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Type Two Diabetes Mellitus Is Associated with The Calcium Channel Blocker Therapy On the Diabetic Hypertensive Patients of the Dr M Djamil General Hospital Padang, Indonesia.

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ABSTRACT

The objective of this study is to evaluate whether type 2 Diabetes Mellitus (DM) on the diabetic-hypertensive patients is associated with CCB therapy. This cross sectional retrospective study was conducted of the Dr. M Djamil General Hospital Padang Indonesia. Data of social demography, medical, drug, family history and social behavior were collected from the patient's medical records which were approved by the guided patient interview. The Chi-Square statistics analysis was used to obtain the Odds ratio and the significance was taken at $p<0.05$. Forty out of the 65 (61.5%) diabetic-hypertensive patients had hypertension before they were diagnosed type 2 DM where, 35 of them (87.5%) were treated with CCB drugs. The patients who used CCB were 5.5 times (95% CI 1.615-18.731) more often to have type 2 DM. This event was occurred even though the patients are <40 years old (OR=∞, p=0.007), non-obese (OR =1.125 (95% CI 0.167-7.6)}, without history of DM and stress (OR of 2 and 2.25 (95% CI 0.296-13.511 and 0.332-15.236) respectively. These indicated that Type 2 diabetes is associated with the CCB therapy on the diabetic-hypertensive patient even though they are less than 40 years old, without diabetic family, smoking and stress histories.

Keywords: CCB, hypertension, CCB associated Type two Diabetes Mellitus, diabetic-hypertension

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INTRODUCTION

According to the WHO (1), there are one billion people in the world suffer from hypertension in 2011 and two-thirds of which are also in low-income developing countries, including Indonesia. The prevalence of this disease is predicted to continue to rise, and by 2025 as many as 29% of adults worldwide suffer from hypertension, while in Indonesia the prevalence reached of 31.7%. On the other hands, diabetes mellitus is a global health problem where the incidence increases by times. In 2013, IDF estimates that 8.3% of adults–382 million people – in the world have diabetes (2), in 2014 this number was increase to 422 million. Compared to that in 1980 where 108 million people leave in diabetes, this global prevalence (age-standardized) of diabetes has nearly doubled (rising from 4.7% to 8.5%)(1). It is estimated that the prevalence of this metabolic disease will continue to increase beyond 592 million in 2035 (2). Yet, 175 million of cases currently undiagnosed, and a vast amount of people with diabetes are progressing towards complications unawares. Moreover, 80% of the total number affected living in low- and middle-income countries, where the epidemic is gathering pace at alarming rates. This situation provides a worrying indication of the future impact of diabetes as a major threat to global development (3).

In 2011, Indonesia situated in a 10th country in the world with the higher DM prevalence (7.3 million), and if it is uncontrolled, it is estimated that by 2030 this number will increase up to 11.8 million (4). Therefore, diabetes is not only a health issue but requires concerted policy action across many sectors.

The goal of pharmaceutical care is to assure that the patients meet their needs of effective, safe and efficient therapy to increase their quality of life. Even though drug manufacturer provides their product with some information of the potential risk of drug used, but practically, certain drug still used clinically due to certain objective(s), such effective, cheap and or other reasons. However, many drugs may induce diseases due to its pharmacodynamics action, drug interaction, idiosyncrasy and other risk factors (5). Most of hypertensive patients require lifelong antihypertensive therapy. Very limited number of patients could maintain their normal blood pressure after discontinuing the therapies. Therefore, the therapy of hypertension can potentially cause chronic side effects, such dried cough that produced by ACE inhibitors (6), erectile dysfunction by thiazide diuretics, bronchospasm by beta blockers and others (7).

Calcium has important functions in the body and its channel spreads throughout the body, includes the pancreas, which has an important role in the body's insulin secretion. Therefore, inhibition of Ca^{2+} channel may lead to the reducing number of Ca^{2+} to enter the pancreatic cells which will result in decreasing insulin secretion (8, 9). Until this paper is published, the use of CCB to treat hypertension is still going on in the Dr. M. Djamil General Hospital, Padang, Indonesia.

The purpose of this study is to determine whether Type II Diabetes Mellitus is associated with the use of Calcium Channel Blockers therapy on diabetic hypertensive patients of the Dr. M. Djamil General Hospital, Padang, Indonesia.

