

77099_Auto_Edited.docx

Name of Journal: *World Journal of Clinical Cases*

Manuscript NO: 77099

Manuscript Type: META-ANALYSIS

Certain sulfonylurea drugs increase serum free fatty acid in diabetic patients: A systematic review and meta-analysis

Yu M *et al.* The association between FFA concentration and SU treatment: A meta-analysis.

Ming Yu, Xiao-Yu Feng, Shuai Yao, Chang Wang, Ping Yang

Abstract

BACKGROUND

Sulfonylurea (SU) are commonly used antidiabetic drugs effective for type 2 diabetes mellitus. Previous studies have reported that the Sulfonylurea treatment could alter the serum free fatty acid (FFA) concentration in diabetic patients, however, their exact effects remain unknown.

AIM

The current analysis is intended to assess the impact of SU on the FFA level in diabetic patients.

METHODS

A systematic literature search was conducted by consulting the PubMed, EMBASE, Cochrane Library, and Web of Science databases from January 1, 1991 to July 30, 2021. Either a fixed-effects model or random-effects model was applied to study the association between SU treatment and FFA concentration according to the heterogeneity test. Two investigators independently performed data extraction. The mean difference (MD) and corresponding 95% confidence interval (CI) were used to measure effect size. R3.5.1 software was utilized for conducting statistical analyses.

RESULTS

A total of 13 studies with 2,273 individuals were selected. Results indicated that FFA concentration increased slightly after treatment with SU (MD=0.08, 95%CI: 0.03-0.12, $p < 0.01$). Besides, we found that SU treatment combined with other antidiabetics could also increase the concentration of serum FFA (MD=0.14, 95%CI: 0.01-0.28, $p < 0.01$). Regarding the type of SU, there was no significant difference in FFA concentration with glimepiride or glibenclamide. FFA concentration was higher at ≥ 12 wk (MD=0.09, 95%CI: 0.04-0.13), not at < 12 wk (MD=0.01, 95%CI: -0.07-0.09).

CONCLUSION

Sulfonylurea treatment could increase the serum FFA concentration in diabetic patients. The fundamental underlying mechanism still needs further investigation.

Key Words: Sulfonylurea; Free fatty acid; Cardiovascular disease; Diabetes mellitus; Systematic review; Meta-analysis.

Yu M, Feng XY, Yao S, Wang C, Yang P. Certain sulfonylurea drugs increase serum free fatty acid in diabetic patients: A systematic review and meta-analysis. *World J Clin Cases* 2022; In press

Core Tip: The effect of sulfonylurea therapy on free fatty acid concentration in diabetic patients has not been determined. This is the first systematic review and meta-analysis to assess the impact of sulfonylurea on free fatty acid. The present study indicated that sulfonylurea therapy could increase free fatty acid concentration in diabetic patients. Further research is required to confirm the association between free fatty acid concentration and sulfonylurea treatment.

INTRODUCTION

The worldwide epidemic of type 2 diabetes mellitus (T2DM) is an important public health problem. ¹ It is predicted that the number of people with diabetes will increase to 642 million by 2040. In 2015, about 5 million people aged 20–79 years died from diabetes, accounting for 12.8% of all-cause mortality worldwide ² [1]. Sulfonylurea (SU) medicines are widely applied for T2DM management [2]. Their mechanism of action is based on enhanced insulin release from the pancreatic beta cells, by binding to ATP-sensitive K⁺ channels [3]. There is also some evidence that SU can limit hepatic glucose production by sensitizing beta cells to glucose [4]. However, SU drugs have limitations, such as being useless against type 1 diabetes or post-pancreatectomy. Several studies have demonstrated that treatment with SU might increase cardiovascular disease-

related death risk and stroke in T2DM patients [5, 6]. SU medications include certain generations of drugs. The first-generation drugs consist of acetohexamide, glycyclamide, carbutamide, *etc.* The second-generation drugs comprise gliclazide, glibenclamide, glipizide, glibornuride, *etc.* The third-generation drugs include glimepiride, which is occasionally considered a second-generation drug as well.

3
Circulating free fatty acids (FFAs), also known as non-esterified fatty acids, are released from phospholipids and adipocyte triglyceride stores after hydrolysis by phospholipases and by lipolysis, respectively [7]. FFA is a key causal factor implied in the association between obesity and T2DM [8]. FFAs play pivotal roles in multiple metabolic processes [9, 10]. They either work by promoting the creation and triglyceride release inducing the enhanced production of very-low-density lipoproteins (VLDLs), thereby leading to the development of atherogenic dyslipidemia [11, 12]. Furthermore, higher VLDL levels may enhance serum FFA flow to the liver, causing inflammation and hepatic insulin resistance [13, 14]. Besides, they inhibit the production and release of insulin, which, alongside insulin resistance, is a cornerstone of T2DM etiology [15]. In recent years, an increasing number of studies has confirmed the association between FFA and heart disease, and serum FFA has been concomitant to an augmented risk of coronary heart disease. High FFA levels reflect the severity of myocardial ischemia and necrosis [16].

