Review Article

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Incidence and risk factors associated with hypoglycemia among patients with chronic kidney disease: A systematic review

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Abstract:

Hypoglycemia is a common complication in patients with chronic kidney disease (CKD), more so if they have diabetes as well. The occurrence of hypoglycemia in CKD is associated with considerable morbidity and mortality, both of which are treatable and preventable. This review summarizes the incidence and risk factors associated with hypoglycemia among patients with CKD. The meta-analysis was performed as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. A search was done on PubMed, EMBASE, SCOPUS, Cochrane Library, Google Scholar, and Cumulative Index to Nursing and Allied Health Literature for cohort studies in English published between January 2000 and August 2019 using search terms related to hypoglycemia (low blood sugar), chronic kidney disease (chronic renal failure OR renal failure), and incidence (risk OR epidemiology OR risk factors). Summary measures were calculated using random-effects model. A total of 5 studies involving 311,817 persons were included in the meta-analysis. The pooled incidence of hypoglycemia in patients with CKD was 0.188 (confidence interval [CI] = 0.097–0.287). The incidence of hypoglycemia was significantly higher in patients with CKD than in patients without CKD (Relative risk [RR] = 1.89, 95% CI = 1.86–1.92, $P < 0.0001$). No heterogeneity was reported between the studies ($I^2 = 0\%$, $P > 0.05$), and publication bias was also found. Females, patients who had diabetes mellitus of long duration, and those on antidiabetic drugs such as insulin and sulfonylureas were at risk of developing hypoglycemia in CKD as per narrative review. The incidence of hypoglycemia in patients with CKD is high. Therefore, there is need to closely monitor affected individuals so that appropriate management protocols could be set up. Further probing of various risk factors for hypoglycemia in CKD patients is necessary for early detection and initiation of timely preventive and curative measures.

Keywords:

Chronic kidney disease, hypoglycemia, incidence, risk factors

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Introduction

The kidneys play a pivotal role in blood glucose homeostasis.[1,2] This is because it is crucial in the metabolism of 30%–40% of circulating insulin.[1] In addition, during prolonged fasting, the kidneys account for about 45% of all gluconeogenesis in the body.[2] In individuals with chronic kidney disease (CKD), there is a substantial alteration in blood glucose homeostasis. More importantly, diabetes is a major risk factor for the development of CKD and end-stage renal disease, with about 40% of patients with diabetes diagnosed with CKD.[3] Usually, individuals with this condition present with glomerular basement

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membrane thickening, mesangial matrix expansion, arteriolar hyalinosis, changes in the tubulointerstitium as well as nodular glomerulosclerosis.[2,4]

CKD together with diabetes predisposes a person to a more morbid condition of hypoglycemia which increases the risk of mortality many folds.[5,6] The underlying pathophysiology leading to hypoglycemia in persons with CKD can be attributed to reduced glomerular filtration rate (GFR) usually <60 ml/min/1.73 m^2 in CKD.[4,5] The degradation of insulin by peripheral renal tissues is noticeably reduced in patients with CKD increasing the blood insulin levels.[5] In cases where CKD is superseded by diabetes, antidiabetic drugs are usually prescribed, but owing to inadequate functioning of the kidney, the drugs are not excreted efficiently. The half-life of these drugs tends to increase, thereby predisposing the patient to frequent episodes of hypoglycemia.[7] Furthermore, the reduced renal mass in CKD hampers the process of gluconeogenesis. The interplay of all these factors tends to contribute to a greater risk for hypoglycemia in patients with CKD.[6,8,9]

Hypoglycemia in CKD commonly manifests as disorientation and dizziness associated with slurred speech, convulsions, and death. It can also lead to a surge in adrenergic activity, resulting in cardiac arrhythmias, coronary ischemia, and even sudden death.[8,9]

A recent meta-analysis summarized such adverse consequences of hypoglycemia to explain the increased risk for hypoglycemia episodes in diabetic patients.[10] Recently, Alsahli and Gerich conducted a narrative review on the current knowledge of the epidemiology, pathogenesis, and morbidity of hypoglycemia in CKD patients, but did not include the summary of its incidence.[11] Most of the studies in the literature have tried to explore the risk factors of hypoglycemia in diabetic patients without stratification for CKD as a risk factor of hypoglycemia.[12-15] However, no studies to date have summarized the risk factors for hypoglycemia in individuals with CKD.

