Diabetes Prevalence, Treatment, Control, and Outcomes Among Hemodialysis Patients in the Gulf Cooperation Council Countries

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Introduction: Diabetes mellitus (DM) is a leading cause of end-stage kidney disease (ESKD). We provide the first description of DM prevalence, related outcomes, and the hemoglobin A1c (HbA1c)/mortality relationship in national hemodialysis (HD) patient samples across the Gulf Cooperation Council (GCC) countries.

Methods: We analyzed data from the prospective Dialysis Outcomes and Practice Patterns Study (DOPPS) in the GCC (2012–2018, $N = 2274$ HD patients ≥ 18 years old). Descriptive statistics were calculated, and all-cause mortality was analyzed for patients with DM versus without DM and by HbA1c levels in patients with DM by Cox regression with progressive confounder adjustments.

Results: DM in the GCC ranged from 45% to 74% in patients with HD by country. Patients with DM were 13 years older (59.9 vs. 46.7 years) and had greater body mass index (BMI), shorter median years on dialysis (1.5 vs. 3.0 years), and higher comorbidity burden. In patients with DM, insulin use was 26% to 50% across countries, with variable oral antidiabetic drug use (2%–32%); median HbA1c levels were 6.1% to 7.5% across countries. Patients with DM (vs. without DM) had higher crude death rates (15.6 vs. 6.2 deaths per 100 patient-years, mean follow-up 1.3 years) and adjusted mortality (hazard ratio [HR] = 1.72 [95% CI 1.23–2.39]). In patients with DM, mortality was lowest at HbA1c 6.5% to 7.5%, with mortality particularly elevated at high HbA1c >9% (HR = 2.13 [95% CI 1.10–4.10]).

Conclusion: Patients with DM in the GCC have high comorbidity burden and mortality rates despite a relatively young mean age. In GCC countries, a holistic strategy for improving diabetes care and outcomes for HD patients is needed at the primary, secondary, and tertiary levels.

DM is a major public health concern owing to the associated end-organ damage and higher morbidity and mortality. Type 2 DM is highly prevalent in the Gulf countries (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates [UAE]), ranging from 8% to 22% of 20 to 79 year-olds by the GCC countries,[1] and has been positively correlated with gross domestic product.[2] A recent report from the International Diabetes Federation indicated that 4

of the 6 GCC countries ranked among the top 16 of 195 countries in the world for diabetes prevalence.[3] In the United States, >40% of dialysis patients have diabetic kidney disease with the associated large health and financial cost.[4] Furthermore, the incidence of ESKD has doubled in 10 years across 9 European countries, mostly owing to diabetes, hypertension, and renovascular disease.[5] Much poorer outcomes have been found in HD for persons having DM. In a study based on data from the United States, diabetic dialysis patients had considerably poorer survival of 34% in 5 years, mainly owing to cardiovascular events.[6] In general, dialysis patients with DM are much more likely to have cardiac disease when compared with patients without diabetes,[7] and the risk of major adverse cardiac events

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in incident HD patients is strongly associated with the presence of DM.[8]

HbA1c is considered a standard-of-care test for monitoring glycemic control in nondialysis patients. Evidence for the importance of monitoring HbA1c levels is considerably weaker for the dialysis population, owing to the lower reliability of HbA1c in dialysis patients.[9] Nonetheless, the most recent guidelines of the Kidney Disease: Improving Global Outcomes recommend use of HbA1c to be prudent for monitoring glycemia.[10] Substantial fractions of dialysis patients are viewed as having undesirable glycemic control, with 22% of patients with DM in a contemporary United States Renal Data System cohort having HbA1c levels >7%.[11] Poorer glycemic control was greater in patients with DM who were younger or inflamed, had higher BMI, or had higher systolic blood pressure.[11] Diabetic dialysis patients with HbA1c <6 and >8 have been associated with poor clinical outcomes, suggesting a J- or U-shaped relationship in this patient population.[12] Relatedly, up to one-third of DM dialysis patients present as "burnt-out DM" and have HbA1c <6% without antidiabetic medication.[6,13,14] Decreased renal and hepatic insulin clearance, reduced gluconeogenesis, and decreased food intake/increased protein-energy wasting are viewed as possible contributors to this phenomenon.[15]

The high prevalence of DM found in the GCC is thought to be related to a number of factors, including obesity, unhealthy lifestyle, increased life expectancy and health care expenditures in recent decades, increased incidence of type 2 DM among children and young persons, and greater genetic susceptibility.[1] Large studies are completely lacking for HD patients in the GCC regarding the level of diabetes, HbA1c levels, clinical outcomes, and how glycemic control is managed. Furthermore, besides special cultural differences, the GCC HD patient population is considerably younger than HD populations in western Europe, Japan, and North America which may affect the outcomes for patients with DM HD in the GCC compared with other regions. In view of this, we have undertaken the present study to address this large gap in knowledge regarding glycemia control, its relationship to mortality, and how glycemia is managed for HD patients having DM in the GCC to help inform the GCC and broader global communities of these key aspects in the care and outcomes of patients with DM HD that undoubtedly will have relevance to other global communities as well.

METHODS

Patients and Data Collection

The DOPPS (http://www.dopps.org) is an international prospective cohort study of HD patients ≥18 years of age. Patients in the DOPPS are enrolled randomly from a representative sample of dialysis facilities within each nation at the start of each study phase, as described previously.[16–18] In the current study, data from 2274 HD patients in GCC countries (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, UAE) participating in DOPPS phases 5 (2012–2015) and 6 (2015–2018) were analyzed. Study approval was obtained by a central institutional review board. Additional study approval and patient consent were obtained as required by national and local ethics committee regulations. Baseline demographic data, comorbid conditions, laboratory values, and medications were abstracted from patient records. Mortality events were collected during study follow-up. The Strengthening the Reporting of Observational Studies in Epidmiology (STROBE) guidelines were followed for reporting results (Supplementary Figure S1).

