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Side Effects of Metformin in Type 2 Diabetes Mellitus: A Systematic Literature Review

Maiyeni Sabrina* and Diana Laila Ramatillah

Pharmacy Faculty, Universitas 17 Agustus 1945 Jakarta, Indonesia

ABSTRACT

Background: Metformin is a Biguanide antihyperglycemic medication, is still considered as the best medications, and the first line of treatment either as monotherapy or in combination with other drugs for type 2 diabetes mellitus. Even though metformin has efficacy, very low risk of hypoglycemia and weight gain, and low cost, it also has side effects that can't be ruled out. The aims of this study to evaluate of side effects of metformin in type 2 diabetes mellitus. Methods: Medline via (via Pub Med) from 2019 until 2024 in English. Term defining side effects of metformin were combined with the term type 2 diabetes mellitus during the search. The studies were chosen based on inclusion criteria.

Results: There were 40 patients (53.3%) had gastrointestinal (GI) effects with persistent use of metformin tablet for 7.8 years in average, including epigastric and abdominal pain, nausea, vomiting, diarrhea, and bloating, and the other research showed that Metformin therapy can reduce testosterone levels in males with T2DM who had normalized blood control, that is indicated that the use of metformin may be another reason of the high prevalence of low testosterone levels in males with T2DM, the same thing also happens with vitamin B12 deficiency that there was a graded increase in the likelihood of vitamin B12 deficiency with increasing dose with those treated with > 2000 mg daily at nearly 40 times the odds compared with those not taking metformin.

Conclusion: from systematic literature review study, it was found that there are side effects of metformin that cannot be ruled out, such as gastrointestinal (vomiting, diarrhea, bloating), decreased testosterone levels and deficiency vitamin B12.

***Corresponding author**

Maiyeni Sabrina, Pharmacy Faculty, Universitas 17 Agustus 1945 Jakarta, Indonesia.

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Introduction

Diabetes mellitus is a chronic disease characterized by hyperglycemia caused by impaired insulin secretion, trauma from decreased insulin action, or both [1]. Internatonal Diabetes Federation (IDF) reveald that in 2015 there were 415 milion people affected by diabetes mellitus (DM) and of that number, 98% were type 2 DM sufferers [2].

Type 2 diabetes melitus (DM) is a chronic and progressive disease, which strict monitoring and control from diagnosis and also through different stages of the disease [3,4]. High prevalence of this disorder imposes a significant burden to the global health, and thus, numerous efforts have been utilized for both prevention and management of this worldwide concern [5,6].

Management of type 2 diabetes mellitus is carried out by applying education, medical nutritional therapy (TNM), physical exercise, and pharmacological therapy [7]. Pharmacological therapy can include insulin and oral antidiabetic drugs (OAD). There are several types of OAD which are the therapy of choice for type 2 diabetes melitus (T2DM), one of them biguainida group.

American Diabetes Association (ADA) recomended that metformin be the first-line oral antidiabetic drug to initiate treatment of type 2 diabetes mellitus (T2DM) if lifestyle interventions are not used to lower blood sugar levels [8]. Based on drug safety, cost, and the level of drug efficacy, it was found that metformin is the oral antidiabetic drug most widely used in patients with T2DM [9].

Metformin has main effect of reducing hepatic glucose production (gluconeogenesis) and improving glucose uptake in peripheral tissues [10]. Molecularly, metformin inhibits the mitochondrial respiratory cycle in liver cells which can then activated the AMP-kinase (AMPK) enzyme. This activation occurs due to an inhibitor of ATP production so that there is little adenosine triphosphate (ATP), while there is more adenosine diphosphat (ADP) and adenosine monophosphat (AMP).

This situation will activate AMPK which will inhibit the phosphorylation of genes that play a role in the gluconeogenesis procces, so production of glucose in the liver is hampered or not at all [11]. Apart from having many adventages, metformin also has side effects such as gastrointestinal which are quite high, namely > 10% [12].

