A Systematic Review of Metformin Therapy and Renal Outcomes in Type 2 Diabetes Mellitus

Kerry Wilbur[1,*] and Kawthar Al Tawengi[2]

[1]*College of Pharmacy, Qatar University, PO Box 2713, Doha, Qatar*

[2]*Heart Hospital, Doha, Qatar*

Abstract: *Background*: Nephropathy is an important sequelae of diabetes. Current clinical study of the potential nephroprotective effects of metformin in diabetes is small and outcomes of individual studies insufficient to arrive at a firm conclusion. The objective of this systematic review is to evaluate the relationship between metformin treatment and specific renal outcomes in patients with Type 2 Diabetes Mellitus (T2DM).

Methods: Two authors independently performed comprehensive searches in relevant health care databases using pre-determined search terms. Included articles described metformin treatment compared to control group(s) whereby baseline and follow-up parameters of relevant renal outcome were adequately described. Study characteristics, outcomes, and methodological quality were extracted according to standard protocols.

Results: Initial search yielded 1,147 articles of which 7(6 prospective and 1 retrospective) studies meeting inclusion criteria were included in the overall analysis totaling 62,993subjects exposed to metformin. Comparators included thiazolidinediones (TZDs), sulfonylureas (SUs) and insulin in studies spanning 12 weeks to 4 years. When change from baseline values is compared, metformin demonstrated a more pronounced increase in albumin to creatinine ratio (ACR) than SUs (mean difference [MD] 14.8 mg/g [-4.2 to 25]), while TZDs were consistently associated with improvements. No significant difference in glomerular filtration rate (eGFR) was observed between metformin and TZD (MD 0.22 mL/min [-0.24 to 0.68]), while data between metformin and SU was conflicting.

Conclusions: The potential nephroprotective effects of metformin in diabetes patients with or without evidence of pre-existing proteinuria are not supported by our findings. Further long-term prospective study among larger populations is needed.

Keywords: Metformin, Type 2 diabetes, nephropathy, systematic review.

BACKGROUND

Metformin is widely recognized as the first therapy shown to offer a reduction in mortality when used as first-line therapy to reach glucose goals in overweight patients with type 2 diabetes mellitus (T2DM) [1-3]. However, metformin may not be offered to all eligible patients. It has been historically contraindicated in patients with conditions that may predispose them to lactic acidosis. In addition, metformin is not recommended in patients suffering from acute illness with liver dysfunction, evidence of alcohol abuse, heart failure, metabolic acidosis, or dehydration [4,5]. Apart from metformin's well-established contraindication for patients undergoing radiocontrast studies or surgery, now many other contraindications are consistently being refuted in the face of epidemiological and study data [4,5]. For example, new study indicates that metformin is at least as safe as other glucose lowering therapy in heart failure patients [6].

Similarly, metformin has recorded contraindication against use in patients with evidence of impaired renal function (serum creatinine values of >1.5 mg/dL men - 1.4 mg/dL women) [7]. Yet, this precaution is consistently ignored in practice throughout the world, without documented negative patient consequences (metabolically or otherwise) [8-10]. A database study of over 50,000 diabetes patients in Sweden found metformin's association with reduced risks of cardiovascular disease and all-cause mortality was also observed in patients with renal impairment (eGFR < 60 mL/min/1.73m^2) [11]. In another observational study, the cardiovascular morbidity and mortality benefits of metformin were preserved even in patients with chronic kidney disease (as defined by the Kidney Disease Outcomes Quality Initiative (KDOQI) stages 1 through 3) [12]. Laboratory data is also emerging that metformin therapy in T2DM may in fact have nephroprotective effects. Several studies have documented the beneficial effects of metformin therapy to ameliorate the pathophysiological alterations observed with diabetic nephropathy (such as fibrosis, inflammation and apoptosis) potentially through metformin's restoration of AMP-activated protein kinase [13-15]. However, current clinical study of the potential nephroprotective effects of metformin in diabetes is small. We undertook a systematic review of the effects of metformin use on renal outcomes in diabetes patients.

*Address correspondence to this author at the College of Pharmacy, Qatar University, PO Box 2713 Doha, Qatar; Tel: 974-4403-5581;
Fax: 974-4403-5551; E-mail: kwilbur@qu.edu.qa

E-ISSN: 2310-9971/16

METHODS

Searching

The two authors independently performed comprehensive searches in relevant health care databases: PubMed (1966-December Week 1 2014); Embase (1947- December Week 1 2014); International Pharmaceutical Abstracts (1970- December Week 1 2014); Cumulative Index to Nursing and Allied Health Literature (1982- December Week 1 2014); EBM Reviews – Cochrane Central Register of Controlled Trials (March 1996 to 4th Quarter 2014); Scopus® (1996-December Week 1 2014); Science Direct® (1995-December Week 1 2014); and Latin American Caribbean Health Sciences Literature (1982- 2014). Predetermined search terms included key words and phrases: "metformin"; "kidney function"; "renal impairment"; "renal function"; "nephro*" or "safety". No language restrictions were applied. Search strategies were modified to accommodate the controlled vocabulary in these databases.

