**TITLE PAGE**

**Title:** Progression towards Diabetic Retinopathy among patients with type 2 Diabetes Mellitus with or without Hypertension (National data- hospital based cross-sectional study from 2010 to 2011)

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ABSTRACT

**Background**: Both Diabetes Mellitus and Hypertension were the common type of non communicable diseases and it was found mostly among people with sedentary lifestyle. Like others non communicable diseases, these two diseases progress towards target organs damages (complications) such as retinopathy, nephropathy and neuropathy if the patients were poorly controlled for long duration. There were many evidences of identified risk factors concerning with getting diabetic nephropathy i.e. uncontrolled sugar level, hypertension, hyperlipidaemia, physical inactivity and smoking etc., but there was little evidence on prevalence and determinants of diabetic retinopathy progression among patients with type 2 Diabetes Mellitus in Thailand.

**Objective**: To investigate prevalence and determinants of Diabetic retinopathy progression among patients with type 2 Diabetes Mellitus with or without hypertension

**Methods**: This study was hospital based cross-sectional study and the study population was those patients diagnosed with type 2 Diabetes and hypertension visiting hospitals in care of Ministry of Public Health and Bangkok Metropolitan Administration in Thailand during 2011, 2012 and 2013. Total numbers of study population were 174,578 from specialist clinics, general medical clinic, general practice clinic and others. Patients were diagnosed having diabetic retinopathy by physicians within 12 months of study period and HbA1c and other clinical parameters were also examined by laboratory within 12 months of last visit.

**Results**: Among study population, 18.4% of patients had had diabetic retinopathy

(95% CI: 18.2% to 18.5%). Bivariate logistic regression was done and it was found that patients with HbA1c level ≥ 7% had had more retinopathy than that of HbA1c < 7% (OR = 4.5, 95% CI: 4.4 to 4.7, *P* = 0.00) and patients with their blood pressure > 130/80 mmHg had had also more retinopathy than that of ≤ 130/80 mmHg (OR = 1.33, 95% CI: 1.30 to 1.37, *P* = 0.000). The mean difference of disease duration (year) of patients with diabetic retinopathy was not clinical significant different with that of patients without retinopathy (-0.00121: 95% CI: -0.00028 to 0.0004, *P* = 0.93) respectively. Multiple logistic regression analysis was done to get adjusted odds ratio for age and sex of patients and it was still high odds ratio for patients with HbA1c level ≥ 7% (OR = 4.6, 95% CI: 4.4 to 4.7, *P* = 0.00) and also high odds ratio for blood pressure > 130/80 mmHg (OR = 1.29, 95% CI: 1.26 to 1.33, *P* = 0.000). Female patients was found to have high odds ratio than male patients (OR = 1.21, 95% CI: 1.26 to 1.33, *P* = 0.000) and odds ratio was increase 1.7% for each one year older in age (OR = 0.983, 95% CI: 0.982 to 0.984, *P* = 0.000).

**Conclusions**: The prevalence of Diabetic retinopathy progression was low compared to other studies. HbA1c level was the most important risk factor to get retinopathy progression and the other important risk factors were the high blood pressure, age and female gender.

**Key words:** diabetic retinopathy, HbA1c,

INTRODUCTION

Progression towards Diabetic Retinopathy, one of the microvascular complications of Diabetes Mellitus, is the leading cause of visual impairment and can be prevented by tight glycemic control (1). Patients with diabetic retinopathy are increasing trend as total numbers of Diabetes Mellitus are also increasing (2,3)and WHO estimate that over 75% of all diabetes patients will be from developing countries by the time of 2025(4). Due to lack of quality health care system and poor self management, Diabetes Mellitus and its complication Retinopathy persists as a serious public health problem in developing countries (1).