Data Analysis

Standard descriptive statistics were used to characterize the prevalence of diabetes by country, the distribution of HbA1c among patients with DM, and characteristics among patients with DM versus without DM by GCC country. Patients were defined as having DM if reported as having DM as a comorbidity at study enrollment or having DM as cause of ESKD. The primary outcome in the current study was mortality, and the primary exposures were (i) DM among all patients and (ii) HbA1c among patients with DM. Among 2274 patients, 574 were excluded owing to inadequate outcome follow-up, for a total analyzed population of 1700 patients. Cox regression was used to analyze the association between HbA1c categories and mortality, stratified by country and phase, accounting for facility clustering using robust sandwich covariance estimators and adjusted for potential confounders. Time at risk started at study enrollment and ended at the earliest of (i) date of death, (ii) 7 days after leaving the facility owing to transplant or transfer to a nonstudy facility, (iii) 7 days after changing modality, (iv) date of loss to follow-up, or (v) the end of the study phase. The median follow-up time was 1.3 years.

Multiple Imputation

Overall, missingness for model adjustment covariates was low: <10% for most of the covariates with the exception of BMI (18%) and single-pool Kt/V (35%). For missing data, we used the sequential regression multiple imputation method implemented by IVEware[19] and analyzed using the MIAnalyze procedure in SAS/STAT 9.4. All analyses used SAS software, version 9.4 (SAS Institute, Cary, NC).

RESULTS

A total of 2274 HD patients were included in the analysis from GCC-DOPPS phases 5 (2012–2015) and 6 (2015–2018), with 60% of the studied HD patients having DM. Overall, 76% of patients with DM also had DM listed as their primary cause of ESKD. The mean age was >13 years greater among patients with DM (59.9 years) versus without DM (46.7 years) HD in the GCC (Table 1). This

Table 1. Patient characteristics in the GCC-DOPPS (2012–2018), by diabetes status

Characteristics	Diabetes	
	Yes	No
Demographics		
Sample patients, n	1373	901
Age, yr	59.9 (13.5)	46.7 (16.1)
Male, %	56	60
Yr on dialysis	1.5 [0.4–3.9]	3.0 [0.9–6.9]
Urine output >200 ml/d, %	32	30
Current smoker, %	6	6
Body mass index, kg/m^2	27.6 (6.7)	24.9 (6.4)
Diabetes as cause of ESKD, %	76	—
Dialysis treatment		
Catheter use, %	39	28
SBP, mm Hg	150 (21)	140 (22)
Treatment time, min	222 (24)	220 (26)
Single-pool Kt/V	1.3 (0.4)	1.4 (0.4)
Comorbidities, %		
Coronary artery disease	39	16
Cerebrovascular disease	13	3
Congestive heart failure	24	16
Other cardiovascular disease	17	11
Peripheral vascular disease	25	7
Hypertension	96	86
Recurrent cellulitis	12	2
Legally blind	4	2
Peripheral neuropathy	28	8
Diabetic retinopathy	51	0
Prior amputation	7	0
Laboratories		
Total calcium, mg/dl	8.7 (0.9)	8.8 (1.0)
Phosphorus, mg/dl	5.0 (1.8)	5.4 (2.0)
Creatinine, mg/dl	8.2 (2.7)	10.5 (3.2)
Albumin, g/dl	3.4 (0.5)	3.6 (0.5)
Hemoglobin, g/dl	10.7 (1.5)	11.0 (1.6)
PTH, pg/ml	302 [149–527]	382 [188–732]
HbA1c, %	7.1 (1.9)	5.5 (1.2)
Medications prescribed,[a] %		
Insulin	39	—
DPP-4 inhibitor	5	—
Metformin	0	—
Sulfonylurea	9	—
No antidiabetic prescriptions	51	—

DOPPS, Dialysis Outcomes and Practice Patterns Study; DPP-4, dipeptidyl peptidase-4; ESKD, end-stage kidney disease; GCC, Gulf Cooperation Council; HbA1c, hemoglobin A1c; PTH, parathyroid hormone; SBP, systolic blood pressure.
[a]Prescription at DOPPS enrollment; no prescriptions observed for the following medications: GLP-1 agonists, SGLT2 inhibitor, alpha glucosidase inhibitors, thiazolidinediones; antidiabetic medications not reported for 47% of patients with diabetes.
Values are illustrated as prevalence, mean (SD), or median [interquartile range].

pattern of substantially older age for patients with DM versus without DM HD was found in each of the 6 GCC nations (Supplementary Table S1). Similarly, BMI was greater in patients with DM (27.6 kg/m^2) versus without DM (24.9 kg/m^2) (Table 1), with this pattern consistently found across all GCC countries as well (Supplementary Table S1). Males constituted 56% of the patients with DM and 60% of the patients without DM HD, whereas the median number of years on dialysis (i.e., dialysis vintage) was 2-fold longer for patients without DM (3.0 years) versus DM (1.5 years) HD (Table 1).

Understandably, comorbidity burden was much higher in patients with DM versus without DM GCC HD for cardiovascular-, peripheral vascular-, cerebrovascular-, or neuropathy-related comorbidities, heart failure, and retinopathy (Table 1). In addition, mean systolic blood pressure and having a history of a previous amputation were substantially higher in patients with DM versus without DM in each GCC country (Supplementary Table S1). Consistent with these comorbidity differences, use of a central venous catheter as vascular access was also higher among patients with DM (39%) versus without DM (28%) HD (Table 1). Mean serum creatinine levels were substantially lower in patients with DM (8.2 mg/dl) versus without DM (10.5 mg/dl), whereas mean serum albumin levels were slightly lower (3.4 vs. 3.6 g/dl) (Table 1).

