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Baseline Anemia Analysis of Hispanic Dialysis Patients with and without Type 2 Diabetes

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Abstract

The complex relationships between chronic kidney disease (CKD), type 2 diabetes, and anemia poses a difficult clinical challenge. The interrelationships between these diseases typically affect hematological profiles in CKD patients. There is a paucity of literature regarding the effects of anemia on patients with CKD and type 2 diabetes in any single ethnic group. We investigated hematologic levels associated with anemia between patients with and without a type 2 diabetes diagnosis within a single ethnic population. A cohort of adult Hispanic, hemodialysis patients attending seven dialysis facilities in San Antonio, Texas was recruited for this retrospective study. Medical record data were collected to ascertain three hematological indicators of anemia: hemoglobin, serum ferritin, and transferrin saturation (TSAT) level. A statistically significant difference for hemoglobin and serum ferritin levels between patients with and without type 2 diabetes was not identified. However, TSAT levels showed a statistically significant difference between both groups. Type 2 diabetic patients exhibited a lower TSAT level of 21.24 ± 9.67%, compared to their non-diabetic counterparts at 23.64 ± 12.19%. Our findings underscore the need for diverse anemia clinical care in patients with a type 2 diabetes diagnosis, and incite the need for further research in this discipline.

Keywords: Neurocysticercosis; Lymphocytes; Plasma cells; Fibroblasts; Astrocytes; Gliosis; *Taenia solium*

Introduction

Chronic kidney disease (CKD) is a common disorder of varying severity that requires a public health approach for prevention, diagnosis, and management. The incidence of CKD is now as high as 200 cases per million per year in many developed countries, with the USA, Taiwan, and Mexico reaching 400 cases per million per year [1]. The National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiatives (K/DOQI) defines CKD as structural or functional abnormalities which cause kidney damage with a glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m^2 that has been present for three or more months [2].

At this point to be Diabetes mellitus is one of the most serious clinical and public health problems facing the world today, with seven million new cases arising each year [3]. Type 2 diabetes is correlated with insulin resistance in target tissues leading to metabolic disturbances that lead to complications including tissue damage, renal dysfunction, and shortened erythrocyte lifespan [3], thereby making it the most common cause of CKD, with the prevalence at 40% among type 2 diabetic adults with some level of CKD [2].

Anemia of inflammation, also known as anemia of chronic disease, is typically characterized by low serum iron and low iron binding capacity in the presence of increased serum ferritin levels [4]. It has been previously reported that patients with chronic renal disease exhibit lower hematological indices due to several factors. Such factors include impaired production of erythropoietin, increased hemolysis, lowered bone marrow erythropoiesis, hematuria, and gastrointestinal blood loss [5]. While the pathogenesis of anemia of CKD includes many factors, it is mainly due to the insufficient production of erythropoietin (EPO) in the failing kidneys [6], with as much as 90% of erythropoietin being produced in the juxtaglomerular apparatus of the kidney [7].

Ethnic minorities show a much greater rate of prevalence of end-stage renal disease (ESRD) with rates of 925 per million for blacks, 501 per million for Hispanics, and 465 per million for Native Americans, compared to 276 per million for non-Hispanic whites [8]. In the past, anemia has been shown to be an independent risk factor for ESRD in high-risk patient groups, yet amelioration of anemia did not prevent the advancement of kidney disease [9].

Most studies observe a heterogeneous group of patients, like those based on the NHANES survey, which have shown that the prevalence of anemia increases in parallel with the severity of CKD [10]. In addition, in patients with type 2 diabetes, the anemia of CKD will occur during earlier stages, be more severe, and is known to trigger a faster progression of renal disease [11]. However, studies looking at a single population, such as that of Chinese patients, concluded that while low hemoglobin may provide some information on the severity of CKD, anemia independently does not have a direct effect on CKD progression [9]. Therefore, further studies must be conducted to show potential relationships between anemia, nephropathy, and renal disease progression, as there has been considerable variation in anemia hematology and nephropathy in patients with diabetes in different ethnicities [9].