METHODS

This research was a historical cross-sectional case control study on the Type II diabetic-hypertensive patients. A number of 65 patients were involved in this study. Data of antihypertensive types therapy, social demography, history of CCB and other antihypertensive therapies before or after they got diabetes of the patients were recorded. From the patients who were treated with CCB, the risk factors such as patients age, obese, smoking and exercise behavior and stress history were also collected from the patient's medical records completed by patient interviewed. Data frequency of drug therapy and duration of therapy were analyzed using descriptive statistic, while the odds of the patient to have diabetes mellitus due to CCB therapy (CCB associated DM) compare to that of control and the odds of all of the above risk factors to the patient's diabetic event were analyzed as Odds ratio using Fisher's Exact analysis and the significant was taken at $p<0.05$ (SPSS 17) (10).

RESULTS

From 65 diabetic-hypertensive patients, most of them (61.5%) were diagnosed hypertension before they got Type Two Diabetes Mellitus, while 38.5% were diagnosed hypertension after they got diabetes mellitus

(Tabel 1). An amount of 75.4% of the patients were with the history of CCB antihypertension while the rest of them were with the history of other antihypertension, such as ARB, ACEI, and diuretics (Tabel 2). Odds Ratio calculation for the possibility of the patients to have CCB associated diabetes mellitus CCB and their relationship to other risk factors is indicated in Tabel 3.

Table 1. Patient distribution based on their hypertensive medical history and duration of the disease experience

Hypertensive medical history	Number of Patients/%	Number / percentage of patient with duration of hypertension (years)			
		≤ 1	1-5	5-10	10-20
Before diabetes	40 61.5%	3/ 4.6	9/ 13.8	10/ 15.4	18/ 27.7
After diabetes	25/ 38.5	1/ 1.5	8/ 12.3	6/ 9.2	10/ 15.4
Total	65/ 100	4/ 6.2	17/ 26.2	16/ 24.6	28/ 43

Table 2. The number of diabetic hypertensive patients based on their antihypertensive therapies

Antihypertensive Therapies	Number	Percentage (%)
CCB	49	75,4
ARB	7	10,8
ACE Inhibitor	6	9,2
Diuretic	3	4,6
Total	65	100

Tabel 3. Odds ratio of CCB therapy and of several risk factors to diabetes mellitus cases

No	Variabels	CCB		OR (95% CI)	p value
		Yes	No		
1.	Hypertension Before DM After DM	 35 14	 5 11	 5.5 (1.615-18.731)	 0.006
		Diabetes mellitus			
		Yes	No		
2.	Sex Male Female	 12 23	 0 5	 ∞	 0.118
3.	Age ≤ 40 yo > 40 yo	 0 35	 1 4	 ∞	 0.007
4.	Obesity Non Obese	 15 20	 2 3	 1.125 (0.167-7.6)	 0.904
5.	Family History No Yes	 20 15	 2 3	 2.0 (0.296-13.511)	 0.477
6.	Exercise No Yes	 15 20	 2 3	 1.125 (0.167-7.6)	 0.904
7.	Smoking Yes No	 6 29	 0 5	 ∞	 0.315
8.	Stress No Yes	 21 14	 2 3	 2.25 (0.332-15.236)	 0.405

It is clearly seen that patients with the history of CCB therapy 5.5x more potential to have diabetes mellitus than the history of other antihypertensive therapy ($p<0.01$). The risk of CCB associated DM is higher

event though the age of these patients <40yo (OR of ∞, p<0.01). The Odds of male to have DM associated with CCB was higher (OR of ∞, p>0.1) compared to female patients, and so as the non-obese (OR of 1.125, p>0.1), smoking (OR of ∞, p>0.1) non-stress (OR of 2.25, p>0.1), not doing exercise (OR of 1.125, p>0.1) or without family history (OR of 2, p>0.1)

DISCUSSION

Until 2014, Pharmacist's Letter still recommend Calcium channel blocker (CCB) for treating hypertension and hypertension with diabetes (11). This recommendation is previously supported by James *et. al*. (12). Therefore, many hospitals in the world still using this drug for such patients, includes Malaysia, USA and Indonesia, even though it is not the drug of choice. On the other hand, American Diabetic Associated (13) had declare not to use CCB to decrease blood pressure of the patients with diabetes. This is due to cardiovascular alteration impact of sing this drug (13, 14).

