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The bidirectional relationship between diabetes mellitus and hyperuricemia, and the best anti-diabetic medication tackling both: A review

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ABSTRACT— Diabetes mellitus and gout are common morbid diseases. They share the unwanted deleterious effects on renal and cardiovascular systems. The current review aimed to investigate the relationship between diabetes mellitus and hyperuricemia and assess the drugs that tackle both diseases. A systematic electronic search was conducted in the Pub Med including E pub and ahead of print and Google Scholar databases. The search was limited to studies assessing the relationship between gout and diabetes mellitus and investigating the effects of anti-diabetic medications on hyperuricemia and published during the period from 2008 to October 2019 with no limitation for the languages or study type. Three hundred-thirty articles were retrieved; the researchers screened the titles and abstracts for eligibility criteria and removal of duplications. Thirty-four articles fulfilled the inclusion and exclusion criteria. Out of 35 full texts approached, seventeen assessed the relationship between diabetes mellitus and gout, all the studies showed that hyperuricemia is a risk factor for diabetes; also the studies concluded a negative correlation between the glycemic control and gout. Salt glucose co-transporters inhibitors-2 (SGLT-2i), metformin, and pioglitazone reduced serum uric acid. Gout (or hyperuricemia) is a risk factor for diabetes; the effects are stronger in prediabetes and early stages of diabetes. However, poor glycemic control improves hyperuricemia due to diuresis. The best medications for hyperuricemia in patients with type 2 diabetes were SGLT-2 inhibitors. In addition, metformin and pioglitazone are suggested.

KEYWORDS: Diabetes mellitus, gout, hyperuricemia, glycemic control, diabetes medications

1. INTRODUCTION

Diabetes mellitus is a global health burden, the disease is now approaching an epidemic, currently 285 million are suffering from the disease and the projection is 438 million by the year 2030 [1]. Diabetes mellitus is essentially a vascular disease leading to macrovascular and microvascular complications (nephropathy, neuropathy, and retinopathy. Gout, the most prevalent inflammatory disease is associated with atrial fibrillation, cardiovascular and renal disease, and premature death [2].

Hyperuricemia has been linked to diabetes mellitus, cardiovascular disease, metabolic syndrome, and chronic kidney disease. The process seemed to be mediated by insulin resistance. The relationship between diabetes and hyperuricemia is bidirectional as patients with type 2 diabetes mellitus are at a higher risk of hyperuricemia, while individuals with hyperuricemia are predisposed to develop type 2 diabetes mellitus [3]. When existing together diabetes and hyperuricemia may exacerbate each other with deleterious consequences.

It is interesting to note that, some diabetic medications had cardio-renal protection, while others are blamed for cardiovascular risks, the same stands for gout as febuxostat (serum uric acid-lowering medication) cardiovascular safety had been debated [4], [5]. [6] found no reduction in diabetes with colchicines use. A case-series study [7] showed that the interleukin-1 receptor antagonist anakinra (100 mg/day improved resistant gout and glycemic control.

Due to the similar effects of diabetes and gout on the cardiovascular and renal systems. Also, some medications used to treat diabetes and gout may negatively affect the cardiovascular system, it is essential to review the literature to investigate the relationship between these two common morbid diseases and to suggest the best treatment. Thus, we conducted this review to assess the relationship between hyperuricemia and glycemic control. We also reviewed the effects of antidiabetic medications on hyperuricemia.

2. Subjects and Methods

Eligibility criteria according to PICOS:
Types of studies:
All articles investigating the relationship of hyperuricemia, diabetes mellitus, and the effects of antidiabetic medication on hyperuricemia and published in the last ten years were approached.

Type of participants:
We included studies on the adult population, animal studies, and cell lines. Studies among children were not included.

Type of outcome measures:
We included studies that investigated at least one of the following:

1. The relationship between hyperuricemia or gouty arthritis and diabetes control
2. The risk of diabetes among patients with hyperuricemia
3. Antidiabetic drugs effects on gout or hyperuricemia

Information sources and search methods:
A systematic electronic search was conducted in Pub Med (including E pub and ahead of print) and Google Scholar databases. The search was limited to articles published during the period 2008-2019 with no limitation in language and type of studies. The terms diabetes mellitus, hyperuricemia, gout, the glycated hemoglobin, HbA1c, antidiabetic medications, metformin, pioglitazone, insulin, salt-glucose co-transporters-2 inhibitors (SGLT-2 inhibitors), glucagon-like peptides agonists (GLP-1) were used.