References of retrieved articles were also hand-searched. Abstracts of unpublished studies were additionally identified by hand-searching American Diabetes Association, International Society of Pharmaceutical Outcomes Research, and International Diabetes Federation-affiliated conference proceedings. Pre-determined search terms were also applied to a general internet search using Google Scholar.

Study Selection and Characteristics

The titles and abstracts of articles identified by the search were screened for potential relevance. Duplicate article titles identified among the searches by the two authors were eliminated. Full-text of potentially relevant studies was retrieved and considered eligible for inclusion according to pre-determined selection criteria:

1) comparison of metformin treatment arm to an active glucose-lowering comparator;

2) evaluation of renal outcomes as primary or secondary endpoints;

3) Data reported in sufficient detail at baseline and follow-up to identify treatment effects on renal outcomes.

Renal outcomes were identified according to study documentation of specific findings:

1) Estimates of glomerular filtration rate (GFR);

2) urinary protein measurements, such as albumin to creatinine ratio (ACR); albumin excretion (UAE); or creatinine to albumin ratio; and

3) new start dialysis. Studies of only adult populations were included.

Articles were excluded if they:

1) were conducted in pediatric populations;

2) examined no active treatment comparator;

3) Failed to either adequately describe the specific renal endpoints that were evaluated or 3) the achieved outcomes according to treatment arm assignment; or

4) Were narrative reviews, commentaries or case reports.

Disagreements about inclusion were resolved in author consensus meetings. The protocol followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered with PROSPERO (systematic review record CRD42015024338) [16].

Validity Assessment

The two authors independently assessed the quality of selected relevant articles according to the *Consolidated Standards of Reporting Trials* (CONSORT) or *Strengthening the reporting of observational studies in epidemiology* (STROBE) guide as applicable according to the studies' methodology. Criteria include the description of trial design, intervention, sample, randomization and blinding (if applicable), results and reporting of limitations and generalizability. Authors paid particular attention to the control of confounding variables known to influence renal outcomes such as blood pressure, smoking status, and use of ACE inhibitors or ARBs. The Agency for Healthcare Research and Quality (AHRQ) guidelines were also used to assess risk of bias and strength of evidence [17].

Data Abstraction

A standardized data extraction form was developed according to the studies' variables of interest: year of publication; country of origin; design; population; baseline measures of renal function; treatment arms;

duration of follow-up; outcome measures of renal function; and statistical comparisons among outcomes, including if other factors influencing renal endpoints were considered. We also recorded any evidence of adverse event evaluation. Final inclusion and exclusion decisions were then made by author consensus

Qualitative Data Synthesis

The methodological heterogeneity across studies including selection and measurement of specific renal endpoints precluded rigorous quantitative assessment (meta-analysis) and so the study results are described and evaluated qualitatively.

RESULTS

Flow of Included Studies

The initial literature search yielded a total of 1,147articles (Figure **1**). After reviewing the titles and abstracts and identifying duplicates, 1,065 articles were excluded. Eighty-two studies remained for full text review, but despite an English abstract, 12 full-texts were not available English; 5 involved pharmacokinetic and not clinical findings for metformin; 32 did not enroll the population of interest; and 28 did not provide sufficient details regarding treatment arm assignment, study duration or renal outcomes evaluated. We included 7 articles in the review.

Study Characteristics

Study characteristics of the included articles are described in Table **1** [18-24]. A total number of 98,832 patients were evaluated in the included studies (5,255 prospectively, from 6 randomized control trials, and 93,577 retrospectively, from 1 database cohort study) with 62,993 (64%) using metformin. All but 2 of the prospective studies enrolled less than 50 subjects per arm. The studies were conducted in health care settings throughout the world including Japan, Europe,

