A REVIEW: DRUG RELATED PROBLEMS ON TYPE 2 DIABETES MELLITUS PATIENTS WITH HYPERTENSION

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ABSTRACT:

Background: Type 2 diabetes (T2DM) patients with hypertension are possible to have drug-related problems (DRPs) due to multiple medications. Nowadays, research in T2DM patients with hypertension still not enough. Therefore, needed to better understand and manage DRP in these patients.

Objective: Reviewing the frequency and type of DRPs and risk factors in T2DM patients with hypertension.

Materials and Methods: Searching bibliographic databases such as PubMed, Google scholar. In this update, the search terms were "Drug-Related Problems Among Type 2 Diabetes Mellitus Patients", and "Diabetes Mellitus type 2 with hypertension", mainly from the year 2010 to 2020 without language restriction.

Results: A total of publications about 198 Drug-Related Problems T2DM with hypertension were identified. A total of 6 studies were selected for the final analysis. This study provides evidence that T2DM with hypertension complications still have drug-related problems. A better understanding of the epidemiology of drug-related problems in T2DM Patients with hypertension is essential to determine, prevent, and resolve drug therapy or potentially interferes with a desired patient outcome.

Conclusion: Drug-related problems that are often found in type 2 diabetes mellitus patients with hypertension are drug selection problems, adverse reactions, and dosage problems are usually caused by drug selection and dosage problems.

Keywords: Diabetes Mellitus Type 2, Drug-Related Problems, Hypertension

PRELIMINARY

Chronic hyperglycemia with disturbance of carbohydrate, fat, and protein metabolism due to disorder in insulin secretion, insulin action or both indicate Diabetes [1]. Diabetes mellitus disease uncontrolled can induce macrovascular complications such as hypertension, dyslipidemia, and obesity while microvascular complications such as retinopathy, nephropathy, and neuropathy. Hypertension means when systolic and diastolic blood pressure equal to or above 140 mmHg and 90 mmHg respectively. The efficient function of vital organs like the brain, heart, and kidneys and for overall health and wellbeing depend on normal level blood pressure [2]. Aldosterone can decrease and serum potassium concentrations could be increased by ACE inhibitors. Hyperkalemia occurs primarily in patients with chronic kidney disease or diabetes [3]. Evidence has associated insulin resistance and hyperinsulinemia with the poor prognosis of hypertension sometimes referred to as the metabolic syndrome. Increased insulin concentrations can induce hypertension when renal sodium retention increased and enhanced sympathetic nervous system activity. Insulin also may elevate blood pressure by increasing intracellular calcium, which leads to increased vascular resistance [4].

Treatment of diabetes mellitus generally requires a long time and is often a treatment that is more than one drug. The complications that occur in diabetes mellitus will increase the complexity of the treatment performed on patients. Patients with diabetes mellitus are prone to drug-related problems because the treatment of diabetes mellitus generally requires a long time and is often a treatment that is more than one drug. Patients with type 2 diabetes mellitus with hypertension often use several drugs and this can cause drug-related problems [5,6]. Drug-related problems are unacceptable events or risks experienced by the patient that involve or are suspected to involve drug therapy, that inhibit or delay someone from obtaining the outcome therapy, and need professional judgment to resolve these problems during the assessment process so that change the personal therapy regimen can be a solution.

Drug-related problems are identified by assessing sociological, pathophysiological, and pharmacological information, disease, and drug therapy collected during the assessment step. The synthesis and application of this knowledge occur in a logical, systematic manner using the Pharmacotherapy Workup when clinicians apply knowledge of patients, diseases, and drugs to this set of inquires, they can make clinical decisions as to whether or not a drug therapy problem exists [8]. If the patient has a drug therapy problem, it can be classified into one of 6 problems based on PCNE V05.01 [7], it is important to identify the cause of each drug-related problem [8].

The risk of DRPs in patients with T2DM with hypertension is relatively high. The contribution among doctors, pharmacists, nurses, and parties related to patient`s direct services prevent drug-related problem [9].

METHODS

By searching bibliographic databases such as PubMed, Google scholar. In this update, the search terms were "Drug-Related Problems Among Type 2 Diabetes Mellitus Patients", and "Diabetes Mellitus type 2 with hypertension", from January 2010 to July 2020 in English-language.

STUDY SELECTION

A total of 198 publications on Drug-Related Problems for Diabetes Mellitus type 2 have been identified. Of the 198 articles that match these keywords. The search results obtained were then checked and 176 abstracts were read that did not match the title of the review article. As many as 22 articles were assessed on the feasibility of the article based on the text as a whole and according to the eligibility criteria, 22 articles were obtained and after being reassessed, 6 articles were obtained which could be used in article reviews. In this study, it provides evidence that T2DM with hypertension complications still has drug-related problems.