The prevalence of diabetic retinopathy varies widely according to the region and a systematic review conducted in Iran found that the prevalence was 30-40% among diabetes patients(5). The major risk factors for retinopathy complication are poor glycemic control, high blood pressure, hyperlipidaemia, disease duration and quality of medical care. More than 60% of type 2 diabetes patients suffer some degree of retinopathy after 20 years of disease duration (6). Regarding to blood glucose control, every percentage of decreased HbA1c level accounts for 35% reduction in occurrence of microvascular complication (6). Male gender is a significant risk factor of progression to microvascular complication (HR: 1.58, 95% CI: 1.18-2.1)(7).

Although global prevalence and determinants for diabetic retinopathy are well known in literature, what are the prevalence and types of retinopathy progression among type 2 diabetes patients for Thailand? Are determinants and strength of association for this complication similar to global situation? This study aim to explore these questions by using national data of the whole country and the results will be used as the baseline data concerning with quality of care of type 2 DM and also for conducting further related studies in this field.

**MATERIALS AND METHODS**

***Study design***

This study was hospital based cross-sectional study and the study population were those patients who had diagnosed with type 2 Diabetes and/or hypertension visiting hospitals in care of Ministry of Public Health and Bangkok Metropolitan Administration in Thailand during 2011, 2012 and 2013. Total numbers of study population were 174,578 from specialist clinics, general medical clinic, general practice clinic and others.

***Study outcome***

This study used diabetic retinopathy as outcome measure i.e. non-proliferative retinopathy, proliferative retinopathy, diabetic macular oedema and others. Patients were diagnosed having diabetic retinopathy by physicians within 12 months of study period during their visits and HbA1c and other clinical parameters were also examined by laboratory within 12 months of last visit. HbA1c level < 7% was used as uncontrolled blood sugar level and HbA1c ≥ 7% as controlled blood sugar level. Blood pressure 130/80 mmHg was used to differentiate the patients with high blood pressure or not. Hba1c and blood pressure level were used as explanatory variables for outcome measure.

***Statistical analysis***

* Data summarization was done by using frequency and percent distribution table for categorical data and, mean and standard deviation for continuous data.
* The proportion of retinopathy patients and 95% CI were calculated to estimate the magnitude of retinopathy outcome among study population. Bivariate logistic regression analysis was done to get the crude odds ratios (ORs) of outcome variables by using explanatory variables i.e. HbA1c level and blood pressure level. To control the covariates effect on outcome variable, multiple logistic regression analysis was done to get the adjusted odds ratios (ORs) and 95% CI of explanatory variables. Demographic characteristics such as age, sex and clinical variables such as duration of disease, treatment status were used to adjust the outcome variables.
* All analyses were performed using Stata version 10.0 (StataCorp, College Station, TX). All test statistics were two-sided and a p-value of less than 0.05 was considered statistical significant. This project was approved by the Human Research and Ethics Committees of the Ministry of Public Health of Thailand.

RESULTS

Total 174,578 patients with type 2 Diabetes Mellitus diseases participated in this study during their follow up visit at specialist clinics, general medical clinic, general practice clinic and others on 2010, 2011 and 2012. The back ground characteristics and clinical variables were record with CRF for quality assessment of medical care among patients with type 2 Diabetes Mellitus and/or Hypertension.

Patients during 2011

Patients during 2010

Patients during 2012

Total 174,578 patients with type 2 Diabetes Mellitus and/or Hypertension

Covariates:

Age, gender, regular treatment, level of health care

Patients with retinopathy (prevalence)