DM prevalence among HD patients varied greatly across GCC countries, ranging from 74% in Kuwait to 72% in Bahrain, 68% in Qatar and the UAE, 59% in Oman, and 45% in Saudi Arabia (Figure 1). Catheter use was more common among patients with DM versus without DM in each GCC country except in Kuwait where catheter use was high overall but slightly lower for patients with DM (59%) versus without DM HD (67%). In half of the GCC countries (Bahrain, Kuwait,
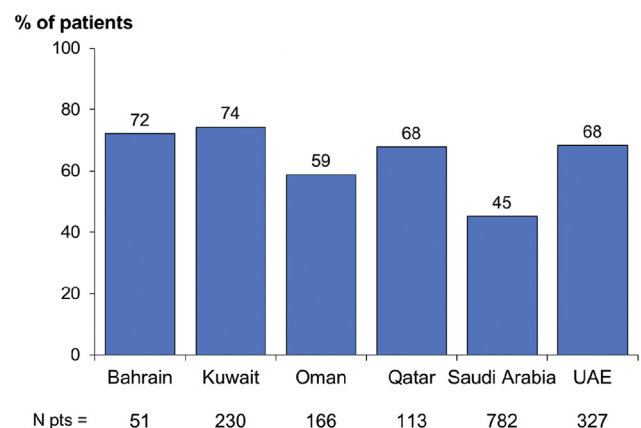

Figure 1. Diabetes prevalence, by country in the initial cross-section of GCC-DOPPS phases 5 (2012–2015) and 6 (2015–2018), weighted by facility sampling fraction. DOPPS, Dialysis Outcomes and Practice Patterns Study; GCC, Gulf Cooperation Council; pts, patients; UAE, United Arab Emirates.

UAE), single-pool Kt/V was lower for patients with DM versus without DM, although it did not differ in the other 3 countries (Oman, Qatar, Saudi Arabia). Mean hemoglobin (Hb) and serum phosphorus levels were lower for patients with DM versus without DM in 4 of the 6 GCC countries (Kuwait, Qatar, Saudi Arabia, and UAE).

Variation was also found in prescription of DM medications in patients with DM HD across 5 of the 6 GCC countries (with medication data not reported for Oman). Prescription of insulin ranged from 26% in Saudi Arabia to 36% in Kuwait and 42% to 50% in Bahrain, the UAE, and Qatar. Prescription of oral diabetic drugs was very low in Kuwait (≤2%), whereas use of sulfonylurea ranged from 6% in Saudi Arabia to 11% in Qatar and 16% in Bahrain and the UAE. Furthermore, prescription of dipeptidyl peptidase-4 inhibitor analogs ranged from 15% in the UAE to 2% to 3% in Kuwait, Qatar, and Saudi Arabia.

The crude death rate per 100 patient-years was 15.6 versus 6.2 for patients with DM versus without DM, respectively. In Cox regression analyses, stratified by GCC region and phase, but not adjusted for any other covariates, the HR of death was 2.73 (95% CI 1.94–3.85) for patients with DM versus without DM (Table 2). After adjusting for covariates pertaining to demographics, years on dialysis, BMI, comorbidities, single-pool Kt/V, catheter use, and laboratory values, the HR of mortality for DM versus non-DM patients was 1.72 (95% CI 1.23–2.39).

Measurement of HbA1c within 4 months of enrollment was quite variable among patients with DM in the GCC, ranging from 25% to 46% for patients in Bahrain, Oman, Saudi Arabia, and the UAE, whereas it was 64% for patients in Kuwait and 95% for those in Qatar (Supplementary Figure S2). Median HbA1c levels in DM patients ranged from 6.1% in Oman to 6.7% in Qatar and the UAE, 7.0% in Kuwait and Saudi Arabia, and 7.5% in Bahrain (Figure 2). The percent of patients having a HbA1c <6% ranged from 44% in Bahrain to 39% in Oman to 24% to 31% in the other 4 countries. Substantial variation was also found in the prevalence
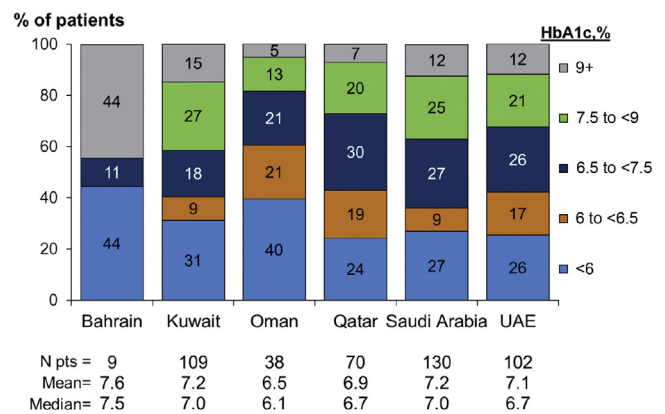

Figure 2. HbA1c distribution among patients with diabetes at DOPPS enrollment, by country in the initial cross-sections of GCC-DOPPS phases 5 and 6 (2012–2018). DOPPS, Dialysis Outcomes and Practice Patterns Study; GCC, Gulf Cooperation Council; HbA1c, hemoglobin A1c; pts, patients; UAE, United Arab Emirates.

of patients with DM having a relatively high HbA1c of 9% or higher, ranging from 5% in Oman, 7% in Qatar, 12% to 15% in Saudi Arabia, UAE, and Kuwait, and 44% in Bahrain. Mean Hb levels were positively related to HbA1c levels and were approximately 0.5 g/dl higher for patients with DM having a HbA1c >7.5% (Hb = 11.1 g/dl) versus HbA1c < 6.5% (Hb = 10.6 g/dl) (Table 2). Among patients with DM with a reported HbA1c, 14% had a Hb <9 g/dl, but 19% to 22% had a Hb <9 g/dl among patients with DM with HbA1c level of 6% to <7.5% (Supplementary Table S2). Antidiabetic medications (including insulin) were not prescribed for 51% of patients with DM (Table 1). Moreover, 27% and 29% of patients with DM having HbA1c of 7.5% to 9% and >9%, respectively, were not prescribed any antidiabetic medication (Table 3). Among DM patients with HbA1c < 6%, 23% were prescribed insulin and another 7% were prescribed an oral antidiabetic medication (Table 3).