After an assessment of the quality of studies from 6 articles can be categorized as high then data extraction is carried

out.   Data analysis is based on the references, title,   results of data extraction can be seen in table 1 below.
objective, research method, result, and conclusion. The

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Tabel1: Drug-related problems in different studies

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No.	References	Methods	Result	Conclusion
1	[10]	retrospective cross-sectional	1. The effect of drug treatment is 49.2% 2. untreated indication and symptoms 21.1% 3. unnecessary drug-treatment 10.7% 4. Hypertensive patients received dual therapy (14 patients) while the appropriate therapy should have been a monotherapy 5. Adverse drug reactions 19% were the most frequent categories of DRPs	suboptimal drug therapy effects, untreated symptoms, unnecessary drug use, and adverse drug reactions are the most common drug-related problems.
2	[11]	Cardiovascular Risk Factors Intervention Strategies (Corfis)	**Classification of DRPs according to PCNE V5.01.** 1. Adverse drug reactions 110 (15.6%). 2. Drug choice problems 67 (9.5%). 3. Dosing problem 24 (3.4%). 4. Drug use problems 235 (33.3%). 5. Drug interaction 4 (0.5%) 6. Others 144 (20.1%). **Classification of DRPs causes found on patients** 1. C1 Drug/Dose selection 353 (50.0%) 2. Drug use process 69 (9.8%) 3. Information 29 (4.1%) 4. Patient/Psychological 228 (32.3%) 5. Logistics 2 (0.3%) 6. Others 25 (3.5%) **Classification of interventions on DRPs found on patients** Outcome of interventions 1. Change made as per pharmacist recommendation, 2. Change made not as per pharmacist recommendation, 3. No change made, medication not dispensed 3. No change made 4. No change required 5. Outcome unknown	Another problem is the problem most often found with percentages 20.1% followed by a Drug use problems 33.3%, Adverse drug reactions 15.6%,
3	[12]	Prospective Study	**Classification of DRPs according to PCNE V5.01.** 1. P1 Adverse reactions 30 (11.4%). 2. P2 Drug choice problem 144 (55.2%). 3. P3 Dosing problem 28 (10.7%) 4. P4 Drug use problem 11 (4.2%) 5. P5 Interactions 47 (18.0%) 6. P6 Others 1 (0.4%). **Classification of DRPs causes found on patients** 1. C1 Drug/Dose selection 184 (62.2%) 2. C2 Drug use process 77 (26.0%) 3. C3 information 16 (5.4%) 4. C4 Patient/Psychological 17 (5.7%) 5. C5 Logistics 2 (0.7%) 6. C6 Others 0 (0%) **Classification of interventions on DRPs found on patients** 1. I1 At prescriber level 43 (27.7%) 2. I2 At patient/carer level 94 (60.7%) 3. I3 At drug level 18 (11.6%) 4. I.4 Other intervention or activity 22 (14.2%)	the problem with the highest percentage is a problem drug choice problems (55.2%). the cause by drug/dose selection.
4	[13]	Retrospective Study	**Classification of DRPs according to PCNE V5.01.** 1. P1 Adverse reactions 25 (6.5%)	Another problem is the problem most often found with percentages of 25.8% because knowledge and management of diabetes with

			2. P2 Drug choice problems 87 (22.5%) 3. P3 Dosing problems 62 (16.0%) 4. P4 Drug use problems 50 (12.9%) 5. P5 Interactions 63 (16.3%) 6. P6 Others 100 (25.8%) **Classification of DRPs causes found on patients** 1. C1 Drug/Dose selection 158 (47.0%) 2. C2 Drug use process 36 (10.7%) 3. C3 Information 13 (3.9%) 4. C4 Patient/Psychological 124 (36.9%) 5. C5 Logistic 5 (1.5%)	hypertension will affect non-compliance. Of all the causes of drug-related problems, the cause of drug/dosage selection was most often found to be the cause of drug-related problems.
5	[14]	retrospective cross-sectional study	**Classification of drug-related problems (DRPs) according to PCNE V8.01.** 1. P1 Treatment effeceiveness problem 270 (23,02%) 2. P2 Treatment safety problems 273 (23,27%) 3. P3 Others problems 267 (22,77%) **Classification of DRPs causes found on patients** 1. C1 Drug selection 271 (16,67%) 2. C2 Drug from 14 (0,86%) 3. C3 Drug selection 330 (20,30%) 4. C4 Dispesing 279 (17,16%) 5. C5 Drug use process 228 (14,02%) 6. C6 Patient related 222 (13,65%) 7. C7 Other 282 (17,34%)	the problem which has the highest percentage is Treatment safety problems, Treatment effeceiveness problem, Others problems.
6	[15]	Deskriptifobservasional with methods cross-sectional	Identification of Drug-Related Problems based on ASCP 2013. Consisted of 2 patients, of which the first patient experienced DRP who experienced drug use without indication and substitution. whereas patients with the second DRPs event experienced untreated indications, adverse drug reactions, and drug interactions	Of the 8 Drug-Related categories, Five (5) of the problems drug-related problems occurred in patients with T2DM with hypertension complications in the ward Hospital LabuangBaji Hospital, Makassar City January-June 2016 period, which is an indication untreated, choice of drugs less precise, sub therapy doses, drug reactions undesirable and drug interactions.

