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Survival Disparities within American and Israeli Dialysis Populations: Learning from Similarities and Distinctions across Race and Ethnicity

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Abstract

There are counterintuitive but consistent observations that African American maintenance dialysis patients have greater survival despite their less favorable socioeconomic status, high burden of cardiovascular risks including hypertension and diabetes, and excessively high chronic kidney disease prevalence. The fact that such individuals have a number of risk factors for lower survival and yet live longer when undergoing dialysis treatment is puzzling. Similar findings have been made among Israeli maintenance dialysis patients, in that those who are ethnically Arab have higher end-stage renal disease but exhibit greater survival than Jewish Israelis. The juxtaposition of these two situations may provide valuable insights into racial/ethnic-based mechanisms of survival in chronic diseases. Survival advantages of African American dialysis patients may be explained by differences in nutritional status, inflammatory profile, dietary intake habits, body composition, bone and mineral disorders, mental health and coping status, dialysis treatment differences, and genetic differences among other factors. Prospective studies are needed to examine similar models in other countries and to investigate the potential causes of these paradoxes in these societies. Better understanding the roots of racial/ethnic survival differences may help improve outcomes in both patients with chronic kidney disease and other individuals with chronic disease states.

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Racial Disparities and High Mortality among US Dialysis Population

Approximately 11% of the United States (US) adult population may have chronic kidney disease (CKD), a progressive and irreversible disease with currently no cure (1). At end-stage renal disease (ESRD), kidney transplantation or chronic dialysis treatment is needed to survive. Racial and ethnic discrepancies in CKD have persisted over the past 30 years (2,3). The ESRD incident rates for African Americans are 3.6 times greater than non-Hispanic whites (4). Similarly, ESRD prevalent rates are higher in African Americans compared to non-Hispanic whites, i.e., 5004 vs. 1194 per million US population, respectively (4). Across virtually all age groups, 1/3 of US dialysis patients are African Americans, when compared to 14% of the US general population (4–6). Examining unresolved racial disparities in CKD is declared a subject for high priority research by the US Agency for Healthcare Research and Quality and many other opinion leaders (3,7), given the high health care expenditure, extremely high CKD burden among minorities, and poor CKD outcomes across all races.

Although dialysis therapy is lifesaving, ~20% of maintenance dialysis patients still die each year in the US, a 5-year survival rate of ~35%, which is worse than most cancer survivals (8). At any given age group, dialysis mortality is several times higher than in nondialysis Medicare patients. Over one-half of the ESRD deaths are caused by cardiovascular or infectious events (9). The etiology of this excessively poor outcome is unknown. Efforts over the past three decades to treat conventional cardiovascular risk factors in dialysis patients, including management of hypercholesterolemia and hypertension, have not substantially changed mortality (10). In two recent randomized trials, the 4D (11) and AURORA (12) studies, neither survival nor cardiovascular outcomes improved in dialysis patients with the use of such HMG coenzyme A reductase inhibitors as atorvastatin or rosuvastatin, respectively. Additional efforts targeting dialysis dose or technique also showed no survival impact (13,14). Discovering novel mechanisms of high CKD mortality in a population where minorities are exceptionally over-represented may help to identify the causes of their poor outcomes.

Survival Disparities across Race

In the US general population, disparities in income, education, and health have been implicated as causes of the higher total mortality and shorter life expectancy of African Americans compared with whites over the past several decades (Fig. 1) (15–17). However, for reasons that have remained essentially unexplainable, racial and ethnic minorities among dialysis patients, in particular African Americans, have greater survival than whites (18,19). These disparities in racial survival in maintenance dialysis patients have persisted for decades (Fig. 2) (18). The greater survival of minority dialysis patients persists irrespective of demographic, residency, dialysis modality (hemo- vs. peritoneal), and dialysis dose or technique (4,18–20). African American dialysis patients are 17% less likely to die of cardiovascular disease than whites (4,20). Examining this unusual disparity may be the key to discovering the factors that can improve longevity in all patients with CKD and possibly in other populations with chronic diseases.