Therefore, based on the explanations above, researchers are interested in conducting a systematic literature review study regarding the description of side effects of metformin in type 2 diabetes mellitus.

Method

This systematic literature review was conducted according to the

preferred reporting item for systematic reviews and meta-analyses (PRISMA) statement [13]. The PRISMA statement includes a checklist for systematic evaluations. Firstly, we included the studies that focus on side effects of metformin in type 2 diabetes mellitus. Secondly, our articles were selected two databases: MEDLINE (via Pubmed) and scholar. Thirdly, we decided that our search strategies should be used in both databases including one Boolean operators; "AND" as keyword to the search (side effects AND metformin AND type 2 diabetes mellitus).

Eligibility Criteria

The Inclusion Criteria Considered While Screening and Selecting the Papers Were Based on the Following:

- Studies related of side effects of metformin in type 2 diabetes mellitus
- Studies that were published in the English language
- Studies published between 2019 until 2024
- Studies published in journal
- Studies that were conducted in type 2 diabetes mellitus

Selection Process

The search using the one databases (Pubmed) indentified 3.861 result. Based on text availability the results are 3.577 full text, after that, we eliminated 2.636 articles based on article type (clinical and rendomized controlled trial), the publication date used since 5 years ago, we get 200 articles. After that, we read the abstract and get 13 articles, and then 3 articles after read full text.

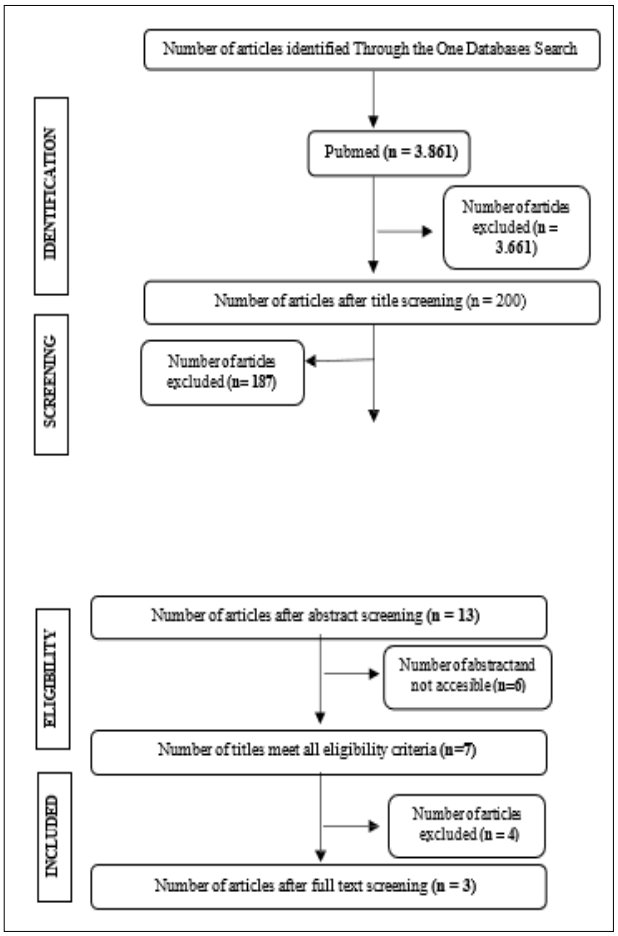

Figure 1: Study Selection Flowchart

Were also removed after reading the full text and not getting useful information about side effects of metformin in type 2 diabetes mellitus, leaving 3 articles for extraction and analysis.

Results

Study Characteristic

The 3 studies originated from 3 different countries, Table 1, shows a range of quantitative and qualitative data that were extracted from the 3 included studies. Quantitative data included sample size and follow up duration (months), whereas qualitative data included country, objective, outcome measures, results, improvement strategies and study limitations.

Discussion

We conducted a systematic review to identify side effects of metformin in type 2 diabetes mellitus. We identified 3 eligible studies that had quantitative and qualitative data. Three articles discussed that there were side efects of metformin in type 2 diabetes mellitus.

