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Managing Diabetes and cardiovascular risk in chronic kidney disease patients

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Introduction

Cardiovascular disease (CVD) is a major clinical problem contributing to significant mortality worldwide, especially in populations with chronic kidney disease (CKD) and diabetes.[1,2] According to the United States Renal Data System (USRDS) and the adult National Health and Nutrition Examination Survey (NHANES), the prevalence of CVD in CKD patients is as high as 63% compared to only 5.8% for non-CKD patients, and is directly related to the severity of CKD.[3] Since CVD mortality rates are 10 to 30 times higher in patients on dialysis than in the general population,[4] patients with CKD are more likely to die of CVD than reach end-stage renal disease (ESRD).[5–7] USRDS 2016 data showed that 41% of deaths in dialysis patients are due to cardiovascular disease. A recent systematic review and meta-analysis of global CKD showed mean CKD prevalence of 13.4% for all 5 stages and 10.6% for stages 3 to 5.[8] According to the World Health Organization (WHO), diabetes had an estimated prevalence of 8.5% in 2014, and evidence suggests that CKD may be even more common.[9]

Diabetes mellitus is the leading cause of CKD in the US, with estimates suggesting that close to 50% of diabetes patients show evidence of CKD.[10,11] Diabetes is also often difficult to control in the CKD population; several antihyperglycemic agents are contraindicated in

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CKD patients, and the pharmacokinetics of others, including insulin, change with declining glomerular filtration rate (GFR).

In this review, we will discuss mechanisms of increased CVD in CKD patients and strategies for managing cardiovascular (CV) risk in CKD patients. Our focus is mainly on decreasing cardiovascular events (CVEs) and progression of microvascular complications by reducing levels of glucose and lipids. We recognize the importance of blood pressure (BP) control in the management of CKD and prevention of CVD events in this population, but a detailed discussion of blood pressure is beyond the scope of this review. We searched PubMed using the terms “mechanisms of increased CVD in CKD,” “CVD and CKD and hyperlipidemia,” “CKD and CVD and diabetes,” “dyslipidemia and CKD,” “ezetimibe and CKD,” “statins and CKD/ESRD,” “glycemic control and CKD,” “glycemic markers,” and “glycosylated albumin and fructosamine and CKD” with no limit on the date of the article. All articles were discussed among all authors. We chose pertinent articles, and searched their references in turn for additional relevant publications.

Mechanisms of increased CVD in CKD

The complex relationship between CKD and CVD involves a combination of cardiovascular risk factors, comprising “traditional factors” (e.g., advanced age, hypertension, diabetes mellitus, and dyslipidemia) and “nontraditional factors” specific to CKD (e.g., anemia, volume overload, mineral metabolism abnormalities, proteinuria, oxidative stress, and inflammation).[12]

An analysis of NHANES data from 2001–2010 encompassing (1) the prevalence of CV-related comorbidities and CV risk factors, (2) the utilization of lipid-lowering and BP-lowering agents, and (3) rates of LDL-C or BP goal attainment in US adults stratified by CKD stage[13] demonstrated that despite a reported increase in lipid and BP treatment, treatment remains sub-optimal. Greater efforts are required to improve CVD reduction in the CKD population.[13]

a) Left Ventricular dysfunction

The leading cardiac abnormality in patients with CKD and ESRD is left ventricular (LV) dysfunction.[12] One study showed that around 74% of ESRD patients starting dialysis suffer from LV hypertrophy, 32% show LV dilatation and another 14.8% have systolic dysfunction.[4] A report from the ADHERE database on outcomes in 118,465 patients hospitalized with acute decompensated heart failure showed that the majority have significant renal impairment (27.4% had mild renal dysfunction, 43.5% had moderate renal dysfunction, 13.1% had severe kidney dysfunction and 7.0% had kidney failure).[14] LV hypertrophy is an adaptive process of the LV in which an increase in cardiac work is induced by an increased afterload (pressure overload), an increased preload (volume overload), or both. Increased afterload may result from arterial hypertension and arterial stiffness, while increased preload may be caused by hypervolemia and anemia.[15]

b) Diabetes mellitus and glucose control

The impact of improved glycemic control in preventing CVD events in patients with diabetes and CKD is controversial. The value of glycemic control in preventing microvascular complications has not been definitively established in advanced CKD, as advanced CKD patients are often excluded from clinical trials.

In one meta-analysis of 7 randomized controlled trials (RCTs) of intensive glycemic control in type 2 diabetes mellitus (T2DM), intensive therapy led to a statistically significant reduction in micro- and macroalbuminuria; however, data regarding the effect of intensive glycemic control on clinical renal outcomes (doubling of serum creatinine, ESRD, or death from renal disease) were inconclusive.[16] The benefits of intensive glycemic therapy for individuals with diabetes and early stage CKD have been well established, but there is no consensus on whether intensive therapy slows the progression of established diabetic nephropathy (DN), particularly among individuals who have a reduced GFR.[17,18] In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, despite intensive control of glucose and other risk factors in patients, CKD progressed in a large number of participants and several biomarkers did not adequately identify or predict progression. Additionally, from a safety perspective, intensive glycemic control in advanced CKD may increase the risk of severe hypoglycemia. Nadkarni et al found that patients with T2DM who developed a sustained decrease in renal function also had elevated levels of urinary monocyte chemotactic protein-1/Cr ratio at baseline compared to those who had minimal or no decline in renal function.[19] This may be a useful urinary biomarker to predict renal failure in patients with T2DM.