The relationship of HbA1c levels with mortality was investigated based on various baseline levels of HbA1c in Cox survival analyses (Figure 3). Although somewhat limited in having HbA1c levels reported for only 481 patients with DM GCC, these analyses suggested that the nadir for mortality risk was in the HbA1c range of 6.5% to 7.5%. Elevated mortality risk was found at high baseline HbA1c >9% (HR = 2.13 [95% CI 1.10–4.10]) (Supplementary Table S3) and with a consistently higher mortality risk found at this high HbA1c level whether or not analyses were adjusted for baseline levels of key laboratory measures (Figure 3). A possibly higher mortality risk was also found at HbA1c levels of >7.5% to 9.0% in the fully adjusted model 3 but not in model 2 which did not contain adjustments for laboratory measures, Kt/V, or catheter use. In sensitivity analyses carried out separately by study phase, the higher mortality

Table 2. Diabetes and mortality, by level of model adjustment among GCC-DOPPS patients (2012–2018)

Model	Adjustments	Diabetes HR (95% CI)
1	Stratified by region/phase[a]	2.73 (1.94–3.85)
2	+Age, sex, years on dialysis, BMI, comorbidities[b]	1.96 (1.42–2.72)
3	+Kt/V, catheter use, laboratories[c]	1.72 (1.23–2.39)

BMI, body mass index; CI, confidence interval; DOPPS, Dialysis Outcomes and Practice Patterns Study; GCC, Gulf Cooperation Council; HR, hazard ratio.
[a]All models account for facility clustering and are stratified by phase of data collection and 2 GCC regions (Saudi Arabia vs. other GCC countries).
[b]Comorbidities include coronary artery disease, congestive heart failure, cerebrovascular disease, and other cardiovascular disease.
[c]Laboratories include creatinine, albumin, and hemoglobin.
Overall: N = 1700 patients, n = 266 deaths.
Diabetes: N = 1016 patients, n = 206 deaths – 15.6 deaths per 100 patient-years.
Nondiabetes: N = 684 patients, n = 60 deaths – 6.2 deaths per 100 patient-years.

Table 3. Patient characteristics of patients with DM HD in the GCC-DOPPS (2012–2018), by HbA1c level

Characteristics	<6%	6% to <6.5%	6.5% to <7.5%	7.5% to <9%	9+%
			HbA1c category		
Demographics					
Sample patients, n (%)	145 (30)	60 (12)	122 (25)	99 (21)	55 (11)
Age, yr	61.7 (13.8)	62.4 (12.4)	58.8 (13.0)	59.1 (11.7)	56.8 (13.5)
Male, %	60	53	54	54	47
Years on dialysis	1.6 [0.3–4.5]	1.9 [0.3–3.9]	1.5 [0.3–3.9]	1.6 [0.4–3.4]	0.9 [0.5–2.8]
Urine output >200 ml/d, %	34	41	37	39	22
Current smoker, %	13	5	6	6	9
Body mass index, kg/m^2	26.7 (6.6)	29.1 (8.7)	27.7 (5.8)	29.7 (6.7)	29.4 (6.8)
Dialysis treatment					
Catheter use, %	33	35	43	37	46
SBP, mm Hg	147 (20)	149 (23)	148 (20)	155 (19)	156 (20)
Treatment time, min	220 (27)	228 (19)	225 (23)	226 (22)	229 (15)
Single-pool Kt/V	1.4 (0.4)	1.4 (0.3)	1.4 (0.3)	1.3 (0.3)	1.3 (0.4)
Comorbidities, %					
Coronary artery disease	39	47	45	42	38
Cerebrovascular disease	15	13	9	13	11
Congestive heart failure	22	22	20	24	18
Other cardiovascular disease	18	27	21	16	20
Peripheral vascular disease	24	37	30	28	35
Hypertension	97	97	95	93	96
Recurrent cellulitis	8	23	18	13	15
Legally blind	4	5	3	4	0
Peripheral neuropathy	19	30	29	34	13
Diabetic retinopathy	37	59	53	46	47
Previous amputation	7	5	8	7	6
Laboratory					
Total calcium, mg/dl	8.9 (0.9)	8.5 (0.9)	8.6 (0.9)	8.7 (0.8)	8.3 (0.8)
Phosphorus, mg/dl	5.0 (1.8)	5.0 (2.1)	4.9 (1.6)	5.0 (1.4)	5.3 (1.3)
Creatinine, mg/dl	8.6 (2.8)	8.3 (2.8)	7.9 (2.8)	8.0 (2.3)	8.1 (2.1)
Albumin, g/dl	3.4 (0.5)	3.3 (0.6)	3.4 (0.5)	3.4 (0.5)	3.3 (0.5)
Hemoglobin, g/dl	10.6 (1.4)	10.5 (1.6)	10.8 (1.8)	11.1 (1.6)	11.0 (1.4)
PTH, pg/ml	354 [147–650]	333 [225–513]	284 [128–515]	367 [189–602]	283 [190–527]
Medications prescribed,[a] %					
Insulin	23	33	54	60	59
DPP-4 inhibitor	7	9	2	11	12
Sulfonylurea	5	12	14	14	9
No antidiabetic prescriptions	70	54	34	27	29

DM, diabetes mellitus; DOPPS, Dialysis Outcomes and Practice Patterns Study; DPP-4, dipeptidyl peptidase-4; GCC, Gulf Cooperation Council; HbA1c, hemoglobin A1c; HD, hemodialysis; PTH, parathyroid hormone; SBP, systolic blood pressure.
[a]Prescription at DOPPS enrollment; <1% for metformin and no prescriptions observed for the following medications: GLP-1 agonists, SGLT2 inhibitor, alpha glucosidase inhibitors, thiazolidinediones; antidiabetic medications not reported for 32% of patients with diabetes with HbA1c values (no differences observed by HbA1c category).
Values are shown as prevalence, mean (SD), or median [interquartile range].

risk found at HbA1c levels >7.5% was consistently found in both DOPPS phases 5 and 6. Nevertheless, although an elevated mortality risk (HR = 1.57 [95% CI 1.01–2.45]) was found for patients having HbA1c of 6.0% to <6.5% (vs. the 6.5% to <7.5% reference group) in the overall study data, a sensitivity analysis revealed that this elevated risk was found only in DOPPS phase 5; no elevation in mortality risk was found in phase 6 for patients having HbA1c of 6.0% to <6.5%.