Gastrointestinal Side Effects

One hundred and three (103) patientes were evaluated and 75 patients participated in this study. 64 patients were on metformin alone and the others were on comination with other antihyperglycemic medications. The mean daily dose of metformin intake was 1000 mg.

40 patients (53.3%) had gastrointestinal (GI) effects with persistent use of metformin tablet for 7.8 years in average, including epigastric and abdominal pain, nausea, vomiting, diarrhea, and bloating, but GI side effects reduced after switching to metformin capsule. GI side effects may be due to delay in release of metformin in stomach, resulting a reduction in stomach irritation and GI side effects.

Some study have shown taking metformin tablets at mealtimes, or using careful dose adjustment to minimize poor compliance with immediate release form of metformin can reduce GI symptoms. However, some patients may discontinue therapy due to higher medications costs [14].

Reduce of Testosterone Levels

This study is secondary analysis of a premix insulin study. Authors selected male patients aged 18-60 who were treated with metformin for three months during the premixed insulin study as the metformin group (n=40). The mean dose of metformin was 1500 mg daily. The control group was selected who were not treated with metformin (n=40).

Glycated hemoglobin (HbA1c) was determined by HPLC, Glycated albumin (GA) was determined by Peroxidase methode, for Total testosterone (TT) and sex hormone were measured by chemiluminescence. The change of testosterone levels was the main observation of this study.

According to international society for sexual medicine (ISSM) guidelines, men with TT < 12nmo/L have a lack of testosterone levels. Of the result, TT, FT, and Bio T levels significantly increased after 3 months of the control group, but the change was lost in metformin group. Patients in metformin group caused superior reductions in TT and Bio-T levels versus the control group.

The study showed that Metformin therapy can reduce testosterone levels in males with T2DM who had normalized blood control, that is indicated that the use of metformin may be another reason of the high prevalence of low testosterone levels in males with T2DM.

M Faure et al. Found that metformin exposure in vitro may contribute to the decrease of cell poliferation and the change

in secretory ability of tersicular sertoli cells. In vivo metformin exposure negatively affected the germ cell population. Sertoli cells are well known to regulate the synthesis and secretion of testosterone by leyding cells. This may contribute to the reduction of testosterone by metformin [15,16].

Deficiency of Vitamin B12

The Fremantle Diabetes Study Phase 2 (FDS2) is a prospective observational study of diabetes in a postcode-defined urban population of approximately 153000 people living in and around the port city of fremantle in western australia (WA). The present study included 1492 out of 1499 (99.5%) participants with clinically diagnosed type 2 diabetes who had a baseline serum total vitamin B12 measured.

All FDS2 participants had a comprehensive assessment at baseline. Demographic and clinical information were documented, physical examinations and associated investigations were carried out, and fasting blood and urine samples were obtained. Medication use, including dose regimens, was documented.

For the purpose study of the present study, and given that metformin tablet strengths are 500, 850 and 1000 mg, daily doses were categorised into four groups as ≤ 1000, > 1000 and ≤ 1700, > 1700 and ≤ 2000, and > 2000 mg.

Vitamin B12 was measured using an E170 immunoasay analyser and reagens supplied by Roche Diagnostics. Deficiency was defined as serum total vitamin B12 < 80 pmol/L and active B12 < 23 pmol/L, and adequate vitamin B12 status was defined as serum concentrations of these analytes above these threshold.

In bivariable analyses, those who were deficient were older and more likely to be metformin-treated than participans in the other two groups. The prevalence of vitamin B12 deficiency in metformin-treated participants was 4.2% and further 3.1% of metformin-treated participants had borderline deficiency.

In multiple logistic regression analysis, age and metformin use were the only independent associates of vitamin B12 deficiency. When metformin dose categories were included instead of metformin therapy as a binary variable, there was a graded increase in the likelihood of vitamin B12 deficiency with increasing dose with those treated with > 2000 mg daily at nearly 40 times the odds compared with those not taking metformin.

