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Glycemic Control in Diabetic Dialysis Patients and the Burnt-Out Diabetes Phenomenon

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Abstract

Diabetes mellitus (DM) is the most common cause of end-stage kidney disease and a major risk of morbidity and mortality. It is not clear whether medical management of DM has any significant beneficial effect on clinical outcomes at the end-stage of diabetic nephropathy with full-blown micro- and macro-angiopathic complications. Both loss of kidney function and dialysis treatment interfere with glucose homeostasis and confound glycemic control. Given unique nature of uremic milieu and dialysis therapy related alterations, there have been some debates about reliance on the conventional measures of glycemic control in particular the clinical relevance of hemoglobin A1c and its recommended target range of <7% in diabetic dialysis patients. Moreover, a so-called "burnt-out diabetes" phenomenon has been described, in that many diabetic dialysis patients experience frequent hypoglycemic episodes prompting cessation of their anti-diabetic therapies transiently or even permanently. By reviewing the recent literature we argue that the use of A1c for management of diabetic dialysis patients should be encouraged if appropriate target ranges specific for these patients (e.g. 6 to 8%) are used. We also argue that "burnt-out diabetes" is a true biologic phenomenon and highly prevalent in dialysis patients with established history and end-stage diabetic nephropathy and explore the role of protein-energy wasting to this end. Similarly, the J-or U-shaped shaped associations between A1c or blood glucose concentrations and mortality are likely biologically plausible phenomena that should be taken into consideration in the

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management of diabetic dialysis patients to avoid hypoglycemia and its fatal consequences in diabetic dialysis patients.

Keywords

Diabetes mellitus; chronic kidney disease; hemoglobin A1c; glycemic control; maintenance dialysis; burnt-out diabetes

Introduction

Diabetes mellitus (DM), especially Type 2 Diabetes (T2D), is the most common cause of chronic kidney disease (CKD) in many countries throughout the world.[1, 2] In the United States DM is pre-existent in almost half of a million maintenance dialysis patients.[3] The US dialysis patient mortality has remained 20% per year, mostly attributable to cardiovascular events.[2, 3] Even though diabetic dialysis patients may have slightly worse prognosis than their non-diabetic counterparts, it is still heavily debated whether medical management of DM has any significant beneficial effect on their outcomes at the end-stage of diabetic nephropathy with full-blown micro- and macro-angiopathies. Loss of kidney function and dialysis therapies may influence the natural course of DM resulting in unusual alterations in glycemic control.

There have been two unique issues pertaining to the management of diabetic dialysis patients. One is what measure of glycemic control is the most reliable in long-term dialysis patients, which specially includes a relevance for use of hemoglobin A1c in this population.[1] The other issue is the phenomenon known as “burnt-out diabetes”, in that in many diabetic dialysis patients normoglycemia or even frequent hypoglycemic episodes are observed. Some of these patients may need permanent cessation of anti-diabetic medications to avoid fatal hypoglycemia.[4, 5] In this article we provide a brief review of recent studies about management of diabetic dialysis patients and the discussions as to what should be specially considered for optimal glycemic control of this patient population.

Hemoglobin A1c in diabetic dialysis patients

Debates about A1c—Glycated hemoglobin, also known as hemoglobin A1c, is usually described as the glycated percentage of the total hemoglobin and is the traditional indicator of overall glycemic exposure over time. Evidence suggests that A1c measurement can be confounded by the uremic milieu in dialysis patients, in that most of the implicating factors such as serum urea concentrations[6] or metabolic acidosis[7] usually lead to an increased A1c levels,[8] whereas there are many more factors that may lower A1c levels in dialysis patients including anemia and shortened erythrocyte lifespan, blood transfusions and the protein-energy wasting, also known as malnutrition-inflammation cachexia syndrome.[1, 4, 5] Recent data based on continued glucose monitoring (CGM) show glycemic variability on dialysis vs. off-dialysis days in patient undergoing intermittent hemodialysis treatment.[9] Glucose values are significantly lower on dialysis days than on non-dialysis days despite similar energy intake.[10] However, even though it has been suggested that glycemic variability mitigates the value of A1c as a surrogate for glycemic control,[11] given stable

(e.g. thrice weekly) dialysis treatment, A1c is expected to represent the time-averaged glycemic burden over a several week interval. With improving CGM technology, its potential use in dialysis populations to address the some of the limitation of A1c could be considered.

