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GLYCEMIC CONTROL AND BURNT-OUT Diabetes IN ESRD

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Abstract

Treatment of early diabetes mellitus, the most common cause of chronic kidney disease (CKD), may prevent or slow the progression of diabetic nephropathy and lower mortality and the incidence of cardiovascular disease in the general diabetic population and in patients with early stages of CKD. It is unclear whether glycemic control in patients with advanced CKD, including those with end-stage renal disease (ESRD) who undergo maintenance dialysis treatment is beneficial. Aside from the uncertain benefits of treatment in ESRD, hypoglycemic interventions in this population are also complicated by the complex changes in glucose homeostasis related to decreased kidney function and to dialytic therapies, occasionally leading to spontaneous resolution of hyperglycemia and normalization of hemoglobin A1c levels, a condition which might be termed "burnt-out diabetes". Further difficulties in ESRD are posed by the complicated pharmacokinetics of antidiabetic medications and the serious flaws in our available diagnostic tools used for monitoring long-term glycemic control. We review the physiology and pathophysiology of glucose homeostasis in advanced CKD and ESRD, the available antidiabetic medications and their specifics related to kidney function, and the diagnostic tools used to monitor the severity of hyperglycemia and the therapeutic effects of available treatments, along with their deficiencies in ESRD. We also review the concept of burnt-out diabetes and summarize the findings of studies that examined outcomes related to glycemic control in diabetic ESRD patients, and emphasize areas in need of further research.

Keywords

end stage renal disease; diabetes mellitus; mortality; glucose control; hemoglobin A1c

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INTRODUCTION

There are currently ~400,000 Americans with chronic kidney disease (*CKD) stage 5, a.k.a., end-stage renal disease* (ESRD), who are dependent on maintenance hemodialysis (MHD) (~92%) or continuous peritoneal dialysis (CPD) (~8%) for their survival.[1] According to US Renal Data System (USRDS) estimates, the number of ESRD patients will surpass one-half million during the 2010's.[2] These individuals experience a low quality of life, high hospitalization rates and a 20% to 25% annual mortality rate, in spite of recent advances in dialysis treatment and technique.[1] Approximately two-thirds of all dialysis patients die within 5 yrs of initiation of dialysis treatment, a 5-year survival worse than that expected in the majority of patients with cancer.[3] Almost half of all CPD and MHD patients presumably die of CV diseases.[1]

DM is the leading cause of CKD including ESRD in the US and most industrialized nations.[1;4] The proportion of incident diabetic dialysis patients in the US has increased from <30% in late 80's to 50% or higher in 2006.[1] Most studies indicate higher comorbidity and poorer outcomes in diabetic dialysis patients as compared to non-diabetic subjects,[5–7] but a large observational study of Medicare beneficiaries showed that while diabetic patients without CKD have significantly worse survival than their non-diabetic counterparts, among those with CKD the mortality is almost equally high in both diabetic and non-diabetic patients.[8]

While strict glucose control in patients with normal kidney function and early stages of diabetes mellitus can result in significant clinical benefits including improved cardiovascular mortality[9;10] and better renal outcomes,[11–16] similar interventions in patients with more advanced diabetes mellitus have produced disappointing results, including in some cases worse outcomes in patients who achieved strict glucose control.[17–19] As a result a more nuanced view of glycemic control may be emerging, with individual patient characteristics determining what therapeutic targets and treatment regimens to be pursued. The issue of long-term outcomes as a function of diabetes control is especially complicated in patients with ESRD in whom there are complex changes affecting glucose homeostasis, independent of the usual diabetic pathophysiology. It is currently unclear whether the altered glucose homeostasis in ESRD combined with medical management of DM has any significant bearing on clinical outcomes of the diabetic dialysis patients.[20] Indeed, some diabetic ESRD patients experience spontaneous improvement in their glycemic control that can occasionally amount to a return to normoglycemia. The occurrence of such "burnt-out" diabetes in ESRD [21] may necessitate the dissociation of the diagnosis of diabetes mellitus (which includes individuals with blood sugar levels ranging from normal to elevated) from that of hyperglycemia, which may occur in some diabetic patients, but could also be a de novo ESRD-related phenomenon.[22] We review the unique features of diabetes mellitus in ESRD, examine available data on the importance or lack thereof of glycemic control in achieving better survival in this patient population, and examine potential causes and consequences of burnt-out diabetes. We also briefly review ESRD-specific aspects of antidiabetic pharmaceuticals.