While it is known that a patient's hematology profile will change depending on the severity of renal failure [5], few studies have looked at what affect Type 2 diabetes has on the hematological profiles of Hispanic patients with anemia of CKD while on hemodialysis. Indeed, only one study was found to use the United States Renal Data System (USRDS) to analyze the laboratory measurements of patients who were receiving maintenance hemodialysis to determine the differences in

anemia care at different dialysis centers around the United States [12]. However, their study was focused on mortality with a heterogeneous population, and did not investigate changes in hematological profiles based on the presence or absence of type 2 diabetes. Therefore, we sought to determine if there is a difference in the hematology profiles between Hispanic hemodialysis patients with and without type 2 diabetes.

Problem statement

Epidemiological data showing the level of risk the general population suffers from a disease is an important and motivating factor when identifying ways to address and treat it. Hematological differences between Hispanic dialysis patients with and without type 2 diabetes are noteworthy. Type 2 diabetes prevalence is 14% in the Hispanic population [13]. This group suffers a higher risk of mortality and micro-vascular complications including renal disease. Anemia can affect patients at any age, but its more severe effects are predominantly observed in the elderly population, many of which suffer renal failure and therefore prescribed maintenance hemodialysis. Hematology levels, including hemoglobin, ferritin, and transferrin saturation (TSAT) levels, therefore, are suitable clinical indicators to determine differences in disease severity and progression between both groups. Studies reveal that an anemia diagnosis between diabetics and nondiabetics may render differences in improvement patterns in hemodialysis patients [5,7,8] and therefore may influence disease stabilization and hematological level restorations. The fact that the number of Hispanics requiring hemodialysis rose by 70% between 1996 and 2001 [14], correlating with observations that this population is the fastest growing demographic in the U.S [15], illustrates the growing public health concern in this specific population.

The problem is the health management of this population of Hispanics requiring hemodialysis is often a generalized "one-size-fits-all" approach because there is a paucity of published literature addressing the specific needs of specific ethnic populations. Given the previously mentioned statistics, which are disproportionately observed in this ethnic population and considering the potential long-term and sometimes catastrophic sequelae which may ensue from fluctuations in hemoglobin, ferritin, and TSAT levels in patients undergoing maintenance hemodialysis, there is a need to investigate if anemia hematology differences exist between diabetic and non-diabetic patients initiating maintenance hemodialysis. Although uncertain, the data on this relationship may reveal specific nutritional policies for dieticians and may help inform clinical staff to design clinical therapeutic interventions regarding tailored, ethnic-specific therapeutic interventions for Hispanic patients with and without type 2 diabetes diagnosis initiating maintenance hemodialysis.

Materials and Methods

We conducted a retrospective examination of the medical records of hemodialysis patients to determine if hematology levels related to anemia differed in a population of adult Hispanic hemodialysis patients with and without a type 2 diabetes diagnosis. Patient medical records were analyzed at baseline to ascertain possible differences in hemoglobin, ferritin, and TSAT levels between patients with and without type 2 diabetes. Baseline for this study was defined as labs drawn on day 1 from patients that were admitted to 1 of 7 dialysis clinics located in San Antonio, Texas.

This study entailed collecting and analyzing data on the health status and renal measures from medical records of Hispanic dialysis patients seen at a worldwide dialysis company in San Antonio, Texas. These records are maintained on all patients admitted to these facilities. With appropriate permission from the company's research department, data were collected from Center for Medicare and Medicaid Services (CMS)-2728 forms. The CMS-2728 government form is a validated data collection instrument that is completed for all new patients who are initiated on dialysis. These forms have clinical data collected by nursing personnel, including anthropometric measures, as well as renal parameters such as BUN-serum creatinine ratios, hemoglobin A1c, lipid profiles, serum albumin, and calcium, phosphorus, and potassium levels documented at treatment onset. Both weekly and monthly lab tests are documented in the patient's medical records. The primary cause of renal failure and ICD-9 codes for diabetes status and associated comorbidities are documented on the patient's medical records.

With appropriate permission from the company's research department, a request was submitted for permission to access patient medical records at seven dialysis centers: Dialysis Center (#8856), Dialysis Center (#1664), Dialysis Center (#1648), Dialysis Center (#8861), Dialysis Center (#8855), Dialysis Center (#6618), and Dialysis Center (#8868) in San Antonio, Texas, to review the medical records of patients attending these facilities. The numbers in parentheses indicate the official clinic facility numbers that were used for identification and reference in this study. These seven facilities are some of the company's largest dialysis centers in the San Antonio region.