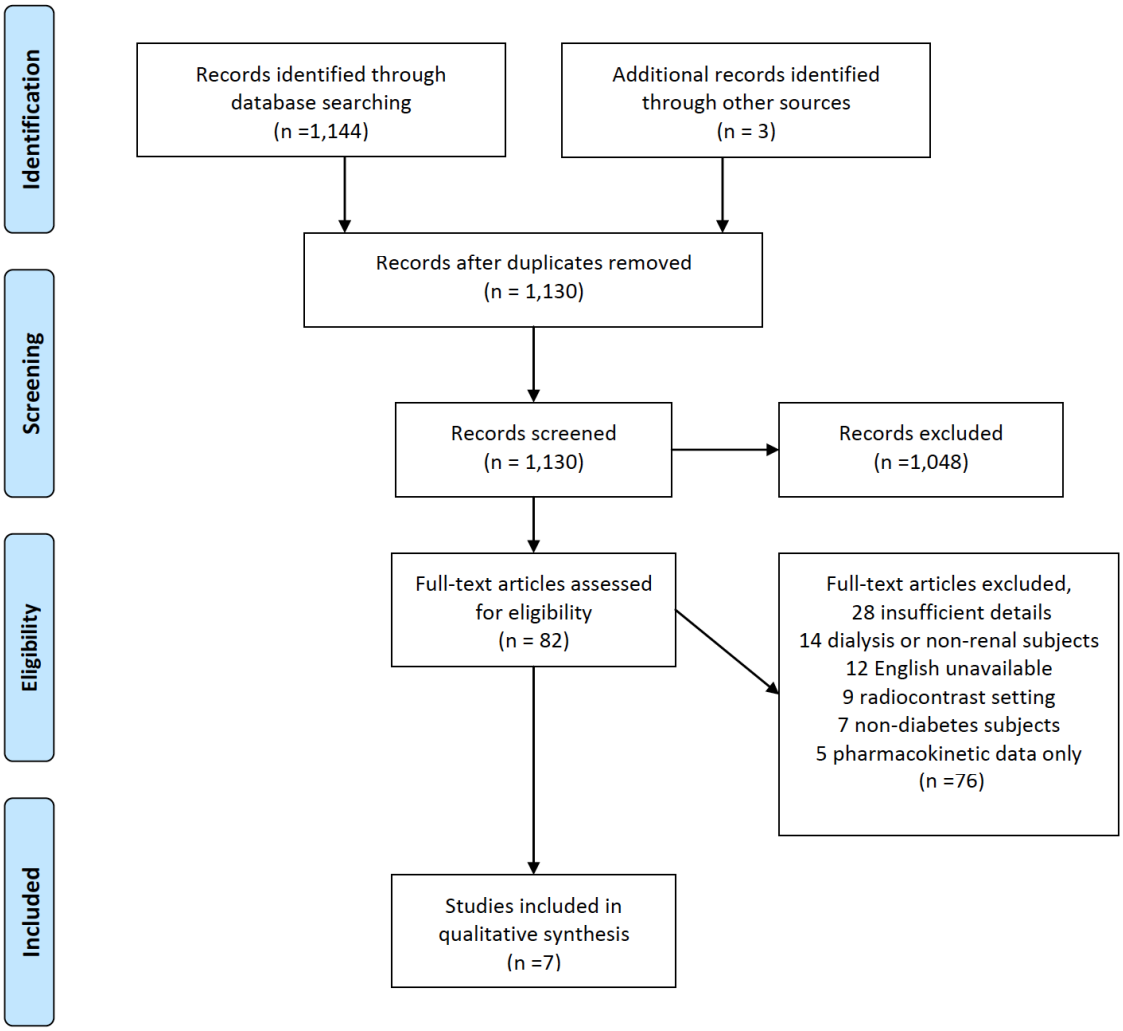

Figure 1: Literature Search and Article Review Process.

Table 1: Study Characteristics

Study	Comparators Maximum Dose	Subjects N, mean age	Duration Methodology	Outcome Baseline	Outcome Follow-Up
Imano *et al.* 1998	M: 500 mg/D T: 400 mg/D	13, 62 years 17, 68 years	12 weeks Prospective Randomized	*ACR (mg/g creatinine):*◆ M: 79 (IQR 64-117) T: 70 (IQR 49-195)	 M: 108 (IQR 78-186) T: 43 (IQR 26-103)** p <.05
Amador-Licona *et al.* 2000	M: 1700 mg/D G: 10 mg/D	28, 49 years 23, 48 years	12 weeks Prospective Randomized	*UAE (mg/dL):*✦ M: 74 (33-200) G: 83 (32-198) *eGFR (mL/min):*# M: 138 ± 28 G: 136 ± 29	 M: 49 (0-244)** p <.05 G: 102 (16.3-255) M: 134 ± 28 G: 151 ± 29 ** p <.05
QUARTET Study Group 2004	M (+SU): 2.55 g/D P (+SU): 45 mg/D	320, 60 years 319, 60 years	52 weeks Prospective Randomized	*ACR* M (+SU): 0.11 ± 0.56 P (+SU): 0.07 ± 0.25	 M (+SU): 0.09 ± 0.01 P (+SU): 0.09± 0.01
PIOCOMB 2011	M (+I): 1.7 g/D P (+I): 30 mg/D M (+P+I): as above Insulin dosed to fasting blood glucose	42, 64 years 40, 61 years 39, 63 years	6 months Prospective Randomized	*Creatinine/Albumin (mmol/mg):*# M (+I): 1.14 ± 0.76 P (+I): 3.47 ± 14.55 M (+P+I): 1.89 ± 3.14 *eGFR (mL/min):*# M (+I): 114.2 ± 34.2 P (+I): 116.9 ± 33.7 M (+P+I): 118.9 ± 47.3	 M (+I): 1.72 ± 3.12 P (+I): 1.19 ± 1.00** p <.05 M (+P+I): 1.54 ± 1.61 M (+I): 115.8 ± 38.9 P(+I): 115.3 ± 36.6 M (+P+I): 117.2 ± 47.9
ADOPT Study Group 2011	M: 2 g/D G: 15 mg/D R: 8 mg/D	1,454, 58 years 1,441, 56 years 1,456, 56 years	4 years Prospective Randomized	*ACR (mg/g creatinine):*^ M: 9.3 (172.3) G: 9.4 (174.4) R: 9.9 (179.5) *eGFR (mL/min):*^ M: 97.1 (24.6) G: 95.7 (27.6) R: 98 (24.6)	mean change, 95% CI M: 20.9 (13.3, 28.9) G: 6.1 (-1.2, 14.0) R: 2.1 (-4.2, 8.8) *p<0.5 vs M mean change, 95% CI M: 1.4 (0.0, 2.9) G: -0.4 (-2.0, 1.2) R: 5.1 (3.6, 6.7) * p<0.5 vs R
Morikawa, *et al.* 2011	M: 0.5-0.75 g/D P: 15-30 mg/D	32, 62 years 31, 62 years	52 weeks Prospective Randomized	*ACR (mg/g creatinine):*^ M: 111 (85, 139) P: 143 (84, 202) *eGFR (mL/min.1.73 m^2):*# M: 75 ± 3.3 P: 79 ± 3.4	absolute values not reported log ACR % change +4.2% log ACR % change -8.3% * p<0.5 vs M M: 75 ± 3.3 P: 78.9 ± 5.0
Hung *et al.* 2012	M S R Doses not reported	61,104, 60 years 30,550, 62 years 1,923, 64 years	0.9 years 0.8 years 0.7 years Retrospective Database Cohort	*eGFR (mL/min):*□ M: 81 (IQR 72, 93) S: 80 (IQR 70, 93) R: 79 (IQR 69, 91)	>25% GFR decline or ESRD: 3.8% 5.0% aHR vs M 1.2 (1.12, 1.28) p<.05 3.2%