It is necessary to assess the risk of hypoglycemia in patients with CKD and explore the various risk factors for hypoglycemia in these patients in order to optimize management strategies. Therefore, the current systematic review was carried out to determine the incidence of hypoglycemia and its risk factors in patients with CKD with or without diabetes mellitus (DM).

Methods

Search strategy and selection criteria

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[16] A prespecified elaborate search strategy was developed with the assistance of an experienced research librarian. All published cohort studies regardless of study setting were included from PubMed, EMBASE, SCOPUS, Cochrane Central Register of Controlled Trials, Google Scholar, and Cumulative Index to Nursing and Allied Health Literature and a manual screen of the references of relevant studies. All studies available in English and published between January 2000 and August 2019 were included. Five major themes were used to search the studies: CKD, hypoglycemia, the incidence, prevalence, and risk factors.

The criteria followed to narrow down the search were as follows:

- Study population: Patients with chronic kidney disease and without chronic kidney disease
- Outcome variables: Hypoglycemia (incidence, number of episodes/person, and its risk factors such as diabetes and antidiabetic drugs).

The following MeSH terms or keywords were used in different combinations and permutations to search for studies in advanced PubMed: “chronic kidney disease,” “hypoglycemia,” “risk factors,” and "diabetes".

The search strategies described above identified potentially eligible studies. The titles and abstracts of all studies retrieved were screened independently. Irrelevant titles or abstracts were discarded in the first attempt. Later, the full-texts of those relevant were analyzed for measurable outcome variables as described above for data extraction and analysis.

Data extraction

For each selected study, the information extracted included the following: first author, publication year, study setting, sample size, patient characteristics (such as age and sex), type of renal disease, diabetes status, number of patients with hypoglycemia, and risk factors of hypoglycemia. Meta-analysis was carried out for the outcomes of only those that had available data in at least two selected studies.

Quality assessment of studies

Each included study was analyzed using the GRACE checklist in order to assess the quality of the study.[17] The GRACE checklist consists of 11 questions addressing the key components of double-arm observational studies. All the studies were reviewed and any differences were resolved by consensus in the group meeting. Finally, after reasoning, found that only those studies which met at least six of the 11 criteria on the GRACE checklist had sufficient quality to be included.

Data analysis

Extracted data were entered and analyzed using MetaXL and Revman 5.3. MetaXL was used to calculate the pooled incidence of hypoglycemia in patients with CKD. Risk ratio or incidence ratio along with 95% confidence interval (CI) of hypoglycemia in patients with CKD and without CKD was used as a summary measure for effect to compare the incidence between these two groups.

Heterogeneity in the studies was evaluated using the Cochran's Q test, and I^2 statistics was used to assess the degree of interstudy variation. I^2 values of 0%–24.9%, 25%–49.9%, 50%–74.9%, and 75%–100% were considered as having no, mild, moderate, and significant thresholds for statistical heterogeneity, respectively. Random-effects model was used to generate summary measures.

Results

Study selection and description

The combined systematic literature search identified around 119 studies with potentially relevant data in their title or abstract. After a review of the title, 30 studies were included for full-text review. Finally, only five cohort studies matched the inclusion criteria.[18-22] The excluded studies were rejected on various grounds, as described in Figure 1.

All studies published from 2008 onward are depicted in Table 1. These studies had been conducted in various parts of the world such as Taiwan, South Korea, the USA, and India. The total sample size of the study population in these studies was 311,817, with ages ranging from 55 to 73 years.