Nowadays, patient safety and treatment effectiveness have become a major concern for health workers, especially on drug-related problems so that patients get optimal treatment effects. Drug-Related Problems based on Pharmaceutical Care Network Europe V5.01. The classification of drug-related problems are 6 main parts of the problem (adverse drug reaction, drug selection issues, dosage problems, drug use problems, interaction, other) and 6 main parts of the causes (drug/dose selection, drug use process, information, patient/psychological, logistics other [7]

Adverse Drug Reactions
There are some side effects in T2DM with Hypertension medication such as hypoglycemia when received antidiabetic drugs and insulin [10,11,13]. Hypoglycemia less weight gain is the most common adverse effects reported with insulin. Hypoglycemia more happens in patients on intensive insulin therapy regimens rather than those on less-intensive regimens [4]. Antihypertensive was reported as adverse reactions of calcium channel blockers, diuretics, and ACE inhibitors. Increasing heart rate and bilateral leg swelling are caused by amlpdipine13. Heart failure was higher with amlodipine versus chlorthalidone in The Antihypertensive and Lipid-LoweringTreatment to Prevent Heart Attack Trial (ALLHAT) 4.

Drug Selection Issues
The problem of drug choice identified mostly lies in the problem of improper drug choice and contraindications. Conservative treatment is no longer effective in sustaining life in end-stage renal disease or renal failure, so renal replacement therapy is performed. Renal replacement therapy available in the unit's renal service is hemodialysis, CAPD (ContinousAmbolatory Peritoneal Disease), and kidney transplant. There are 5 patients with ESRD (End Stage Renal Disease) take a pill of ACE inhibitor [16]. Aspirin is also given to patients with severe renal impairment who have a creatine clearance of less than 10 mL/minute. Besides, several drugs that are not appropriate for use in the elderly and are classified as high risk under the modified Beers criteria, namely ticlopidine, amitriptyline, diphenhydramine, liquid paraffin, and chlorpheniramine. The problem of choice of drugs involves the use of contraindicated drugs. There are three drugs most commonly prescribed in the presence of contraindications are metformin, aspirin, and fondaparinux 13. Drug choice problems category the use of contraindicated drugs involved a woman planning to get pregnant but was prescribed a combination of irbesartan and hydrochlorothiazide [11]. Angiotensin receptor II antagonists are potassium-sparing (IRBESARTAN), on the other hand, loop-diuretics (hydrochlorothiazide) is potassium-depleting. Angiotensin receptor II antagonist with a diuretic has an impact increase, a decrease, or no change to the potassium levels, although logically adding an angiotensin II receptor antagonist to proved treatment with a diuretic would seem more likely to enhance potassium, and vice versa. Elderly patients or patients with

heart failure, renal impairment who take medication of angiotensin II antagonists should be monitoring the level of serum potassium [17]. The problem of drug choice was that no drug was prescribed but clear indications were found in 5 studies [10,11,12, 13,14], and Drug use without indication was found in the 2 studies 10,15. Where the administration of salbutamol to treat symptoms of shortness of breath due to bronchial constriction such as asthma and chronic obstructive pulmonary disease (COPD). From complaints and physical examination of patients with breathing 20x / minute which is a normal value of breathing, it shows that there is no problem with the respiratory system and allergies that require patients to receive therapy from both drugs and it is found that untreated indications occur in patients who do not receive therapy to treat SGOT- SGPT that exceeds the normal value [15].

Dosage Problems

Dose problems were found in two studies. The patient was given a statin for only a week and another who has still prescribed a statin even though his cholesterol level was only 2.9 mmol/L and his low-density lipoprotein (LDL) was 1.3 mmol/L [11]. The duration of treatment is too short and the duration of treatment is too long than necessary was only on oseltamivir given for three days for the treatment of hypertension and oral azithromycin 500 mg was administered once daily for six days [13]. The problem of drug doses being too low was also found. That patients complained of nausea and vomiting [15].