c) Hypertension (HTN)

HTN and CKD have a unique relationship: Each is both a cause and a consequence of the other. Among NHANES (2009) participants with CKD Stages 4–5, 84% had hypertension, compared to just 23% of those without CKD.[3] Furthermore, 80% of NHANES participants with CKD Stages 3–4 had hypertension and only 20% of cases were adequately controlled. In 2010, in the Chronic Renal Insufficiency Cohort (CRIC) of over 3,600 patients with a broad spectrum of renal disease severity, 67% of patients reached their BP goal of <140/90mmHg and 46% reached their goal of <130/90mmHg,[20] compared to a 50% rate of HTN control for the general population from 2007 to 2008.[21] Even with many well-designed RCTs and observational studies, uncertainty and controversy remain amongst the guideline committees concerning the optimal blood pressure (BP) target required to halt CKD progression.

d) Dyslipidemia of CKD

There are several processes responsible for dyslipidemia of *CKD* including 1) impaired lipolysis, 2) impaired reverse cholesterol transport, and 3) low and altered HD, which are summarized in Table 2 and discussed in detail below.

e) Cardiovascular calcifications

In patients with CKD, accelerated calcifying atherosclerosis and valvular heart disease is a result of uremic cardiovascular disease. Cardiovascular calcifications in CKD are highly

prevalent as CKD progresses and are strong predictors of CV mortality in CKD patients. Vascular calcification manifests as both intimal plaque calcification and medial calcification.[22] Many data sources (including registry data, cross-sectional analyses, experimental and clinical data) have shown that increased calcium phosphate product (Ca × P), caused by hyperphosphatemia and/or hypercalcemia, may be a key determinant of cardiovascular mortality and progression factors of undesirable calcifications in uremia.[23–26]

The natural history of disease progression in CKD patients is being evaluated in the Chronic Renal Insufficiency Cohort (CRIC) study, a United States multicenter observational cohort study that recruited an ethnically and racially diverse patient population (more specifically, the study oversampled black Americans and individuals with diabetes).[27] The study's goals are to 1) examine risk factors for progression of CKD and cardiovascular disease, 2) develop models that identify high-risk subgroups, and 3) assist in the development of treatment trials and therapies. The CRIC study will likely be instrumental in revealing controlling factors that contribute to mortality and morbidity in CKD patients. In the meantime, we can improve our knowledge of currently known worsening factors, and most importantly, focus on prevention and screening for kidney disease in high-risk populations.

Is lipid lowering therapy beneficial in CKD?

The HMG-CoA reductase inhibitors (statins) have been shown to reduce CVEs by 20–25% in clinical trials. However, patients with moderate to severe CKD and dialysis patients were either limited in numbers or excluded in trials.[28] Hence, treating dyslipidemia with statins to reduce CV events in moderate to severe CKD and dialysis patients lacks a strong evidence basis. Patients with diabetes and CKD are at higher risk of developing CVD compared to either CKD alone or diabetes alone or general population.[29] Trials such as the Deutsche Diabetes Dialyse Studie (4D), and A Study to Evaluate Use of Rosuvastatin in subjects on Regular Hemodialysis (AURORA) question the efficacy of statins in moderate to severe CKD and dialysis patients.[30,31]

Several possibilities exist for the lack of benefit of statins in CKD (summarized in Table 1). First, CKD-related dyslipidemia is characterized by hypertriglyceridemia and normal cholesterol level.[32,33] Second, in addition to CKD dyslipidemia, hypercoagulability, autonomic dysfunction, electrolyte disturbance, LV hypertrophy, and chronic volume overload collectively increase the risk of cardiovascular deaths.[34,35] Third, uremic patients' coronary intima and media are distinct; coronary plaques are heavily calcified and infiltrated with active macrophages, making them more vulnerable to plaque destabilization than patients with normal renal function.[36] Fourth, increased inflammation, oxidative stress, protein energy malnutrition, sympathetic over activation, and endothelial dysfunction play critical roles in the development of vascular disease combination of which dilutes effects of statins as compared to presence of only traditional risk factors in the general population.[37,38] Fifth, chronic hyperglycemia impairs endothelial function and potentiates coronary vasoconstriction and thrombosis, ultimately decreasing myocardial blood flow, especially in diabetic CKD patients.[39] Finally, the optimal LDL-C goal in CKD is unknown and it is unclear whether we should target a lower LDL level in this population.