TREATMENT ARMS: G: glyburide; I: insulin; M: metformin; T: troglitazone; P: pioglitazone; R: rosiglitazone; S: sulfonylurea.
RENAL OUTCOMES: ACR: urinary albumin to creatinine ratio; eGFR: estimated glomerular filtration rate; UAE: urinary albumin excretion.
OUTCOMES REPORT: ◆ median and 25th and 75th percentile interquartile range; ✦ mean and range; # mean and standard deviation; ^ geometric mean and 95% coefficient of variance.
aHR: adjusted hazard ratio and 95% confidence interval; ESRD: end-stage renal disease.
** p-values reported for within group comparisons (baseline vs follow-up).

and North America spanning evaluation time periods from 12 weeks to 4 years (mean 60 weeks). The majority was conducted among adult diabetes populations in their 60's. Metformin was compared to a thiazolidinedione therapy in 6 studies (one involving the randomized addition of metformin, pioglitazone or the

combination to existing insulin treatment and another one using metformin or pioglitazone in patients failing maximum sulfonylurea dosing), and compared to a sulfonylurea therapy in three. No study included non-sulfonylurea insulin secretagogues, alpha glucosidase inhibitors, or incretin-based therapies in a comparator arm.

Estimated GFR was the predominant renal outcome evaluated (in 5 of 7 studies) and combined with measures of protein excretion in 4 of these (ACR in three and one study each with UAE and with creatinine to albumin ratio). Renal outcomes were among the primary endpoints in all but two studies whose main objective was to evaluate inflammatory markers of cardiovascular risk [20,21]. Three studies enrolled diabetes patients with pre-existing evidence of nephropathy, whereby two studies purposely excluded these potential subjects. One study expressly excluded recruitment of subjects with elevated creatinine, but did not restrict according to elevated urinary albumin values (ultimately found in 17% of their study population at baseline) [22]. The retrospective study excluded patients with elevated creatinine/impaired eGFR, but reported 3% assessed in their database had evidence of microalbuminuria [24].

The six prospective randomized trials described a well-defined study question with appropriate inclusion and exclusion criteria and appropriate comparator interventions. Three of the prospective studies were not evaluating renal parameters as a primary endpoint, but as either secondary endpoints or as a priori defined separate subgroup analysis [20-22]. Risk of bias is considered medium to high among the 4 studies enrolling a small number of subjects and absence of statistical assessment of known confounding variables.

Data Synthesis

In studies comparing treatment of T2DM with metformin or sulfonylurea therapy, metformin demonstrated significant reductions in the difference in UAE measurements from baseline, (-25 vs 19.0, mean difference -44 mg/dL, 95% CI -84 to -3.7) (Table **1**) [19]. However, when ACR is evaluated, the mean increase from baseline among glyburide patients is less pronounced (6.1 vs 20.9, mean difference -14.8mg/g creatinine, 95% CI -25.3 to -4.2) [22]. Findings for eGFR were conflicting; while creatinine clearance estimates at baseline were largely sustained at follow up among metformin study arms, at least one study demonstrated significant improvements with glyburide (mean increase of 59 mL/min) [19]. Retrospective evaluation of diabetes therapies found significantly more patients experiencing >25% reductions in eGFR or reaching end-stage renal disease in the sulfonylurea groups (5.0%) compared with either metformin (3.8%) or rosiglitazone (3.2%) [24]. When evaluable studies are aggregated, the mean difference in change in eGFR between metformin and sulfonylurea is -1.94 mL/min, 95% CI -3.86 to -0.01) [19,23].