Drug Use Problems

Three of the six articles identified drug use problems in the study.Were seen from the patient's medical records that the drugs were not taken or given by them before entering [13]. DRPs with the highest percentage occurred in the problem of drug use. Noncompliance with antidiabetic and antihypertensive is common and problems also occur with drugs not taken or not given at all [11].

Interaction

Potential drug interactions were found when used aspirin and clopidogrel [13]. The need for the use of low-dose aspirin simulants and anticoagulant or antiplatelet agents is common for patients with cardiovascular disease. The combination of these two drugs can increase the risk of bleeding because it affects platelet function. Clopidogrel can potentiate the inhibition of platelet aggregation due to the presence of aspirin. Aspirin has an effect on platelet function in the blood. The interaction of aspirin with clopidogrel affects hemodynamic function, increasing the bleeding effect [18]. The problem of potential drug interactions the use of enalapril with allopurinol which may increase the risk of leucopenia and hypersensitivity [11]. Three cases of Stevens-Johnson syndrome (one fatal) and two cases of hypersensitivity have been attributed to the use of captopril with allopurinol. Anaphylaxis and myocardial infarction occurred in one man taking enalapril when given allopurinol. The combination of ACE inhibitors and allopurinol may increase the risk of leucopenia and serious infection, especially in renal impairment 17. Fenofibrate and atorvastatin may increase the risk of myopathy [11]. Potential drug interactions have also been found in two studies [12,15]. Interacting drugs Glucophyl and Ramipril can simultaneously increase the effectiveness of Gluchopil which can cause severe/excessive hypoglycemia. This interaction occurs because ACE inhibitors increase insulin sensitivity. Giving Harnal and Ramipril together can cause a decrease in the effectiveness of Ramipril as an antihypertensive drug so that the goal of hypertension treatment is not achieved. Concurrent administration of Mefenamic Acid and Ramipril can also cause a decrease in the effectiveness of antihypertension from Ramipril so that hypertension treatment therapy is also not achieved. Giving Ranitidin and Glucophyl together can cause an increase in Glucophyl levels so that excessive hypoglycemia will occur. The concomitant administration of Ketorolac and Mefenamic Acid can increase plasma concentrations because both are NSAIDs, thereby increasing side effects (cumulative / accumulation), also, administration of Ketorolac causes an increase in SGOT and SGPT concentrations in serum [15].

Others

Another problem was found in some research. First problems with patients not achieving their desired glycemic goals or suboptimal treatment effects, poor glycemic control can be related to factors such as lifestyle modification, the presence of other comorbidities, and also non-compliance of patients [10, 14]. The second problem is related to the lack of awareness or knowledge of health for an illness. For example, many patients do not have less knowledge about type 2 diabetes mellitus and do not know the management of the disease and its complications. Other problems with cost-effectiveness, unnecessary drug treatment, and complaint problems were not clearly [14].

Causes Of Drug-Related Problems

From several studies conducted by three researchers found that drug selection/dose had the highest percentage of causes of drug-related problems [11, 12, 13]. Drug/dose selection is the main source of drug-related problems among patients with type 2 diabetes mellitus with hypertension. Some problems may have several causes and may have no cause at all [14]. Drug interaction problems do not have a cause, drug selection problems and dosage problems are associated with causes of drug selection or dosage, drug use problems, and other problems generally caused by patients or psychologically followed by drug use processes [13]. The causes of drug-related problems found in this study were patient/psychological where patient non-compliance was the main factor, it could be related to forgetfulness, refusal to take medication, the cost of medication that was not available, and also found the cause of the drug selection problem category [10]. The identified cause of drug-related problems is drug selection problems [15].

Intervention

Pharmacists give intervention for DRPs resolution by providing personal counseling and education to families. Direct pharmacist involvement in patients with type 2 diabetes mellitus with hypertensive complications can provide a solution in the early detection of DRPs [12].

The importance of a Pharmacist conducting a study regarding drug-related problems and can also be useful to minimize errors in drug administration in patients with type 2 diabetes mellitus with hypertension complications, and also can provide information about the rationality of drug administration, especially in patients with type 2 diabetes mellitus with hypertension complications.

Drug-Related Problems also have a relationship with patients' quality of life. Drug-related problems can reduce the quality of life of patients [19]. Drug-related problems

can result in ongoing symptoms of the disease or new symptoms that can affect the patient's quality of life. A patient with osteoarthritis uses several different drugs (for example NSAIDs) to find an effective and tolerable drug [19].

CONCLUSION

It can be concluded from several studies above those drug-related problems often found in type 2 diabetes mellitus patients with hypertension are drug selection problems, adverse reactions, and dosage problems are usually caused by drug selection/dosage problems. Pharmacists and other health workers play an important role in handling cases of drug-related problems in patients with type 2 diabetes mellitus with hypertension so that patients get outcome-therapy.

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