Study selection and data extraction:
The results were searched manually for relevant articles. The authors independently screened the titles and abstracts. They checked all articles for eligibility according to the mentioned selection. Out of 330 articles retrieved, only thirty-four articles fulfilled the inclusion and exclusion criteria. The author name, country,

year of publication, type of study, number of patients, the duration of follow-p, and the outcomes were extracted. The different phases of the systematic review were reported in Figure 1

Ethical considerations: Ethical approval was obtained from the ethical committee of the University of Tabuk, Saudi Arabia to conduct the current review

For the assessment of study quality, the risk of bias assessment according Ottawa Newcastle scale was applied.

3. Results

Out of 330 articles retrieved, thirty-four manuscripts remain after the removal of duplication and irrelevant articles. Out of the manuscripts reviewed, fifteen were from Asia, nine manuscripts were from Europe, six manuscripts were published in the USA, three from Africa, and one from Canada. In the current review, seventeen studies assessed the relationship between diabetes and gout, while eighteen touched the effects of antidiabetic medications on hyperuricemia. The studies observed the increased risk of diabetes among patients with gout. Among patients with diabetes, good glycemic control and prediabetes were associated with higher serum uric acid levels directly or through associated comorbidities. The present review showed that metformin, pioglitazone, and SGLT-2 inhibitors reduce serum uric acid levels among patients with type 2 diabetes. Tables 1-4.