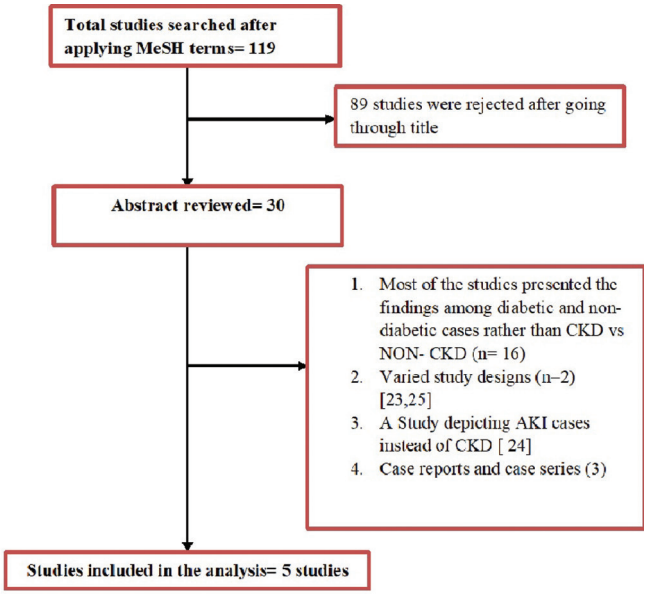

Figure 1: Flowchart showing selection of studies

Furthermore, three studies presented data for a single arm reporting the incidence of hypoglycemia in patients with chronic renal disease.[18-20] In the other two articles, data were available for a comparison of the risk of hypoglycemia in patients with CKD versus patients without CKD.[21,22] Based on the data available, we estimated a summary measure for the risk of hypoglycemia in CKD patients.

Quality assessment of selected studies

The quality of the included studies was found to be satisfactory according to the GRACE checklist. Except for studies by Chu *et al*., Khyalappa and Devdikar, and Hsiao *et al*.,[18,20] all other articles were double-arm analytical studies. The studies conducted by Yun *et al*., Chu *et al*., and Hsiao *et al*. had addressed confounding factors at the analysis stage for sex, duration of diabetes, type of antidiabetic drugs being administered, and history of past hypoglycemic episodes.[18,19,22] All the other quality assessment criteria such as the objectivity of the primary outcome (risk of hypoglycemia) and comparison of hypoglycemia in patients with CKD and non-CKD were fulfilled by all studies. The quality assessment of the studies is shown in Table 2.

Incidence of hypoglycemia among chronic kidney disease patients

The risk of hypoglycemia in patients with CKD in the studies included varied from 0.11 to 0.46.[18-22] The reason for this variation could be the differing stages of CKD and mixed populations of individuals with and without DM. The pooled incidence was found to be 0.188 with 95% CI of 0.097–0.287 with large heterogeneity among the studies ($I^2 = 99.88\%$, $P < 0.05$) based on the random-effects model [Figure 2]. The funnel plot in Figure 3 shows there is no publication bias as there is lack of small sample size studies.

As shown in Figure 4, the incidence of hypoglycemia was significantly higher in patients with CKD than in patients without CKD (relative risk = 1.89, 95% CI = 1.86–1.92, $P < 0.0001$). No heterogeneity was reported between the studies ($I^2 = 0\%$, $P > 0.05$).[18-25] There was zero heterogeneity among the selected studies for this outcome measure ($\tau^2 = 0.00$, df = 1, $P = 0.52$, $I^2 = 0\%$).

Risk factors leading to hypoglycemia

Only two studies presented data on risk factors for hypoglycemia in CKD patients, and other studies reported varying risk factors. Therefore, it was decided to present the results as qualitative data. Two studies by Yun *et al*. and Chu *et al*. found that females were more at risk of hypoglycemia than males (20.5% among females vs. 17.89% in males), and the risk increased with the severity and duration of diabetes. The history of a previous episode of hypoglycemia

Table 1: Summary matrix for studies included in the systemic review

First author, years	Country	Study design	Study period	Study population	Sample size	Age (years)	Groups	Number of patients developing hypoglycemia
Moen *et al*. 2009	USA	Retrospective cohort	2004-2005	General population developing CKD and diabetes	243,222	73±0.04	Hypoglycemia in CKD	16,977/70,169
							Hypoglycemia in patients without CKD	22,161/173,053
Khyalappa *et al*. 2012	India	Prospective cohort	2009-2011	CKD Stage V with and without diabetes	100	NA	Hypoglycemia in patients with CKD	46/100
Yun *et al*. 2013	South Korea	Prospective longitudinal cohort	2000-2012	All patients with Type II DM	871	55.3±9.8	Hypoglycemia in micro- and macroalbuminuria	33/190
							Hypoglycemia in normoalbuminuria	71/681
Chu *et al*. 2017	Taiwan	Longitudinal cohort	2002-2008	ESRD with diabetes	20845	NA	Single arm	3998/20,845
Hsiao *et al*. 2019	Taiwan	Retrospective cohort	1997-2011	DM and ESRD	46,779	60.45±3.96	Single arm	5379/46,779

