**TITLE PAGE**

**Title: Effects of Oral Hypoglycemic Agents, Insulin (Pharmacological treatment) And Life style modification (Non-pharmacological treatment) on glycemic control of Type 2 Diabetes patients in Thailand**

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 **Effects of Oral Hypoglycemic Agents, Insulin (Pharmacological treatment) And Life style modification (Non-pharmacological treatment) on glycemic control of Type 2 Diabetes patients in Thailand**

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**ABSTRACT**

**Background**: Diabetes Mellitus (DM) is a clinical syndrome characterized by hyperglycemia due to absolute or relative deficiency of insulin which is one of the global pandemic which involves Type 2 DM.

It is a chronic illness that requires continuing medical care, ongoing patient self-management education and support, life style modification and regular monitoring of their blood glucose level to maintain their blood glucose level within normal limit.

**Objective**: To assess the effects of oral hypoglycemic agents, insulin (pharmacological treatment) and life style modification (non-pharmacological treatment) on glycemic control (HbA1c level) of Type 2 Diabetes patients.

**Methods**: A hospital based cross-sectional study was conducted by using DAMUS study data. Nationally representative sample surveys of 59750 patients with Type 2 DM and/or hypertension were interviewed at 549 hospitals which were based on medical records in Thailand during 2011. Among these, 8421 patients with Diabetes alone were used in this study. Level of HbA1c was the outcome of this study. Both of pharmacological treatments and non-pharmacological treatments (life style modification) were assumed as treatment of Diabetes according to American Diabetes Association. Multiple logistic regression was used to analyze.

**Results**: In this study, almost all of the patients were on pharmacological treatments (98.21%) and the rest 1.79% was non-pharmacological treatment. In pharmacological treatments patients, 8.42%, 77.69%, 12.10% were on treatment with Insulin alone, OHA alone and both of them respectively. The odds of patients with lifestyle modifications is x.xx times ( OR= x.xx. 95%CI x.xx\_x.xx) more controlled that patients with pharmacological treatments after adjusting of the other factors.

**Conclusions**: In conclusion, lifestyle modification is the most effective treatment for Type2 DM patients compared with pharmacological treatments in Thailand.

**Key words**: Pharmacological treatment, Oral Hypoglycemic Agents, Insulin, Non-pharmacological treatment, Life style modification, Type2 DM, HbA1c.

**Introduction**

Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces.(1) There are about 346 million people worldwide have diabetes. In 2000, the estimated prevalence of diabetes for all age-groups worldwide was around 2.8%and is projected to be 4.4% in 2030. In Thailand, burden of diseases defined as total disability-adjusted life year (DALY) loss attributed to diabetes was 1.7 million years (3.1%) in men and 2.7 million years (6.4%) in women.(2) DM can cause several complications including acute and chronic complications, which impose enormous burden on the individual and on health care system.

HbA1c occurs when hemoglobin joins with glucose in the blood. When glucose sticks to these molecules it forms a glycoslated hemoglobin molecule, also known as A1c and HbA1c. The more glucose found in the blood the more glycated hemoglobin (HbA1c) will be present (3). We can make a laboratory test for HbA1c that shows the average level of blood sugar (glucose) in the past 3 months. It shows how diabetes is well controlling. Reasonable A1c goal for many adults is <7%. (4)

According to the guideline of American Diabetic Association for Type 2 DM patients, lifestyle modifications including modified diet, increased physical activity, and weight loss are critical for all diabetes patients. For highly motivated patients with an HbA1c less than 7.5%, the guidelines recommend pursuing lifestyle intervention for 3 to 6 months before starting medications. Metformin(one of the types of OHA); if not contraindicated and if tolerated, is the preferred initial pharmacological agent for type 2 diabetes. In newly diagnosed type 2 diabetic patients with markedly symptomatic and/or elevated blood glucose levels or HbA1c, consider insulin therapy, with or without additional agents, from the outset. If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the A1c target over 3–6 months, add a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin. Due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes. (4)

According to the above evidence, Diabetes is one of the global pandemic chronic diseases and it needs continuing medical care and lifestyle modifications to maintain their blood glucose level within normal limit. Treatment with lifestyle modifications, OHA, Insulin is known to reduce glycemia in patients with type 2 diabetes mellitus, but which treatment most frequently attains target HbA1c below7% is unknown. So this study was done to assess the effects of lifestyle modifications, OHA and Insulin on glycemic control in Thailand.