At the time of data collection there were: n=125, n=159, n=140, n=106, n=104, n= 97, and n=106 patients attending #8856, #1664, #1648, #8861, #8855, #6618, and #8868, respectively. Between the seven facilities, there were approximately 837 cumulative patients, undergoing weekly dialysis therapies. Of these patients, Hispanics account for approximately 56%, 75%, 75%, 95%, 95%, 98%, 85% attending #8856, #1664, #1648, #8861, #8855, #6618, and #8868, respectively. Approximately 75% of the Hispanics patients receiving treatments at these facilities have a Type 2 diabetes diagnosis. Dialysis Center #8856 had 56% (n=70/124) Hispanic diabetic patients. Dialysis Center #1664 had 72% (n=115/159) Hispanic diabetic patients. Dialysis Center #1648 had 66% (n=92/140) Hispanic diabetic patients. Dialysis Center #8861 had 70% (n=74/106) Hispanic diabetic patients. Dialysis Center #8855 had 63% (n=66/104) Hispanic diabetic patients/ 106) Hispanic diabetic patients. While the number of diabetic patients at each facility Dialysis Center #6618 had 67% (n=65/97) Hispanic diabetic patients. Dialysis Center #8868 had 66% (n=70 fluctuates slightly over the years, overall the large Hispanic, diabetic and non-diabetic population in these facilities at any given year provided a suitable number of medical records to access for review.

The study population consisted of a cohort of adult, hemodialysis patients attending seven local dialysis facilities in San Antonio, Texas. Each facility followed the exact dialysis treatment protocols and utilized the same documentation system and instrumentation provided by the clinical services department. The same data for both diabetic and non-diabetic patients were collected for each patient from CMS-2728 forms at treatment onset based on their treatment schedules. For older patient records, those prior to 2012, data were extracted from paper records. For patients records documented after 2012, the data were collected and amassed from electronic medical records; the same data were extracted from both paper and electronic records and information about how the transition between paper and

electronic records was implemented, and whether there were any differences in data uniformity in terms of the type of data collected, data documentation and entry, data compilation, and data storage was also documented. To ensure data collection quality control, duplicate entry or spot checks of a small population sample (10%) at each clinic was conducted. The sample population was randomly selected and then divided into two groups, those with a type 2 diabetes diagnosis and those without one.

For this study, IBM Statistical Package for the Social Sciences (SPSS V23) was used for data collection and analysis. SPSS is a widely used and powerful statistical analysis software suite that facilitates data collection and analysis.

Results

To investigate if there is a difference between anemia hematology profiles between hemodialysis patients with and without type 2 diabetes, an independent samples t-test with bootstrap resampling was conducted. The baseline measures of anemia evaluated were hemoglobin, ferritin, and TSAT level. These baseline measures of anemia were from initial blood draw collections upon admission to the dialysis clinics. The bootstrap resampling was set for 1000 samples with replacements. Confidence intervals were set for 95%. The total sample size [N=647] consisted of patients with Type 2 diabetes [n=421] and of patients without Type 2 diabetes [n=226].

The overall baseline measure of hemoglobin level was [M=10.10, SD=3.78, SEM=0.15, 95% CI (9.87, 10.40); Skewness=18.68, SES=0.10, 95% CI (-2.04, 19.74); Kurtosis=432.36, SEK=0.19, 95% CI (5.01, 462.64)]. The baseline measure of hemoglobin level was slightly higher for Type 2 diabetes patients [M=10.13, SD=4.55, SEM=0.22] over patients without type 2 diabetes [M=10.04, SD=1.54, SEM=0.10]. However, the difference in means was not statistically significant [p>0.05] and the Levene's test for equality of variances was also not statistically significant [F=0.29, p>0.05]. With equal variances assumed, the independent samples t-test calculated [MD=0.09, SED=0.31, 95% CI (-0.53, 0.70)]. These results were further supported by bootstrap resampling. The bootstrap resampling baseline measure of hemoglobin level was slightly wider for type 2 diabetes patients 95% CI [9.80, 10.62] over patients without type 2 diabetes 95% CI [9.85, 10.24]. With equal variances assumed, the independent samples t-test with bootstrap resampling calculated [MD=0.09, SED=0.25, 95% CI (-0.33, 0.62)]. Similar results were found for ferritin levels (Table 1).