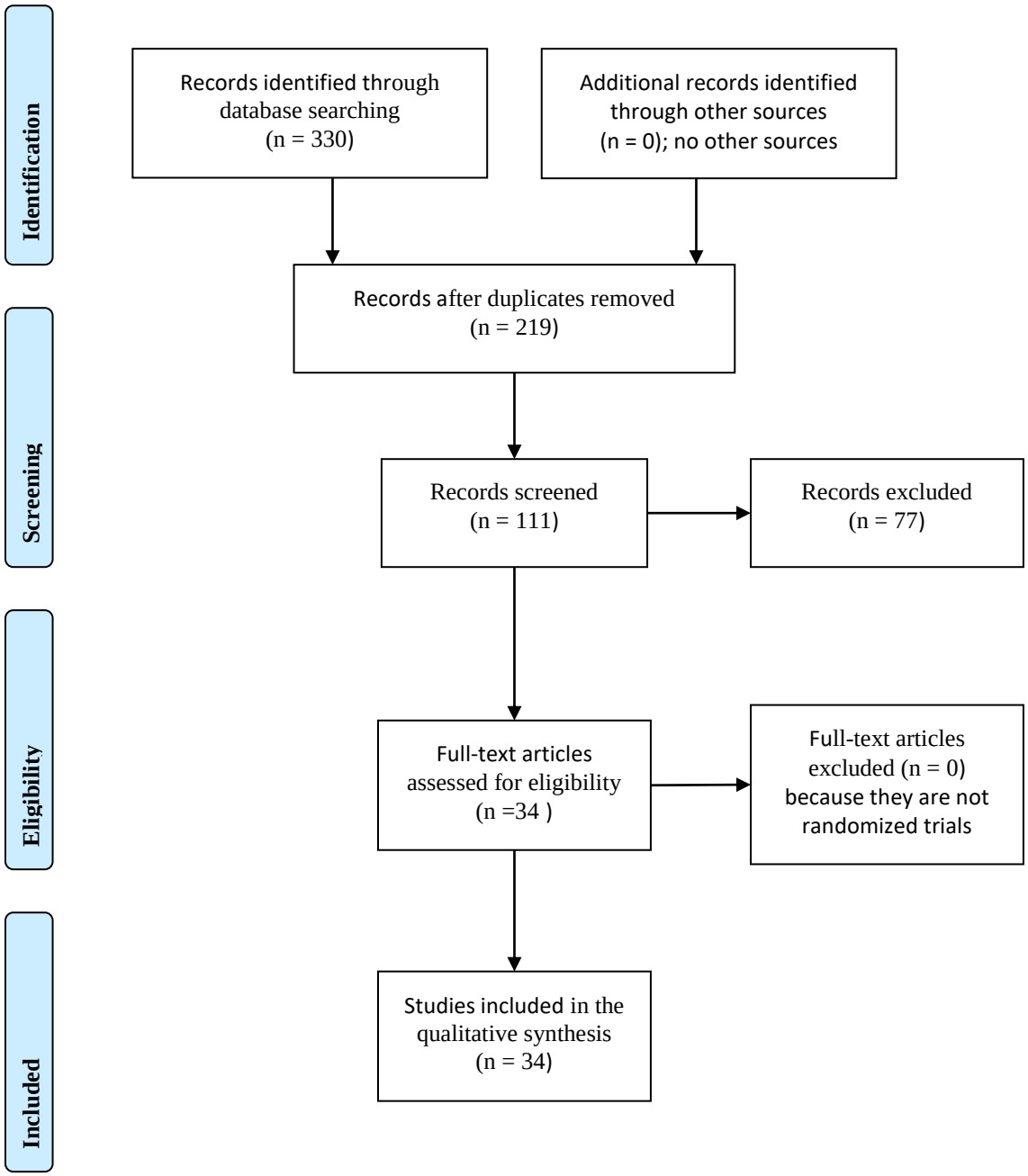

Figure 1. Flow diagram through the different phases of the systematic review (PRISMA flowchart).

Table 1. The association between type 2 diabetes mellitus and hyperuricemia

Author	Year	Country	Type of study	Patients no	Follow-up	Results
[8]	2010	Japan	Cross-sectional longitudinal study	193 normoglycemic patients		No correlation between serum uric acid and $HbA1_c$
[9]	2010	UK	Retrospective	24 768 and 50000 controls		Patients with diabetes are at a lower risk of gout
[10]	2011	Spain	Retrospective	82980		Uric acid may be high in prediabetes and good glycemic control than poorly controlled patients
[11]	2012	China	Cross-sectional experimental	533		Serum uric acid acute insulin response (AIR) and acute C-

						peptide response (ACPR) and maybe an independent predictor of beta-cell function
[12]	2012	Taiwan	Case-control Gene analysis	20 patients with gout and 42 unrelated controls		Patients with gout and Type 2 diabetes shared the common genetic factors
[18]	2013	USA	Retrospective	1923 patients with gout		Excess risk of diabetes was observed among Veterans with gout
[19]	2014	Italy	Hospital-based cross-sectional	3280		DM and glycemic control are not independent predictors of hyperuricemia, BMI, and TG are.
[13]	2015	Switzerland	A case-control study	7536		Increased A1c decreased incident gout, insulin, sulphonylureas, and pioglitazone are not
[14]	2015	Netherlands	Retrospective	221,117		Diabetes is associated with gout in men and may be related to co-morbidities
[15]	2015	USA	Commercial insurance cohort	54,075 with gout vs162,225 OA patients.	1.9 years	Gout was associated with DM incidence, more among women
[16]	2016	USA	Electronic database records cohort	Among 35 339		Gout was associated with risk of diabetes
[17]	2016	Taiwan	Retrospective	89295		Gout is an independent risk of diabetes more in females
[20]	2016	Nepal	Crosse-sectional	50		Serum uric acid not correlated with $HbA1_c$
[21]	2019	New Zealand	Electronic health records based cohort	Stroke survivors		Gout may be independently associated with an increased risk of hypertension and diabetes mellitus in patients with stroke
[22]	2019	New Zealand	Retrospective	10,117		The relationship of DM and gout is bidirectional among patient with pancreatitis
[23]	2019	China	Cross-sectional longitudinal	6466	9 months	A linear association between TG and hyperuricemia.
[24]	2019	Vietnam	A population-based study	1542		Significant association of hyperuricemia with glycemia especially among women

Table 2: Metformin and hyperuricemia

Author	Year	Country	Type of study	Patients no	Follow-up	Results
[25]	2018	Libya	Case-control, insulin, glibenclamide, and metformin tested	162		A direct effect on xanthine metabolism is suggested (mediated by obesity, no effects on antidiabetic medications)

[26]	2019	Netherlands	In vivo study using immune cells			MTOR inhibition was proposed as a novel therapeutic target for hyperuricemia
[27]	2019	Canada	Retrospective	135,301 new users of anti-diabetic medications		Metformin users were less likely to have gouty attacks
[28]	2019	China	Experimental study			AMPK activation may temporarily compensate for HUA-induced renal injury
[29]	2017	China	Experimental study			Metformin reversed gout induced insulin resistance in muscle
[30]	2009	Russia	A prospective study	30	12 months	Metformin reduces the production of uric acid

Table 3. Pioglitazone effects on hyperuricemia

Author	Year	Country	Type of study	Patients no	Follow-up	Results
[31]	2016	Egypt	Animal study On 35 males rats		4 weeks	Pioglitazone treatment significantly reduced uric acid
[32]	2015	Egypt	Metabolic syndrome rats model			Pioglitazone ameliorated hyperuricemia
[33]	2013	Japan	Experimental study	68	12 w2eeks	Pioglitazone down-regulated uric acid
[34]	2014	China	Experimental study on rats gouty model		2 days	Pioglitazone had anti-inflammatory effects on gouty arthritis
[35]	2018	Taiwan	A retrospective study	30/100		Incidence of gout was less among pioglitazone users