Approximately 75.4 % of hypertensive patients in the Dr. M. Djamil Padang Indonesia are treated primarily with CCB. This number is large enough to create drug related problem on this population, ie. type 2 diabetes mellitus. In this research, large number of the patient (61.5%) were diagnosed diabetes mellitus long after they got hypertension, while 38.5 % of them got hypertension after they were diagnosed diabetes mellitus. Since most of these hypertensive patients experienced to use CCB compared to other antihypertensive therapy, it is indicated that the probability of these CCB treated hypertensive patients to have type 2 DM is 5,5 time. There is the reason behind this statement will be discussed later on.

Ca+2 ion is an important second messenger of electrical signaling every aspect of cell activities. Ca serves as the initiating intracellular events such as contraction, secretion, synaptic transmission and gene expression (15, 16). By controlling ion permeability, ion channels at the membrane (i.e. Ca+2 channels) will regulate both electrical activity and signal transduction. Even though cell membrane Ca+2 channel (dihydropyridine type) was first described from muscle cells, but it is postulated that there is similarity between the Ca2+ channels of endocrine cells and those of smooth muscle and other excitable cells (16, 17).

Pancreatic β-cells also needs Ca+2 to produce insulin. The α and β cells are electrically excitable and use electrical signals to couple changes in blood glucose concentration to stimulation or inhibition of hormone release. In both cell types, influx of extracellular Ca^{2+} through voltage-gated Ca^{2+} channels with resultant elevation of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) triggers exocytosis of the hormone-containing secretory granules (18). This statement was approved by (9, 19). Therefore, inhibiting the membrane Ca++ channels by drugs (CCB) will block beta cell depolarization and thus stop insulin release as described by (18).

According to Rasmussen *et. al.* (20), the regulation of insulin secretion occurs in three stages: cephalic, early enteric, and later enteric. In this view, the crucial event occurring during the first two phases is the agonist induced translocation of protein kinase C (PKC) to the plasma membrane under conditions in which an increase in Ca^{2+} influx does not occur. PKC is now in a cellular location and a Ca^{2+}-sensitive conformation such that an increase in Ca^{2+} influx rate occurring during the third phase leads to its immediate activation and an enhanced rate of insulin secretion. Furthermore, under physiological circumstances, an optimal insulin secretory response is dependent on a correct temporal pattern of signals arising from neural and enteric sources. If this pattern is deranged, an abnormal pattern of insulin secretion is observed.

As described earlier, Voltage-gated T-type and L-type Ca^{2+} channels as well as Na^{+} channels participate in glucose-stimulated electrical activity and insulin secretion. Ca^{2+} activated big potassium (BK) channels are required for rapid membrane repolarization. Exocytosis of insulin-containing granules is principally triggered by Ca^{2+} influx through P/Q-type Ca^{2+} channels (21). CCB drugs such as nifedipine, nitrendipin, felodipin, amblodipin etc. act by blocking the entry of **calcium** ion into excitable cells. Thus, it will reduce electrical conduction within the cells and block insulin release.

Actually, Calcium channel blockers comprise three chemical groups, all of them bind the L-type Ca++ channel, but each class binds to different binding sites of the same channel. Phenilalkylamines CCB (verapamil) is the only drug in this group, binds to the V binding site. Benzothiazepines CCB (diltiazem) binds to the D binding site in the L-type Ca++ channel, while Dihydropyridines CCB, the prototype and first generation agent in this group is nifedipine, binds to the N binding site. Second generation agents include isradipine, nicardipine, and

felodipine. Amlodipine is considered a third generation dihydropyridine also bind to N type of Ca channels (22). All excitable tissues contain voltage dependent calcium channels and the high affinity, reversible and stereospecific binding sites for calcium channel-inhibiting drugs, even though not affect every tissue equally (23). So, even though it is known that most of the CCB drugs act primarily on the L type of Ca channels, but it is very possible that it could act on other type of channels, such as P/Q type, the one that available on the pancreatic cells. The result of this study approved this assumption, where the patients that received CCB for their hypertension therapy is 4.5 times more probable to get type two DM.

From those explanations above, it can be concluded that type II diabetes mellitus is associated with the CCB therapy on diabetic hypertensive patients of the Dr. M. Djamil General Hospital, Padang, Indonesia.

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ABREVIATIONS

CCB; calcium channel blocker, DM; diametes mellitus, OR; ods ratio, ACE; angiotensin converting enzyme, ACI; angiotensin converting enzyme nhibitor, ADA: American Diabetic Association, IDF; International Diabetic Federation, WHO; World Health Organization

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