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Adherence to Sulfonylureas in Comparison to Metformin among T2DM Patients: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Improved adherence to oral anti-hyperglycemic drugs (OAHs) may improve glucose control while also lowering diabetes morbidity, mortality, and long-term health resource consumption. **Aim:** This study aims to compare the adherence of type 2 diabetes mellitus (T2DM) patients to sulfonylureas with metformin.

Methods: This systematic review and meta-analysis followed the PRISMA 2020 guidelines. A systematic search was done in PubMed, MEDLINE through Clarivate, Web of Science through Clarivate, and EBSCO. Studies retrieved were managed in Rayyan–Intelligent systematic reviews website for duplicate removal and screening. Review Manager 5.4 was used to generate forest plots to estimate pooled odds ratios using a random-effect model. We used the Higgin's I2 test for assessing between-study heterogeneity. We used funnel plots for assessment of publication bias.

Results: This review included data from 11 studies on 274,202 T2DM patients. Random effect meta-analysis revealed that the odds for higher proportion of adherence favoured sulfonylurea group (OR = 1.34, 95% CI [1.08-1.65]). The comparison between sulfonylurea and metformin adherence using OR was significant (p=0.007).

Conclusion: The study concludes that T2DM patients were significantly more adherent to sulfonylurea than metformin, however, the analysis showed significant heterogeneity. We recommend adherence measures to be devised when prescribing OHAs.

Keywords: Adherence; Metformin; Sulfonylurea; T2DM.

INTRODUCTION

Diabetes mellitus is a centuries-old illness that is still a global issue, with an alarming rise in frequency and a tremendous health impact. Diabetes mellitus is a long-term hyperglycemia illness that is often accompanied by other metabolic abnormalities. Type 1, Type 2, gestational diabetes, and other forms of diabetes were defined by the World Health Organization (WHO) based on their etiologies [(1)]. Type 2 diabetes mellitus (T2DM) is the most prevalent type of diabetes, and it is defined by insulin dysfunction in peripheral tissues, or decreased insulin production from pancreatic beta cells, or both. There is also an extraordinary rise in hepatic glucose production, as well as aberrant carbohydrate, lipid, and protein metabolism, resulting in a markedly elevated blood glucose level [(1,2)]. T2DM has previously been associated with the elderly, although it is now increasingly being detected in younger individuals and even children [(3)].

T2DM that is not well controlled can cause long-term organ damage, malfunction, and failure. Poor glycemic management leads to macrovascular and microvascular problems, both of which contribute to a high risk of death and morbidity. Microvascular complications are damage to smaller blood vessels that cause nephropathy, neuropathy, and retinopathy, requiring dialysis, amputation, and vision loss; on the other hand, macrovascular complications increase the risk of cardiovascular and cerebrovascular events, causing damage to other peripheral vascular systems, necessitating dialysis, amputation, and loss of vision. T2DM imposes a significant health and economic burden as a result of these problems, including repeated hospitalization, pharmaceutical expenditures, and lost productivity owing to different impairments. Furthermore, it has a significant influence on the patients' lifespan and quality of life, as well as their family members indirectly [(4)].

Insulin has been widely used for diabetic therapy since its discovery in 1921 by Frederick Banting and his student Charles Best. In the 1950s, oral hypoglycemic medications were launched, revolutionizing the treatment of diabetes mellitus [(5, 6)].

The most effective glucose-lowering drug has been found is insulin. Patients' psychological insulin resistance is one of the most significant hurdles to starting insulin treatment [(7-9)].

Oral hypoglycemic agents (OHAs) are the most common therapy for diabetics with type 2 diabetes. These drugs are designed to provide continuous blood glucose control, which reduces microvascular complications including nephropathy and retinopathy [(10)]. Noncompliance with OHAs, on the other hand, continues to be one of the leading causes of poor glycemic control [(11)]. Patients' self-reports may be used to monitor adherence in a simple and effective way [(12)]. Issues with inadequate pharmacological treatment self-management may worsen the diabetic burden [(13)]. Understanding why patients do not adhere is critical to improving patient adherence. Forgetfulness and spontaneous actions owing to a lack of self-discipline, poor intellect, or a fearless attitude about the consequences of diabetes are some of the most often stated causes for non-adherence to oral medication

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regimes [14,15]. Only 37.7% of patients treated with OHAs had glycosylated haemoglobin (HbA1c) levels of less than 7% [5]. However, after a prescription is issued, it is up to the patient to decide whether or not to take the medication. There is a significant and continuous gap between evidence-based recommendations and the actual treatment that patients get for such chronic medical illnesses [16].

