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Burnt-Out Diabetes: The Impact of CKD Progression on the Natural Course of Diabetes Mellitus

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Abstract

Many individuals with diabetic nephropathy, the leading cause of chronic kidney disease (CKD) in the United States, progress to stage 5 of CKD and undergo maintenance dialysis treatment. Recent data indicate that in up to one-third of the diabetic dialysis patients with the presumptive diagnosis of diabetic nephropathy, glycemic control improves spontaneously with the progression of CKD, loss of residual renal function and the initiation of dialysis therapy, leading to normal to low hemoglobin A1c (<6%) and glucose levels, requiring cessation of insulin or other diabetic medications. Potential contributors to this so-called “burnt-out diabetes” include decreased renal and hepatic insulin clearance, decline in renal gluconeogenesis, deficient catecholamine release, diminished food intake due to anorexia and/or diabetic gastroparesis, protein-energy wasting with resultant weight and body fat loss, and hypoglycemic effect of dialysis treatment. Although the concept of “burnt-out diabetes” appears in sharp contradistinction to the natural history of diabetes mellitus, studying this condition and its potential causes and consequences including the role of genetic factors may lead to better understanding of the pathophysiology of metabolic syndrome and diabetes mellitus in the CKD population and in many other individuals with chronic disease states associated with wasting syndrome that can confound the natural history of diabetes.

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Keywords

Diabetic nephropathy; chronic kidney disease (CKD); hemoglobin A1c; glycemic control; maintenance dialysis

Brief Case Report

Mr. H. is a 54-year-old Filipino man who has been undergoing maintenance hemodialysis for 3 years. He was first diagnosed with diabetes mellitus (DM) type 2 approx. 25 years ago and initially treated with oral hypoglycemic agents. Several years later the patient required insulin injections for refractory hyperglycemia (>350 mg/dl), high hemoglobin A1c levels (>8%) and polyuria due to osmotic glucosuria. His BMI was 35 kg/m2 then. In addition to insulin, he also received anti-hypertensive medications including ACEI-inhibitors for hypertension, statins for LDL-hypercholesterolemia (>160 mg/dL), and pain medications for diabetic neuropathy with severe burning pain in his feet. In-between he underwent quadruple bypass surgery for extensive coronary artery disease and laser treatment for diabetic proliferative retinopathy. The patient required progressively higher doses of insulin until 5 years ago, when he presented to emergency room with hypoglycemic episode, which led to lowering his insulin dose for the first time. At that time, his serum creatinine was 1.7 mg/dL, and he had 5 gm of daily proteinuria. He was diagnosed with chronic kidney disease (CKD) stage 3 presumably due to diabetic nephropathy. As his CKD progressed, he required even less insulin and was eventually off insulin several months prior to the dialysis initiation while maintaining glypizide 5 mg twice daily orally. At the start of hemodialysis treatment his BMI was 28 kg/m2 and his urination frequency only once to twice daily. After one year of thrice weekly hemodialysis treatment, his glypizide was discontinued for recurrent hypoglycemia, his A1c was 5.5%, LDL-cholesterol was <70 mg/dl while being off statin for over a year. His residual renal function declined to one urination episode per every 3 to 4 days. In the past 2 years he has been relatively stable on maintenance hemodialysis and off any oral or injectible diabetic medication or statins with quarterly A1c ranging in 5.5 to 5.9% range, LDL-cholesterol below 70 mg/dl and BMI at 30 to 32 kg/m2.

DM and CKD

DM type 2, also known as adult onset DM, is invariably described as a chronic progressive disease with worsening hyperglycemia over time. It is the most common cause of CKD in the United States (US) and most westernized countries.[1] Indeed, in the US almost half of all patients who start dialysis treatment have the underlying diagnosis of diabetic nephropathy, [2] and the cost of diabetic nephropathy is estimated to surpass $15 billion annually in the US. [3] Many contemporary nephrologists believe that a renal biopsy is not necessary to ascertain the diagnosis of diabetic nephropathy in a patient with preexisting DM, significant proteinuria, worsening renal function, normal to large kidney size in imaging studies, and prior history of diabetic retinopathy or neuropathy.

Since the natural course of DM is progressive worsening, and since several clinical trials have shown that optimal glycemic control mitigates the risk of diabetic complications, it is generally assumed that patients with CKD stages 3 to 5 due to diabetic nephropathy would also benefit from tight glycemic control.[4] However, prevention of diabetic nephropathy is clearly not a goal any more in patients who have reached CKD stage 5 and require maintenance dialysis therapy.[1] Nevertheless, many CKD patients without prior diagnosis of DM develop insulin resistance, metabolic syndrome and eventually DM type 2 after the start of renal replacement therapy, esp. after renal transplantation.[5]

Dose CKD Confound the Natural Course of DM?

