EDITORIAL

Insulin use and the risk of hypoglycemia in people with renal disease

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INTRODUCTION

In the United States, more than 30 million persons have diabetes mellitus (DM). Diabetic nephropathy is the most common cause of chronic Kidney Disease (CKD), with over one-third of diabetics getting kidney disease. Despite the relevance of renal illness in people with type 2 diabetes (T2D), there is a scarcity of information on the best medication for glycemic control in this group. Fundamental questions remain unanswered, such as the role of insulin in glycemic control in CKD. Insulin needs are thought to decrease with advanced CKD because insulin gets eliminated by the kidney. Cross-sectional studies, on the other hand, reveal that those with advanced CKD need more insulin. Hypoglycemia is a significant side effect of insulin therapy that can lead to ER visits or hospitalization. While insulin therapy is an established risk factor for hypoglycemia [1], whether advanced CKD is related with an increased risk of hypoglycemia has been a point of contention. In a study of veterans, the incidence of hypoglycemia, defined as blood glucose below 70mg/dl, was greater in individuals with more severe CKD. Hypoglycemia was prevalent in people with moderate to severe CKD, but not more so than in people with maintained GFR, according to a prospective observational study of people with T2D who used continuous glucose monitors.

The topic of whether insulin use and advanced CKD are both linked to an increased risk of hypoglycemia may have therapeutic implications for glycemic management in people with T2D and CKD, as hypoglycemic episodes are linked to an increased risk of CKD progression [2], stroke, and mortality. As a result, we tested the hypothesis that the need for insulin for glycemic control in T2D is lower in people with advanced CKD in the current study. We also looked at whether the risk of significant hypoglycemia episodes is higher in people with advanced CKD and heightened in people with advanced CKD who are on insulin. Within 180 days following the index date, prevalent insulin use was discovered through a review of the patient's prescription records. The first time a patient got a prescription for insulin after the index date was used to determine the incidence of new insulin use in those who were not on insulin at baseline [3]. Serious hypoglycemic occurrences were classified as those that necessitated medical attention, as shown by an emergency room visit with a hypoglycemia diagnosis and/or hospitalization with a primary discharge diagnosis of hypoglycemia codes. From the index date through the censor date, a previously validated criteria was utilized to detect hypoglycemia incidents from ICD 9/10 codes from emergency room visits or hospitalizations.

Chronic kidney disease (CKD) is an independent risk factor for hypoglycemia, and it increases the risk that patients with diabetes already have [4]. Furthermore, CKD limits ant diabetic treatment options and increases the risk of cardiovascular disease and death. This review is an update and enhancement of a recent paper we published on the issue, with a more in-depth look at the therapeutic alternatives and limits that care providers face in this prevalent clinical setting. Diabetes mellitus, hypoglycemia, chronic kidney disease, diabetic nephropathy, diabetic kidney disease, and chronic renal insufficiency were all searched for in PubMed and MEDLINE from January 1989 to January 2015 [5]. The presence of CKD adds to the risk factors for hypoglycemia that already exist in diabetic patients. Affected drug metabolism, drug-drug interactions (e.g., angiotensin-converting enzyme inhibitors), albuminuria, autonomic neuropathy, anorexia, malnutrition, infections, dialysis-related problems, associated cardiac and hepatic disease, and impaired renal glucose release are some of the additional factors. Both the liver (through glucagon) and the kidney (by catecholamine) contribute equally to the increase in glucose release into the circulation during hypoglycemia counter regulation in healthy people; this is mostly accomplished through gluconeogenesis [6]. Hypoglycemia and CKD are both linked to an increased risk of morbidity and mortality, especially from cardiovascular disease. Renal illness is linked to hypertension, hyperlipidemia, and diabetes, all of which are

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substantial cardiovascular risk factors. Hypoglycemia is currently being debated as to whether it is an extra risk factor or simply a sign of cardiovascular fragility. Hypoglycemia's effects on oxidative stress, endothelial dysfunction, ST-segment lengthening, and arrhythmia precipitation via sympathetic nervous system activation are among the theoretical, experimental, and clinical aspects that point to a causal effect [7].

We first ran a multivariable Cox regression analysis in the whole analytic cohort (N=855,133) with the same covariates as before to see if insulin use and eGFR categories were independently linked with major hypoglycemia incidents. We conducted the multivariable Cox regression model for serious hypoglycemia events in a propensity score matched population (N=305,570) to further eliminate the likelihood of indication bias between veterans not on and on insulin at baseline [8]. The propensity scores were calculated using the multivariable logistic regression model with baseline insulin as the dependent variable, as described above.

The study's primary findings were that insulin use was higher in people with more advanced CKD, and that insulin use and advanced CKD were both independent risk factors for significant hypoglycemia episodes. Furthermore, individuals who took insulin and had an eGFR of less than 30ml/min/1.73 m2 had a roughly 5.3-fold higher risk of major hypoglycemia episodes than those who had intact renal function and were not on insulin [9]. Because the kidney is responsible for the bulk of exogenous insulin clearance, patients with diabetes and CKD with poorer renal clearance rates have higher blood insulin levels and may require less insulin than those without CKD, according to previous research. In contrast to popular opinion, the findings of this study show that the demand for insulin for glycemic control is inversely related to renal function, with a graded increase in baseline insulin use and subsequent insulin use as CKD progresses. There are biological explanations for this discovered phenomenon. Insulin resistance is widespread in CKD, and it's thought to be linked to pro-inflammatory cytokines like interleukin-6 and tumor necrosis factor, as well as oxidative stress, which are implicated in intracellular insulin resistance processes. Second, pancreatic beta-islet cells have low antioxidant enzyme expression and are very vulnerable to oxidative stress as a result of their low antioxidant capacity. Experimental evidence suggests that beta cell dysfunction may develop in CKD due to increased oxidative stress caused by uremic toxins buildup [10].