Table 4. SGLT-2 inhibitors and hyperuricemia

Author	Year	Country	Type of study	Patients no	Follow-up	Results
[36]	2018	USA	A review			SGLT-2 inhibitors decreased hyperuricemia
[37]	2018	China	A review of 62 randomized controlled trials (RCTs)	34 941 patients		SGLT-2 inhibitors especially empagliflozin reduced hyperuricemia
[38]	2019	China	A meta-analysis of 31 RCTs	6813,650		SGLT-2 inhibitors significantly decreased serum uric acid

[39]	2017	USA	Post hoc analysis of pooled data from four placebo-controlled phase III studies	2313	26 weeks	Canagliflozin reduced serum uric acid
[40]	2018	Serbia	A Review			SGLT-2 inhibitors attenuated hyperuricemia
[41]	2017	France	A review			SGLT-2 inhibitors are preferred over DPP-4 inhibitors in patients with gout

4. Discussion

In the present review, [8] assessed 193 normoglycemic patients in a cross-sectional longitudinal study and found no correlation between serum uric acid and $HbA1_c$, [9] conducted a large database-nested study and stated that patients with diabetes are at a lower risk of gout. The above findings can be explained by that in the early staged of diabetes and prediabetes there is insulin resistance that increases gout, also, the lack of dieresis from high glucose is absent. A retrospective study conducted in Spain [10] concluded that uric acid may be high in prediabetes and good glycemic control than poorly controlled patients, [11] in their cross-sectional study including 533 patients with diabetes observed that serum uric acid correlate with acute insulin response (AIR) and acute C-peptide response (ACPR) and maybe an independent predictor of beta-cell function, [12] suggested that patients with gout and Type 2 diabetes shared the common genetic factors, a case-control study (7536 participants) published in Switzerland [13] found a negative relationship between the glycated hemoglobin and gout. Regarding gout and diabetes risk, previous retrospective studies [14- 19] found a positive relationship either directly or through associated co-morbidities. On the other hand, [20] found no association of gout and the glycated hemoglobin. A recent study conducted among patients with stroke [21] found that gout may be independently associated with an increased risk of hypertension and diabetes mellitus in patients with stroke, another recent study [22] observed a bidirectional relationship between gout and diabetes among patients with pancreatitis. It is important to note that pancreatogenous diabetes (type 3c diabetes may be misdiagnosed as type 2 diabetes as pancreatitis may be silent in some cases. A cross-sectional longitudinal study [23] with a large sample size (6466) and followed for nine months showed a linear association between triglycerides (TG) and hyperuricemia, it is essential to note that patients with diabetes mellitus have high TG among other unwanted lipid abnormalities. A more recent population-based study [24] including 1542 patients concluded the significant association of hyperuricemia with glycemia, especially among women. Regarding the effects of metformin on serum uric acid level, a case-control study [25] conducted among 162 patients with diabetes stated that a direct effect on xanthine metabolism is suggested (mediated by obesity, no effects on antidiabetic medications), another study conducted on human cell line [26] and proposed MTOR inhibitors as noble therapeutic target for hyperuricemia, [27] conducted a retrospective study and observed less gouty attacks among metformin users, two experimental studies [28], [29] showed AMPK activation may temporarily compensate for HUA-induced renal injury and a decreased insulin resistance in muscles, and a recent prospective study [30] with one year follow-up concluded the reduction of serum uric acid with metformin use. The five retrieved studies [31- 35] found regarding the effects of pioglitazone on serum uric acid (four animal studies and a retrospective cohort) found that pioglitazone reduce uric acid, while one study also showed anti-inflammatory effects on gouty arthritis. The strongest level of evidence in the current review is SGLT-2 inhibitors reduction of serum uric acid (three reviews, a review of randomized controlled trials, a meta-analysis of randomized controlled trials, and one post hoc analysis of pooled data from four placebo-

controlled phase III studies [36- 41].

5. Conclusion

Gout increases the risk of diabetes. However, the counterintuitive appearance of a protective effect of diabetes mellitus on hyperuricemia is due to loss of beta-cell function and flushing of uric acid by the osmotic effects of glycosuria in the later staged of diabetes mellitus. SGLT-2 inhibitors are the best drugs tackling both serum uric acid and hyperglycemia in addition to their cardio-renal protection. However, metformin and pioglitazone are also suggested.

Conflicts of interest: The author declares that there are no conflicts of interest

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