Given the above data on glycemic variability in dialysis patients and due to a lack of association between A1C levels and mortality in some of the preliminary studies in the past, [12] it was once suggested that A1c had no role in dialysis patients.[13] Such opinion leaders have also advocated the use of alternative glycemic measures including fructosamine and glycated albumin in lieu of A1c.[14-17] However, although it is possible that fructosamine offers the advantage of gauging shorter-term glycemic control, it does not correlate strongly with fasting plasma glucose and is a relatively insensitive measure for determining the diagnosis of type 2 diabetes (T2D).[18] Glycated albumin testing may have some utilities in certain settings in which A1c proven less reliable including anemic or malnourished dialysis patients.[14] However, it is use also remains subject to such confounders as obesity, smoking, and hyperuricemia, all of which exhibit high prevalence among CKD patients.[18] Hence, the question about the most reliable measure of glycemic control in dialysis patients remains to be determined.

A1c and Clinical Outcomes—For over 3 decades A1c has been used to monitor glycemic control by targeting A1c <7% or even <6.5% in clinical practice. However, A1c levels exhibit a J-shaped association with outcomes in non-CKD patients.[19] This may be a biologically plausible phenomenon refuting the assumption of the-lower-the-better for glycemic exposure. The continued discussion on the reliability of A1c in dialysis patients has generated a large degree of confusion among both physicians and patients. Most data, however, are supportive of A1c testing in the CKD population. From early 90's to mid 00's several small studies (≤150 subjects in each study) found an association between higher A1c levels and worse clinical outcomes in the CKD (mostly dialysis) populations.[20-23] Wu *et al.* studied 137 hemodialysis (HD) patients with T2D and reported that cumulative survival rates were lower in the poor glycemic control group than in the good glycemic group.[20] In another observational study in 114 diabetic HD patients in Japan, the 7.5 year death risk of patients with A1c ≥8% was higher than those with A1c <6.5%.[23]

In recent years the two largest dialysis organization in the United States, i.e., Fresenius Medical Care and DaVita, each with over 100,000 dialysis patients, have contributed to leading epidemiologic studies about glycemic control in dialysis patients.[12, 24•] The first large and nation-wide study published in 2006 by Williams *et al.*. found no associations between one-time-measured A1c level at baseline and survival at 12 months in 24,875 diabetic dialysis patients from the largest dialysis organization in the US (Fresenius Medical Care).[12] However, this study had major limitations including the short-term follow-up period and use of a single measurement of A1c at baseline without repeated measure over time. Other methodological issues included non-time dependent survival models and lack of stratified analyses to detect interactions. Unfortunately, however, upon its publication the Williams study led to major confusion among both physicians and patients about the role of glycemic control in diabetic dialysis patient care.[25] Indeed it was even suggested that the guidelines on glycemic controls should not be extrapolated to dialysis population.[12, 25]

Whereas the latter suggestion has some merit, we believe that categorical dismissal of glycemic monitoring in these patients without scientific qualification is unwarranted.

Approximately a year after the publication of the Williams study,[12] a new nationally representative cohort study from DaVita patients was reported by Kalantar-Zadeh et al.[24•] In 23,618 HD patients who were followed over a 3 year cohort (7/2001-6/2004), unadjusted mortality risk was paradoxically higher with lower A1c values, but after adjusting for potential confounders, higher A1c >6% were incrementally and linearly associated with increased death risks over 3 year. The association between higher A1c values and mortality was even more prominent among younger patients, those who had undergone longer dialysis, and those with higher protein intake, blood hemoglobin, or serum ferritin levels. The authors of this DaVita cohort study concluded that the apparently counterintuitive associations between the poor glycemic control and greater survival in diabetic HD patients could be confounded by demographics, anemia and nutritional factors.[24•]