Renal mass is reduced in people with moderate to severe CKD, resulting in a lower capacity for renal glucose release. Furthermore, these patients may be malnourished or have muscle wasting, which limits hepatic glycogen reserves and gluconeogenic substrate availability. Finally, acidosis limits the liver's ability to compensate through hepatorenal reciprocity (reciprocal changes in hepatic and renal glucose release to maintain normoglycemia). Third, in severe CKD, several anti-diabetic medicines are contraindicated [11]. As a result of decreased insulin production, peripheral insulin resistance, and contraindications to other drugs, exogenous insulin may be required for glycemic management in CKD. There could possibly be biological reasons for the links between advanced CKD and an increased risk of hypoglycemia. In healthy individuals, renal gluconeogenesis plays an important role in preventing hypoglycemia. People with moderate to severe CKD have less renal mass, which means they have a lower capability for releasing glucose from the kidneys, thereby increasing the risk of hypoglycemia. However, previous research on whether CKD is a risk factor for hypoglycemia has shown mixed results. Some earlier studies, but not all, found a link between the two. When GFR goes below 15mL/min/1.73 m2-20mL/min/1.73 m2, the renal clearance of insulin decreases. A decrease in hepatic insulin metabolism is also observed at this time, which is assumed to be owing to the effects of uremic toxins on the liver. Dialysis treatment for CKD lowers insulin resistance and enhances insulin breakdown, which leads to an improvement in hepatic insulin metabolism. Furthermore, glucose is the most often utilized osmotic agent in peritoneal dialysis, and glucose-containing dialysis solutions can cause alternating hyperglycemia and hypoglycemia in many patients unless their ant diabetes treatment and dialysis schedule are closely monitored [12].

We discovered that not only did patients with advanced CKD require more insulin, but that CKD and insulin use are both independent factors that add to the risk of a hypoglycemic incident, with the risk being highest in patients with advanced CKD on insulin. This study has clinical implications for glycemic control therapy choices in advanced CKD, as hypoglycemia has been linked to an increased risk of death, cardiovascular illness, cognitive impairment, and CKD progression. Hypoglycemic episodes were most common in insulin users in patients hospitalized due to an acute kidney injury, according to a previous study. Insulin's safety profile in advanced CKD should be compared to that of newer glycemic medicines such SGLT-2 inhibitors and GLP-1 analogues in randomized controlled trials to find the best glycemic control therapy for this population [13].

The observational character of the analyses, despite the use of propensity score matching, is a key drawback of the current investigation, as there may be residual confounding from unknown factors that were not included in the construction of propensity scores. While using data from electronic medical records to define hypoglycemia is a constraint, we used a previously validated definition. Even though we employed a large national database of veterans, major hypoglycemia incidents treated at non-VA medical facilities may have gone unnoticed. However, such underreporting will almost certainly bias the study in favor of the null hypothesis; therefore the current findings are likely conservative estimates of the relationships between insulin use and advanced CKD and the likelihood of hypoglycemia incidents. Finally, because the study participants were mostly men (97%), more research on hypoglycemia in both men and women is needed [14].

In conclusion, we discovered that, contrary to popular belief, severe CKD is associated with a lower demand for insulin, insulin consumption was higher in T2D patients with more advanced CKD. Furthermore, this study discovered that insulin use and CKD are both independent risk factors for hypoglycemia, with patients with severe CKD who use insulin having the highest risk [15]. In individuals with T2D and advanced CKD, future randomized controlled trials will be needed to assess the safety of insulin against newer glycemic treatments. Hypoglycemia is frequently the limiting factor in obtaining adequate glycemic control in diabetic patients, and it is linked to significant morbidity and mortality. Up to 40% of persons with diabetes have CKD, defined as a GFR of less than 60 mL/min/1.73 m2. It is an independent risk factor for hypoglycemia, raises the risk of cardiovascular disease and death in patients with diabetes, and augments the risk of hypoglycemia that is already

present. People with CKD may have other risk factors for hypoglycemia, such as altered medication metabolism, albuminuria, malnutrition, reduced renal glucose release and insulin clearance, and dialysis-related issues, in addition to inadequate hormonal counter regulation. The presence of CKD complicates the selection of effective anti-diabetic medicines for diabetic patients. Glipizide, meglitinides, DPP-4 inhibitors, thiazolidinedione, albiglutide, dulaglutide, orlistat, colesevelam, and insulin are some of the medicines that can be utilized in all types of CKD if used with caution or at a lower dose. Other drugs (metformin, glibenclamide (glyburide), glimepiride, gliclazide, exenatide, liraglutide, alpha glycosidase inhibitors, and SGLT2 inhibitors) are not recommended in people with moderate to severe CKD (eGFR 45 mL/min/1.73 m2-60 mL/min/1.73 m2) because their efficacy is reduced and/or the risk of hypoglycemia.

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