Clinic	**1648 N=113**	**1664 N=125**	**6618 N=61**	**8855 N=79**	**8856 N=139**	**8861 N=79**	**8868 N=80**
Age	M=65.3 SD=13.4	M=63.8 SD=12.6	M=64.1 SD=12.2	M=63.7 SD=12.9	M=66.9 SD=12.3	M=64.2 SD=12.5	M=64.8 SD=12.3
Gender							
Male	(n=48) 53.9%	(n=53) 45.3%	(n=36) 60.0%	(n=36) 48.0%	(n=54) 54.5%	(n=40) 55.6%	(n=32) 45.7%
Female	(n=41) 46.1%	(n=64) 54.7%	(n=24) 40.0%	(n=39) 52.0%	(n=45) 45.5%	(n=32) 44.4%	(n=38) 54.3%
Ethnicity							
Hispanic or Latino	(n=56) 62.9%	(n=72) 61.5%	(n=52) 86.7%	(n=68) 90.7%	(n=41) 41.4%	(n=59) 81.9%	(n=57) 81.4%
Non-Hispanic or Latino	(n=33) 37.1%	(n=45) 38.5%	(n=8) 13.3%	(n=7) 9.3%	(n=58) 58.6%	(n=13) 18.1%	(n=13) 18.6%
Diabetic	(n=54) 60.7%	(n=75) 64.1%	(n=43) 71.7%	(n=50) 66.7%	(n=66) 66.7%	(n=42) 58.3%	(n=51) 72.9%
Non-diabetic	(n=35) 39.3%	(n=42) 35.9%	(n=17) 28.3%	(n=25) 33.3%	(n=33) 33.3%	(n=30) 41.7%	(n=19) 27.1%

Table 1: Summary of Participant Anthropometrics and Diabetes Status by Clinic Based on Medical Records Review.

The overall baseline measure of ferritin level was [M=423.91, SD=671.40, SEM=26.40, 95% CI (376.66, 478.64); Skewness=10.29, SES=0.10, 95% CI (1.85, 11.35); Kurtosis=144.32, SEK=0.19, 95% CI (4.55, 200.07)]. The baseline measure of ferritin level was slightly lower for type 2 diabetes patients [M=399.93, SD=610.72, SEM= 29.76] over patients without type 2 diabetes [M=468.58, SD=771.31, SEM=51.31]. However, the difference in means was not statistically significant [p>0.05] and the Levene's test for equality of variances was statistically significant [F=1.16, p<0.05]. With equal variances assumed, the independent samples t- test calculated [MD=-68.65, SED=55.34, 95% CI (-177.32, 40.03)]. These results were further supported by bootstrap resampling. The bootstrap resampling baseline measure of ferritin level was slightly more narrow for Type 2 diabetes patients 95% CI [350.04, 462.52] over patients without type 2 diabetes 95% CI [388.68, 575.53]. With equal variances assumed, the independent samples t-test with bootstrap resampling calculated [MD=-68.65, SED=57.62, 95% CI (-188.40, 30.29)]. Opposing results were found for TSAT levels.

The overall baseline measure of TSAT level [M=22.08, SD=10.67, SEM=0.42, 95% CI (21.30, 22.97); Skewness=1.25, SES=0.10, 95% CI (0.95, 1.53); Kurtosis=2.59, SEK=0.19, 95% CI (1.32, 4.00)]. The baseline measure of TSAT level was slightly lower for Type 2 diabetes patients [M=21.24, SD=9.67, SEM=0.47] over patients without type 2 diabetes [M=23.64, SD=12.19, SEM=0.81]. Further, the difference in means was found to be statistically significant [p<0.05] and the Levene's test for equality of variances was also found to be statistically significant [F=11.49, p>0.05]. With equal variances not assumed, the independent samples t-test calculated [MD=-2.40, SED=0.94, 95% CI (-4.24, -0.56)]. These results were further supported by bootstrap resampling. The bootstrap resampling baseline measure of TSAT level was slightly more narrow for Type 2 diabetes patients 95% CI [20.34, 22.16] over patients without type 2 diabetes 95% CI [22.07, 25.35]. With equal variances not assumed, the independent samples t-test with bootstrap resampling calculated [MD=-2.40, SED=0.92, 95% CI (-4.35, -0.64)].