CKD: Chronic kidney disease, DM: Diabetes mellitus, ESRD: End-stage renal disease, NA: Not available

Table 2: Quality assessment of studies

GRACE checklist	Moen *et al*. 2009	Khyalappa *et al*. 2012	Yun *et al*. 2013	Chu *et al*. 2017	Hsiao *et al*. 2019
D1. Were treatment and/or important details of treatment exposure adequately recorded for the study purpose in the data sources?	Yes	Yes	No	Yes	Yes
D2. Were the primary outcomes adequately recorded for the study purpose?	Yes	Yes	Yes	Yes	Yes
D3. Was the primary clinical outcome measured objectively rather than subject to clinical judgment?	Yes	Yes	Yes	Yes	Yes
D4. Were primary outcomes validated, adjudicated, or otherwise known to be valid in a similar population?	Yes	Yes	Yes	Yes	Yes
D5. Was the primary outcome measured or identified in an equivalent manner between the intervention group and the comparison groups?	Yes	Yes	Yes	Yes	Yes
D6. Were important covariates that may be known confounders or effect modifiers available and recorded?	No	No	Yes	Yes	Yes
M1. Was the study (or analysis) population restricted to new initiators of treatment or those starting a new course of treatment?	Yes	Yes	Yes	Yes	Yes
M2. If 1 or more comparison groups were used, were they concurrent comparators? If not, did the authors justify the use of historical comparison groups?	Yes	Yes	Yes	Yes	Yes
M3. Were important confounding and effect modifying variables taken into account in the design and/or analysis?	No	Yes	Yes	Yes	Yes
M4. Is the classification of exposed and unexposed person-time free of "immortal time bias"?	Yes	Yes	Yes	Yes	Yes
M5. Were any meaningful analyses conducted to test key assumptions on which primary results are based?	NA	NA	NA	NA	NA

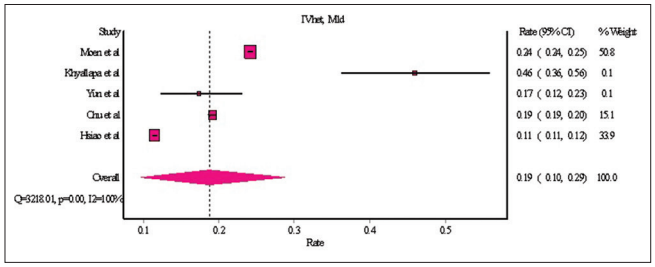

Figure 2: Forest plot depicting risk of hypoglycemia in chronic kidney disease patients

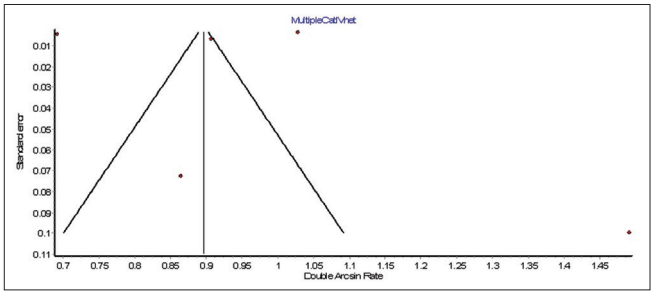

Figure 3: Funnel plot showing publication bias

was also found to be significantly associated with the development of hypoglycemia.[18] Hsiao *et al*. found that the risk of hypoglycemia was higher in patients on antidiabetic drugs, and the risk was more among insulin users than glyburide users followed by glipizide (insulin > glyburide > glipizide).[19]

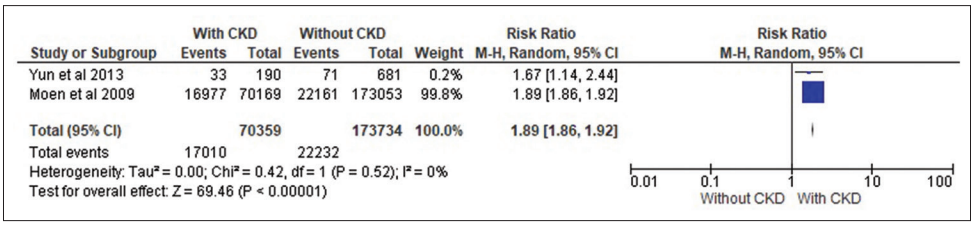

Figure 4: Hypoglycemia incidence in patients with and without chronic kidney disease