Fatty acid metabolism is considered an effective factor during the SU-mediated treatment of T2DM [17]. However, because of the presence of different SUs and their varied combination with other antidiabetic drugs, such as metformin, rosiglitazone, or pioglitazone, the exact effect of SU therapy on serum FFA concentration remains unclear. As a result, the current meta-analysis searched for the possible link between SU therapy and serum FFA concentration. The analysis could help gain a better understanding of SU-mediated treatment impact on FFA of T2DM patients.

MATERIALS AND METHODS

Search strategy

This meta-analysis was conducted according to PRISMA statement guidelines. A systematic literature search was conducted by consulting the PubMed, EMBASE, Cochrane Library, and Web of Science databases to find articles dedicated to the study of the relationship between SU therapy and plasma FFA concentration. A literature search was performed independently by two of the authors (Yu M and Feng XY) using keywords: “sulfonylurea”, “glyburide”, “glipizide”, “glibenclamide”, “gliclazide”, “glimepiride”, “free fatty acids”, “FFA” and “non-esterified fatty acids” in different combinations. For any further possibly eligible research, suitable references from all prospective papers were also retrieved and studied. In the literature review, no language restrictions were implemented. The last retrieval was made on July 30, 2021. The approval of the ethics committee was not needed because this meta-analysis does not contain patient personal information.

Selection criteria

The titles and abstracts of the primary studies were screened independently by two authors. The original studies were added in our meta-analysis if the below-mentioned conditions were met: (1) Studies using SU treatment for diabetic patients; (2) Studies where SU drugs used alone or in combination were equated to placebo or other active medications; (3) Studies examining the effect of SU treatment on serum concentration of FFA; (4) Studies with sufficient data on FFA concentration at baseline and endpoint. Studies were omitted if they were: (1) Duplicate studies; (2) Non-human research; (3) Studies without sufficient data to extract the detailed information; (4) Pooled studies, comments, and review articles; (5) Irrelevant studies.

Data extraction

The studies were thoroughly examined, and data were extracted using a predefined criterion. Data extraction was performed by two investigators independently, and disagreements were resolved by consensus. The following data were extracted: first author’s name, publication year, study location, ethnicity, number of participants in the

SU and control groups, age, disease, median body mass index (BMI), and concentrations of serum FFA within the treatment group, and control group.

Risk of bias assessment

The Cochrane criteria were used to undertake a systematic assessment of methodological quality in the selected studies. The items used for evaluating studies were as follows: randomization method, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete/missing outcome data, selective reporting and other potential bias. The quality was checked by two authors independently, and the disagreement was resolved by mutual discussion.

Statistical analysis

The after-before FFA value change was measured according to the Cochrane handbook recommended formula if the study provided only endpoint and baseline FFAs values, and the correlation coefficient was 0.5. There was a uniform unit for FF; thus, mean difference (MD) with a 95% confidence interval (CI) was used to assess the effect sizes by evaluating the association between SU therapy and FFA concentration. I^2 index was used to assess the heterogeneity, and a random-effect model or fixed-effect model was used according to the test of heterogeneity. I^2 of $\geq 50\%$ and a P of < 0.1 indicating statistical heterogeneity were present between studies, and a random-effect model was implemented. Otherwise, the fixed-effect model was applied. The values were merged into a single group by the inverse variance method when performing the overall subgroup analysis if more than one SU group was provided. R3.5.1 software was utilized for conducting all the statistical analyses.

RESULTS

Selection process

The procedure for the selection of studies is shown in Figure 1. Initially, 116 studies were selected by comprehensively searching the electronic database. Following an

assessment of the titles and abstracts, 91 studies were excluded as irrelevant. Then, the remaining 25 studies were carefully assessed for eligibility through full-text reading. Among them, six studies were excluded without sufficient data to extract. Three studies were excluded as they were reviews, while two studies were non-human research, and one study was conducted without interventional design. Eventually, 13 studies comprising 16 treatment arms were used in our meta-analysis.

Characteristics of included studies

Data of 2,273 individuals were included in the present study, comprising 995 subjects in the control group and 1,278 subjects in the SU treatment group. Thirteen studies included in our meta-analysis were published from 1991 to 2010. Among them, four were conducted in China, three were conducted in Germany, and two were conducted in Japan. Four studies were conducted in Italy, Finland, Greece, and America, respectively. SU treatment time ranged from 2 wk to 52 wk. Two studies focused on non-insulin-dependent diabetes, and the rest focused on T2DM. Two studies were published in the Chinese language, while the rest were in the English language. Glibenclamide was used as a therapeutic drug in five randomized controlled trials (RCTs). Gliclazide was used as a therapeutic drug in two RCTs, and glimepiride was used as a therapeutic drug in seven RCTs. Four studies used SU combined with rosiglitazone, pioglitazone, or metformin. All detailed information is listed in Table 1.