In 2008, a 2nd cohort study from Fresenius dialysis patients focusing on hospitalization was published, which found that extremely high and low A1c values of >11% and <5% were associated with higher hospitalization risks in 23,829 diabetic HD patients.[26] The 3rd Fresenius dialysis cohort study published in 2010 by Williams *et al.* to supplements the authors' previous analysis (which had found no correlation between A1c levels and mortality rates at one year[12]) by extending the follow-up period to 3 years and using time-dependent survival models with repeated measures.[27•] In these 24,875 diabetic HD patients (including 94.5% with T2D), adjusted time-dependent Cox models indicated that only extremes of glycemia were associated with poor survival. However, higher A1c values were associated with lower survival rates in type 1 diabetic patients. The Fresenius Study authors again concluded that sustained extremes of glycemia were only variably and weakly associated with decreased survival in the diabetic dialysis population, and suggested that aggressive glycemic control cannot be routinely recommended for all diabetic HD patients. In 2010, no relationship between average blood glucose levels and mortality rates was reported in a much smaller and short-term follow-up (median of 1.5 years) study with 1,484 Canadian diabetic HD patients.[13]

However, three additional studies have recently emerged from DaVita dialysis cohorts. [28-30] These studies indicated that both high and very low levels of A1c in dialysis patients are indeed associated with poor outcomes. Duong *et al.* examined mortality-predictability of A1c and random serum glucose in a 6-year (2001-2007) DaVita cohort of 2,798 diabetic peritoneal dialysis (PD) patients with repeated A1c measures.[28] Serum glucose concentrations correlated with A1c levels (r=0.51). Adjusted all-cause death hazard ratio (HR, and 95% confidence interval) for time-varying A1c increments of 7.0-7.9%, 8.0-8.9%, 9.0-9.9%, and ≥10%, compared with 6.0-6.9% (reference), were 1.10 (0.96-1.27), 1.28 (1.07-1.53), 1.34 (1.05-1.70), and 1.81 (1.33-2.46), respectively. The results supported an incremental and linear association between A1C levels and death rates. This association, however, was modified by hemoglobin levels such that higher mortality was evident only in non-anemic patients. This was the first study with large and nationally representative cohort of diabetic PD patients, in whom glucose laden peritoneal dialysate fluid expose an even higher glycemic burden. In a novel effort to examine the association of pre-transplant

glycemic control during dialysis treatment with post-transplant outcomes in kidney transplant recipients, Molnar *et al.* linked the 5-year national DaVita dialysis cohort to the Scientific Registry of Transplant Recipients.[29] They found that in 2,872 diabetic HD patients who underwent first kidney transplantation, mortality HR for time-averaged pre-transplant A1c categories of 7.0-7.9%, 8.0-8.9%, 9.0-9.9%, and ≥10%, compared with 6.0-6.9% (reference), were 0.89 (0.59-1.36), 2.06 (1.31-3.24), 1.41 (0.73-2.74), and 3.43 (1.56-7.56), respectively.

Finally, Ricks *et al.* examined mortality predictability of A1c levels and random serum glucose concentrations over time in the 6-year DaVita cohort of 54,757 diabetic HD patients.[30•] Although unadjusted mortality HR was paradoxically lower in higher baseline A1c levels, after fully adjusting for confounders, mortality HR for baseline A1c increments of 8.0-8.9, 9.0-9.9, and ≥10%, compared with 7.0-7.9% (reference), was 1.06 (1.01-1.12), 1.05 (0.99-1.12), and 1.19 (1.12-1.28), respectively and for time-averaged A1c 1.11 (1.05-1.16), 1.36 (1.27-1.45), and 1.59 (1.46-1.72). It was noteworthy that a symmetric increase in mortality also occurred with time-averaged A1c levels in the low ranges of 6.0-6.9, 5.0-5.9%, and ≤5%, of which HR was 1.05 (1.01-1.08), 1.08 (1.04-1.11), and 1.35 (1.29-1.42), respectively. In patients with adequate hemoglobin levels, these findings became more robust. Figure 1 shows a J-shaped A1c-death association above mentioned in the subgroup of patients with hemoglobin levels of 10.0 to 12.0 g/dl (n=21,579) which is recommended levels for dialysis patients and means their renal anemia is well controlled (Figure 1). More interestingly, this J-shaped A1c-death association was also recently reported in a large Canadian cohort of 23,296 non-dialysis-dependent diabetic CKD patients with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2.[31] Over the median follow-up period of 46 months, and regardless of baseline eGFR, both higher and lower A1c levels of <6.5% and >9.0% were associated with excess risks of most of the five outcomes studied (death, progression of kidney disease based on a doubling of serum creatinine level, or new end-stage kidney disease (ESKD), cardiovascular events, all-cause hospitalization), whereas the increased ESKD risk of higher A1c levels was attenuated at a lower eGFR.