Study Aim

This systematic review aims to compare the levels of adherence to metformin and sulfonylurea among T2DM patients.

Methodology

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Search strategy

We systematically searched four major databases, namely, PubMed, MEDLINE through Clarivate, Web of Science through Clarivate, and EBSCO, for eligible studies. Keywords used for searching the databases were "adherence," "metformin," "sulfonylurea," and "diabetes." We used Boolean operators (AND, OR, and NOT) for the search. MeSH terms were used on PubMed database. No time or language restriction were applied.

Eligibility criteria

Inclusion criteria

Studies were eligible if they were:

- Analytical, observational studies,
- Including T2DM patients,
- Studies reporting adherence in number of patients and percentage to each drug separately.

Exclusion criteria

We excluded studies if they were:

- Interventional studies,
- Incomplete or inaccurate reporting on adherence data,
- Including combination therapy

Study screening and data extraction

Studies that were initially retrieved from the database search were extracted to Rayyan–Intelligent systematic review website [17] for duplicate removal and screening process. For data extraction from included studies, we used an Excel sheet that included study ID, title, author(s), study year, study design, study population, number of participants, level of adherence to sulfonylurea and metformin.

Data management and study quality assessment

We used the Newcastle-Ottawa Scale (NOS) for assessing quality of the included studies [5]. Review Manager 5.4 software was used to perform a random effect meta-analysis. We used Higgin's I-square test to assess the inter-study heterogeneity across studies with significant heterogeneity's cut-off point at I^2>50%. Funnel plot was used in order to assess publication bias by visual inspection.

Statistical analysis

The data was not analyzed using any software. The information was gathered using a specific form that included (Authors' names, country, year of publication, methods, and results). The data were analyzed by the authors to assess the initial outcomes. To ensure the validity of the results and minimize errors, each member's results were double-reviewed.

RESULTS

Search results

Initial search of the databases yielded 731 study, of which 322 duplicates were removed. The remaining 409 underwent title and abstract screening and 358 studies were excluded. Fifty-one studies were enrolled for retrieval and full-text assessment, of which only eleven studies were eligible for quantitative data synthesis (Figure 1).