Dyslipidemia of CKD (summarized in Table 2)

There are several processes responsible for dyslipidemia of CKD: 1) Impaired lipolysis: Apo CIII levels are higher in patients with CKD with or without diabetes, which leads to impaired lipolysis by chylomicrons, and Very Low Density Lipoproteins (VLDL) leads to increased levels of Triglyceride(TG) and VLDL.[40] Apo B48 levels are elevated in diabetic and nondiabetic ESRD.[41] 2) Impaired reverse cholesterol transport: Plasma Lecithin-Cholesterol Acyltransferase (LCAT) activity is decreased in chronic uremia[42] and normalizes after renal transplant.[43] As a result, decreased LCAT activity, decreased esterification of cholesterol, and maturation of HDL ultimately decreases HDL 2 (mature HDL).[44] HDL 2 carries antioxidant enzymes, and decreased HDL 2 level leads to an increase in oxidized LDL level.[45] Hepatic lipase activities depend upon HDL 2, and decreased HDL 2 levels lead to accumulation of IDL. Inflammation in CKD patients also decreases ABCA1 expression[32], preventing efflux of cholesterol from lipid laden macrophages to cholesterol poor HDL.[46] Dialysis patients have high VLDL and IDL, high cholesterol/TG ratio, and low HDL and LDL.[47] 3) –CKD-HDL anti-atherogenic properties are affected through impaired reverse cholesterol transport. CKD-HDL causes uncoupling of nitric oxide synthase and impairs vascular relaxant properties.[48]

Clinical Trials of the statins in mild to severe CKD patients (Table 3)

Statins in patients with mild CKD

The Scandinavian Simvastatin Survival Study group (4S) trial was conducted to evaluate the effect of simvastatin in CVD for secondary prevention. In the 4S trial, subgroup analysis in patients with GFR <75 ml/min, simvastatin decreased relative risk (RR) of all-cause mortality by 31% and reduced nonfatal MI and coronary mortality by 35%. Though subgroup analysis failed to show improvement in all-cause mortality in CKD patients with GFR <60 ml/min, all-cause mortality rate doubled in the diabetic subgroup with GFR < 75 ml/min compared to the simvastatin group, and the trend was similar for reduction of major coronary events in the simvastatin group. Limitations of subgroup analysis in diabetic CKD patients include small sample size (95 patients) and post hoc analysis.[49]

In a subgroup analysis of three randomized control trials (WOSCPOS, CARE and LIPID), Tonelli et al studied the effects of pravastatin in patients with mild CKD. In 571 diabetic patients with CKD, pravastatin did not decrease all-cause mortality but decreased RR by 25% of composite outcome (Myocardial Infraction-MI, coronary death or revascularization procedure rate).[29] The Heart Protection Study (HPS) evaluated the effects of simvastatin on all-cause mortality and fatal and non-fatal vascular events in 20,000 United Kingdom patients. Subgroup analysis of 1,329 patients with mildly elevated creatinine (>1.24 mg/dl for women and >1.47 mg/dl but < 2.26 mg/dl for men) reduced major CVEs by 28% compared to placebo group, similar to other cohorts.[50]

Statins in advanced CKD and dialysis patients

In the 4D trial, 1255 hemodialysis (HD) patients with T2DM were randomized to atorvastatin 20 mg or placebo to evaluate possible CV reduction benefit in dialysis patients. Total reduction of LDL cholesterol reduction was similar to that seen in non-dialysis

patients. Atorvastatin did not significantly decrease mortality from cardiac causes or nonfatal MI, but suggested a downward trend in terms of cardiac death. There was an increased trend of death from cerebrovascular accident (CVA) (CI 0.81–1.55) and increased incidence of statistically significant fatal stroke (HR = 2.03 CI (1.05–3.93), P value 0.04). Lack of benefit of statins is possibly due to dyslipidemia of CKD, delayed treatment with statin, or low dose of statin, as 15 % patient in placebo group used statin and 25 % discontinued Atorvastatin in intervention arm.[30]

In the AURORA trial, 2,776 dialysis patients (731 patients with diabetes) were randomized to receive Rosuvastatin 10mg vs placebo. Results showed no benefit of statins on major CVEs and all-cause mortality. The results were similar to the 4D study except there was no increase in the incidence of fatal stroke. The study excluded patients who were previously on statins, so the question remains whether it would show beneficial effects if dialysis patients with previous statin therapy were included in the trial.[31]

The Study of Heart and Renal protection (SHARP) trial was a randomized trial of 9,027 patients with advanced CKD and dialysis with primary prevention of CVEs as primary outcome. Results showed that simvastatin 20 mg plus Ezetimibe 10 mg reduced major atherosclerotic events by 17% without an increase in side effects.[51] However, the study lacks adequate power to assess separate elements of major atherosclerotic events in CKD patients. Study participants had a diabetes incidence of 23%, and there was no evidence of the comparative RR on major atherosclerotic events between patients with or without diabetes with intervention.[51] Subgroup analysis among non-dialysis subjects showed relative risk reduction (RRR) of 22% for major atherosclerotic events. The subgroup analysis of 3,023 patients on dialysis showed no difference in incidence of major atherosclerotic events or all-cause mortality, despite receiving statin and ezetimibe. (Of note: 1/3 of non-dialysis patients were started on dialysis during the trial). These encouraging results in the non-dialysis subgroup strengthen the possibility of a beneficial effect of interaction in the dialysis group.[51]