In summary, the recent studies indicate that when A1c is used to risk-stratify diabetic dialysis patients, longitudinal A1c values are more reliable than single baseline measurements. Moreover, low glycemic levels are also clearly associated with high mortality risks in this patient population given the J-shaped association in most recent studies.

Considerations in Use of A1c—The appropriate use of A1c as glycemic indicator and outcome predictor in dialysis patients should be continued and even encouraged, as long as the following several points are carefully considered. First, both high (A1c >8% or more unequivocally >9%) and low (A1c <6%) levels are associated with poor outcomes. The latter association is consistent with recent data indicating similar J-shaped associations. Whether the A1c range of 6-8% or 6-9% should be recommended needs additional considerations. Second, the A1c-death association appears more robust in patients with higher hemoglobin levels or better nutritional status. The stronger A1c-death association is in younger patients and those with higher protein intake (>1 g/kg/day) or with higher hemoglobin levels (>11 g/dl).[24•] In anemic patients or those with protein-energy wasting, lower A1c levels may be a surrogate of poor nutritional status, then may be associated with mortality. Given the

aforementioned interaction of nutrition and anemia with indices of glycemic control in dialysis patients, an unusually low A1c <6% may warrant additional work-up rather than being considered as a favorable range. Finally, A1c monitoring should be based upon repeated measures and examining moving averages and trends over time, rather than a single baseline measurement. Time-average or time-dependent A1c models showed a more robust, linear and incremental outcome-predictability rather than baseline A1c.[27-30]

Burnt-out diabetes in dialysis patients

Alterations in glucose homeostasis when declining kidney function—In many diabetic dialysis patients with established DM a decline in insulin requirements and even spontaneous hypoglycemia can also occur.[32] The reasons for alterations in glucose homeostasis involve various mechanisms related to both decreased kidney function and dialysis therapies (Figure 2).[4] Renal clearance of insulin is significantly diminished once GFR declines below 15-20 ml/min.[32] Hepatic clearance of insulin also tends to decline in uremia, although it may improve after dialysis initiation.[32] Nevertheless, an increase in insulin resistance and diminished insulin secretion may also happen in ESKD. The cause of increased insulin resistance in ESKD is not fully understood. Inferred from improving of insulin sensitivity by dialysis[33-35], it may be related to unspecified uremic toxin possibly acting on the muscle tissue.[36] The exact reason for the diminished insulin secretion is also unclear. It may be because of hyperparathyroidism and activated vitamin D deficiency. Insulin secretion appears to improve after the treatment of hyperparathyroidism and after administration of activated vitamin D.[37, 38] The consequences of insulin resistance and deficiency in ESKD are complex and may influence to patients' outcomes beyond glucose homeostasis. Some studies showed that they were associated with muscle protein breakdown through the ubiquitin–proteasome pathway via suppression of phosphatidylinositol-3 kinase.[39-41] It suggests that insulin resistance and deficiency may contribute to a protein-energy wasting relating to higher mortality in dialysis population.[42] Diminished kidney function may affect renal gluconeogenesis.[43] The resultant deficient gluconeogenesis combined with impaired renal insulin clearance, uremic malnutrition, and deficient catecholamine release can contribute to a lower than usual threshold for clinical hypoglycemia, which is a common complication associated with adverse outcomes in dialysis patients.[44]