DISCUSSION

To the best of our knowledge, this is the first description of DM prevalence, related outcomes, and

the HbA1c/mortality relationship in national HD patient samples across the GCC countries. Notably, the GCC HD population is significantly younger than in western European countries, Japan, and North America.[20] A clear finding from this work is the great health burden related to DM in GCC HD patients. Not only is this DM prevalence in GCC HD patients one of the highest reported in the international DOPPS, but crude mortality rates are high for patients with GCC DM HD (15.6 deaths per 100 patient-years), and median survival time on dialysis is only 1.5 years despite having a mean age of only 59.9 years. Moreover, comorbidity burden also is much higher in patients with DM than without DM GCC HD, including coronary artery
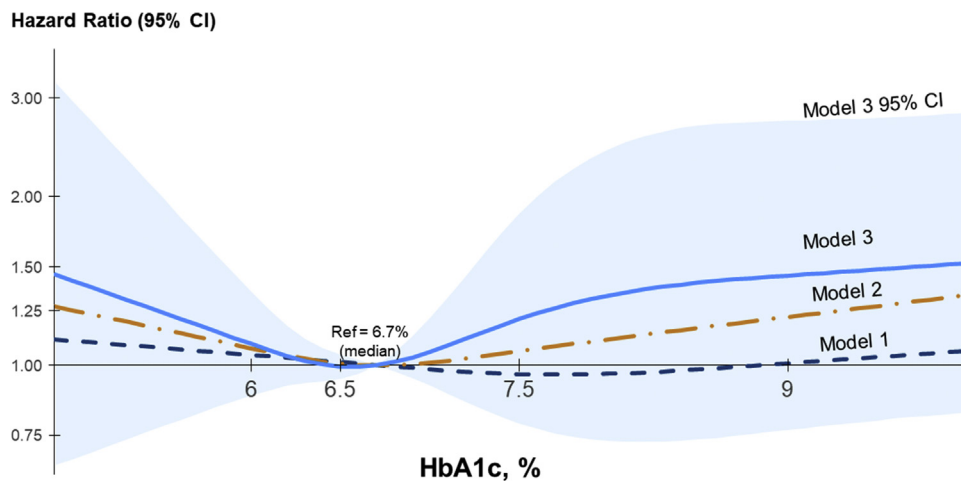
Figure 3. HbA1c categories and mortality among GCC-DOPPS patients with diabetes (2012–2018), effect of progressive adjustment. $N = 481$ patients with diabetes ($n = 92$ deaths). Model 1: Stratified by phase of data collection and 2 GCC regions (Saudi Arabia vs. other GCC countries). Model 2: Additionally adjusted for age, sex, years on dialysis, BMI, comorbidities (coronary artery disease, congestive heart failure, cerebrovascular disease, and other cardiovascular disease). Model 3: Additionally adjusted for Kt/V, catheter use, and laboratories (creatinine, albumin, and hemoglobin). Spline regression used to create the figure with knots at HbA1c levels of 6%, 6.5%, 7.5%, and 9.0%; the median HbA1c value (6.7%) was used as a reference when plotting the figure. BMI, body mass index; DOPPS, Dialysis Outcomes and Practice Patterns Study; GCC, Gulf Cooperation Council; HbA1c, hemoglobin A1c; Ref, reference.

disease, cerebrovascular disease, heart failure, peripheral vascular disease, amputation, peripheral neuropathy, proliferative retinopathy, and cellulitis. These data confirm previously published studies regarding the high comorbidity burden found for patients with DM HD and is a main expectation of the disease.[21–23] One peculiarity raised by our findings, however, is that approximately 50% of patients with GCC DM were not prescribed any type of antidiabetic drug, with nearly 30% of patients with high HbA1c (>9%) not prescribed an antidiabetic medication. This raises the question of possible undertreatment of some patients with DM and the impact on outcomes for these patients.

The prevalence of DM in HD patients was especially high in some GCC countries, ranging from 74% in Kuwait to 72% in Bahrain and the UAE, 68% in Qatar, 59% in Oman, and 45% in Saudi Arabia. This is substantially higher than the summarized estimate of 47.8% recently reported by Hassanien *et al.*[24] from >40 studies, but many of these used substantially older data. Nevertheless, this high DM prevalence in GCC HD patients is consistent with the underlying high DM prevalence in the Gulf region noted by Meo *et al.*[2] and by the recent report from the International Diabetes Federation.[3] The DM prevalence among Saudi Arabia HD patients (45%) observed in this 2012 to 2018 DOPPS sample is consistent with the 54% prevalence reported in the recent 2019 SCOT annual report[25] resulting from an exponential increase in DM that has doubled in 10 years.

The age difference for patients with DM versus without DM HD in the GCC was particularly striking,

with the mean age >13 years older among patients with DM (59.9 years) versus without DM (46.7 years) HD. In view of patients with DM having a relatively short median dialysis vintage of 1.5 years (vs. 3.0 years for patients without DM), these results indicate that patients with DM are starting ESKD at a much older age on average than for patients without DM and that the onset and progression of chronic kidney disease (CKD) differ substantially for patients with DM versus without DM HD in the GCC. Understanding the drivers of ESKD in patients without DM GCC HD at such an early age would be important to explore in future analyses. The age difference between patients with DM versus without DM HD in the GCC is much larger than the 2-year mean age difference found previously by Combe *et al.*[23] in DOPPS phase 2 data (2002–2004) for the United States, Canadian, European, and Japanese HD patients. In addition, mean ages have been much more similar for patients with DM versus without DM in UK Renal Registry data, whereas in ANZDATA, patients with incident ESKD with diabetic nephropathy were 6 years older on average versus patients without DM in Australia and New Zealand.[26] The much older age of patients with DM GCC HD may be a key reason for the substantially lower serum creatinine and phosphorus levels in patients with DM because serum creatinine and phosphorus levels often are lower in older HD patients,[27,28] and may reflect higher coprevalence of malnutrition found in other patient cohorts with DM HD.[29,30] Furthermore, the considerably higher prevalence of cardiovascular and peripheral vascular comorbidities found for patients with DM in

the GCC may not only be a result of the pathogenesis of DM but also a consequence of the older age of patients with DM; they have had more time to accumulate these and other pertinent comorbidities.