Correction of hypertriglyceridemia and low HDL

Hypertriglyceridemia and low HDL are common in diabetes patients.[32,33,40,42] For T2DM related dyslipidemia, many physicians believe that fibrates are the logical first choice.[52] In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group (VA HIT), 2,531 patients with similar lipid abnormalities participated.[53] The overall trial showed that treatment with gemfibrozil 1200 mg daily resulted in a RRR of 24% in combined outcome of death from nonfatal MI, CHD or stroke, though there was no statically significant change in all-cause mortality. In a post hoc analysis of 297 patients with diabetes and eGFR <75 ml/min showed 42% RRR in major CVEs. However, the study did not have adequate power for subgroup analysis.[53]

The lipid arm of the ACCORD trial was performed to identify CV benefits of a combination of simvastatin and fenofibrate in 5,000 patients with T2DM, low HDL and high TG. Patients were randomized to receive simvastatin + fenofibrate vs simvastatin alone to assess CV benefits for both primary and secondary prevention. The study did not show a statistically

significant difference in CV outcome with simvastatin + fenofibrate, though a statistically nonsignificant downtrend was present after a median follow up of 4.3 years. There were 734 patients with GFR 30–50 ml/min requiring dose adjustment of fenofibrate, and 96 patients with GFR <30 ml/min requiring discontinuation of drugs. Subgroup analysis of 734 patients with CKD-3 did not have adequate power to show beneficial effects of the combination. Post hoc analysis showed a subgroup of patients with TG>204 mg/dl and HDL <34 mg/dl may have had decreased rate of CVEs with combination therapy.[54]

In another study, Fenofibrate Intervention and Event Lowering in Diabetes (FIELD), 9,795 patients with T2DM and dyslipidemia (5,218 patients with e GFR 60–89 ml/min and 519 patients with e GFR 30–59 ml/min[55]) were randomly assigned to fenofibrate or placebo group. Fenofibrate reduced RR of CVEs by 14% in patients with low HDL, by 23% in patients TG >204 mg/dl, and by 27% in patients with combined low HDL and high TG.[56] However, the study was performed in the background of usual care, and patients with moderate to severe CKD were excluded[52,56] In addition, fibrates increase creatinine and are cleared by the kidneys, so their use in severe CKD and dialysis patients is contraindicated.[57]

Will lowering LDL target be beneficial in high risk and extremely high risk patients with CKD?

Doubling the dose of a statin further reduces plasma LDL by only 6%, but adding another drug to enable combination therapy has a greater effect in lowering LDL.[58] Would lowering LDL target further in high risk or extremely high risk individuals be beneficial?[58] This hypothesis has been tested in several clinical trials including the Improve IT trial and the FOURIER study, and other trials are ongoing.

The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (Improve IT) tested the benefits of lowering LDL by randomizing 18,000 acute coronary syndrome patients (3,261 patients with e GFR 30–60 ml/min, 7,026 patients with e GFR 60–90 ml/min and 40% patients with diabetes) to determine whether the addition of ezetimibe to statin would provide additional benefits. Nonfatal MI and stroke, hospital admission requiring unstable angina or coronary revascularization showed RRR of 6.4 % (HR = 0.936 CI (0.887–0.988), P value = 0.016) in the intervention group, without increasing side effects except for a non-statistically significant increase in event of hemorrhagic stroke. The benefit was particularly pronounced in patients with diabetes (27% of study population) and patients age >75 years. However, the study excluded patients with severe CKD (GFR<30 ml/min) and dialysis patients at the time of randomization.[59] The Further Cardiovascular Outcomes Research with proprotein convertase subtilism/kexin type 9 (PCSK 9) Inhibition in Subjects with Elevated Risk (FOURIER) study was a randomized placebo controlled trial in 27,500 patients (36% patients with diabetes) on background statin therapy to evaluate the benefits of intensive LDL reduction with evolocumab. Evolocumab reduced LDL cholesterol by 59% - LDL <70, <40 and <25 mg/dl in 87%, 67% and 40% respectively. RR of primary endpoint (cardiovascular death, MI, stroke, hospitalization for unstable angina) was reduced by 15% in evolocumab group. 20% RRR in secondary end point (cardiovascular death, MI and

stroke). Results were consistent across major subgroups. Patients with GFR <20 ml/min were excluded from the study.[60]

In summary, at present, there is no evidence of nephrotoxicity of statins and the dose does not need to be modified until GFR is <30 ml/min, except with atorvastatin and fluvastatin.[57,61] Based on current evidence, early detection and treatment of CKD dyslipidemia is critical in order to decrease mortality from cardiovascular disease. Early treatment with statins may allow for long term statin benefit in mild to moderate CKD patients, but the benefits are less clear in patients with more advanced disease. Patients on statins who become dialysis dependent can continue statin therapy but may need some dose adjustments. Based on current evidence, dialysis dependent patients who are not on a statin should not be started on statins.[61,62] In patients with severe CKD and LDL above target, raising statin dose increases the risk of side effects.[61,62] Ezetimibe, which was also tested in the SHARP trial, can be used in combination with statins. Fibrates and PCSK 9 inhibitors should not be used in patients with GFR <30. Newer studies (TIMI and FOURIER) in high risk or extremely high risk patients indicate that intensive LDL lowering therapy reduced CVEs. However, severe CKD and dialysis patients were excluded, so further studies are needed to determine the role of intensive lipid lowering therapy on cardiovascular outcomes (CVOs) in those populations.