Effect of dialysis on glucose homeostasis—The initiation of dialysis therapy *per se* may lead to improved insulin sensitivity and glucose tolerance, and production.[34, 35, 45] Other than the favorable effects of dialysis, these treatments can complicate the management of diabetes by the glucose load provided by both hemo- and peritoneal dialysates. The latter especially can result in significantly higher glucose loads if higher dialysate glucose concentrations are required to achieve adequate ultrafiltration. The glucose load delivered by PD can be as much as 10–30% of total energy intake.[46] This glucose load in PD patients sometimes requires higher insulin dose for glycemic control resulting in patient's inconvenience, unintended hypoglycemic episode, and central obesity. In the view of nutrition, the total nutrient intake of these patients is often inadequate despite the additional glucose load, possibly because of a loss of appetite related to continuous glucose absorption[47, 48] and the mechanical effects of large filling volumes.[49]

Clinical Relevance of Burnt-out diabetes—Hypoglycemic episode may occur during hemodialysis treatment, even though the hemodialysates usually have high glucose levels up to 200 mg/dl.[50] A recent study of 23,618 diabetic HD patients showed that 33% of them had A1c levels below 6%.[24•] Even though in this cohort higher A1c values was 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. As previously mentioned, in this year a study of a contemporary cohort of 54,757 diabetic HD patients, which is a 6-year cohort from 2001 to 2007, reported similar results.[30•] Percentage of patients with A1c below 6% increased by 39.7% and even those who had A1c below 5% were also 10.6%. The distribution of A1c in the study is shown in Figure 3. Time-averaged A1c and mortality curve showed J-shaped association and a notable increase in mortality occurred with time-averaged A1c levels in the low range in fully adjusted models. Hence, at least according to these nationally representative studies, approximately 30-40% of all prevalent diabetic HD patients in the US have A1c levels within the “normal range” of the general population. Many of these patients probably do not need insulin injections, even though they usually have full-blown sequela of DM such as proliferative retinopathy, polyneuropathy, and peripheral vascular disease or other cardiovascular disorders.

The clinical significance of alterations in glucose homeostasis and normoglycemia without anti-diabetic treatment, so-called “burnt-out diabetes” in dialysis patients remains unclear. Furthermore, it is far less clear what approach has to be taken in the considerable number of dialysis patients whose A1c decreases to approach normal or even subnormal levels. While a lower A1c may be perceived as advantageous in general, we believe that patients with burnt-out diabetes may be at higher risk for morbidity and mortality. The advantages of a normal blood sugar level likely take a very long time to become manifest[53, 54], but on the short run these patients may in fact be more prone to develop clinically relevant hypoglycemic episodes. At present it seems to be sure that burnt-out diabetes is a complication of ESKD rather than a benefit of it. It is important to note that in the randomized trials ACCORD[51] and the ADVANCE,[52] targeting A1c levels <6.5 and <7%, respectively, in non-dialysis dependent T2D patients with a high cardiovascular disease risk have not shown to confer any cardiovascular benefit, and indeed trends towards higher cardiovascular events have been observed with lowering A1c, the so-called U-or J-shaped phenomenon. Hence, similar to dialysis patients, the-lower-the-better A1c principle does not appear to apply here either. However, in the ACCORD study the increased cardiovascular events with lowering A1C could not be attributed to hypoglycemic episodes. Hence, at least for now, neither the burnt-out diabetes phenomenon nor such other modifying factors of A1c as the uremia, anemia, acidosis, and shortened RBC life span should be directly implicated for these observations. Given the fact that diabetic dialysis patients have an exceptionally high burden of cardiovascular disease, it is possible that factors other than burnt-out phenomenon or non-glycemic modifiers of A1c could be playing a role in the U-shape A1c-event association in dialysis population as well.