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GLYCEMIC CONTROL IN ESRD: THE CONCEPT OF BURNT-OUT DIABETES

While diabetes is one of the most important causes of CKD, the gradual decline in kidney function in itself causes significant changes that alter glucose homeostasis in patients with kidney disease.[23] Abnormal glycemic control has been described as a complication of advanced CKD [24] independent of underlying diabetic status, as even non-diabetic patients with CKD can display mild fasting hyperglycemia and abnormal glucose tolerance.[22] Interestingly enough though, in some patients with established diabetes mellitus a decline in insulin requirements and even spontaneous hypoglycemia can also occur with advancing stages of CKD.[22;25] A recent 2-year cohort study of 23,618 diabetic hemodialysis patients showed that 33% of them had A1c levels below 6%.[26] Even though in this cohort higher A1c values were incrementally associated with increased death risk after controlling for demographics and other confounders, low A1c, especially if below 5%, was also associated with poor survival. This nationally representative study shows that approximately one-third of all prevalent diabetic hemodialysis patients in the United States have a normal to low A1c level despite the ironic fact that they sustained ESRD as a result of diabetic nephropathy.[26]

The reason for these alterations in glucose homeostasis are multifactorial and involve various mechanisms related to both decreased kidney function and dialytic therapies (Table 1).[23] Once glomerular filtration rate declines below 15–20 ml/min, the renal clearance of insulin decreases significantly.[22] Concomitantly, hepatic clearance of insulin also declines, likely due to the inhibitory effect of unidentified uremic toxin(s), as the initiation of dialysis seems to mitigate this effect.[22] Counterbalancing diminished insulin clearance is lower insulin production and increased insulin resistance. The exact reason(s) for the diminished insulin secretion is unclear; it may be due to hyperparathyroidism and activated vitamin D deficiency, as insulin secretion appears to improve after the treatment of hyperparathyroidism and after administration of activated vitamin D.[27–31] Even though activated vitamin D can lower parathyroid hormone (PTH) levels, its effect on insulin secretion is believed to be independent of the PTH lowering effect,[31] and may be one of the explanations for the improved outcomes associated with these medications.[32;33]

The mechanism of increased insulin resistance in ESRD is also not fully clarified. It may be related to another unspecified uremic toxin possibly acting on the muscle tissue, [34;35] as insulin sensitivity is improved with dialysis.[36–40] The consequences of insulin resistance and deficiency in ESRD are complex and reach beyond glucose homeostasis, as they are associated with muscle protein breakdown through the ubiquitin-proteasome pathway[41;42] via suppression of phosphatidylinositol-3 kinase,[43;44] thus contributing to a state of protein-energy wasting which and may also play a major role in the higher mortality seen in this population. Decreased kidney function is also associated with deficient renal gluconeogenesis,[45] which along with malnutrition, deficient catecholamine release and impaired renal insulin degradation and clearance can contribute to a lower threshold for clinical hypoglycemia.[25]

Aside from the salutary effects of dialytic therapies on insulin production and sensitivity, [36–39] these treatments can complicate the management of diabetes by the glucose load provided by both hemo- and peritoneal dialysis. The latter especially can result in

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significantly higher glucose loads if higher dialysate concentrations are required to achieve ultrafiltration goals. The impact of the often significant glucose load delivered by peritoneal dialysis (which can be as much as 10–30% of total energy intake[46]) is complex. In spite of the added nutritional value of glucose the total nutrient intake of these patients is often below ideal,[47] possibly because of a loss of appetite related to continuous glucose absorption[48–50] and the mechanical effects of large filling volumes (in the case of PD).[51] Glucose absorbed during dialysis could at the same time lower patients' energy expenditure,[52] limit amino acid losses and stimulate insulin secretion.[53]

The practical significance of the listed changes in glucose homeostasis in ESRD remains unclear. While changes inducing worsening hyperglycemia would result in heightened efforts to better control the blood sugar of such patients, it is less clear what approach should be taken in the considerable number of dialysis patients whose A1c decreases to levels approaching normalcy.[26] It is not entirely clear what distinguishes such patients with normoglycemic or "burnt-out" diabetes from their counterparts who continue to display hyperglycemia, and studying them may offer further insights into the natural course of diabetes not only in dialysis patients, but also in other populations such as those suffering from chronic illnesses [54] or in the elderly, who may experience an altered course of this disease. While in today's benchmark-driven environment a lower A1c may be perceived as advantageous, we believe that patients with burnt-out diabetes may on the contrary be at higher risk for poor outcomes including mortality. The advantages of a normal blood sugar level likely take a very long time to become manifest,[55;56] and on the short run these patients may in fact be more prone to develop clinically relevant hypoglycemic episodes. Observational studies in dialysis patients indeed suggest that patients with the lowest A1c levels suffer significantly higher mortality rates,[26] thus emphasizing the need to relate to burnt-out diabetes as a complication of a disease (ESRD) rather than as a benefit of it.