Diabetes, glycemia and chronic kidney disease (CKD)

The management of glycemia is challenging in patients with CKD due to inconclusive data on the value of intensive control, challenges with measurement metrics such as HbA1c, and changes to the pharmacokinetics and pharmacodynamics of various drugs. Some diabetes medications are contraindicated in advanced CKD. Further, hypoglycemia may be more severe in CKD patients. As a result, glycemic control is often poor in patients with CKD.

Benefits of glycemic control in patients with diabetes and CKD

The Diabetes Control and Complications Trial (DCCT) showed that maintaining A1C at <7% resulted in decreased microvascular complications, and the United Kingdom Prospective Diabetes Study group (UKPDS) confirmed this. However, both DCCT and UKPDS excluded participants with advanced kidney disease. In patients with CKD, not on dialysis, it is not clear whether good glycemic control delays progression of DN and CVEs.[63] The DCCT trial only included participants with early stage DN and found decreased microvascular complications.[64] In patients with T2DM, both albuminuria and eGFR have been found to be independent risk factors for CVD, renal disease and mortality.[64–66] Unfortunately, most large studies analyzing the benefits and risks of glycemic control did not include patients with advanced CKD. In a subgroup analysis of CKD in the ACCORD study, 3,636 patients met the criteria for CKD stage 1–3. These participants had an increase in all-cause mortality (HR 1.3, 95% CI =1.0–1.6) and increased CV mortality (HR 1.4, 95% CI= 1.05–1.90).[67] A large retrospective observational study of 23,296 people with T2DM and eGFR <60 mL/min/1.73 m2 found higher mortality with A1C both less than 6.5% and greater than 8%.[68] This study did not find more adverse events (AEs) in those with stage 4 CKD and A1C 7–9% when compared to A1C <7% in the same population. More studies are

needed to evaluate the risks and benefits of strict glycemic control in patients with CKD using additional biomarkers such as glycated albumin.

A1C as an indicator of glycemic control in CKD

Diabetes is the leading cause of CKD, and the incidence of diabetes continues to rise by 4.4% per year.[69] It is therefore crucial to have reliable glycemic markers in this patient population. A1C has been used in clinical practice since 1976[70] as a marker to assess glycemic control in patients with diabetes. American Diabetes Association (ADA) guidelines from 2017 recommend checking A1C every 3 months in patients with diabetes who have had a change in therapy or are not meeting glycemic goals. Different recommendations do not exist for patients with both diabetes and CKD. Decreased reliability of A1C in CKD may be due in part to the shorter life span of red blood cells (RBCs).[71] Decreased RBC life span includes uremia which causes increased breakdown. There may also be mechanical damage from the dialysis itself. The mechanical effect of HD is small and transient; it has not been noted to cause a decrease in hemoglobin concentrations.[72] Patients on peritoneal dialysis (PD) do not have the mechanical damage of HD but do have decreased RBC survival due to the uremic environment, although possibly to a lesser extent.[72] In uremia there is increased phosphatidylserine, resulting in increased degradation by erythrocytes.[73] Patients with CKD were noted to have impairment in phospholipid asymmetry; this did not seem to be affected by the presence or absence of dialysis.[73] In fact, uremia is the likely cause of altered phospholipid asymmetry, which can decrease the life span of RBCs.[74] Various studies have looked at the survival of RBCs in dialysis patients, but results vary widely; decrease of RBC life span ranges from 20%[72] to 70%.[75] There is conflicting data regarding whether improvement of the uremic state results in improved RBC survival.[76–78] In addition, some individuals may glycate hemoglobin faster than others, resulting in differences in A1C.[79] In ESRD patients, differences in acid base balance and hemoglobin concentration can also affect glycation of RBCs.[80]

Erythropoietin production is decreased in ESRD, and a significant proportion of patients with ESRD receive erythropoietin treatment for normocytic normochromic anemia.[71] Erythropoietin use results in increased production of young RBCs, which are reported to glycate at a slower rate than older cells.[81] Diabetes patients on dialysis receiving erythropoietin were found to have lower levels of A1C than patients who were not receiving erythropoietin.[71,82,83]

In a uremic environment there is increased production of carboxylate hemoglobin, which may be assayed incorrectly as A1C[84], resulting in overestimation of A1C levels. Uremia can also suppress bone marrow function.[85,86]

A1C is a result of non-enzymatic glycation of RBC; therefore, any condition that affects the half-life or metabolism of RBC can affect A1C values. Several studies have shown a positive correlation coefficient between serum plasma glucose (PG) levels and A1C in patients with stage 3 and 4 CKD,[87] ESRD on HD[71,85,88–92] and ESRD on PD.[93] In these studies, the correlation coefficient ranged from 0.5 to 0.8 and the strongest correlation coefficient was seen in a study conducted by Chen et al which analyzed the GA and PG in stage 3 and 4 CKD.[87] Poor correlation has been noted between stage 4 and 5 CKD and A1C; this may be

secondary to anemia, decreased RBC survival[71] and use of erythropoietin. Many studies have shown lower than estimated A1C in diabetic patients with ESRD compared to diabetic patients without CKD,[71,87,91,92] suggesting that in this patient population, A1C may underestimate glycemic control. The lower A1C value may also be due to a combination of anemia and erythropoietin injections.[82,94] Inaba et al showed that the regression slope between PG A1C was steeper in patients with diabetes who did not have CKD when compared to patients with diabetes and ESRD.

