2.3)

ranged from 12.0 to 22.3 kg/m^2 (15.9±2.8). All patients received insulin treatment, 35 (81.4%) patients were treated with premix insulin twice daily, 8 were treated with multiple daily insulin injections 3-4 times per day with an insulin analogue (rapid onset and long acting basal insulin). Fifteen patients (34.9%) had been monitored for serum lipids and 14 patients (32.6%) required lipid-lowering agents. Five patients (11.6%) had hypertension and need antihypertensive drugs. SMBG was conducted by 21 patients (48.8%). The characteristics of the 43 patients are summarized in Table 1. The mean HbA1c ranged from 5.2 to 17.6% (9.6±3.1); 6 patients (14.0%) had a Hb1c < 7%. Chronic complications were documented in 13 patients, 7 patients had more than one complication (Table 2). Nephropathy (18.6%) was the most common chronic complication and retinopathy (16.3%) was the second most common chronic complication. A comparison of the data in T1DM patients with and without chronic complications is summarized in Table 3.

DISCUSSION

Long-term poor glycemic control, long duration of diabetes, older age at onset and puberty are the main risk factors known to contribute to diabetic complications (Krolewski *et al,* 1985). The Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) study showed intensive glycemic control results in a significant risk reduction for microvascular and macrovascular complications (DCCT, 1993; EDIC, 2003; Nathan *et al,* 2005). Our results show longer duration of T1DM and older age at onset were significant risk factors for chronic diabetic complications, similar to the findings of a multicenter study of 195 T1DM patients from 11 tertiary hospitals in Thailand (Likitmaskul *et al,* 2006). The mean duration of T1DM among patients with complications was 2 times longer than among patients without complications. Glycemic control and elevated HbA1c level were not significant risk factors for complications since most of our patients (86%) had high HbA1c levels (poor glycemic control) and more than 80% of our patients were treated with a conventional insulin regimen.

Chronic elevation of blood glucose level is associated with damage of blood vessels. It was demonstrated in a cohort of 27,805 T1DM patients from Germany that longer diabetes duration, high HbA1c levels, high LDL cholesterol levels and high blood pressure were risk factors for the development of microalbuminuria and nephropathy (Raile *et al,* 2007). Among 11,618 Swedish T1DM patients, female sex and prepubertal age at onset of T1DM were associated with a prolonged time to development of renal disease. These age and sex differences in development of renal disease may be explained by differences in lifestyle, diet, renal and glomerular size, glomerular hemodynamics and effect of sex hormones (Mollsten

Table 3
Comparison of T1DM patients with and without chronic diabetic complications.

Data	With chronic complications	Without chronic complications	OR (95% CI)	*p*-value
Number of patients	13	30		
Sex (%)				
Male	3 (23.1)	15 (50.0)	1.00	0.16
Female	10 (76.9)	15 (50.0)	3.33 (0.65 - 22.02)	
Age at onset (years)				
Range (M±SD)	6.0-28.1 (15.0±6.0)	0.9-20.0 (9.3±5.0)		0.005*
Duration of DM (years)				
Range (M±SD)	4.0-19.0 (10.1±4.6)	1.1-13.0 (5.3±3.3)		0.001*
Mean HbA1c				
Range (M±SD)	6.9-12.4 (9.2±2.0)	5.2-17.6 (9.8±3.4)		0.409
Insulin injections/day (%)				
Twice daily	8 (61.5)	27 (90.0)	0.18 (0.02 - 1.20)	0.459
Multiple times daily	5 (38.5)	3 (10.0)		1.00
Insulin dosage (units/kg/day)				
Range (M±SD)	0.6-1.5 (1.0±0.3)	0.5-1.6 (1.0±0.3)		0.824
Self monitoring of blood glucose (%)	5/13 (38.5)	16/30 (53.3)	0.55 (0.11 - 2.47)	0.558

* $p < 0.05$ = significant difference; OR, odds ratio; CI, confidence interval

et al, 2010). Animal studies suggested estrogens slow the progression rate of renal disease (Mankhey *et al*, 2005).

Genetic contribution to hyperglycemia-induced nephropathy was suggested by a study that found 83% of T1DM patients with a sibling who had T1DM and nephropathy also had evidence of nephropathy, compared to only 17% of T1DM siblings without nephropathy (Sequist *et al*, 1989). Recent studies of genetic associations for susceptibility to diabetic nephropathy revealed a strong association between nephropathy and two novel candidate loci on chromosome 9q and 11p near the FRMD3 and CARS genes (Pezzolesi *et al*, 2009).

For retinopathy, poor glycemic control, long duration of diabetes, puberty and pregnancy are known risk factors for retinopathy among T1DM patients (Olsen *et al*, 2004). The presence of retinopathy is associated with a doubling or tripling of risk for stroke, coronary heart disease and heart failure independent of cardiovascular risk factors (Cheung *et al*, 2007). These findings suggests retinopathy is a sign of widespread microcirculatory damage and needs careful cardiovascu-

lar monitoring and follow-up (Cheung and Wong, 2008). Variations within the aldose reductase (AKR1B1) genes are significantly associated with diabetic retinopathy irrespective of ethnicity (Abhary *et al*, 2009). Identification of genetic risk factors for diabetic complications will assist in further understanding this complex and debilitating diabetic complication (Pezzolesi *et al*, 2009).

Abnormalities of the retina and kidneys may occur within a few years of the onset of diabetes. Early detection and treatment of microvascular complications has a pivotal role in prevention of blindness and end-stage renal disease in childhood diabetes (Bailey *et al*, 1999; Twyman *et al*, 2001). Besides metabolic control, regular screening for retinopathy and nephropathy are important in pediatric diabetes care. ISPAD Clinical Practice Consensus Guidelines (2009) recommend screening for retinopathy every 2 years beginning at age 11 years and screening for nephropathy every 5 years beginning at age 9 years. Lipid level screening should be conducted every 5 years beginning at age 12 years in all T1DM patients (Donaghue *et al*, 2009).

The most common macrovascular complication in this study was hypertension (11.6%), a risk factor for cardiovascular disease (CVD). Studies of glycemic control and the development of CVD (DCCT, 1993; EDIC, 2003) showed better glycemic control reduced the risk of CVD and coronary artery calcification among patients with T1DM (Wajchenberg *et al*, 2008).

In conclusion, chronic diabetic complications are common in our Thai subjects where most had poor glycemic control and a long duration of DM. These were the main risk factors for developing chronic diabetic complications. Early detection and intensive treatment of complications should be provided for all T1DM patients in Thailand.

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