DIAGNOSTIC TESTS OF GLYCEMIC CONTROL IN ESRD

There have been ongoing questions on what is the most reliable marker of long-term glycemic control in these patients. HbA1c has long been the assay of choice for determining long-term glycemic control among diabetic dialysis patients.

Glycated hemoglobin refers to a series of minor hemoglobin components formed by the adduction of various carbohydrate molecules to hemoglobin. The minor fractions include HbA1a, HbA1b, and HbA1c.[57] HbA1c is the largest fraction formed and the most consistent index of the prevailing ambient concentration of circulating glucose.[58] Glycation rate is determined by temperature, pH, hemoglobin concentration, glucose concentration, and length of exposure to glucose. There are various glycated hemoglobin assays available with normal ranges that vary between laboratories so that test results may not be directly comparable.

HbA1c measurements can be confounded in the uremic milieu, by formation of carbamylated hemoglobin[59] or by metabolic acidosis which increase the rate of HbAlc formation,[60] but the practical significance of these have been questioned.[61;62] Other factors that could affect HbAlc levels in patients on dialysis include a shortened erythrocyte

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life span, blood transfusion, and accelerated erythropoesis due to routine use of erythropoietin. However, the life span of erythrocyte is close to normal in well dialyzed patients treated with ertythropoesis stimulating agents and routine blood transfusions are rarely needed nowadays. HbA1c was found to underestimate glucose measurements in diabetic patients on hemodialysis due to anemia and use of erythropoietin compared to glycated albumin,[63–66] and there have been recent suggestions to use a correction factor based on the degree of anemia and the dosage of erythropoietin.[64] Aside from all the above limitations, HbAlc is still considered to be a reasonable index of glycemic control even in patients with ESRD.[67–70]

The uses of other marker of long-term glycemic control that are devoid of HbAlc's drawbacks in dialysis patients have been proposed. Fructosamine is formed by the non-enzymatic reaction between fructose and ammonia or an amine and can form when the carbonyl group of glucose reacts with an amino group of a protein. Therefore, fructosamine is a general measure of glycated serum proteins, 90% of which is represented by glycated albumin.[71] Fructosamine level correlates well with measurements of mean blood glucose and HbAlc,[72] it has therefore been suggested as an alternative method for monitoring glycemic control in diabetes patients. Fructosamine level reflects integrated glycemia during a period of 2 to 3 weeks compared to 2- 3 months for HbAlc.[73] Thus, fructosamine may be a better choice in situations when HbA1c cannot be reliably measured. As with HbAlc, fructosamine level may be less reliable in renal failure,[68;74] and may not be superior to HbA1c in diabetic patients with ESRD.[68;70] High urate levels often seen in patients with CKD may interfere with the fructosamine assay and levels may be falsely low in the setting of decreased protein levels such as nephrotic syndrome or liver disease, and also affected by increased protein turn over related to dialysis.[20] Use of this marker is further hampered by its lack of availability in routine practice and the lack of established reference levels.

Glycated albumin and the percentage of glycated albumin have also received much attention lately as a potentially more accurate measure of glycemic control in diabetic hemodialysis patients. Glycated albumin was a more accurate measure of glycemic control in two recent studies.[63;65] Both of these studies showed that HbAlc underestimated blood glucose levels in diabetic hemodialysis patients mainly because of erythropoietin use and anemia. In addition to being a significant marker of hyperglycemia in diabetic patients on hemodialysis, higher glycated albumin is also associated with diabetic complications such as increased arterial stiffness,[75] peripheral vascular calcification,[76] and increased cardiovascular morbidity and shortened survival in diabetic patients with ESRD.[77;78] It is unclear, however, what therapeutic target level of glycated albumin should be used for glycemic control, and in what stages of CKD its application should replace or supplement HbAlc. Glycated albumin has limitations in diabetic patients on peritoneal dialysis due to increased albumin turnover, and in non-oliguric patients with significant proteinuria.