Glycated albumin as an indicator of glycemic control in CKD

Several studies have suggested that glycated albumin (glycosylated albumin) (GA) may be a superior indicator of glycemic control in CKD.[71,90,92] Albumin has a half-life of about 2 weeks and therefore is a marker of glycemic control over a shorter duration than A1C.[71,95] GA can be affected by many conditions which lower serum albumin such as nephrotic syndrome,[96] thyroid function,[97] chronic liver disease[98], blood loss and burns.[99] There may also be increased protein loss during dialysis.[100,101] In addition, GA is lower than expected in Cushing's syndrome,[102] and thyroid hormone levels were found to be inversely related to GA. GA has also been found to be lower in obese patients with diabetes compared to non-obese patients with diabetes,[99,103,51] likely due to the increased microinflammation in obese patients.[51] High serum albumin has been associated with less glycation, and low albumin levels are associated with increased glycation.[104] As CKD worsens the rate of proteinuria and albuminuria increases and the serum albumin levels decrease. Of note, no significant correlation has been found between GA and PG when serum albumin was < 3.5 g/dL.[51,97–99,105,106]

Comparison of A1C to glycated albumin

Some studies have shown that GA may be a better marker than A1C for glycemic control,[71,90,92] while others show that A1C correlated more closely with PG.[85] Chronic liver disease can affect both A1C and GA due to increased turnover of RBCs and decreased levels of serum albumin.[98] Likely due to increased RBC turnover, A1C values in chronic liver disease patients were lower than the estimated A1C based on PG values. and GA levels where increased when compared to PG.[98] Inaba et al found a significant and positive correlation between A1C and GA in patients with diabetes with both ESRD and diabetic patients without CKD.[71] Vos et al found a poor and non-significant correlation between A1C and PG in stage 4 and 5 CKD patients, whereas GA showed significant and positive (r=0.54) correlation in patients with and without CKD stage 4 and 5. Two observational studies have shown that in patients with diabetes on HD, GA but not A1C was a good predictor of all-cause mortality and CV mortality.[107,108] Harada et al found a positive correlation between PG and GA when eGFR was >30 mL/min/1.73 m2; they did not find a significant correlation if the eGFR was < 30 mL/min/1.73 m2.[105]

Fructosamine as an indicator of glycemic control in CKD

Fructosamine is composed of glycated serum proteins that have become stable ketoamines though non-enzymatic glycation. Albumin makes up about 90% of fructosamine.[95] The different proteins that make up fructosamine have different half-lives and react differently with glucose. In addition, serum urea and uric acid can influence fructosamine levels.[109]

Several studies have suggested that fructosamine should be corrected for serum albumin or protein levels.[110,111]

Self-blood glucose monitoring and continuous glucose monitoring in CKD

Regardless of which glycemic marker is chosen, self-monitoring blood glucose (SMBG) and/or continuous glucose monitoring (CGM) is essential in patients with end stage DN given the high degree of glycemic variability. Jin et al found lower blood glucose levels in patients with diabetes on dialysis days, with increased mean amplitude of glycemic excursions compared to non-dialysis days.[112] Hypoglycemia has also been noted on CGM without symptoms in patients with end stage diabetic nephropathy.[112] SMBG or CGM is essential in this patient population given the chance of asymptomatic hypoglycemia. In addition, studies suggest that glucose fluctuation is an independent risk factor for diabetes complications.[113]

Glycemic markers in summary

In summary, some recent studies have suggested that GA may be a better glycemic indicator in patients with diabetes with CKD.[71,90,92] It should be noted that a significant correlation has not been found between GA and PG when the serum albumin was <3.5 g/dL.[51,97–99,105,106] Several of these studies looked at a limited number of blood glucose values to determine the average blood glucose, but these values may be more dynamic in patients on dialysis. In addition, further studies directly comparing A1C, GA and serum albumin levels are warranted. In our review, when choosing a glycemic marker in patients with eGFR <30 mL/min/1.73 m2 who also have serum albumin ≥3.5 g/d, GA appears to be superior to A1C.

Treatment of diabetes in CKD

Diabetic kidney disease carries an increased risk of hypoglycemia. In a fasting state, an estimated 20–25% of glucose released into circulation originates from renal gluconeogenesis.[114,115] In addition, renal gluconeogenesis increases following a meal, which in turn may contribute to hepatic glycogen stores.[114,115] Renal impairment leads to decreased renal gluconeogenesis, and there is also decreased sympathetic response due to autonomic neuropathy.[116] Renal insulin clearance is decreased and uremic toxins decrease insulin metabolism in the liver.[117] Prevention of hypoglycemia is crucial in this patient population. Summarized in Table 4 are various antihyperglycemic treatment options with recommended dose adjustments for the CKD population.