When compared to metformin, thiazolidinedione therapy is consistently associated with improvement in ACR [18,20,22]. Unlike concomitant pioglitazone, metformin's addition to insulin did not demonstrate lowering of creatinine to albumin ratio (0.58 vs -2.28, mean difference -2.86 mmol/mg, 95% CI -7.8 to 2.1). Although in one study where subjects receiving rosiglitazone had significantly greater eGFR improvements from baseline at the four-year follow-up when compared to metformin, there was no significant difference overall when other studies were considered (mean difference -0.22 mL/min, 95% CI -0.68 to 0.24) [21-23].

Glucose control, as measured by A1C, was evaluated in 5 studies with metformin and comparator arms all demonstrating reductions from baseline [18-21,23]. Only the retrospective cohort database study adjusted for the effects of glucose (and blood pressure treatment) on renal outcomes but no consideration for other variables known to influence kidney function such as blood pressure, body mass index (BMI), cholesterol, or smoking status were recorded in any included study.

Adverse events were evaluated in 5 prospective studies [18-21,23]. No serious side effects occurred in any study. Metformin exhibited more reported gastrointestinal intolerances during the initial phase of two studies [19,20]. In another, peripheral edema and weight gain were more prevalent among thiazolidinedione arms when combined with insulin or with sulfonylurea [20,21]. None reported elevated serum lactate values in metformin treated subjects.

DISCUSSION

Nephropathy is a serious sequelae of diabetes worldwide, accounting for an estimated one-third of all end-stage-renal disease [25]. It is additionally associated with non-renal complications in diabetes patients, including independent increased risk for cardiovascular events [26]. As options for therapy to control glucose continue to expand, it is prudent to also

consider the effects of these treatments on mitigating micro- and macrovascular complications. In this systematic review, we found metformin therapy exhibits overall more favourable effects on measures of renal function than sulfonylurea, but less so than thiazolidinediones.

As an alternative for glucose control in T2DM, metformin is considered a first line therapy [3,27,28]. While desirable pharmacologic properties include reductions in glucose, in triglyceride and cholesterol synthesis and neutral effects on weight, its preferential position in treatment is largely supported by the cardiovascular mortality benefits observed among obese T2DM patients in the UKPDS34 trial [1,2]. While subjects with impaired renal function were excluded from this study, uncomplicated use of metformin is pervasive in this population throughout the world [7-10]. Despite the dogma of safety concerns, such experience further reinforces the dearth of clinical evidence to support avoidance metformin in patients with renal impairment [29]. No study in our review identified increased adverse events in subjects receiving metformin compared to those in comparator arms. These particular studies, which followed subjects for at least one year similarly, found no evidence of lactic acidosis and is consistent with other reviews indicating low overall prevalence among diabetes patients and uniform across administered glucose-lowering therapies [30].

Despite metformin's preferred choice as initial monotherapy in T2DM, additional glucose-lowering medication is often required to reach desired targets, either at treatment outset in patients with marked metabolic elevation (AIC> 9%) or in time as β–cell function is progressively lost [31,32]. As such, study of the effects of metformin (or any other monotherapy) on renal outcomes is incomplete. In the one investigation of combined therapy we included, secondary outcomes of eGRF were no different following 6 months of concomitant metformin and/or pioglitazone with insulin [21]. In a retrospective review a British diabetes population cohort, undefined "renal complications" occurred at similar rates in patients receiving metformin combinations with either sulfonylurea (2.2 event rate per 1000 person-years) or insulin (2.3 events per per 1000 person-years) studied over a mean follow-up period of 2.8 years [33]. While studies evaluating combination therapies in our review of metformin are lacking, what does arise from our data is the observed beneficial renal effects of thiazolidinedinone monotherapy. In animal models, PPARγ activators are shown to inhibit induced tubular necrosis and associated inflammatory responses [34,35]. Rosiglitazone has demonstrated improvements in glomerular endothelial function, as evident by increased nitric oxide bioavailability, among diabetes patients with advanced nephropathy [36]. In a previous meta-analysis exploring the renal benefits of rosiglitazone and pioglitazone, authors called for further prospective study to further elucidate the clinical impact of the significant decreases in urinary albumin and protein excretion observed among the small and heterogenous studies they reviewed [37].

Studies included in our review included both measures of protein and estimated GFR as markers of renal function. Spot urine albumin measurements (expressed as albumin concentration or urinary albumin-to-creatinine ratios) are advocated as baseline screening for newly diagnosed Type 2 diabetes patients with follow-up 24-hour total urine protein collection and estimates of GFR if urine albumin measurements are found to be abnormal [27,38]. As such, the included studies used accepted evaluations of renal outcomes. Investigation into the best predictor of end-stage renal disease among diabetes populations has largely demonstrated that those with poorer eGFR and greater evidence of proteinuria experience more rapid progression in renal function decline as well as higher rates of all-cause mortality [39,40]. However, in some instances serum creatinine measurements and associated eGFR may be preserved in the presence of micro- or macroalbuminuria [41]. It seems prudent then to ensure consideration of both eGFR and protein measures in concert in all future study of treatment effects on renal outcomes.