**MATERIALS AND METHODS**

Study design

This research utilized data that is part of the study: “An Assessment on Quality of Care among Patients Diagnosed with Type 2 Diabetes and Hypertension Visiting Ministry of Public Health and Bangkok Metropolitan Administration Hospitals in Thailand (Thailand DM/HT)” which was conducted in 2011. Nationally representative samples of 59750 patients with diabetes and/or hypertension were randomly selected from 249 hospitals across Thailand. The samples were selected based on the probability proportional to size of the patients for each hospital. Data collection involved medical record review conducted by well trained research nurses. This paper involved a total of 8421 Diabetes alone patients and excluded the patients with Hypertension alone and Diabetes with Hypertension patients. The target goal for in this study of HbA1c level was defined according to American Diabetes Association, if HbA1c level is <7%, diabetes is well control and if HbA1c is >=7%, it means uncontrol of diabetes.

 Study Outcome

Independent variables of Socio-demographic characteristics, Pharmacological treatments (Insulin alone, OHA alone, both Insulin and OHA), Non-pharmacological treatment (life style modification) which are diet, reduce body weight and physical exercise and dependent variable of (Plasma glucose level) HbA1c level (>=7% as uncontrol and <7% as control) were used to assess the outcome of this study.

Statistical Analysis

Sample size calculation was based on the main statistical methods that used to estimate the magnitude of effect. Thus the sample size for logistic regression was used. The calculation was based on methods proposed by Hsieh (1991).

Inependent variables were described by using frequency and percentage for categorical data and mean, standard deviation were used for continuous data. For dependent variables, HbA1c <7% as a control group and HbA1c>=7% as uncontrol group in this study. We considered the outcome could be more similar within than between the study sites and affected by a number of potential confounding factors. Thus we analyzed the data using logistic regression implemented under generalized estimating equations (GEEs) framework. We initially explored (bivariate analysis) the relation between .HbA1c and pharmacological treatments and non-pharmacological treatments and also the other variables including gender, age, BMI, duration of diabetes, occupation , Acute complications , Diabetes Retinopathy, Diabetes Nephropathy and Acute Renal Failure , expressed both as percentages and as odds ratioswith 95% confidence intervals.

The initial model contained all variables that were known to be bio-sociologically important and those with p-value of bivariate analysis was 0.2 or less. Interaction terms that were clinically meaningful and p-value of 0.2 or less were also included. Backward elimination were used as methods for variable selection following methods proposed by Kleinbaum (1996). We then obtained fully adjusted odds ratios and 95% confidence intervals.

Model adequacy assessments were performed by examining for goodness of fit and most influential observation. Sensitivity analysis was also performed for the appearance of influential observations and missing values. We regarded a two sided p-value less than 0.05 or a 95% confidence interval .All analyses were performed using Stata version 12.0 (StataCorp, College Station, TX). All test statistics were two-sided and a p-value of less than 0.05 was considered statistical significant.

**Results**

A sample of 59750 patients with diabetes and/or hypertension were listed in these database in 2011 were the population of this study. As this study was only based on Diabetes alone patients, 32890 patients of Hypertension alone and 18207 of Diabetes with Hypertension patients were excluded .. Fig: 1

Total number of patients

(n=59750)

Exclude the patients with Hypertension alone

Number of patients with Diabetes alone and Diabetes with Hypertension(n=26860)

Exclude Diabetes with Hypertension patients

Number of patients with Diabetes alone ( n=8653)

Exclude diabetes alone patients with others treatments and exclude the missing data.

Total number of diabetes alone patient who were on non pharmacological and pharmacological treatments (n=8421)

Fig1:Inclusion flow chart

Socio-demographic characteristics

Of 8421 type 2 diabetes mellitus patients, most of them 71% are female with the mean age of 56.17 years old , range (20-98) . About half of the type 2 DM patients from this study have normal BMI (50.70%) and most of them 49.81% have duration of diabetes < 5years. Among total participants of this study, 77.69% of type 2 DM patients took pharmacological treatments of OHA alone and only 1.78%of patients were on non-pharmacological treatment of lifestyle modifications.