Patients without retinopathy

Figure 1. Flow chart diagram of study concept

***Demographic characteristics***

**Table 1.** Demographic characteristics of study population

| **Characteristics** | **Total**  **(n=xx,xxx)** | **Types of health care institution** | | |
| --- | --- | --- | --- | --- |
| **Specialist hospitals**  **(n=xx,xxx)** | **General hospitals**  **(n=xx,xx)** | **Others**  **(n=xx,xxx)** |
| Age (years) |  |  |  |  |
| ≤ 40 | xx.x | xx.x | x.x | x.x |
| 40 – 59 | xx.x | xx.x | xx.x | xx.x |
| 60 or greater | x.x | x.x | x.x | x.x |
| Mean ± standard deviation | xx.x± x.x | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x |
| Range (Min:Max) | xx.x- xx.x | xx.x - xx.x | xx.x - xx.x | xx.x - xx.x |
| Gender |  |  |  |  |
| Male | x.x | x.x | x.x | x.x |
| Female | xx.x | xx.x | xx.x | xx.x |
| Present diagnosis |  |  |  |  |
| Diabetes Mellitus only | xx.x | xx.x | xx.x | xx.x |
| Hypertension only | xx.x | xx.x | x.x | xx.x |
| Diabetes and Hypertension | x.x | x.x | - | x.x |
| Disease duration |  |  |  |  |
| Mean ± standard deviation | xx.x± x.x | xx.x ± x.x | xx.x ± x.x | xx.x ± x.x |
| Treatment |  |  |  |  |
| Regular | xx.x | xx.x | xx.x | xx.x |
| Not regular | xx.x | xx.x | xx.x | xx.x |

The mean age of study population was xx.x years and ranged from xx years to xx years. Female patients were xx.x percent of study population and male were xx.x percent. xx.x percent of study population were diabetic patients, xx.x percent were hypertensive patients and xx.x percent were both Diabetic and hypertensive patients. The mean disease duration was xx.x years and xx.x percent took regular treatment.

***Diabetic Retinopathy progression prevalence***

Table 2. Retinopathy prevalence and types among study population

| **Characteristics** | **Total**  **(n=xx,xxx)** | **Types of health care institution** | | |
| --- | --- | --- | --- | --- |
| **Specialist hospitals**  **(n=xx,xxx)** | **General hospitals**  **(n=xx,xx)** | **Others**  **(n=xx,xxx)** |
| Retinopathy |  |  |  |  |
| Present | xx.x | xx.x | x.x | x.x |
| Absent | xx.x | xx.x | xx.x | xx.x |
| Retinopathy type |  |  |  |  |
| Non-proliferative | xx.x | xx.x | xx.x | xx.x |
| Proliferative | xx.x | xx.x | xx.x | xx.x |
| Diabetic macula oedema | xx.x | xx.x | xx.x | xx.x |
| Others | xx.x | xx.x | xx.x | xx.x |

The study found that xx,xxx (xx.x%) patients had had retinopathy complication (95% CI: xx.x% –xx.x%). Among them, non-proliferative retinopathy was found in x,xxx (xx.x%) patients, proliferative retinopathy was found in x,xxx (xx.x%) patients and diabetic macular oedema was found in x,xxx (xx.x%) patients.

***Multiple logistic regression analysis for retinopathy outcome by using explanatory variables and covariates***

Table 3. Odds ratios (ORs) of getting retinopathy and their 95% confidence intervals for each factor, and adjusted for all other factors presented in the table using logistic regression

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Factors** | **Number** | **% retinopathy** | **Crude OR** | **Adjusted OR** | **95%CI** | **P-value** |
| HbA1c |  |  |  |  |  | 0.xxx |
| < 7% | xx,xxx | xx.x | x.xx | x.xx | x.xx-x.xx |  |
| ≥ 7% | xx,xxx | xx.x | x.xx | x.xx | x.xx-x.xx |  |
| Blood pressure |  |  |  |  |  | 0.xxx |
| < 130/80 | xx,xxx | xx.x | x.xx | x.xx | x.xx-x.xx |  |
| ≥ 130/80 | xx,xxx | xx.x | x.xx | x.xx | x.xx-x.xx |  |
| Age (years) |  |  |  |  |  | 0.xxx |
| ≤ 40 | xx,xxx | xx.x | x.xx | x.xx | x.xx-x.xx |  |
| 40 – 59 | xx,xxx | xx.x | x.xx | x.xx | x.xx-x.xx |  |
| 60 or greater | xx,xxx | xx.x | x.xx | x.xx | x.xx-x.xx |  |
| Gender |  |  |  |  |  | 0.xxx |
| Male | xx,xxx | xx.x | x.xx | x.xx | x.xx-x.xx |  |
| Female | xx,xxx | xx.x | x.xx | x.xx | x.xx-x.xx |  |
| Present diagnosis |  |  |  |  |  | 0.xxx |
| DM only | xx,xxx | xx.x | x.xx | x.xx | x.xx-x.xx |  |
| Hypertension | xx,xxx | xx.x | x.xx | x.xx | x.xx-x.xx |  |
| Both | xx,xxx | xx.x | x.xx | x.xx | x.xx-x.xx |  |
| Treatment |  |  |  |  |  | 0.xxx |
| Regular | xx,xxx | xx.x | x.xx | x.xx | x.xx-x.xx |  |
| Not regular | xx,xxx | xx.x | x.xx | x.xx | x.xx-x.xx |  |