A number of limitations to our study merit consideration. While the majority of eligible studies were prospective in size, the sample population enrolled among most of these randomized control trials was each less than 100 subjects. Valuable articles meeting most of our inclusion criteria were lacking in sufficient detail to permit contribution to our aggregated findings [33,42]. The landmark UKPDS 34 study (evaluating metformin's effect on glucose control, macrovascular, and microvascular complications in almost 10,000 Type 2 diabetes patients did evaluated renal death, but due to the small numbers of outcome experienced (total 4), we did not include in our analysis [43]. Separate reports related to other renal parameters offered further information related to albuminuria and eGFR in the UKPDS 34 trial, but failed to describe comparison of these findings among metformin,

sulfonylurea, or insulin assigned treatment groups [44]. Since our review concluded, a retrospective analysis has identified metformin users with stage 5 kindey disease in Taiwan were less likely to reach chronic dialysis as an outcome, but had greater risk of overall mortality, further supporting ongoing contraindication of metformin in patients with advanced renal failure [45].

All studies we found eligible evaluated eGFR as an endpoint, but measurement of important renal outcomes related to evidence of micro- or macroalbuninuria were inconsistent making estimates of aggregate treatment effect sizes inadequate. Similarly, any effects of metformin on diabetic nephropathy must be considered in the context of the short time frame for evaluation. Sustained changes (or preservation) of renal outcomes observed over years (instead of months) would better substantiate the potential nephroprotective roles of glucose-lowering therapy, with additional assessment of clinically meaningful endpoints such as dialysis or death. Unfortunately, the lack of control for known confounding variables affecting renal function and the composition of diabetes patients with pre-existing evidence of proteinuria among the studies in our review make conclusions about the impact of metformin (or the other glucose lowering strategies) on the development or progression of nephropathy in diabetes patients difficult.

CONCLUSION

While the body of literature supports the safe use of metformin in diabetes patients with (or at risk of) renal impairment and data is emerging that it may be associated with reduced cardiovascular risks in this population, we did not find conclusive evidence of a nephroprotective effect with metformin treatment. Prospective study of larger diabetes cohorts is necessary to determine potential renal benefits of glucose lowering therapies in T2DM.

FUNDING

This publication was made possible by the NPRP award [NPRP 7-1189-3-04] from the Qatar National Research Fund (a member of The Qatar Foundation). The statements made herein are solely the responsibility of the author[s].

AUTHOR CONTRIBUTIONS

All authors conducted the data search and analysis. K.W. wrote the manuscript. K.T. reviewed/edited the manuscript, contributed to discussion.

REFERENCES

[1] UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352: 854-65. http://dx.doi.org/10.1016/S0140-6736(98)07037-8

[2] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359: 1577-89. http://dx.doi.org/10.1056/NEJMoa0806470

[3] International Diabetes Federation. Global guideline for Type 2 Diabetes [article online], 2012. Available from http: //www.idf.org/publications/global-guideline-type-2-diabetes. Accessed 4 July 2015.

[4] Bristol-Myers Squibb. Glucophage (metformin hydrochloride) tablets package insert. Princeton, NJ. 2010.

[5] Marquess JG. Managing special populations among patients with type 2 diabetes mellitus. Pharmacotherapy 2011; 31(12 Part 2): 65S-72S. http://dx.doi.org/10.1592/phco.31.12.65S

[6] Eurich DT, Weir DL, Majumdar SR, *et al*. Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure. Circ Heart Fail 2013; 6: 395-402. http://dx.doi.org/10.1161/CIRCHEARTFAILURE.112.000162

[7] Lipska K, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care 2011; 34: 1431-7. http://dx.doi.org/10.2337/dc10-2361

[8] Holstein A, Nahrwold D, Hinze S, Egberts EH. Contra-indications to metformin therapy are largely disregarded. Diabet Med 1999; 16: 692-6. http://dx.doi.org/10.1046/j.1464-5491.1999.00115.x

[9] Emslie-Smith AM, Boyle DI, Evans JM, *et al*. Contraindications to metformin therapy in patients with type 2 diabetes: a population-based study of adherence to prescribing guidelines. Diabet Med 2001; 18: 483-8. http://dx.doi.org/10.1046/j.1464-5491.2001.00509.x

[10] Koro CE, Lee BH, Bowlin SJ. Antidiabetic medication use and prevalence of chronic kidney disease among patients with type 2 diabetes mellitus in the United States. Clin Therapm 2009; 31: 2608-17. http://dx.doi.org/10.1016/j.clinthera.2009.10.020

[11] Ekstrom N, Schioler L, Svensson AM, Eeg-Olofsson K, Miao Jonasson J, Zethelius B, *et al*. Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. BMJ Open 2012; 2(4). http://dx.doi.org/10.1136/bmjopen-2012-001076