As exemplified in our case report (see above), in long-standing diabetic patients who required high doses of insulin for years, the emergence of hypoglycemic episodes may herald worsening kidney function due to progressive diabetic nephropathy. A decline in insulin requirements may occur with advancing stages of CKD, underscoring the complex nature of the uremic dysregulation of glucose homeostasis in CKD.[6] The reason for the abnormal glucose homeostasis in CKD is postulated to be multifactorial as listed in Table 1. Renal clearance of insulin is diminished as the GFR declines.[6] Hepatic clearance of insulin also tend to decline in uremia, although it may improve after dialysis initiation.[1,6] Nevertheless, an increase in insulin resistance and diminished insulin secretion may also happen in more advanced CKD stages, which may be related to secondary hyperparathyroidism and activated vitamin D deficiency and which may be improved after treatment of hyperparathyroidism or administration of activated vitamin D.[7,8] Diminished kidney function may affect renal gluconeogenesis.[9] The resultant deficient gluconeogenesis combined with uremic malnutrition, also known as protein-energy wasting or kidney disease wasting,[10] deficient catecholamine release and impaired renal insulin degradation and clearance can contribute to a lower than usual threshold for clinical hypoglycemia, which is a common complication associated with adverse outcomes in CKD.[11]

In addition to the direct impact of uremia and renal insufficiency on glycemic status, the initiation of dialysis therapy *per se* may lead to improved insulin sensitivity and glucose tolerance.[12–14] Hypoglycemic episode may happen during hemodialysis treatment, even though the hemodialysate usually have high glucose levels up to 200 mg/dL.[15] There appears to be mixed data, however, pertaining to the effect of the peritoneal dialysis on glycemia.[1] Even though peritoneal dialysis may be superior to hemodialysis in achieving better insulin sensitivity,[16] it can result in significantly higher glucose intake from peritoneal dialysate especially with higher dialysate glucose concentrations. Other contributors to the seemingly improved hyperglycemia in peritoneal dialysis patients include diminished appetite related to continuous glucose absorption [17] or due to the mechanical effects of large filling peritoneal dialysis volumes.[18] Lowered patient energy expenditure, [19] limited amino acid losses and effect of peritoneal glucose absorption to stimulate insulin secretion may be other mechanisms to this end.[20]

Measures of glycemic control in CKD

Glycosylated hemoglobin, also known as hemoglobin A1c, is usually described as the percentage of the total hemoglobin and is the traditional indicator of overall glycemic control. The currently recommended A1c target for optimal glycemic control in diabetic patients, i.e., A1c below 6.5% or 7%, is derived from studies in the general diabetic population without renal insufficiency.[21] The A1c measurement can be confounded in the uremic milieu, although most of the implicating factors such as serum urea [1,22] or metabolic acidosis [23] usually lead to an increased, rather than decreased, A1c levels.[24] Factors that may lower A1c levels in CKD include severe anemia, shortened erythrocyte lifespan in inadequately dialyzed patients and blood transfusions, i.e., conditions that happen rather rarely in the contemporary dialysis patients.[1] Hence, A1c should be a reasonable measure of glycemic control even in dialysis patients, as long as they are not overtly anemic. However, other measures of long term glycemic control in uremia including glycated fructosamine and glycated albumin.[25–28]

A recent study of 23,618 diabetic hemodialysis patients who were followed between 2001 and 2003 showed that 33% of them had A1c levels below 6% (Figure 1).[29] Even though in this cohort higher A1c values was incrementally associated with increased death risk after controlling for demographics and other confounders, low A1c, esp. if below 5%, was also

associated with poor survival. Hence, at least according to this nationally representative study, approximately one-third of all prevalent diabetic hemodialysis patients in the US have an A1c within the "normal range" of the general population.[29] Many of these patients probably do not need insulin injections, even though they usually have full-blown sequalae of DM such as proliferative retinopathy, nephropathy (which has led to end-stage renal disease), polyneurpathy, and peripheral vascular disease or other cardiovascular disorders. Our case report is a typical example of what we call the "burnt-out diabetes" of advanced CKD.

Conclusions

Recent data indicate that in up to one-third of diabetic patients with the presumptive diagnosis of diabetic nephropathy, glycemic control may improve spontaneously with the progression of CKD, loss of residual renal function and the initiation of dialysis therapy. Many of these long-standing diabetic patients have full-blown diabetic microangiopathies (proliferative retinoapthy, nephropathy and neuropathy) and macroangiopathies (coronary artery disease, peripheral vascular disease, and limb amputations); nevertheless, they may not need insulin or other diabetic medications any more, as their A1c levels shifts within normal range and their serum glucose goes into normal or even low ranges, especially if such medications continued to be administered with the same doses or frequencies as before.