ANTIDIABETIC DRUGS IN ESRD

The complex pathophysiology of glucose and insulin homeostasis and the imperfect diagnostic and monitoring tools available in patient with ESRD make therapy aimed at glycemic control in these patients challenging. Therapeutic interventions are made even

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more complicated by concomitant comorbidities such as sepsis, malnutrition, liver disease and congestive heart failure that could exacerbate hypoglycemia,[25] and also by the pharmacokinetic alterations caused by the decrease (or lack) of kidney function. The medications used to treat DM can be affected to various extents in CKD and ESRD (Table 2).

Insulin therapy

Insulin requirements usually diminish as kidney function declines, but no uniform recipe can be provided for dose adjustment, which has to be individualized. Patients receiving PD are in a unique situation as they can receive insulin by injection into their dialysate. One advantage of this approach is that intraperitoneal delivery of insulin provides a more reliable and more physiologic delivery of insulin compared to the subcutaneous route. Direct insulin delivery to the liver stimulates endogenous insulin secretion and inhibits hepatic gluconeogenesis and ketogenesis compared to the subcutaneous route,[79] and has been reported to result in better insulin sensitivity.[37] Peritoneal insulin delivery can result in fewer hyper- and hypoglycemic episodes and results in smaller diurnal variation in blood glucose levels.[80;81] Potential disadvantages of intraperitoneal insulin delivery include the possibility of an increased incidence of peritonitis,[82] lowered plasma HDL levels [83] and rare reports of subcapsular hepatic steatonecrosis[84] and malignant omentum syndrome.[85] Controlled clinical trials would be needed to fully describe the net impact of intraperitoneal insulin administration in PD.

Oral (and other) antidiabetics

The number of non-insulin type antidiabetic medications (which are not exclusively oral any more, see Table 2) has proliferated in the past decade. These medications depend on renal excretion to various extents; hence they may or may not require adjustments with advancing stages of CKD. Biguanides (metformin) represent a special category in that they should be withheld in patients with an even modest decline of kidney function (the exact degree of which remains ill-defined), due to the rare but potentially fatal lactic acidosis caused by the accumulation of this drug.[86] The other hypoglycemic agents may or may not require dose adjustments, as shown in Table 2. Unfortunately, there is no uniformity in how kidney function is quantified in the individual medications' dosing recommendations. As a general rule the use of non-insulin antidiabetic medications in ESRD requires a familiarity with the individual medications' pharmacokinetics and careful monitoring of the therapeutic effects of such medications.

DIABETES IN ESRD: TO TREAT OR NOT TO TREAT?

The beneficial impact of glycemic control in patients with normal GFR and/or early stages of CKD appears to be settled, as glucose control has been found to lower the incidence of new onset microalbuminuria in both retrospective [87;88] and prospective studies [11;12] of type I and type II DM. Worsening of established diabetic nephropathy (defined both as worsening of albuminuria [11;12;89;90] and as a progressive decline in GFR [13–16]) can also be retarded through strict glycemic control. It is not clear what the benefit of blood glucose control is on progression in patients with DN who have advanced (stage 3 and

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beyond) CKD, and in patients who have reached ESRD worsening kidney function represents a much less acute (albeit not negligible) concern. In the latter group glycemic control would be of primary interest as a means to lower future micro- and macrovascular complications, and ultimately to beneficially affect mortality.

Mortality and morbidity

Several studies have examined the effect of glycemic control on morbidity and mortality in patients with normal kidney function and with early stages of CKD. The impact of blood glucose control on mortality in patients with type I DM, normal serum creatinine and variable degrees of albuminuria was examined in a study of 939 adults with type I DM followed over 10 years.[91] This study found that a higher HbA1c concentration was associated with higher all-cause mortality.[91] The incidence of cardiovascular disease in patients with type I DM and early diabetic nephropathy was studied in the DCCT/EDIC study, where intensive insulin therapy lowered progression of carotid intima-media thickness [92] and improved cardiovascular survival.[9] In the UKPDS study strict glycemic control resulted in a trend towards lower cardiovascular events in patients with type 2 diabetes.[12] The Steno-2 study examined multiple risk factor modification in non-CKD patients with type 2 diabetes (including treatment of hyperglycemia) and showed a 50% reduction in cardiovascular events.[93]