 Table 1. Baseline characteristics, in participants (n=8421)

|  |  |  |
| --- | --- | --- |
| Baseline Characteristics | Number (n) | Percentage (%) |
| **Gender**MaleFemale | 24425978 | 2971 |
| **Age in years**<50 50-69.9>60Mean=, SD=1Medium=, Range= |  |  |
| **BMI in kg/m2**18.5-24.99 (normal)>=25 (overweight)>=30 (obesity)Mean=24.77 , SD=4.08Medium=4.08, Range=11.11-48.04 | 408527021270 | 50.7033.5415.76 |
| **Duration of Diabetes**<5years5-10years>10years | 365423481334 | 49.8132.0118.18 |
| **Occupation**Not daily workerDaily workerOwn Business |  |  |
| **Acute Complications of DM**YESNO |  |  |
| **Dibetes Retinopathy**YESNO |  |  |
| **Diabetes Nephropathy**YESNO |  |  |
| **Acute Renal Failure**YESNO |  |  |
| **Patients with pharmacological treatments**Only InsulinOnly OHABoth OHA and Insulin | 70965421019 | 8.4277.6912.10 |
| **Patients with non-pharmacological treatments**Lifestyle modifications( diet, reducing weight, exercise) | 151 | 1.79 |
|  |  |  |

**Table 2..**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Socio-demographic Characteristics | Number (n) | Percentage (%) | Crude OR | 95% CI | P-value |
| **Gender**MaleFemale | 24425978 | 2971 |  |  |  |
| **Age in years**<50 50-69.9>60Mean=, SD=1Medium=, Range= |  |  |  |  |  |
| **BMI in kg/m2**18.5-24.99 (normal)>=25 (overweight)>=30 (obesity)Mean=24.77 , SD=4.08Medium=4.08, Range=11.11-48.04 | 408527021270 | 50.7033.5415.76 |  |  |  |
| **Duration of Diabetes**<5years5-10years>10years | 365423481334 | 49.8132.0118.18 |  |  |  |
| **Occupation**Not daily workerDaily workerOwn Business |  |  |  |  |  |
| **Acute Complications of DM**YESNO |  |  |  |  |  |
| **Dibetes Retinopathy**YESNO |  |  |  |  |  |
| **Diabetes Nephropathy**YESNO |  |  |  |  |  |
| **Acute Renal Failure**YESNO |  |  |  |  |  |
| **Patients with pharmacological treatments**Only InsulinOnly OHABoth OHA and Insulin | 70965421019 | 8.4277.6912.10 |  |  |  |
| **Patients with non-pharmacological treatments**Lifestyle modifications( diet, reducing weight, exercise) | 151 | 1.79 |  |  |  |
|  |  |  |  |  |  |

**Table 3..**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Socio-demographic Characteristics | Number (n) | Percentage (%) | Crude OR | AdjustedOR | 95% CI | P-value |
| **Gender**MaleFemale | 24425978 | 2971 |  |  |  |  |
| **Age in years**<50 50-69.9>60Mean=, SD=1Medium=, Range= |  |  |  |  |  |  |
| **BMI in kg/m2**18.5-24.99 (normal)>=25 (overweight)>=30 (obesity)Mean=24.77 , SD=4.08Medium=4.08, Range=11.11-48.04 | 408527021270 | 50.7033.5415.76 |  |  |  |  |
| **Duration of Diabetes**<5years5-10years>10years | 365423481334 | 49.8132.0118.18 |  |  |  |  |
| **Occupation**Not daily workerDaily workerOwn Business |  |  |  |  |  |  |
| **Acute Complications of DM**YESNO |  |  |  |  |  |  |
| **Dibetes Retinopathy**YESNO |  |  |  |  |  |  |
| **Diabetes Nephropathy**YESNO |  |  |  |  |  |  |
| **Acute Renal Failure**YESNO |  |  |  |  |  |  |
| **Patients with pharmacological treatments**Only InsulinOnly OHABoth OHA and Insulin | 70965421019 | 8.4277.6912.10 |  |  |  |  |
| **Patients with non-pharmacological treatments**Lifestyle modifications( diet, reducing weight, exercise) | 151 | 1.79 |  |  |  |  |
|  |  |  |  |  |  |  |