[12] Roussel R, Travert F, Pasquet B, *et al*. Reduction of Atherothrombosis for Continued Health (REACH) Registry Investigators. Metformin use and mortality among patients with diabetes and atherothrombosis. Arch Intern Med 2010; 170: 1892-9. http://dx.doi.org/10.1001/archinternmed.2010.409

[13] Satriano J, Sharma K, Blantz RC, Deng A. Induction of AMPK activity corrects early pathophysiological alterations in the subtotal nephrectomy model of chronic kidney disease.. Am J Physiol Renal Physiol 2013; 305: F727-F33. http://dx.doi.org/10.1152/ajprenal.00293.2013

[14] Alhaider AA, Korashy HM, Sayed-Ahmed MM, Mobark M, Kfoury H, Mansour MA. Metformin attenuates streptozotocin-induced diabetic nephropathy in rats through modulation of oxidative stress genes expression. Chem Biol Interact 2011; 192: 233-42. http://dx.doi.org/10.1016/j.cbi.2011.03.014

[15] Kim J, Shon E, Kim CS, Kim JS. Renal podocyte injury in a rat model of type 2 diabetes is prevented by metformin. Exp Diabetes Res 2012 2012(210821). http://dx.doi.org/10.1155/2012/210821

[16] Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic re- views and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009; 339: b2700. http://dx.doi.org/10.1136/bmj.b2700

[17] Owens DK, Lohr KN, Atkins D, Treadwell JR, Reston JT, Bass EB, *et al*. Grading the strength of a body of evidence when comparing medical interventions - Agency for Healthcare Research and Quality and the Effective Health Care Program. J Clin Epidemiol 2010; 63: 513-23. http://dx.doi.org/10.1016/j.jclinepi.2009.03.009

[18] Imano E, Kanda T, Nakatani Y, Nishida T, Arai K, Motomura M, *et al*. Effect of troglitazone on microalbuminuria in patients with incipient diabetic nephropathy. Diabetes Care1998; 21: 2135-9. http://dx.doi.org/10.2337/diacare.21.12.2135

[19] Amador-Licona N, Guizar-Mendoza JM, Vargas E, Sanchez-Camargo G, Zamora-Mata L. The short-term effect of a switch from glybenclamide to metformin on blood pressure and microalbuminuria in patients with Type 2 Diabetes Mellitus. Arch Med Res 2000; 31: 571-5. http://dx.doi.org/10.1016/S0188-4409(00)00241-1

[20] Hanefield M, Brunetti P, Schernthaner GH, Matthews DR, Charbonnel EH on behalf of the QUARTET Study Group. One-year glycemic control with a sulfonylurea plus pioglitazone versus sulfonylurea plus metformin in patients with Type 2 diabetes. Diabetes Care 2004; 27: 141-7. http://dx.doi.org/10.2337/diacare.27.1.141

[21] Hanefeld M, Pfutzner A, Forst T, Kleine I, Fuchs W. Double-blind, randomized, multicentre, and active comparator controlled investigation of the effect of pioglitazone, metformin, and the combination of both on cardiovascular risk in patients with type 2 diabetes receiving stable basal insulin therapy: the PIOCOMB study. Cardiovasc Diabetol 2011; 10: 65. http://dx.doi.org/10.1186/1475-2840-10-65

[22] Lachin JM, Viberti G, Zinman B, Haffner SM, Aftring RP, Paul G, *et al*. Renal function in type 2 diabetes with rosiglitazone, metformin, and glyburide monotherapy. Clin J Am Soc Nephrol 2011; 6: 1032-40. http://dx.doi.org/10.2215/CJN.09291010

[23] Morikawa A, Ishizeki K, Iwashima Y, Yokoyama H, Muto E, Oshima E, *et al*. Pioglitazone reduces urinary albumin excretion in renin-angiotensin system inhibitor-treated type 2 diabetic patients with hypertension and microalbuminuria: the APRIME study. Clin Exp Nephrol 2011; 15: 848-53. http://dx.doi.org/10.1007/s10157-011-0512-3

[24] Hung AM, Roumie CL, Greevy RA, Liu X, Grijalva CG, Murff HJ, *et al*. Comparative effectiveness of incident oral antidiabetic drugs on kidney function. Kidney Int 2012; 81: 698-706. http://dx.doi.org/10.1038/ki.2011.444

[25] Rossing P, de Zeeuw D. Need for better diabetes treatment for improved renal outcome. Kidney Int 2011; 79(Supplement 120): S28-S32. http://dx.doi.org/10.1038/ki.2010.513

[26] Currie G, Delles C. Proteinuria and its relation to cardiovascular disease. Int J Nephrol Renovasc Dis 2014; 7: 13-24.

[27] Association AD. Standards of Medical Care in Diabetes - 2015. Diabetes Care 2015; 38(Supplement 1).