The effect of blood glucose control on outcomes in patients with ESRD is less well-studied, with the limited number of published studies showing somewhat inconsistent results (Table 3).[94–100] Except for one non-randomized trial [96] these studies are all observational, and all but two of them have small sample sizes. In one of the two available large observational studies Williams et al [98] found no statistical association between HbA1c and survival at 12 months in 24,875 US diabetic dialysis patients. The lack of survival association in this study could have been due to the short duration of follow-up or other methodological limitations including the use of non-time dependent (fixed covariate) survival models and residual confounding from unmeasured surrogates of malnutrition, inflammation and anemia. This was substantiated by a subsequent study by Kalantar-Zadeh et al,[26] which examined 23,618 diabetic patients receiving maintenance hemodialysis, and it too found a paradoxically lower unadjusted mortality associated with higher HbA1c levels. However, after adjusting for a variety of confounders, most importantly for markers of malnutrition and inflammation, higher HbA1c levels became associated with higher mortality (Figure 1).[26] The results of this study indicate that in diabetic dialysis patients competing risk factors related to nutrition and mortality may confound the association between glycemic control and survival. The time varying malnutrition-inflammation-cachexia syndrome (MICS) and anemia can lead to apparently low levels of HbA1c and to concurrent poor survival, but such an association would not indicate a cause-effect relationship, since lower HbA1c levels would merely be surrogate markers of a state of more severe illness. These pitfalls can be overcome by more sophisticated analytical methods in observational studies, or by randomized controlled trials. Unfortunately, only a single interventional study examined clinical outcomes in 83 dialysis patients undergoing intensive diabetes-related intervention compared to standard care.[96] Patients in the intensive intervention arm had better glycemic

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control and experienced improved quality of life and a reduction in the need for amputations and hospitalizations.[96]

It is also unclear what the ideal target level should be for glycemic control in ESRD patients. Aside from the above mentioned pitfalls of imperfect diagnostic tests, complex pharmacology and complicated glucose homeostasis, recent studies in patients with normal kidney function but advanced diabetes mellitus indicated that attempts to improve blood glucose control towards levels resembling normoglycemia can become deleterious,[17–19] possibly because of consequences of hypoglycemic events. In our opinion the concerns raised by these studies would only be magnified in diabetic ESRD patients, as most of them would have suffered from advanced diabetes mellitus and cardiovascular disease, and the potential for clinically relevant hypoglycemic episodes would be much larger (vide supra). Larger clinical trials are thus indispensable to conclusively test the concept that better glycemic control is beneficial in patients with ESRD, and most importantly to establish what an ideal blood glucose level should be in these patients. For the time being, hyperglycemic patients with ESRD are usually treated in clinical practice based on guidelines established for patients with normal kidney function. While this is probably better than not treating them at all (the authors' personal opinion), significantly more effort needs to be devoted to assure that undesirable complications of overenthusiastic therapy are avoided.

CONCLUSIONS

Diabetes mellitus represents an important comorbidity in the CKD population and especially in ESRD patients who are dialysis dependent, and is associated with adverse outcomes such as cardiovascular disease and peripheral vascular disease. Strangely, in up to one-third of dialysis patients the hyperglycemia that caused their micro- and macrovascular disease appears to be alleviated and often "cured" by complex pathophysiologic mechanisms, leading to a phenomenon of normoglycemic or "burnt-out diabetes". While sounding provocative, studying the causes and consequences of this phenomenon may lead to better understanding of the pathophysiology of metabolic syndrome and DM in not only the CKD population but in many other conditions with chronic disease states, such as chronic heart failure,[54] that are associated with wasting syndrome and that may confound the natural course of DM. If for instance these CKD patients with burnt-out diabetes have distinguished genotype or phenotypes, such genetic or acquired distinction may help modulate the glycemic control and treat or prevent DM more effectively. Nevertheless, it is important to appreciate that even if diabetes may be burnt out in up to one-third of diabetic patients, the remainder continue to struggle with poor glycemic control and consequences of hyperglycemia. The benefit of better glycemic control in dialysis patients remains however unproven and further testing of this hypothesis in clinical trials will be very important, as the application of guidelines meant for the general population may not be possible and could indeed prove deleterious. This is especially relevant in light of the high short-term mortality seen in dialysis patients, most of whom do not have the long life expectancy needed to experience the benefits of tight glucose control, but who are in fact more likely to suffer from the hypoglycemic events brought about by ill-advised and overzealous attempts to satisfy incorrect or unfounded benchmarks. The unique pathophysiology of glucose homeostasis, the imperfect nature of our diagnostic tools measuring long-term glycemic

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control and the complex pharmacokinetics of antidiabetic medications in ESRD should prompt efforts to develop approaches that specifically address the needs of this vulnerable population.