In those with vitamin B12 deficiency, whether definite or borderline, there was no statistically significant relationship with Distal symmetrical polyneurophaty (DSPN) or anemia. These findings argue againts regular or opportunistic measurement of serum vitamin B12 in metformin-treated patients, which should be reserved for situation with a clear clinical indication [17].

Table 1: Characteristics of the Selected Studies

Author, Year, Contry	(Sample size/follow-up (months))/ (outcome measure/ metodelogy)	objective	Results	Improvement strategies	Limitations
Mansor S, Maid T, Ali MS, Niloufar R. 2017. Iran	(75sample)/ (6 months)/ (prospective interventional study)	This study was designed to compare the severity of GI side efects in type 2 DM patients receiving tablet or capsule forms of metformin	There were patients had Gastrointestinal side effects with presistent use of metformin tablet including, epigastric and abdominal pain, nausea,vomiting, diarrhea,and bloathing	-GI side effects were reduced after switching to metformin capsule -The results indicated that switching to metformin capsule led to a greater patients satisfaction	-Open-label design with no comparator -leaving a number of patients during the study due to repeated attendance at clinic -using sample questioning techniques rather than validated QOL measures to record GI side effects
Cai T, Hu Y, Ding B, Yan R, Liu B, Cai L, Jing T, Jiang L, Xie X, Wang Y, Wang H, Zhou Y, He K, Xu L, Chen L, Cheng C and Ma J. 2021. China	(80 sample)/ (3 months)/ (clinical trial with 40 men as a control and another 40 men as a cases)	All eligible subects received intermitten Flash glucose monitoring (FGM) once a month for 3 months. Doctors adjusted the hypoglicemia treatment, and diabetes specialist nurse provided educations according to the FGM data every months.	-TT, FT, and Bio-T levels significantly increased after 3-month in the control group, but the change was lost in metformin group -patients in metformin group caused superior reductions in TT and Bio-T versus the control group	-additional studies are needed to clarify the mechanisms that metformin reduces testosterone in male with T2DM	-The study population is patients using premixed insulin -Although there is a control group, the efect of changes in the dose of insulin or other hypoglycemic drugs cannot be completely excluded in the real-world study.

Timothy M.E.D, Stephen A.P.C, Kristen E.P, Wendy E.D. 2023. Australia	(1.492 sample)/ (not mentioned) / (prospective observational study)	The present study included 1492 out of 1499 (99,5%) participants with clinically diagnosed type 2 diabetes who had a baseline serum total vitamin B12 measured, and then they were given metformin tablets strenght are 500, 850 and 1000 mg, daily doses were categorised into four groups.	Most FDS2 participants were vitamin B12 replate, 2.0% were deficient and the remainder borderline. metformin treatment increased the odds deficiency in a dose- dependent fashion for >2000 mg daily compared with no treatment ($p < 0.001$). metformin increased the likelihood of anemia, especially at high dose, independent of vitamin B12 deficiency.	-it was necessary to periodically measure serum B12 -Further study needs to be conducted regarding the ethiology of the causing factors of anemia that occur in this participant.	-it had cross-sectional design which relected, in part, the fact that fuul blood count was done only at the baseline FDS2 assessment so that analysis of the serial change observed in other studies was not possible. -any affects of metformin on vitamin B12 status and its consequences would likely have been realised by the time reqruitment.

Limitation

The search of database via Pubmed was considered suitable for gathering all qualifying papers by the proposed topic and objectives, but this restriction may have missed some relevant articles, and some identified articles were not accessible to the research team. The main limitation of this research lies in the fact that the source articles obtained were to few, so that results cannot be generalized appropiately for all countries with different characteristics and cultures.

Conclusion

from systematic literature review study, it was found that there are side effects of metformin that cannot be ruled out, such as gastrointestinal (vomiting, diarrhea, bloating), decreased testosterone levels and deficiency vitamin B12.

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