[28] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, *et al*. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015; 38: 140-9. http://dx.doi.org/10.2337/dc14-2441

[29] McCormack J, Johns K, Tidesley H. Metformin's contraindications should be contraindicated. CMAJ 2005; 173: 502-4. http://dx.doi.org/10.1503/cmaj.045292

[30] Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and non-fatal lactic acidosis with metformin use in type 2 diabetes mellitus: systematic review and meta-analysis. Arch Intern Med 2003; 163: 2594-53. http://dx.doi.org/10.1001/archinte.163.21.2594

[31] Berkowitz SA, Krumme AA, Avorn J, *et al*. Initial choice of oral glucose-lowering medication for diabetes mellitus: A patient-centered comparative effectiveness study. JAMA Internal Medicine 2014; 174: 1955-62. http://dx.doi.org/10.1001/jamainternmed.2014.5294

[32] Harper W, Clement M, Goldenberg R, Hanna A, Main A, Retnakaran R, *et al*. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: pharmacologic management of type 2 diabetes. Can J Diabetes 2013; 37(Supplement 1): S61-S8. http://dx.doi.org/10.1016/j.jcjd.2013.01.021

[33] Currie CJ, Poole CD, Evans M, Peters JR, Morgan CL. Mortality and other important diabetes-related outcomes with insulin vs other antihyperglycemic therapies in type 2 diabetes. J Clin Endocrinol Metab2013; 98: 668-77. http://dx.doi.org/10.1210/jc.2012-3042

[34] Reel B, Guzeloglu M, Bagriyanik A, Atmaca S, Aykut K, Albayrak G, *et al*. The effects of PPAR-γ agonist pioglitazone on renal ischemia/reperfusion injury in rats. J Surg Res 2013; 182: 176-84. http://dx.doi.org/10.1016/j.jss.2012.08.020

[35] Calkin AC, Giunti S, Jandeleit-Dahm KA, Allen TJ, Cooper ME, Thomas MC. PPAR-α and -γ agonists attenuate diabetic kidney disease in the apolipoprotein E knockout mouse. Nephrol Dial Transplant 2006; 21: 2399-405. http://dx.doi.org/10.1093/ndt/gfl212

[36] Pistrosch F, Passauer K, Herbrig K, Schwanebeck U, Gross P, Bornstein SF. Effect of thiazolidinedione treatment on proteinuria and renal hemodynamic in type 2 diabetic patients with overt nephropathy. Horm Metab Res 2012; 44: 914-8. http://dx.doi.org/10.1055/s-0032-1314836

[37] Sarafidis PA, Stafylas PC, Georgianos PI, Saratzis AN, Lasaridis AN. Effect of thiazolidinediones on albuminuria and proteinuria in diabetes: A meta-analysis. Am J Kidney Dis 2010; 55: 835-47. http://dx.doi.org/10.1053/j.ajkd.2009.11.013

[38] Kidney Disease Improving Global Outcomes (KDIGO) 2012. Clinical practice guideline for the Evaluation and managmeent of chronic kidney disease. Kidney Int 2013; 3(1): Supplement 1.

[39] Hemmelgarn BR, Manns BJ, Lloyd A, *et al*. Relation between kidney function, proteinuria, and adverse outcomes. JAMA 2010; 303: 423-9. http://dx.doi.org/10.1001/jama.2010.39

[40] Hoefield RA, Karla PA, Baker PG, Souda I, Diggle J, Gibson MJ, *et al*. The use of eGFR and ACR to predict decline in renal function in people with diabetes. Nephrol Dial Transplant 2011; 26: 887-92. http://dx.doi.org/10.1093/ndt/gfq526

[41] Newman DJ, Mattock MB, Dawnay AB, Kerry S, McGuire A, Yaqoob M, *et al*. Systematic review on urine albumin testing for early detection of diabetic complications. Health Technol Asses 2005; 9(30).

[42] Solini A, Penno G, Bonora E, Fondelli C, Orsi E, Trevisan R, Vedovato M *et al*. for the Renal Insufficiency and Cardiovascular Events Study Group. Age, renal dysfunction, cardiovascular disease, and antihyperglycemic treatment in

type 2 diabetes mellitus: findings from the renal insufficiency and cardiovascular events Italian multicenter study. JAGS 2013; 61: 2353-61. http://dx.doi.org/10.1111/jgs.12381

[43] UK Prospective Diabetes Study (UKPDS) Group. Risk factors for renal dysfunction in Type 2 diabetes. (UKPDS 74). Diabetes 2006; 55: 1832-1839. http://dx.doi.org/10.2337/db05-1620

[44] UK Prospective Diabetes Study (UKPDS) Group. Development and progression of nephropathy in Type 2 diabetes: The United Kingdom Prospective Diabetes Study(UKPDS 64). Kidney Int 2003; 63: 225-232. http://dx.doi.org/10.1046/j.1523-1755.2003.00712.x

[45] Hung SC, Chang YK, Lius S, *et al*. Metformin use and mortality in patients with advanced chronic kidney disease: national, retrospective, observational cohort study. Lancet Diabetes Endocrinol 2015; 3: 605-614. http://dx.doi.org/10.1016/S2213-8587(15)00123-0

Received on 20-04-2016 Accepted on 01-07-2016 Published on 09-09-2016

DOI: http://dx.doi.org/10.12970/2310-9971.2016.04.01.1