Strategies to improve overall metabolic control

Owing to CKD association with high CV risk, morbidity and mortality, in addition to a lack of studies demonstrating methods to decrease CV risk as compared to populations without CKD, for many treatments we must resort to applying data results obtained from non-CKD population studies. To improve overall metabolic control, healthcare providers should pay close attention to what we commonly think of as the “traditional factors” (e.g., advanced age, hypertension, diabetes mellitus, and dyslipidemia) as well as the “nontraditional factors” specific to CKD (e.g., anemia, volume status, mineral metabolism abnormalities, and proteinuria).

As covered above, treatment of CKD-associated dyslipidemia is important in order to decrease mortality from cardiovascular disease. A majority of studies showed a positive effect of statins in mild to moderate CKD; however, risk and benefits should be closely evaluated and statin doses should be adjusted once the patient is dialysis dependent. Since diabetes is the leading cause of CKD, and as the incidence of diabetes continues to rise, more studies are needed to evaluate and identify a glycemic threshold to slow the progression of CKD. For now, due to lack of such data, goals similar to those for non-CKD patients are used to prevent microvascular complications, paying special attention to avoid hypoglycemia. Another difficult part of diabetes control in CKD is the lack of one ideal marker to assess and follow glycemic control. Again, most large studies analyzing the benefits and risks of glycemic control did not include patients with advanced CKD.

Exercise, smoking cessation, optimal protein intake, and treatment of anemia and deficiency of active vitamin D are other factors that should be monitored in CKD patients. In addition to specific data reviews on lipids and diabetes in this article, and BP control addressed in Farheen K Dojki and George L Bakris' article "Blood pressure control and cardiovascular and renal outcomes," in this issue, optimizing volume status, correcting anemia and ensuring the patient is on appropriate treatment to decrease proteinuria are essential. Pharmacologically, focusing on treatment that targets multiple risk factors with low risk for side effects is optimal for CKD patients. Evidence from clinical trials indicates that mild to moderate CKD is also much easier to treat, and we assume similar benefits to non-CKD patients with slight medication dose adjustment. Further studies are needed on severe CKD and dialysis patients to determine the effects of controlling traditional and nontraditional cardiovascular factors.

Conclusion

Diabetes is the leading cause of CKD, and the incidence of diabetes continues to rise. Treatment and control of CVD risk factors among people with CKD and diabetes remains poorly understood, mostly due to a lack of studies on CVD risk in CKD patients. Therefore, for many treatments, we resort to applying results obtained from non-CKD population studies to decrease CV risk in CKD patients. Due to a lack of studies including advanced CKD populations, combined with the lack of a reliable marker of glycemic control in patients with CKD and high risk of hypoglycemia, the benefits of good glycemic control on CV risk has not been clearly shown in advanced CKD patients. Conversely, most studies show that statins benefit mild to moderate CKD, although statin doses may need to be adjusted once the patient is dialysis dependent. Further research on screening, preventative methods, and the development of medications targeting these specific patients is necessary in order to improve CKD treatment and prevent cardiovascular mortality.

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Table 1

Possible Reasons for lack of benefit of statins in CKD

1	CKD dyslipidemia is different compared to simple elevation of cholesterol.[32,33]
2	Many cardiovascular deaths in dialysis patients may be due to a combination of chronic volume overload-induced cardiomyopathy or electrolyte disturbance.[34,35]
3	Coronary plaques are prone to destabilization in uremic patients[36]
4	Increased inflammation, oxidative stress and pro-atherogenic factors in CKD attenuate effect of statins.[37,38]
5	Chronic hyperglycemia reduces vasodilation and myocardial blood flow in diabetic CKD patients[39]

Table 2

Dyslipidemia related to CKD

1) Impaired lipolysis	Plasma Apo CIII is higher in patients with CKD with or without diabetes and leads to impaired lipolysis.[40]
	Apo B48 levels are elevated in diabetic and nondiabetic ESRD.[41]
2) Impaired reverse cholesterol transport	Plasma LCAT activity is decreased in chronic uremia,[42] so lower LCAT activity decreases mature HDL production.[44]
	Increased plasma oxidized LDL and IDL result from a decrease in mature HDL.[45]
	Inflammation decreases ABCA1 expression[32] and prevents reverse cholesterol transport.[46]
3) Low and Altered HDL	CKD-HDL impairs vascular relaxant properties[20]

Table 3

Summary of clinical trials of lipid lowering therapy in mild to severe CKD patients