The concept of "burnt-out diabetes" that we have advanced herewith is not a novel condition in our opinion. However, to the best of our knowledge, this is the first time that this condition has been described systematically by referring to the national A1c data of the hemodialysis patients in the USA (Figure 1)[29] and by presenting the comprehensive list potential etiologies of the "burnt-out diabetes" (Table 1). Although the concept of burnt-out diabetes may sound provocative and in sharp contradistinction to the natural history of DM, it appears to be a real entity, the study of which 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,[30] that are associated with wasting syndrome and that may confound the natural course of DM. If for instance these one-third CKD patients with burnt-out diabetes have distinguished genotype or phenotypes, such genetic or acquired distinction may help module the glycemic control and treat or prevent DM more effectively. Studying the causes and consequences of the burnt-out diabetes may be a mean to that end.

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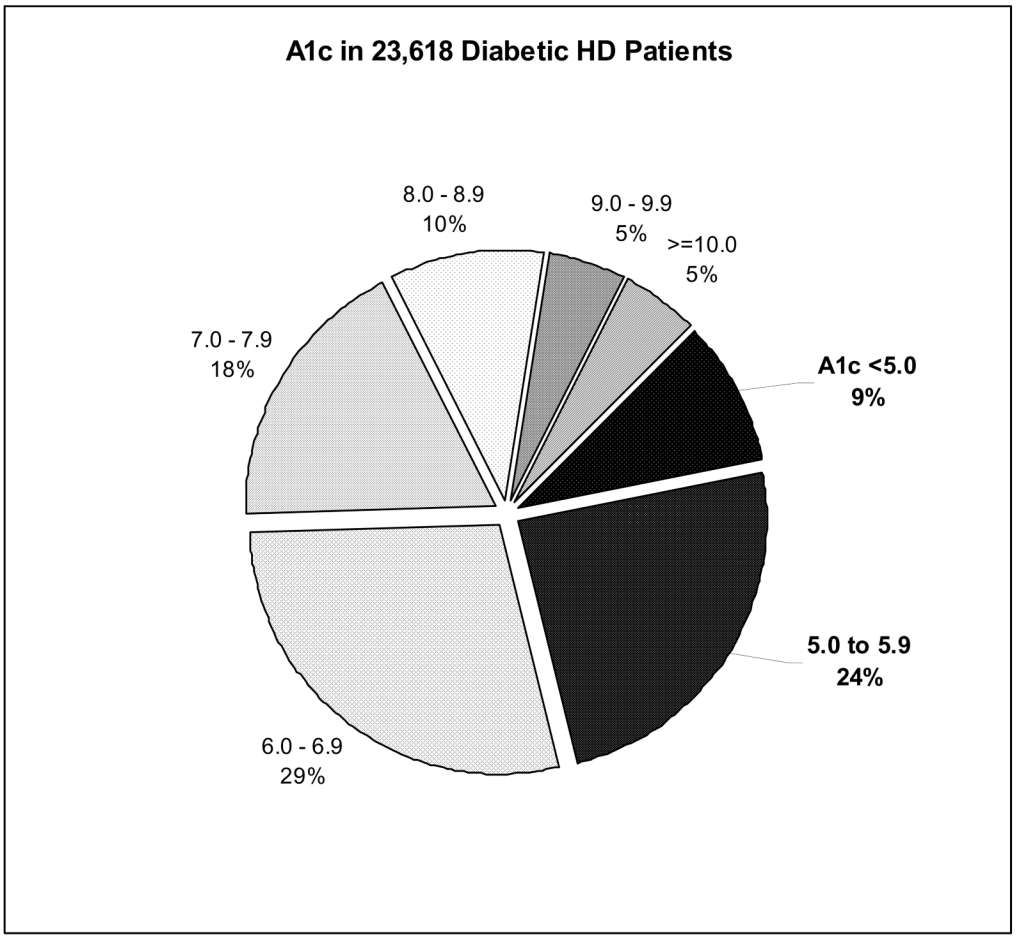

Figure 1.
Distribution of hemoglobin A1c in 23618 diabetic hemodialysis patients in the United States (these data are derived from all DaVita dialysis clinics between July 2001 and June 2003) [29]

Table 1

Potential contributors of the "burnt-out diabetes" in patients with CKD stage 5.

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. Comorbiod 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