Quality assessment

The detailed information on the risk of bias assessment is shown in Figure 2. Seven (53.8%) of the included studies generated random sequences adequately. Eight (61.5%) studies concealed allocation of treatment sufficiently, while two (15.4%) studies had a high risk of blinded participants and personnel. Six (46.2%) studies reported a low risk of outcome assessors. Three (23.1%) studies had an elevated risk of incomplete outcome data, and one (7.7%) study had an increased risk of selective reporting. Finally, all included studies had a low risk of other bias. Overall, the included studies were of high quality.

Main analysis

A total of 13 RCTs described the outcome of SU on the concentration of FFA. ¹ According to the heterogeneity test ($I^2 = 76\%$, $p < 0.01$), a random-effect model was utilized to evaluate the effect of SU treatment on the serum FFA concentration. The results indicated that FFA concentration was slightly increased after the treatment with SU (MD = 0.08, 95%CI: 0.03–0.12, $p < 0.01$) (Figure 3A). Besides, four studies reported the treatment with SU combined with rosiglitazone, pioglitazone, or metformin. The results indicated that treatment with SU combined with other antidiabetics could effectively raise the serum FFA concentration (MD = 0.14, 95%CI: 0.01–0.28, $p < 0.01$) (Figure 3B). Regarding SU types, there was no significant difference in effect on FFA concentration using treatment with glimepiride or glibenclamide (interaction $P = 0.72$). Summaries of subgroup analyses are provided in Table 2. When the data were stratified by treatment length, serum FFA concentration was higher in subsets of time spanning several weeks, i.e., ≥ 12 wk (MD = 0.09, 95%CI: 0.04–0.13), and not in time durations of < 12 wk (MD = 0.01, 95%CI: -0.07–0.09) (Figure 4A). Thus, 12 wk was identified as a critical assessment point. Furthermore, elevation of FFA concentration was seen in both Asians (MD = 0.10, 95%CI: -0.01–0.20) ⁴ and Caucasians (MD = 0.06, 95%CI: 0.02–0.11) (Figure 4B). The effect of SU medications on FFA concentration was also proved in the age group of ≥ 55 years (MD = 0.09, 95%CI: 0.04–0.14) and in the age group of < 55 (MD = 0.05, 95%CI: -0.02–0.11) (Figure S1A). We also assessed the effect of SU drugs on FFA concentration in the group with a BMI of ≥ 28 (MD = 0.08, 95%CI: 0.03–0.12) ¹ and in the group with a BMI of < 28 (MD = 0.08, 95%CI: -0.01–0.17) (Figure S1B). The results showed that there was no significant difference between the two groups.

Sensitivity analysis

By removing one study apiece, the sensitivity examination was done to explore the robustness of our results. The data indicated that the significance of the comprehensive effect size did not significantly change throughout the analysis, suggesting that our results were relatively steady (Figure 5).

DISCUSSION

Different FFA concentrations have been shown to alter various biological processes in metabolism [18]. High expression of FFA has been reported to induce oxidative stress insulin resistance and facilitate inflammation by modulating the nuclear factor-kappa B pathway [14]. As a result, the altered FFA concentration might have important clinical roles in regulating the risk of cardiovascular disease and atherogenesis progression. FFA can be produced from adipose tissue lipolysis *via* lipase [19]. FFA interacts with peroxisome proliferator-activated receptors (PPARs) after being derived from lipolysis. PPARs activation boosts FFA oxidation, decreases triglyceride levels, raises plasma HDL, and lowers VLDL production and secretion [20]. The current study attempted to examine the effects of SU therapy on FFA in-depth and produce a reliable conclusion by merging as many valuable studies as feasible. This could be the first meta-analysis to investigate the relationship between SU and FFA.

In the present study, the results indicated that SU treatment could increase the concentration of FFA (MD = 0.08, 95%CI: 0.03–0.12). Importantly, when combined with other antidiabetics, such as rosiglitazone, pioglitazone, or metformin, the effects of SU treatment on FFA concentration were more pronounced (MD = 0.14, 95%CI: 0.01–0.28). To further elaborate our findings, we performed a subgroup analysis, which assisted us in reaching a firmer conclusion. We found that there was no significant difference in the efficacy of different SU types. Besides, no apparent alteration of the effects was found between the Asian and Caucasian populations, indicating that ethnicity could not affect the impact of SU treatment on FFA concentration. Furthermore, we discovered that serum FFA had no discernible effect on SU therapy in highly obese (BMI of ≥ 28) individuals compared to moderately underweight people (BMI of < 28). Additionally, the elevation of FFA was only observed when T2DM patients were treated with SU for duration time ≥ 12 wk.