Conclusions

In summary, A1c remains a useful and reliable surrogate marker for glycemic control and clinical outcomes even in dialysis populations. Its target range and clinical interpretation can

be more appropriately adjusted for dialysis patients rather than following blindly the same target ranges as in non-CKD populations. Recent data indicate that in up to 30~40% of diabetic dialysis patients in the U.S. have a near or lower normal A1c level, and lower A1c is closely associated with higher mortality. The-lower-the-better seems to be true no more in dialysis patients. The concept of burnt-out diabetes that we have advanced herewith is not a novel condition. Although the concept of burnt-out diabetes may sound provocative and may be contradistinctive to the natural history of DM, it appears to be a real entity. Further studies about delicate and effective care for patients with this condition are urgently needed.

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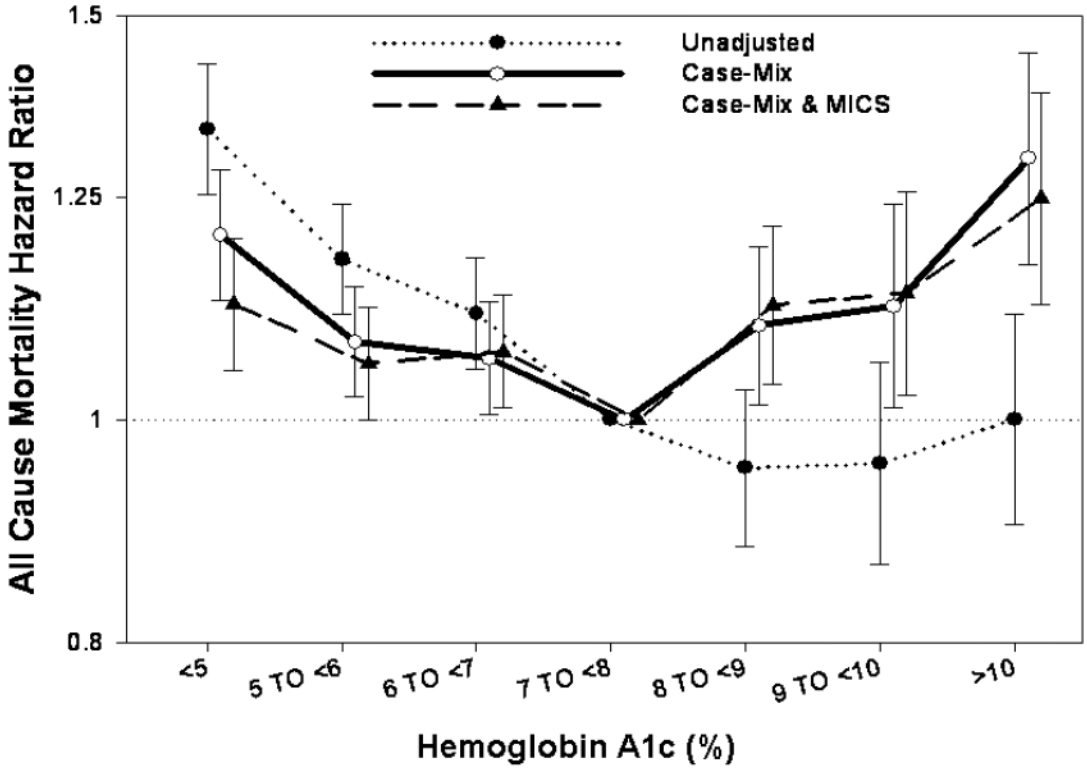

Figure 1.

HRs of all-cause mortality of the entire range of A1c in 21,579 hemodialysis patients with adequate hemoglobin levels (10.0-12.0 g/dl) using time-averaged Cox proportional hazards regression model.

Case-mix model is adjusted for age, gender, race and ethnicity, categories of dialysis vintage, primary insurance, marital status, dialysis dose as indicated by Kt/V (single pool), and residual renal function during the entry quarter.

Malnutrition-inflammation complex (or cachexia) syndrome (MICS) adjusted model includes all of the case-mix covariates as well as body mass index, normalized protein catabolic rate, serum levels of albumin, total iron-binding capacity, ferritin, creatinine, phosphorus, calcium, bicarbonate, blood white blood cell count, lymphocyte percentage, and hemoglobin.