Discussion

In this meta-analysis, Five studies that followed various methodologies were included to determine the incidence of hypoglycemia in patients with CKD and explore the risk factors for hypoglycemia in these patients. The incidence of hypoglycemia in adults with CKD varied from 0.115 to 0.460 in the studies with an overall pooled incidence of 0.188 or pooled incidence of 188 cases of hypoglycemia per 1000 CKD patients. Despite the large heterogeneity, the risk measure was found to be within acceptable limits in comparison to individual studies. The reasons for the variations in the studies may be the differences in the study population, geographical location, stages of CKD, and other patient characteristics. We also found that the incidence of hypoglycemia was 1.89 times higher in patients with CKD than in patients without CKD as the individual studies had also reported. Owing to the inclusion of evidence from cohort studies and zero heterogeneity, this finding was statistically significant.

The high pooled incidence of hypoglycemia in CKD patients with or without diabetes indicates the need to closely monitor and manage the condition as such patients had been shown to have increased mortality.[18,26,27] Besides, hypoglycemia may contribute to the high cardiovascular morbidity and mortality observed in individuals with CKD.[21,28,29]

Given that hypoglycemia and CKD have been shown to have a multiplicative effect on morbidity and all-cause mortality in individuals with DM through an unclear mechanism,[27,28] this finding needs to be confirmed by further studies.

In this study, we have tried to enumerate various risk factors which influence the development of hypoglycemia in CKD. It was found that females were more prone to the condition than males. Patients with long duration of DM were also more affected as well as individuals on antidiabetic drugs, particularly insulin and sulfonylureas. In diabetic patients with CKD, increased risk of hypoglycemia may be due to lower urinary insulin clearance because of the CKD resulting from a rise in the half-life of circulating insulin in the blood.[27] Furthermore, owing to damage to the kidneys, renal gluconeogenesis which contributes to glucose homeostasis is also impaired.[27,30] Sulfonylureas may predispose diabetic patients with CKD to an increased risk of hypoglycemia by an increase in the secretion of insulin from the pancreas whose half-life has been prolonged on account of impaired urinary excretion and altered pharmacodynamic and pharmacokinetic responses to this medication in CKD patients.[12,27,30] However, more studies are needed to explore the relationship of estimated GFR gradient and its effect on hypoglycemia along with other factors such as age, smoking status, and other comorbidities as potential risk factors.[31]

Our systematic review has some strengths and limitations. Considering the extensive literature search, this is the first meta-analysis done to assess the risk and risk factors of hypoglycemia in patients with CKD. Another strength of this meta-analysis is the inclusion of studies from both developed (the USA) and developing nations (Taiwan and India) which increases its potential for generalization. However, the absence of enough literature, differences in study design, patient population, and the availability of only large sample-sized studies as well as the analysis of the funnel plot indicate the possibility of publication bias. Consequently, more studies across population groups and stages of CKD are required. Despite this limitation, our review is important because it strengthens the argument of a multiplicative adverse effect between CKD and hypoglycemia and vice versa.[27] Furthermore, further research is required to explore the effect of various confounders on the occurrence of hypoglycemia in patients with CKD. For this, prospective studies with large sample size and sufficient power will be more beneficial to provide evidence-based findings to inform clinical care and policy.

Conclusion

The high incidence of hypoglycemia calls for the need to closely monitor affected individuals and the institution of appropriate management. Females, patients with DM of long duration, and those on antidiabetic drugs such as insulin and sulfonylureas are at risk of developing hypoglycemia in CKD as per narrative review. Hence,

the choice of antidiabetic drugs becomes important in these cases. Efforts are required to train and improve the skills of community physicians at primary health-care centers, to be able to diagnose this condition promptly and give the necessary emergency care before the patient is referred to a higher health facility. The identification of risk factors for hypoglycemia in CKD patients is, therefore, necessary for early detection and the initiation of timely preventive and curative measures.

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Conflicts of interest
There are no conflicts of interest.

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