Interestingly, another meta-analysis provided a slightly different conclusion compared to our findings. Chen's study ^[21] has focused on the lipid alteration after administration of SU in T2DM treatment. Our study specifically focused on the FFA concentration after SU treatment in diabetic patients. Moreover, Chen's study has only included 8 RCTs, which reported the effect of SU on FFA concentration in T2DM (based on their criteria for inclusion). They excluded all other studies focusing on the FFA concentration instead of lipids. We also investigated the impact of FFA changes when paired with other antidiabetics. Following treatment with SU, both studies found an increase in FFA concentration. However, Chen's study that enrolled 3 RCTs has reported that FFA elevation was only observed after glibenclamide treatment. Our results were more robust compared to Chen's analysis.

The underlying mechanism of this FFA concentration alteration after SU treatment is still unknown. It has been reported that SU could open Ca^{2+} channels in pancreatic beta cells; thus, the influx of calcium ions increases. This ultimately leads to enhanced insulin secretion. The potassium channel, which regulates lipid metabolism, is another essential membrane protein ^[22]. SU could form proteins, anchored to membranes, and interact with yeast glycosyl-phosphatidyl-inositol (GPI) ^[23]. Thus, SU could affect the FFA concentration in patients with diabetes. However, the specific mechanism still needs further research.

Despite a thorough review, there are several limitations to our research. The most important is the existence of significant heterogeneity between the studies. Although we conducted the subgroup analysis to find the potential for bias, the heterogeneity still existed. The random-effect model was used to check the variation of treatment effect and limit heterogeneity, yet it still existed. It could be due to variations in patients' age, a dose of a drug, *etc.* Secondly, the quality assessment indicated that not all studies generated random sequences adequately. Thus, they might have influenced the outcome of our analysis. Finally, the sample size in several included studies was

comparatively small. Hence, more studies concentrating on the association between FFA concentration and SU treatment are encouraged.

CONCLUSION

SU treatment may raise the serum FFA concentration in T2DM patients. The elevated FFA concentration was also observed when SU was combined with other antidiabetics. The change in FFA is more sensitive than that of triglycerides and total cholesterol. Therefore, FFA levels can be tested regularly for diabetic patients as a reference indicator of whether their lipid metabolism is well controlled.

ARTICLE HIGHLIGHTS

Research background

Previous studies suggested that FFA concentration was potentially associated with anti-diabetic drugs of SU. The results were inconsistent. We assess the effects of SU on the level of FFA concentration in diabetic patients.

Research motivation

SU are one of the most commonly used anti-diabetic medications. Several studies reported that SU treatment increases the risk of cardiovascular death and stroke in diabetic patients. Despite the reason for this result is unclear, but may be related to the effect of SU on FFA and blood lipids.

Research objectives

The primary objective was to perform a meta-analysis of diabetic patients treated with SU and analyze changes in FFA concentration.

Research ⁵methods

We reviewed PubMed, EMBASE, Cochrane Library, and Web of Science databases to identify studies using SU for diabetic patients. The after-before FFA value change was

measured. A random-effect model or fixed-effect model was used according to the test of heterogeneity, and I^2 index was used to assess the heterogeneity.

Research results

We included 13 observational studies comprising 16 treatment arms in the meta-analysis. FFA concentration was increased after the treatment of SU in diabetic patients. When combined with other antidiabetics, the effects of SU treatment on FFA concentration were more pronounced. There was no significant different effect of FFA concentration when treatment with Glimepiride or Glibenclamide.

Research conclusions

Some sulfonylurea drugs increase serum free fatty acid concentration in diabetic patients.

Research perspectives

The association between FFA concentration and SU treatment requires more studies and longer follow-up.

ORIGINALITY REPORT

3%

SIMILARITY INDEX

PRIMARY SOURCES

1	www.ncbi.nlm.nih.gov Internet	39 words — 1%
2	www.hindawi.com Internet	16 words — < 1%
3	Zhao, Y.F.. "Contribution of adipocyte-derived factors to beta-cell dysfunction in diabetes", International Journal of Biochemistry and Cell Biology, 200605/06 Crossref	14 words — < 1%
4	www.endocrinologyadvisor.com Internet	14 words — < 1%
5	www.cambridge.org Internet	12 words — < 1%

EXCLUDE QUOTES ON
EXCLUDE BIBLIOGRAPHY ON

EXCLUDE SOURCES < 12 WORDS
EXCLUDE MATCHES < 12 WORDS