**Discussion**

The participant findings of the dependent variable indicate that only 21.60% of Type 2 DM patients got the target HbA1c level <7%. It means that most of the type 2 DM patients didn’t get control well. The previous study by Thai Diabetes Registry Project on 2006 also revealed that only 26.3% of their participants got control of HbA1c <7%.(5) It show Type 2 DM patients from Thailand need to emphasize on controlling for their blood glucose level.

Although the controlled diabetes patients was low, this study was to assess the effects of pharmacological treatments and non-pharmacological treatments on glycemic control. Hence found out the percentage of patients who were on pharmacological treatments and non-pharmacological treatments. Among Type 2 DM patients in Thailand, 98.21%were on pharmacological treatments ( 8.42%, 77.69%, 12.1%) of Insulin alone, OHA alone and both of them respectively and only 1.79% were on non-pharmacological treatment of lifestyle modifications(diet, reducing body weight and exercise).According to that results most of Type 2 DM patients took pharmacological treatments and OHA alone is the most common use of drug in this study. This show that for Type 2DM patients OHA is the first choice in pharmacological treatments for Type 2 DM and this is consistent with the guides of treatments for Diabetes by American Diabetes Association. (6).Only 1.79% were on non-pharmacological treatments of lifestyle modifications. According to guidelines, the first choice of treatment is lifestyle modifications and if not get control with lifestyle modifications change to OHA. So if the patient is in pre-diabetes state or their disease severity is not so severe, patients can get the target HbA1c <7% by intensive lifestyle modifications. Severity of disease depends on duration of diabetes, present of micro vascular and macro vascular complications.

On finding the effects of pharmacological treatments on glycemic control, 11% , 23.83% , 10.40% of OHA alone, Insulin alone And both OHA and Insulin get control of HbA1c level respectively. So in pharmacological treatments group, OHA is the best effective treatments to get target HbA1c level and this is also consistent with the previous study.(7)

In non pharmacological treatments group in which patients took intensive lifestyle modifications, 50.33% got target HbA1c level .Half of Type 2 DM patients from Thailand got control of diabetes by intensive lifestyle modifications. Even though the literature and previous articles show that OHA is the most effective treatment compared with lifestyle modifications(diet, reduce weight and exercise)and Insulin alone to get control of blood glucose level, this study show that intensive lifestyle modifications can get more control of the blood glucose level compared with pharmacological treatments.(8)As this was the secondary data, there was lacking data for how they take intensive lifestyle modifications . So this study can’t assess among the intensive lifestyle modifications(diet, reducing body weight, exercise), whis was the most effective for glycemic control.

In conclusions , most of Type 2 DM patients from Thailand were uncontrol of their blood glucose level.But among the control group of blood glucose level, they were on pharmacological treatments and and only some of patients were on non pharmacological treatments of intensive lifestyle modifications. Even though some of them took lifestyle modifications , half of them got control of their blood glucose level. Therefore , in Thailand, Type 2 DM patients can get target HbA1c level to<7% by intensive lifestyle modifications.

**Recommendation for further research:**

Recommend for other study to do effects of Intensive lifestyle modifications on glycemic control and which of the Intensive lifestyle modifications is the best effective treatment for getting control of the blood glucose level.

**Acknowledgement**

This research utilized data provided by the study: “An Assessment on Quality of Care among Patients Diagnosed with Type 2 Diabetes and Hypertension Visiting Ministry of Public Health and Bangkok Metropolitan Administration Hospitals in Thailand (Thailand DM/HT)”, a collaborative clinical study supported by the Thailand National Health Security Office (NHSO) and the Thailand Medical Research Network (MedResNet). The data was archived at the web site <http://www.damus.in.th> maintained by MedResNet.  This manuscript was not prepared in collaboration with Investigators of the Thailand DM/HT study and does not necessarily reflect the opinions or views of the Thailand DM/HT study, the Thailand NHSO or the Thailand MedResNet.

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