BMI was higher in patients with DM versus without DM HD (27.6 and 24.9 kg/m^2), which is not surprising for people with type 2 DM. Even though lower mortality has been observed in obese versus nonobese patients without DM HD, DM has been reported to be an effect modifier with higher mortality found in obese versus nonobese patients with DM HD.[31] Sanguankeo and Upala[32] have suggested that in dialysis patients, metabolic syndrome may be more detrimental than whatever survival advantages are gained by a larger BMI alone.

Reporting of HbA1c in a 4-month study period differed greatly by country, from 95% of patients with DM HD in Qatar, 64% in Kuwait, 36% to 46% in Saudi Arabia, Oman, and the UAE, and 25% in Bahrain. The 2020 Diabetes Management Guidelines of the Kidney Disease: Improving Global Outcomes for patients with CKD[10] recommend monitoring long-term glycemic control by HbA1c twice per year as being reasonable but as often as 4 times per year if the glycemic target is not met or after changing antihyperglycemic therapy. Thus, the percentage of patients with GCC DM HD with a reported HbA1c seems to be substantially lower in some GCC countries than recommended in the updated guidelines. Nevertheless, the guideline committee noted that in DM dialysis patients, the optimal HbA1c range and glycemic targets are unknown, with more research being needed; inaccuracy and imprecision of HbA1c may be greater in dialysis patients and HbA1c values should be interpreted with these limitations in mind. The current study, based on a single baseline HbA1c measurement, contributes evidence revealing elevated mortality at HbA1c levels ≥9% (HR = 2.13 [95% CI 1.10–4.10]) in the GCC HD patient population. Possible elevated mortality risk was also suggested at HbA1c levels of 7.5% to 9.0% (HR = 1.39 [95% CI 0.66–2.92]), but additional evaluation is needed in future studies with larger sample sizes. The elevated mortality risk observed here at high HbA1c levels provides further evidence of the value of HbA1c as a tool for managing glycemia in patients with DM HD. The HbA1c range of 6.5% to 7.5% was chosen as the reference group for analyses based on previous studies typically having found lower mortality risks in HD patients in this HbA1c range.[33] We were surprised to find substantially elevated mortality risk among DM HD patients having HbA1c of 6% to 6.5%. However, a sensitivity analysis found this elevated risk only in DOPPS phase 5 but not phase 6, suggesting a lack of consistency in this finding and pointing to the need for

additional future data to continue evaluating this relationship.

As noted in the Guidelines of the Kidney Disease: Improving Global Outcomes, HbA1c level is lower when erythrocyte survival or age is shortened. In HD patients, greater hemolysis and shorter erythrocyte lifespan have both been well-documented, with lower HbA1c levels found with use of erythropoiesis-stimulating agents and iron replacement therapies.[10] In GCC HD patients, mean Hb levels were 0.5 g/dl lower for patients with DM with HbA1c <6.5% (Hb = 10.6 g/dl) versus HbA1c >7.5% (Hb = 11.1 g/dl). Overall, 14% had Hb <9 g/dl, but notably 19% to 22% had Hb < 9 g/dl among patients with HbA1c level of 6% to <7.5%. This difference in Hb levels for patients with DM versus without DM HD differs considerably from what has been found in previous HD cohorts, which have revealed little difference.[34,35] It is conceivable that HbA1c under-represents the true level of hyperglycemia in such highly anemic patients with DM. Poorer outcomes for these patients may occur not only owing to their severe anemia but also owing to actual levels of hyperglycemia not being recognized and treated appropriately if glycemia control is only being evaluated by HbA1c. Anemia correction in combination with close evaluation and treatment of hyperglycemia would seem to be especially important considerations in the care of such patients.

After accounting for anemia in the current study, the relationship of HbA1c with mortality in patients with GCC HD DM is consistent with that found in other HD patient populations. In an earlier DOPPS study based on 2006 to 2010 HD data from 12 countries, Ramirez et al.[33] found a U-shaped HbA1c/mortality relationship with HbA1c 7% to 7.9% displaying the lowest mortality. In Japan DOPPS, a similar U-shaped HbA1c/mortality relationship was found, with the lowest mortality found at HbA1c levels between 6% and <7%.[36] A meta-analysis of 10 studies in HD patients concluded that the lowest mortality was at HbA1c values >6.5% to 7.4%, whereas HbA1c levels ≥8.5% had increased mortality.[37] Similarly, a meta-analysis of 46 studies in patient populations with DM versus without DM found higher mortality risk at HbA1c levels <6% and >8%.[38] The importance of glycemic control in cardiovascular mortality has been found by the 4D Study Group, which revealed a 2-fold higher risk of sudden death in patients with HbA1c >8% versus ≤6%, and with an 18% increase in sudden death for every 1% increase in HbA1c levels.[39] Thus, as concluded by Galindo et al.,[9] HbA1c level of 7% to 8% may be the most favorable for the best outcomes for DM patients in advanced CKD. Furthermore, Navaneethan et al.[40] reported lowest mortality

for nondialysis patients with CKD at HbA1c levels of 6% to 9%. The explanation of the higher mortality found at HbA1c <6% is difficult to ascertain, although hypoglycemia is common in DM dialysis patients. Hypoglycemic agent use was found in nearly half of patients with DM having HbA1c of 6% to 6.5% and in 30% of those with HbA1c <6% in the present study.

Our observational study design limits causal inference owing to possible residual confounding, despite analyses accounting for many factors. Furthermore, our sample size provided some limitations in being able to meaningfully describe mortality risk at all HbA1c levels. Despite these limitations, our study has strong points, including a large DM cohort sample based on randomly selected national samples of HD facilities and patients in each country, and the inclusion of many different patient factors in evaluating the relationships described here.