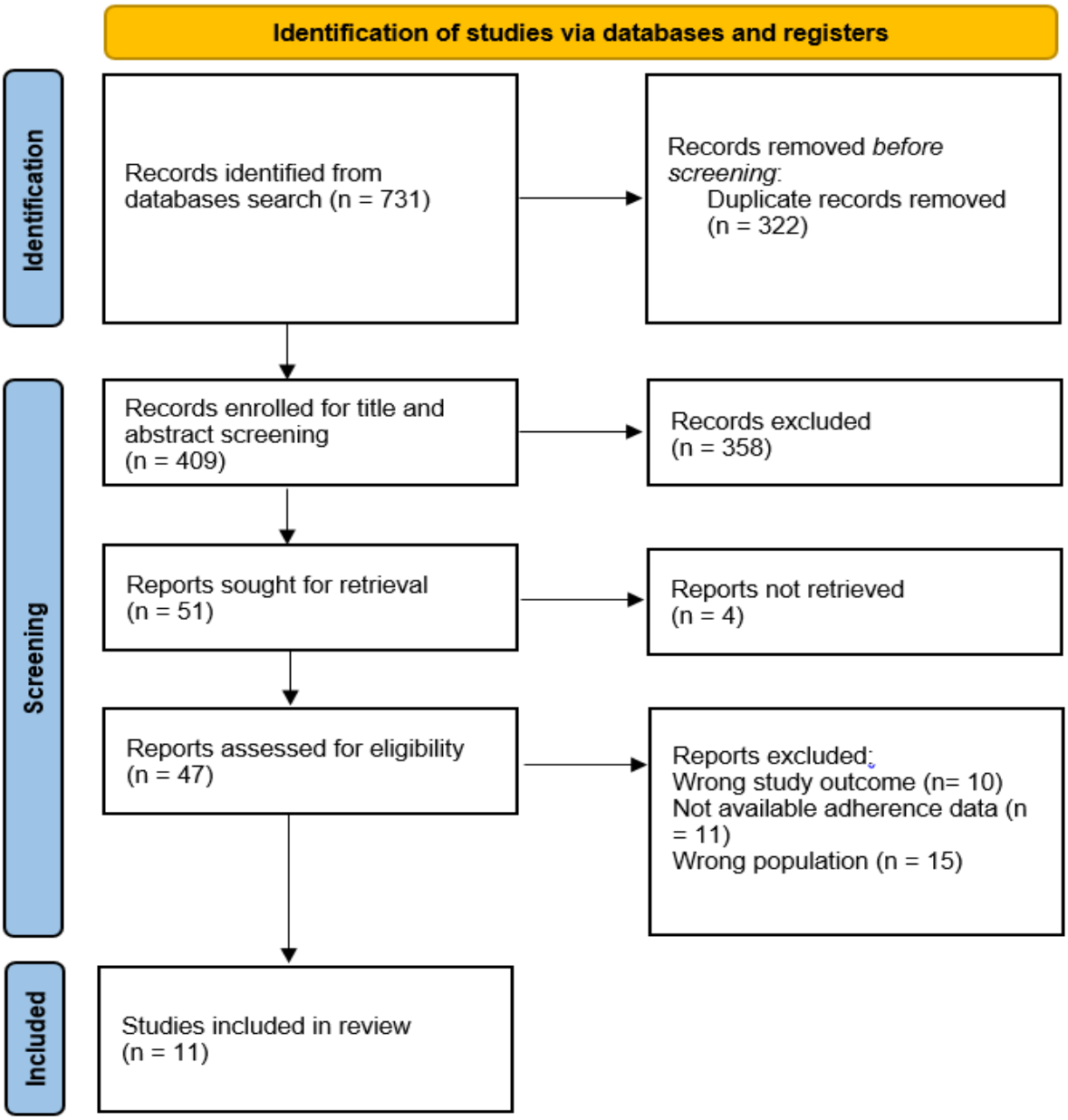

Figure 1: PRISMA flow chart for study screening process

Characteristics of the included studies

This review included data from 11 studies on 274,202 T2DM patients from four countries [17-27]. There were five studies from the USA [16, 22-25], four studies from the UK [19, 20, 27], one study from Canada [18], and one study from Iran [22] (Table 1).

Table 1: Characteristics of the included studies (n=11)

Study	Study design	Country	Sulfonylurea cohort	Adherence (%)	Metformin cohort	Adherence (%)	NOS
Calip *et al.*, 2015[17]	Retrospective cohort	USA	195	77	149	30.9	5
Chong *et al.*, 2014[18]	Retrospective cohort	Canada	26155	52.2	46847	59.2	7
Donnan *et al.*, 2002(21)	Retrospective cohort	UK	1321	31.3	825	33.9	6
Evans *et al.*, 2002[22]	Retrospective cohort	UK	2537	63	1519	50	4
Farmer *et al.*, 2016[23]	Retrospective cohort	UK	10070	88.1	13823	81.2	7
Farsaei *et al.*, 2011[24]	Prospective cohort	Iran	123	65	204	60.3	7
Flory *et al.*, 2017[25]	Retrospective cohort	USA	1970	84	4117	81	6
Hansen *et al.*, 2010[26]	Retrospective cohort	USA	44916	61.3	52156	56.7	6
Quilam *et al.*, 2013[27]	Retrospective cohort	USA	9817	76.4	55043	70.4	8
Rozenfeld *et al.*, 2008[28]	Retrospective cohort	USA	1081	65.8	1274	63.9	8
White *et al.*, 2012[29]	Prospective cohort	UK	28	89.3	32	53.1	7
NOS: Newcastle-Ottawa Scale							

Quantitative data synthesis

Random effect meta-analysis revealed that the odds for higher proportion of adherence favoured sulfonylurea group (OR = 1.34, 95% CI [1.08-1.65]). The comparison between sulfonylurea and metformin adherence using OR was significant (p=0.007) (Figure 2).