Multiple logistic regression analysis was done and it was found that HbA1c level was the main determinant factors which crude OR (x.xx, 95%CI: x.xx-x.xx) and adjusted OR (x.xx, 95%CI: x.xx-x.xx) were largest and not much change after adjusting other covariates. The effect of blood pressure on retinopathy was small i.e. crude OR (x.xx, 95%CI: x.xx-x.xx) and adjusted OR (x.xx, 95%CI: x.xx-x.xx). Older age and female patients were more prone to have retinopathy with crude OR (x.xx, 95%CI: x.xx-x.xx) and adjusted OR (x.xx, 95%CI: x.xx-x.xx) for 40 or greater age and crude OR (x.xx, 95%CI: x.xx-x.xx) and adjusted OR (x.xx, 95%CI: x.xx-x.xx) for female.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Factors** |  | **Odds ratio** | **95% CI** | **p-value** |
|  |  |  |  |  |
| Hba1c (≥ 7%) |  | x.xx | x.xx – x.xx | 0.xxx |
| Blood pressure (≥ 130/80) |  | x.xx | x.xx – x.xx | 0.xxx |
| Age (≥ 40) | | x.xx | x.xx – x.xx | 0.xxx |
| Gender (female) |  | x.xx | x.xx – x.xx | 0.xxx |
| ???    .50  0 |  | x.xx | x.xx – x.xx | 0.xxx |
|  | 2  1 |  |  |  |
|  |  |  |  |  |

**Figure. 2.** Effect of HbA1c and blood pressure on retinopathy progression, presented as odds ratio adjusted for age, gender, disease duration, treatment effect, using multiple logistic regression

HbA1c was predominantly the strongest factor of progression towards retinopathy, i.e., it was x.xx folds the risk of retinopathy for patient with HbA1c (≥ 7%) compared to patients with HbA1c (< 7%) (OR = x.xx; 95%CI: x.xx –x.xx; *p* < 0.xxx) (Figure. 2).

**DISCUSSIONS**

* Prevalence of retinopathy progression among study population- by age group (<40 and ≥ 40), by gender and health care institutional level-compare with other studies
* Major risk factors for diabetic retinopathy
* Strength of association changes after controlling covariates

***Strength of the study***

* National data with large sample size

***Limitation of the study***

* Hospital based study – just we see tip of the ice berg, many left in the community
* Secondary data analysis – should consider on Data validity
* Confounders can be controlled by data analysis phase

***Conclusions***

The prevalence of Diabetic retinopathy progression was low compared to other studies. It reflects the national quality of diabetic care. HbA1c level was the most important risk factor towards retinopathy progression and the high blood pressure and female gender were more likely to get retinopathy complication. The percentage of HbA1c <7% and blood pressure <130/80 among study population should be increased to prevent progression towards diabetes retinopathy and other complications.

***Recommendations***

* National survey concerning with Diabetes Mellitus and its complication should be conducted to reflect the community.
* Continuous monitoring of HbA1c level among Diabetes Mellitus and tight glycemic control by medication
* Awareness raising campaign concerning with risk factors of Diabetes Mellitus, its complication and prevention methods
* Quality health care setting at the community level with high accessibility and affordability

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