The persistent observation that African Americans dialysis patients have greater survival despite their less favorable socioeconomic status, high burden of cardiovascular risk factors, including hypertension and diabetes, and excessively high CKD prevalence, is counterintuitive and puzzling. An understanding of the causes of these disparities could provide information relevant to clinical and public health, not only for CKD but for other chronic disease states with poor survival. If the biologic basis for these survival disparities can be identified, if these survival differences are proven to have biologic plausibility, and if such factors and conditions as the nutritional or bone-mineral status or the psycho-social

factors, rather than the traditional cardiovascular risk factors, are shown to protect against early death in such multimorbid dialysis patients and lead to such survival disparities across races/ethnicities in sharp contradistinction to all expectations, then they need to be examined urgently via biologically plausible hypotheses. Such discoveries may be an important step in medicine and public health as strategies might be developed to improve clinical outcomes of millions of people with chronic diseases worldwide (21).

Other Relevant Minority Models in the US

Whereas the lower dialysis mortality of African Americans contrasts sharply with the general population where African Americans have a shorter life expectancy than whites, this is not the only outcome paradox observed in minorities (15–17). A similar phenomenon is observed in preterm black infants who are more likely to survive than preterm white infants, although term baby survival is the opposite (22,23). US Hispanics have a lower than average incidence of most chronic illnesses but better than expected survival despite their relatively poor socioeconomic status, the so-called Hispanic Paradox (24–27). Yet they are twice as likely to develop CKD as non-Hispanic whites (28–30), what has been referred to as a “Hispanic paradox-within-a-paradox” (5). Indeed, even though the prevalence of type 2 diabetes is 2–5 times higher in Hispanics (31,32), when diabetic Hispanics undergo dialysis treatment, they are more likely to survive than non-Hispanic white diabetics (33,34), which can be considered as yet another example of a paradox-within-paradox (5). Obesity is generally more common in Hispanics (35,36), a condition predisposing to many adverse complications but which paradoxically may act protectively in Hispanics with ESRD who are at high risk for protein energy wasting (PEW) (5). Although Hispanics exhibit same the hypertension rate as in the general population, their incidence of hypertensive ESRD is 2.5 times higher (37,38).

Israeli Model

Arab citizens of Israel account for approximately 20% of the Israeli citizens. Different socioeconomic status and other differences for Arabs may create a backdrop that parallels African Americans in the US. By contrast, the retention of cultural heritage, the lack of a relatively recent period of enslavement, and a less dramatic physical distinction are among many of the factors that distinguish the contextual milieu of the two groups (Table 1).

According to the data from the Renal Registry of the “Israeli Society of Nephrology and Hypertension” and “Israel Center for Disease Control,” at the end of 2007 there were 4800 dialysis patients in Israel including 23% Ethnic Arabs (consisting of Muslim and Christian Arabs) (39). At this same time, Arabs constituted 19% of the total population of Israel (40), indicating a 1.2 times higher dialysis prevalence in this ethnic group. Between 1990 and 2007, there was a 71% increase in the incident rate of dialysis patients in Israel (40). The average age ($\pm$ SD) of incident dialysis patients increased from 55.6 ± 19.0 years in 1990 to 64.6 ± 17.1 years in 2007. The dialysis incident rate increased in both ethnic Arabs and non-Arabs, who are essentially Jewish Israelis. The age- and gender-adjusted dialysis patient incidence rates per 100,000 population among Israeli Jews increased from 11 in 1990 to 20 in 2007 (an increase of 84%). The same adjusted incidence rate among Israeli Arabs rose even more strikingly during the same period, i.e., from 13 to 43 per 100,000 population, indicating a 330% increase, which was 2.1 times higher than that of the Jewish population in 2007 (Fig. 3) (39). The main cause of ESRD is diabetes mellitus, which has increased in both Arab and Jewish patients from 18% to 42%.