Trials and Total number of patients	Intervention	Number of patients with mild to moderate CKD	Number of patients with severe CKD and Dialysis	Primary Result
4S 4,420	Simvastatin vs Placebo	2,314 patients with GFR<75 Average GFR 65 in these patients with CKD	Excluded	RRR of all-cause mortality decreased by 31%, nonfatal MI and coronary mortality by 35%
4D 1,250	Atorvastatin 20 mg Vs Placebo	N/A	1,255 Dialysis patients	No difference in mortality form cardiac causes, nonfatal MI
AURORA 2,776	Rosuvastatin 10 mg vs placebo	N/A	2,776 Dialysis Patients	No difference on major CV events and all-cause mortality
SHARP 9,027	Simvastatin 20 mg + Ezetimibe 10 mg Vs Simvastatin 20 mg	88 Patients with GFR > 60 ml/min 2,155 patients with GFR 30–60 ml/min	2,526 patients with GFR 15–30 ml/min 3,623 Dialysis patients	Decreased major atherosclerotic events by 17%, but not in those on dialysis.
VA HIT 2,531	Gemfibrozil 1200 mg q24h	297 Patients with GFR <75 ml/min	Excluded	RRR of 24% of combined outcome of death from nonfatal MI, CHD or stroke
ACCORD (Lipid arm) 5,000	Simvastatin + Fenofibrate Vs Simvastatin alone	734 Patients with GFR 30–50 ml/min	Excluded	No difference in CVS outcome
FIELD 9,795	Fenofibrate Vs Placebo	5,218 patients with GFR 60–89 ml/min 519 patients with GFR 30–50 ml/min	Excluded	Decrease of CVD events by 14% in patients with low HDL, by 23% in patients TG >204 mg/dl and 27% in patients with both
Improve IT 18,000	Simvastatin 40 mg + Ezetimibe 10 mg Vs Simvastatin 40 mg + Placebo	3,261 patients with GFR 30–60 ml/min 7,026 patients with GFR 60–90 ml/min	Excluded	RRR of 6.4% in nonfatal MI and stroke, hospital admission requiring unstable angina or coronary revascularization

Abbreviations:

4S = “The Scandinavian Simvastatin Survival Study,” 4D = the “Deutsche Diabetes Dialyse Studie,” AURORA = “A Study to Evaluate Use of Rosuvastatin in subjects on Regular Hemodialysis,” SHARP = “The Study of Heart and Renal protection,” VA HIT = “Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group,” ACCORD = “Action to Control Cardiovascular Risk in Diabetes,” FIELD = “Fenofibrate Intervention and Event Lowering in Diabetes,” IMPROVE IT = “Improved Reduction of Outcomes: Vytorin Efficacy International Trial,” RRR = relative risk reduction; CV = cardiovascular; NSS = no statistical significance

Table 4

Recommended dose adjustments in CKD for antihyperglycemic drugs

Drug Class/Drug	Recommended dose adjustments with Impaired GFR	Rationale
Insulin	Decrease dose	Prolonged half-life due to decreased renal metabolism of exogenous insulin
Biguanides:		
Metformin	eGFR >45: Dose adjustment not required eGFR 30–45: Do not start treatment; if patient is already on it, monitor renal function changes carefully eGFR<30: do not use	Concern for lactic acid accumulation in kidney disease
Thiazolidinediones:		
Pioglitazone and Rosiglitazone	Dose adjustment not required, avoid use in advanced CKD	Causes fluid retention therefore avoid use in advanced CKD. Does not cause hypoglycemia, metabolized by the liver.
Sulfonylureas:		
Glyburide	Avoid Use	Accumulation of active metabolites can result in hypoglycemia
Glimepride	Start at 1 mg daily	Causes less hypoglycemia than glyburide
Glipizide	Dose adjustment not required	Metabolized by the liver to inactive metabolites
Meglitinides:		
Repaglinide	eGFR <30: start 0.5 mg with meals	Decreased renal clearance; increased risk of hypoglycemia[80] Lower dose recommended in CKD
Nateglinide	eGFR<30: start 60 mg with meals	
α-Glucosidase inhibitors:		
Acarbose and miglitol	Use with caution if eGFR < 30	Plasma levels can increase in CKD[118]
Dipeptidyl Peptidase-4 Inhibitors:		
Linagliptan	Dose adjustment not required	Mainly excreted by enterohepatic circulation
Sitagliptan	eGFR.> 50: 100 mg daily eGFR 30–50: 50 mg daily eGFR <30: 25 mg daily	Varying renal excretion ranging from 12% to 80% SGLT2 may have decreased function in renal impairment.
Saxagliptan	eGFR >50: 5 mg daily eGFR≤50: 2.5 mg daily	
Alogliptan	eGFR >60: 25 mg daily eGFR30-60: 12.5 mg daily eGFR <30: 6.25 mg daily	
Glucagon-Like Peptide 1 Receptor Agonists:		
Exenatide	eGFR<30: not recommended	Renally excreted, clearance decreased by 64% if eGFR is < 30[119] May be associated with acute kidney injury and worsening kidney function[120, 121]
Liraglutide	Dose adjustment not required as per manufacturer	Kidneys are not the main organ of elimination[122] More G.I. adverse effects may occur in CKD[123]
Lixisenatide	eGFR 30–59 dosage adjustment not required, close monitoring recommended eGFR 15–29, limited clinical experience, monitor kidney function eGFR< 15: avoid use	
Albiglutide	eGFR>15, dosage adjustment not required	
Dulaglutide	dose adjustment not required per manufacturer	
Amylinomimetic:		

Drug Class/Drug	Recommended dose adjustments with Impaired GFR	Rationale
Pramlintde	Avoid use in stage 4 CKD	Primarily metabolized and excreted by kidneys
Sodium Glucose Cotransporter 2 inhibitors:		
Canaglifozin	eGFR>60: No dose adjustements eGFR 45–59: 100 mg daily eGFR<45: Avoid use	
Dapaglifozin	eGFR <60: Avoid starting eGFR<30: Contraindicated	
Empaglifozin	eGFR≥45: Dose adjustment no required eGFR<30: Contraindicated	