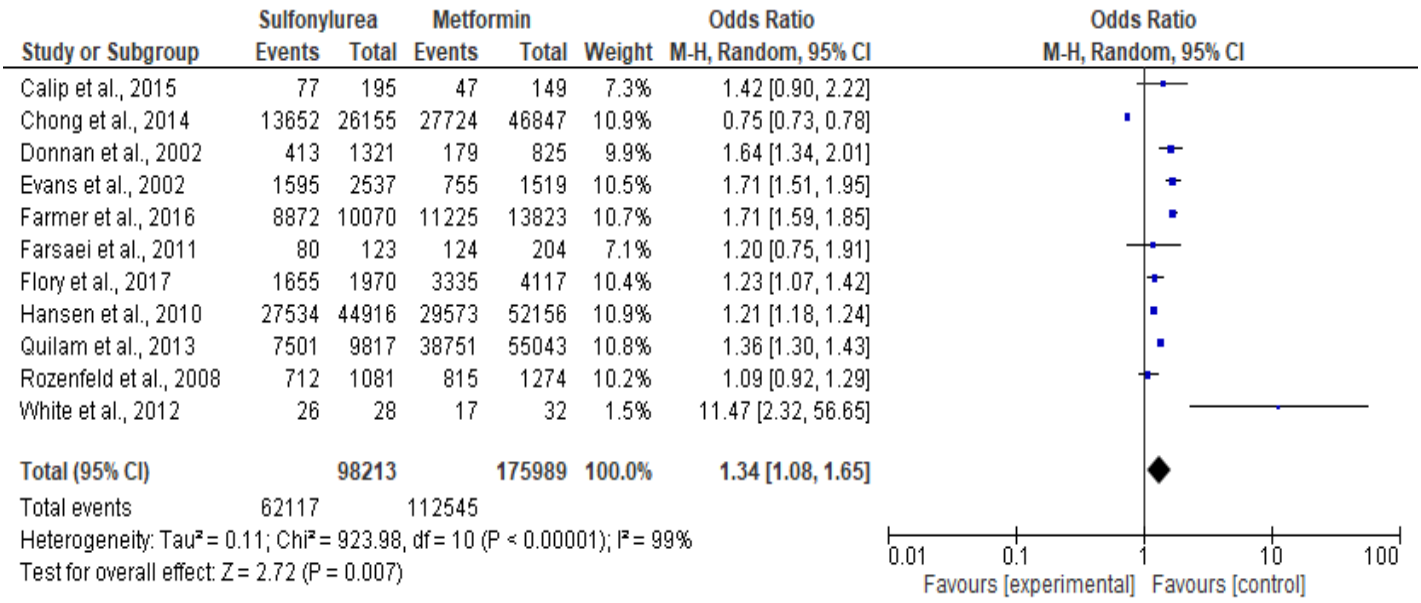

Figure 2: Forest plot of comparing sulfonylurea and metformin adherence and T2DM patients

Inter-study heterogeneity and publication bias

There was a significant heterogeneity in our pooled analysis (I^2 = 99%) (Figure 2). Funnel plot inspection reveals a nearly symmetrical distribution of the plotted ORs (Figure 3).