CONCLUSIONS

In conclusion, DM is highly prevalent among HD patients in the GCC with relatively poor outcomes found among patients with DM HD with an overall higher crude mortality rate, shorter median survival on HD, and considerable associated comorbidity despite having a relatively young mean age of 59.9 years. Primary prevention of diabetes, close monitoring, and maintaining acceptable glycemia control among patients with CKD/ESKD DM and decreasing progression to ESKD should be prioritized by national health systems. Almost half of the patients with GCC DM ESKD are not prescribed antidiabetic medications despite high HbA1c, which may explain the higher negative outcome. The lowest mortality was found at the nadir HbA1c 6.5% to <7.5% in a U-shaped curve of HbA1c with mortality. Thus, numerous challenges are faced by care providers and patients for improving outcomes for this large population of persons with DM receiving maintenance HD in the GCC.

DISCLOSURE

AUTHOR CONTRIBUTIONS

BB, RLP, BMR, AAS, IAS, MAR, SMA, and FAA substantially contributed to conception and design, or acquisition of data, or analysis and interpretation of data. BB, RLP, BMR, AAS, IAS, MAR, SMA, FAA, and AAA drafted the article or revised it critically for important intellectual content; gave final approval of the version to be published; and agree be accountable for all aspects of the work. SMGA confirms that he has had full access to the data in the study and final responsibility for the decision to submit for publication.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)
Figure S1. STROBE Statement.
Figure S2. Percent of patients with diabetes with HbA1c measured within 4 months of DOPPS enrollment, by country in the initial cross-sections of GCC-DOPPS phases 5 and 6 (2012–2018).
Table S1. Patient characteristics in the GCC-DOPPS (2012–2018), by country and diabetes status.
Table S2. HbA1c distribution, by hemoglobin level among GCC-DOPPS patients with diabetes at study enrollment (2012–2018).
Table S3. HbA1c categories and mortality among GCC-DOPPS patients with diabetes (2012–2018), effect of progressive adjustment.

REFERENCES

1. Aljulifi MZ. Prevalence and reasons of increased type 2 diabetes in Gulf Cooperation Council Countries. *Saudi Med J*. 2021;42:481–490. https://doi.org/10.15537/smj.2021.42.5.20200676

2. Meo SA, Sheikh SA, Sattar K, et al. Prevalence of type 2 diabetes mellitus among men in Middle East: a retrospective

study. *Am J Mens Health*. 2019;13:1557988319848577. https://doi.org/10.1177/1557988319848577

3. IndexMundi. Diabetes prevalence (% of populations ages 20–79)—country ranking. IndexMundi. Accessed October 25, 2021. https://www.indexmundi.com/facts/indicators/SH.STA.DIAB.ZS/rankings

4. Doshi SM, Friedman AN. Diagnosis and management of type 2 diabetic kidney disease. *Clin J Am Soc Nephrol*. 2017;12:1366–1373. https://doi.org/10.2215/CJN.11111016

5. Postma MJ, de Zeeuw D. The economic benefits of preventing end-stage renal disease in patients with type 2 diabetes mellitus. *Nephrol Dial Transplant*. 2009;24:2975–2983. https://doi.org/10.1093/ndt/gfp352

6. Rhee CM, Leung AM, Kovesdy CP, Lynch KE, Brent GA, Kalantar-Zadeh K. Update in the management of diabetes in dialysis patients. *Semin Dial*. 2014;27:135–145. https://doi.org/10.1111/sdi.12198

7. Xue JL, Frazier ET, Herzog CA, Collins AJ. Association of heart disease with diabetes and hypertension in patients with ESRD. *Am J Kidney Dis*. 2005;45:316–323. https://doi.org/10.1053/j.ajkd.2004.10.013

8. Hase H, Tsunoda T, Tanaka Y, et al. Risk factors for de novo cardiac events in patients initiating hemodialysis with no previous cardiac symptoms. *Kidney Int*. 2006;70:1142–1148. https://doi.org/10.1038/sj.ki.5001726

9. Galindo RJ, Beck RW, Scioscia MF, Umpierrez GE, Tuttle KR. Glycemic monitoring and management in advanced chronic kidney disease. *Endocr Rev*. 2020;41:756–774. https://doi.org/10.1210/endrev/bnaa017

10. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int*. 2020;98:S1–S115. https://doi.org/10.1016/j.kint.2020.06.019

11. Rhee JJ, Ding VY, Rehkopf DH, Arce CM, Winkelmayer WC. Correlates of poor glycemic control among patients with diabetes initiating hemodialysis for end-stage renal disease. *BMC Nephrol*. 2015;16:204. https://doi.org/10.1186/s12882-015-0204-4

12. Park J, Lertdumrongluk P, Molnar MZ, Kovesdy CP, Kalantar-Zadeh K. Glycemic control in diabetic dialysis patients and burnt-out diabetes phenomenon. *Curr Diab Rep*. 2012;12:432–439. https://doi.org/10.1007/s11892-012-0286-3

13. Kalantar-Zadeh K, Kopple JD, Regidor DL, et al. A1C and survival in maintenance hemodialysis patients. *Diabetes Care*. 2007;30:1049–1055. https://doi.org/10.2337/dc06-2127

14. Kovesdy C, Park JC, Kalantar-Zadeh K. Glycemic control, and burnt-out diabetes in ESRD. *Semin Dial*. 2010;23:148–156. https://doi.org/10.1111/j.1525-139X.2010.00701.x

15. Kalantar-Zadeh K, Derose SF, Nicholas S, Benner D, Sharma K, Kovesdy CP. Burnt-out diabetes: impact of chronic kidney disease progression on the natural course of diabetes mellitus. *J Ren Nutr*. 2009;19:33–37. https://doi.org/10.1053/j.jrn.2008.11.012

16. Young EW, Goodkin DA, Mapes DL, et al. The Dialysis Outcomes and Practice Patterns Study: an international hemodialysis study. *Kidney Int*. 2000;57:S74–S81. https://doi.org/10.1046/j.1523-1755.2000.07413.x

17. Pisoni RL, Gillespie BW, Dickinson DM, Chen K, Kutner MH, Wolfe RA. The Dialysis Outcomes and Practice Patterns Study (DOPPS): design, data elements, and methodology. *Am J Kidney Dis*. 2004;44(suppl 2):7–15. https://doi.org/10.1053/j.ajkd.2004.08.005