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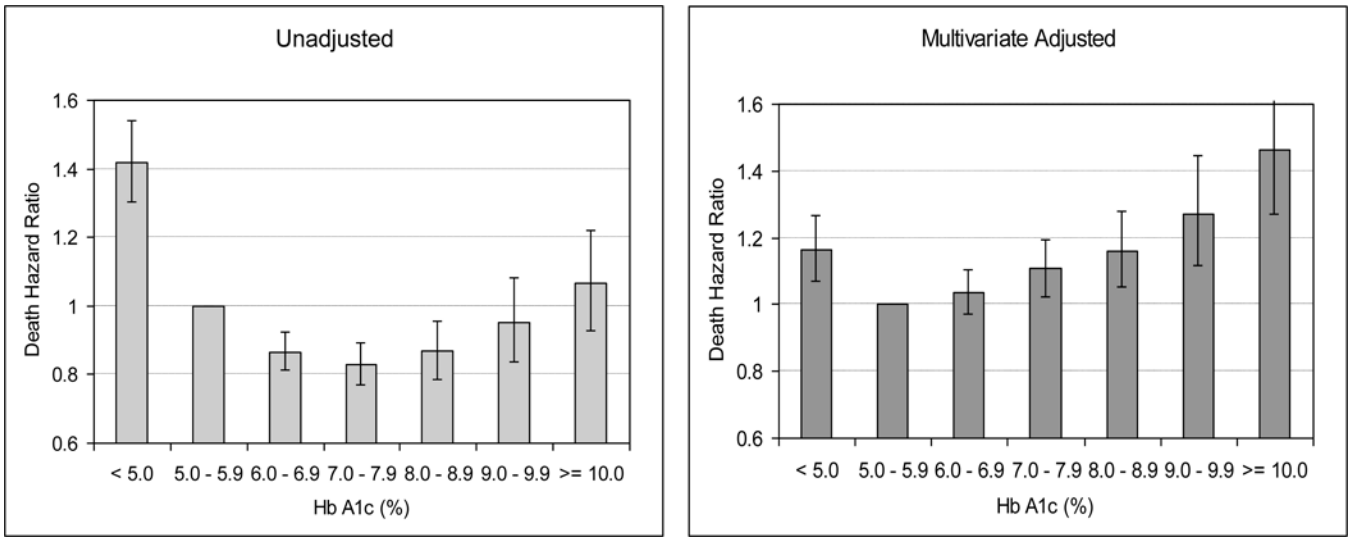

Figure 1.

Unadjusted and multivariable adjusted hazard ratios of all cause mortality associated with various levels of hemoglobin A1c levels in 23,618 diabetic patients on maintenance hemodialysis. The group with hemoglobin A1c level of 5–5.9% served as referent. Adapted from [26].

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Table 1

Possible causes of the "burnt-out diabetes" in maintenance dialysis patients (adapted from [21]).

1.	Decreased renal clearance of insulin
2.	Decreased hepatic clearance of insulin
3.	Impaired renal insulin degradation
4.	Increased insulin half-life *
5.	Decline in renal gluconeogenesis
6.	Deficient catecholamine release
7.	Other impacts of uremia on glucose homeostasis
8.	Diminished food intake due to anorexia, diabetic gastroparesis, etc.
9.	Protein-energy wasting (malnutrition-inflammation complex)
10.	Loss of body weight and fat mass
11.	Comorbid conditions
12.	Hypoglycemia during hemodialysis treatments
13.	Effects of peritoneal dialysis on glucose metabolism
14.	Prescribed medications
15.	Imposed dietary restrictions
16.	Apparently low A1c due to confounding by uremia or anemia

*Due to conditions other than those under 1 through 3

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Table 2

Available antidiabetic medications and their CKD-specific adjustments.