Discussion

The results of our study showed no statistically significant difference for hemoglobin and serum ferritin levels between those patients with type 2 diabetes compared to those without type 2 diabetes. However, a statistically significant difference in TSAT levels between the two groups was identified.

Diabetic and non-diabetic patients had hemoglobin levels below norm anemic levels of 13 g/dL for men and 12 g/dL for women as published by the WHO [15]. These findings were expected, as they corresponded with the established literature that patients suffering from diabetes and micro-vascular disease exhibit a declination of hemoglobin and GFR levels in parallel with their debilitating disease [16]. It has previously been reported that patients with chronic renal disease have lowered hematological indices due to several factors. Such factors include impaired production of EPO, increased hemolysis, lowered bone marrow erythropoiesis, hematuria, and gastrointestinal blood loss [5]. Our findings, showing no significant difference in hemoglobin levels between both the diabetic and non-diabetic patient groups, reflect similar findings by Cana-Ruiu, et al. [17].

Serum ferritin levels are a key hematological indicator and are a standard clinical measurement to determine the status of iron in patients [18]. Serum ferritin is an acute phase reactant and indicator of acute and chronic inflammation and is elevated in multiple inflammatory diseases including CKD. This elevation indicates higher levels of total body iron storage, yet these iron stores are not available for hematopoiesis partly leading to anemia of inflammation. While we found no significant difference in ferritin levels between patients with type 2 diabetes and those without, it is notable that ferritin levels were lower in those with diabetes compared to those without the disease. These findings are in contrast with Cana-Ruiu, et al. which reported higher ferritin levels in patients with type 2 diabetes.

Transferrin is a protein that captures iron that has been absorbed from the GI tract and released from macrophages to deliver it to maturing red blood cells. Patients with CKD are known to have decreased transferrin levels, impairing iron mobilization, and increasing the risk for bleeding and iron loss. Hemodialysis patients are particularly at risk of iron loss due to the chance for blood loss during dialysis [15]. The patients with type 2 diabetes in our study were found to have a mean TSAT percentage of 21.24 ±9.67%, while those patients without type 2 diabetes had a mean TSAT percentage of 23.64 ± 12.19%, a statistically significant difference. These percentages are indicative of patients suffering from anemia with severe iron deficiency and correlate with the findings of Lau et al. [19]. TSAT, in relation to circulating iron, is the serum iron content divided by the total iron-binding capacity. A TSAT level below 20% is associated with absolute iron deficiency, according to the K/DOQI [20]. A difference in TSAT percentage between the two patient groups is not entirely surprising, as type 2 diabetes is known to produce numerous long-term physiological complications including shortened erythrocyte lifespan due to oxidative damage [4], which makes TSAT restoration efforts in dialysis patients with type 2 diabetes a clinical challenge.

Conclusion

There is a strong conceptual premise, clinical basis, and biological plausibility to suggest that anemia manifests dissimilarly in patients with and without type 2 diabetes. The conventional standards of care among dialysis clinicians are to provide standardized anemia therapy for all dialysis patients as a homogenous group. However, there is no empirical evidence to fully support these standardized anemia therapeutics. Currently, there is no diversity in anemia management for patients with a type 2 diabetes diagnosis, despite the theoretical concerns. The lack of statistical significance, specifically for hemoglobin and serum ferritin, should not be interpreted to mean that these levels in the diabetic group should not be addressed differently than those without a type 2 diabetes diagnosis from a clinical perspective; it only means that it was not entirely demonstrable in this specific study. Additionally, the lack of statistical significance for these two hematology levels should not be dismissed as not supporting their potential to modulate hemoglobin and ferritin levels in this group. This study represents one sample population that may not have demonstrated the expected results that align with the existing body of knowledge.

Although the results for hemoglobin and serum ferritin support the null hypothesis, they do have intrinsic value. While previous studies have shown differences in hematological indices [5], other studies have not [8,12]. These contradictory results may spawn further research investigations that may help reconcile this research contradiction. Our research findings may be of significant interest, particularly the hematological differences that exist between Hispanic diabetic and non-diabetic patients, to both nephrology and diabetology disciplines. We recommend further prospective time series analyses to identify possible patterns in anemia levels through the course of their dialysis treatments. This can help further illuminate the intricate, complex relationship between anemia, type 2 diabetes, and progressive renal disease.

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