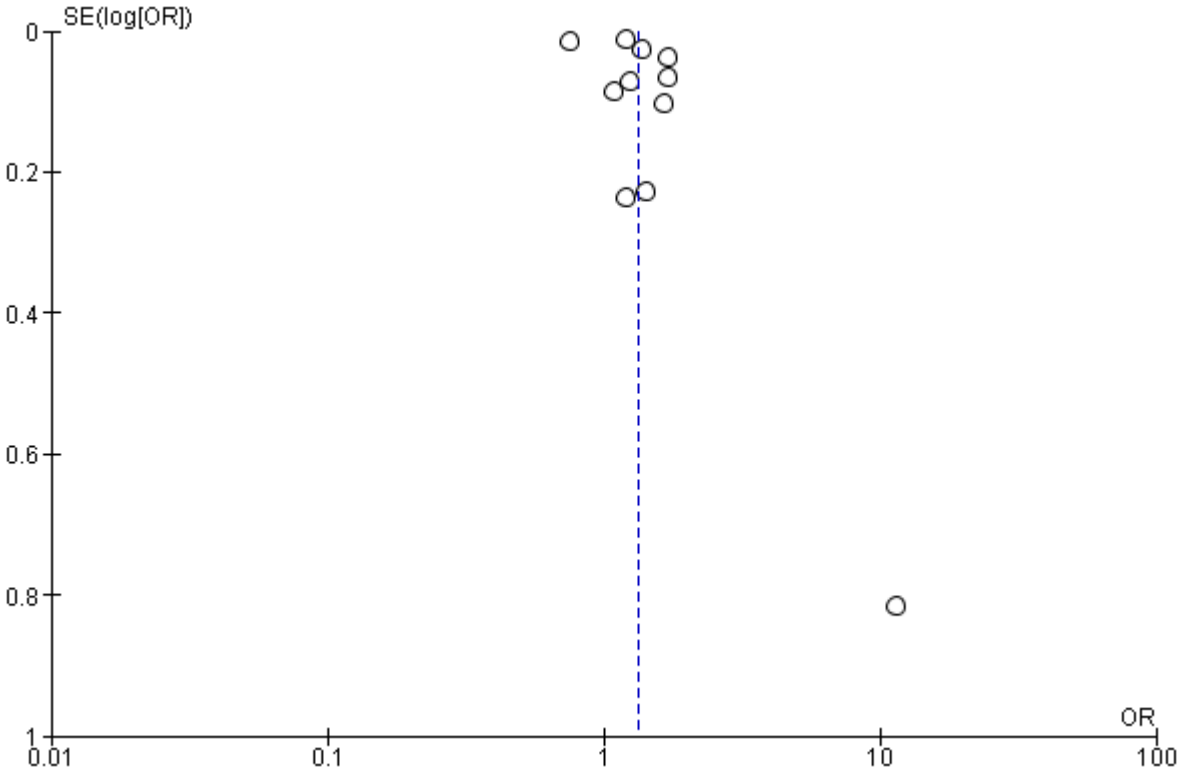

Figure 3: Funnel plot for assessment of publication bias

DISCUSSION

Among all diabetic patients, 90% have T2DM, of whom 58% are treated by oral anti-hyperglycemic drugs (OAHs) [26]. Improved adherence to these drugs may improve glucose control while also lowering diabetes morbidity, mortality, and long-term health resource consumption (including expenditures) [27].

Non-adherence to prescriptions can be a serious issue on managing diabetes [26]. Primary non-adherence, in which patients do not receive the first prescription for a drug, can occur in 16 percent to 32 percent of new prescriptions for diabetes drugs [28], while about half of patients develop poor adherence during subsequent observation (secondary non-adherence) or stop taking the new diabetes drug entirely within a year [29].

This meta-analysis aimed to compare the level of adherence to sulfonylurea with metformin among T2DM patients. The study found significantly higher adherence to sulfonylurea than metformin drugs (OR = 1.34, 95% CI [1.08-1.65].

Several studies have compared sulfonylureas to other types of diabetic medications in terms of adherence and durability. Inconsistent with our findings, a German survey of primary care practices [30] and a US claims-based research, patients on sulfonylureas were shown to have lower persistence than those taking DPP-4 inhibitors [31].

Another study comparing the DPP-4 inhibitor sitagliptin to sulfonylureas as an add-on medication to metformin found that patients using a sulfonylurea had worse adherence and persistence than those taking sitagliptin [32]. When compared to patients beginning metformin, patients starting a sulfonylurea had a higher chance of stopping their antidiabetic medicine and a lower likelihood of taking another antidiabetic drug following their initial therapy [33].

Adherence and persistence are often compared amongst antidiabetic drugs and/or prescription classes because of the link between antidiabetic medication adherence and better outcomes. According to a review paper published in 2011, 37 studies investigated at the association between antidiabetic drug adherence and a variety of health outcomes, 22 of the studies measured adherence using pharmaceutical claims or refill information. Better adherence was linked to improved glycemic control, according to **Asche and colleagues**. Glycemic control is crucial in diabetes care to avoid microvascular damage. Better adherence to anti-diabetes drugs was also linked to lower healthcare usage, according to the previously mentioned review paper [34].

The cost, availability, dose regimen, and complications related with the therapy all have a role in medication compliance [33]. Multiple therapies for type 2 diabetes are generally required to lower the risk of microvascular and macrovascular disease [35], but our findings show that complicated "optimal therapy" is unlikely to be successful unless adherence measures are developed.

CONCLUSION AND RECOMMENDATIONS

The study concludes that T2DM patients were significantly more adherent to sulfonylurea than metformin, however, the analysis showed significant heterogeneity. We recommend adherence measures to be devised when prescribing OHAs.

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Author Contributions

Authors contributed equally in search implementation as well as data extraction and manuscript writing.

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Conflict of Interest

The authors declare that there are no conflicts of interests.

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