Class	Mechanism of action	Medication	Dose	Adjustment/Restriction in CKD
Insulin	Replaces/supplements endogenous insulin	Various formulations and brands.	Individualized	Half life may be prolonged and dose reduction may be necessary.
Biguanide	Decreases hepatic glucose production and intestinal glucose absorption, increases insulin sensitivity, possibly through activation of AMP-activated protein kinase.	Metformin HCl (Fortamet®, Glucophage®, Glucophage XR®, Glumetza®, Riomet®)	Varies with different brands.	Contraindicated with renal impairment, due to potential severe lactic acidosis.*
Thiazolidinediones	Increased insulin sensitivity through PPAR-gamma activation.	Pioglitazone HCl (Actos®)	15–30 mg qd	No adjustment; dosing in RRT not defined.
		Rosiglitazone Maleate (Avandia®)	4–8 mg/day	No adjustment; HD/CAPD: no supplement.
Sulfanylureas	Insulin secretagogues, through binding to (and thus closure of) the K_{ATP} channel in the pancreatic beta cells.	Tolazamide (generic)	100–250 mg qd	No adjustment; dosing in RRT not defined.
		Tolbutamide (generic)	250–3000 mg qd	No adjustment; HD/CAPD: no supplement.
		Chlorpropamide (Diabinese®)	100–500 mg qd	CrCl >50: decrease dose 50%; CrCl<50: avoid use.
		Glimepiride (Amaryl®)	1–4 mg qd	Renal impairment: start 1 mg daily, increase slowly and monitor glucose.*
		Glipizide (Glucotrol®, Glucotrol XL®)	2.5–20 mg qd-bid (Glucotrol®); 5–10 mg qd (Glucotrol XL®)	CrCl<50: decrease dose 50%; dosing in RRT not defined.
		Glyburide (Diabeta®, Micronase®, Glynase®)	1.25–20 mg qd	CrCl<50: avoid use.
Meglitinides	Non-sulfonylurea insulin secretagogues, through binding to (and thus closure of) the K_{ATP} channel in the pancreatic beta cells.	Repaglinide (Prandin®)	0.5–4 mg before meals, max 16 mg/day	CrCl 20–40: start 0.5 mg before each meal, titrate with caution; CrCl<20: not defined.
		Nateglinide (Starlix®)	60–120 mg tid before meals	No adjustment; dosing in RRT not defined.
Alfa glucosidase inhibitors	Block enzymatic degradation of complex carbohydrates in the gut, through inhibitin of pancreatic alfa-amylase and membrane-bound intestinal alfa-glucosidase hydrolase enzymes.	Miglitol (Glyset®)	50–100 mg tid	Cr>2 mg/dl: avoid use.
		Acarbose (Precose®)	50–100 mg tid	Cr>2 mg/dl: avoid use.
DPP-4 inhibitor	Increase in insulin synthesis/release and decrease in glucagon synthesis, through slowing of incretin metabolism	Sitagliptin Phosphate (Januvia®)	100 mg qd	CrCl 30–50: 50 mg qd; CrCl <30: 25 mg qd; HD/CAPD: no supplement.
Incretin mimetic	Stimulation of insulin secretion in a glucose-specific manner, inhibition of gastric emptying, suppression of glucagon secretion, and central anorexic activity.	Exenatide (Byetta®)	5–10 mcg bid**	CrCl 30–80: no adjustment; CrCl<30: not recommended.

*Degree of renal impairment remains undefined.

**Subcutaneous injection.

PPAR: peroxisome proliferator-activated receptor.

RRT: renal replacement therapy.

DPP: dipeptydil peptidase

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Table 3

Studies on association of glycemic control with survival in diabetic dialysis patients.

Authors and year of publication	Type of the study	Number and type of patients	Results
Tzamaloukas et al.[100] 1993	Observational	226, chronic dialysis	Decrease in mortality with good diabetic control.
Tzamaloukas et al.[99] 1993	Observational	110, CAPD	Decrease in mortality with good diabetic control.
Wu et al.[94] 1997	Observational	137, hemodialysis	Decrease in mortality with good diabetic control.
Morioka et al.[95] 2001	Observational	150, incident hemodialysis	Decrease in mortality with lower HgbA1c.
McMurray et al.[96] 2002	Non-randomized trial	83, hemodialysis	No survival benefit from lower HgbA1c, but better quality of life.
Oomichi et al.[97] 2006	Observational	114, hemodialysis	Decrease in mortality with lower HgbA1c.
Williams et al.[98] 2006	Observational	24,875, hemodialysis	No difference in survival across A1c increments.
Kalantar-Zadeh et al.[26] 2007	Observational	26,187, hemodialysis	Decrease in mortality with lower HgbA1c.