Figure 2.
Diagram for potential contributors of the “burnt-out diabetes” in dialysis patients.

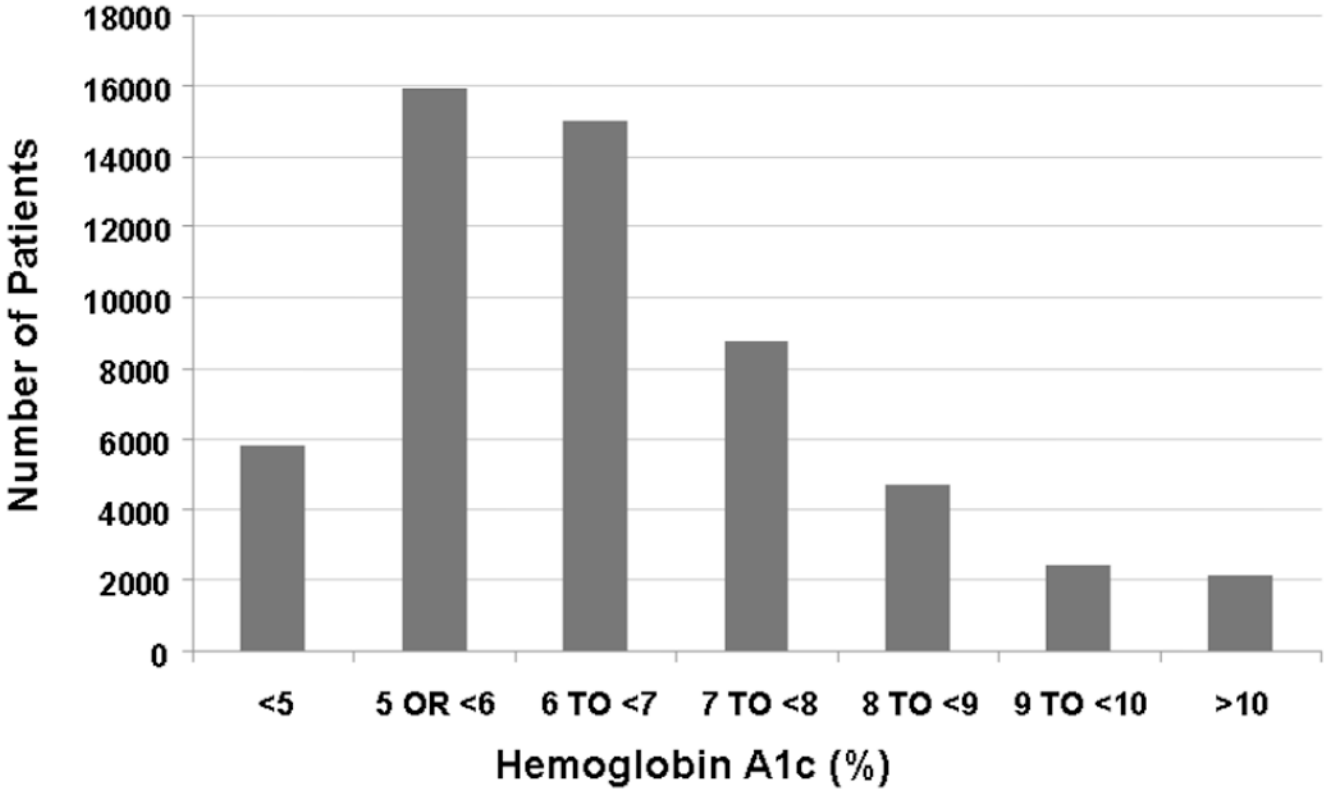

Figure 3.

Distribution of A1c in the study by Ricks et al. [27] with 54,757 hemodialysis patients. A1c levels below 5.0% and of 5.0-5.9% were observed in 5,800 (10.6%) and 15,933 (29.1%) patients, respectively. Cumulative frequency of patients with A1c level below 6.0% was 21,733 (39.7%).