18. Pisoni RL, Bieber BA, Al Wakeel J, et al. The dialysis outcomes and practice patterns study phase 5 in the Gulf Cooperation Council countries: design and study methods. *Saudi J Kidney Dis Transpl*. 2016;27(suppl 1):S1–S11. https://doi.org/10.4103/1319-2442.194878

19. Raghunathan T, Solenberger P, Van Hoewyk J. *IVEware: Imputation and Variance Estimation Software User Guide*. 2002.

20. AlSahow A, AlRukhaimi M, Al Wakeel J, et al. Demographics and key clinical characteristics of hemodialysis patients from the Gulf Cooperation Council countries enrolled in the dialysis outcomes and practice patterns study phase 5 (2012–2015). *Saudi J Kidney Dis Transpl*. 2016;27(suppl 1):S12–S23. https://doi.org/10.4103/1319-2442.194885

21. Akmal M. Hemodialysis in diabetic patients. *Am J Kidney Dis*. 2001;38(suppl 1):S195–S199. https://doi.org/10.1053/ajkd.2001.27443

22. Al-Thani H, Shaban A, Hussein A, et al. Cardiovascular complications in diabetic patients undergoing regular hemodialysis: a 5-year observational study. *Angiology*. 2015;66:225–230. https://doi.org/10.1177/0003319714523672

23. Combe C, Albert JM, Bragg-Gresham JL, et al. The burden of amputation among hemodialysis patients in the Dialysis Outcome Practice Pattern Study (DOPPS). *Am J Kidney Dis*. 2009;54:680–692. https://doi.org/10.1053/j.ajkd.2009.04.035

24. Hassanien AA, Al-Shaikh F, Vamos EP, Yadegarfar G, Majeed A. Epidemiology of end-stage renal disease in the countries of the Gulf Cooperation Council: a systematic review. *JRSM Short Rep*. 2012;3:38. https://doi.org/10.1258/shorts.2012.011150

25. Saudi center of organ transplantation annual report 2019. Accessed July 24, 2021. www.scot.gov.sa.

26. Lim WH, Johnson DW, Hawley C, et al. Type 2 diabetes in patients with end-stage kidney disease: influence on cardiovascular disease-related mortality risk. *Med J Aust*. 2018;209:440–446. https://doi.org/10.5694/mja18.00195

27. Lopes AA, Bragg-Gresham JL, Elder SJ, et al. Independent and joint associations of nutritional status indicators with mortality risk among chronic hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Ren Nutr*. 2010;20:224–234. https://doi.org/10.1053/j.jrn.2009.10.002

28. Canaud B, Tong L, Tentori F, et al. Clinical practices and outcomes in elderly hemodialysis patients: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Clin J Am Soc Nephrol*. 2011;6:1651–1662. https://doi.org/10.2215/CJN.03530410

29. Qureshi AR, Alvestrand A, Danielsson A, et al. Factors predicting malnutrition in hemodialysis patients: a cross-sectional study. *Kidney Int*. 1998;53:773–782. https://doi.org/10.1046/j.1523-1755.1998.00812.x

30. Cano NJ, Roth H, Aparicio M, et al. Malnutrition in hemodialysis diabetic patients: evaluation and prognostic influence. *Kidney Int*. 2002;62:593–601. https://doi.org/10.1046/j.1523-1755.2002.00457.x

31. Deger SM, Ellis CD, Bian A, Shintani A, Alp Ikizler T, Hung AM. Obesity, diabetes and survival in maintenance

hemodialysis patients. *Ren Fail*. 2014;36:546–551. https://doi.org/10.3109/0886022X.2013.876351

32. Sanguankeo A, Upala S. Metabolic syndrome increases mortality risk in dialysis patients. A systematic review and meta-analysis. *Int J Endocrinol Metab*. 2018;16:e61201. https://doi.org/10.5812/ijem.61201

33. Ramirez SPB, McCullough KP, Thumma JR, et al. Hemoglobin A1c levels and mortality in diabetic hemodialysis patients. *Diabetes Care*. 2012;35:2527–2532. https://doi.org/10.2337/dc12-0573

34. Pisoni RL, Bragg-Gresham JL, Young EW, et al. Anemia management and outcomes from 12 countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis*. 2004;44:94–111. https://doi.org/10.1053/j.ajkd.2004.03.023

35. Akizawa T, Pisoni RL, Akiba T, et al. Japanese haemodialysis anaemia management practices and outcomes (1999–2006): results from the DOPPS. *Nephrol Dial Transplant*. 2008;23:3643–3653. https://doi.org/10.1093/ndt/gfn346

36. Hoshino J, Larkina M, Karaboyas A, et al. Unique hemoglobin A1c level distribution and its relationship with mortality in diabetic hemodialysis patients. *Kidney Int*. 2017;92:497–503. https://doi.org/10.1016/j.kint.2017.02.008

37. Hill CJ, Maxwell AP, Cardwell CR, et al. Glycated hemoglobin and risk of death in diabetic patients treated with hemodialysis: a meta-analysis. *Am J Kidney Dis*. 2014;63:84–94. https://doi.org/10.1053/j.ajkd.2013.06.020

38. Cavero-Redondo I, Peleteiro B, Álvarez-Bueno C, Rodriguez-Artalejo F, Martínez-Vizcaíno V. Glycated haemoglobin A1c as a risk factor of cardiovascular outcomes and all-cause mortality in diabetic and non-diabetic populations: a systematic review and meta-analysis. *BMJ Open*. 2017;7:e015949. https://doi.org/10.1136/bmjopen-2017-015949

39. Drechsler C, Krane V, Ritz E, März W, Wanner C. Glycemic control and cardiovascular events in diabetic hemodialysis patients. *Circulation*. 2009;120:2421–2428. https://doi.org/10.1161/CIRCULATIONAHA.109.857268

40. Navaneethan SD, Schold JD, Jolly SE, Arrigain S, Winkelmayer WC, Nally JV Jr. Diabetes control and risks of ESRD and mortality in patients with CKD. *Am J Kidney Dis*. 2017;70:191–198. https://doi.org/10.1053/j.ajkd.2016.11.018