Survival rates of Israeli maintenance dialysis patients are rather similar to the United States and Western European countries, i.e., 75–85% per year. Among 17,420 incident dialysis patients who began dialysis treatment between 1990 and 2007, 80%, 67%, and 55% of

patients survived the first, second and third year of dialysis treatment, respectively (39). However, there appears to be a noticeable survival disparity between Arab and Jewish dialysis patients; 85% of Arab and 79% of Jewish maintenance dialysis patients survived at least 1 year of initiation of renal replacement therapy (Fig. 4). These data stand in contrast to the life expectancy of Israeli Arabs without CKD, which is slightly (3–4 years) lower than that of the Jewish populations (40,41). The main causes of death in the Israeli Arabs without CKD are chronic diseases and attributed mainly to higher rates of heart disease and diabetes mellitus (40).

The 5-year and 10-year survival rates among Arab vs. Jewish maintenance dialysis patients are 48% vs. 35% and 22% vs. 11%, respectively (39). Whereas Arab dialysis patients in Israel are slightly younger than the Jews, their prevalence rate for diabetes is higher. It is important to note that these are crude data and that adjustment for some parameters including age, gender, dialysis vintage, and primary renal disease mitigates the statistical significance. Additional adjustment for detailed comorbid states and/or laboratory data such as those related to nutritional status and inflammation would help identify the main contributors to these differences.

There are more Israeli Arab patients with ESRD per Arab population living with a functioning kidney transplant compared to Jewish renal transplant recipients per Jewish population (39). Indeed, the prevalence rates of renal transplantation among Arabs and Jews were 8.6 and 7.7 per 100,000 population in 1990, which, by 2007, had increased in both groups by 4.7-fold to 40.3 and 36.5 per 100 000, respectively (Fig. 5). According to a recent study, the allocation of cadaveric kidneys between young Jewish and Arab dialysis patients did not differ and was associated with comparable waiting times, identical renal transplant scores, and similar long-term outcome (42). This is a remarkable finding in the face of the unequal race allocation of renal transplant in the United States. Putting together, these data indicate that Israeli Arab patients with ESRD have maintained both a greater survival and a higher transplantation.

Potential Etiologies of Dialysis Survival Disparities

Several hypothetical mechanisms may lead to the racial survival disparities regarding CKD in the United States (Fig. 6): (5,6) (i) racial/ethnic differences in nutritional inflammatory status and diet (43), (ii) differences in mineral-and-bone disorders (MBD) including in hyperparathyroidism and vitamin D (44–46), (iii) differences in psychosocial status, subjective perception of quality of life and coping mechanisms (47–49), (iv) differences in dialysis treatment and techniques (50), and (v) genetic and other inherent differences related to CKD progression (6,51–53), in particular the role of nonmuscle myosin heavy chain 9 (MYH9) gene in Nephropathy of African Americans (53). MYH9 polymorphisms may affect clinical outcomes in severe kidney disease; such gene effects are rarely encountered in practice (53). Notwithstanding the potentially important role of genotype, we feel that a priority research is the nutritional, anti-inflammatory, and dietary axis as the most promising line of investigation, whereas each of these hypotheses may represent biologically plausible and intervention-amenable areas to be examined as alternative and/or coexisting mechanisms to this end (Table 1).

Race/Ethnicity and Protein-Energy Wasting

The recent “International Society of Renal Nutrition and Metabolism” (ISRNM) Consensus Conference defined “PEW” as a common condition in patients with CKD (54) and acknowledged the need for race- and ethnicity-specific research on PEW criteria. For instance, the body composition measures or biomarkers may be significantly different across diverse racial and ethnic subgroups. Whereas a BMI of 22 kg/m² may be considered within

the desired range for a non-Hispanic Caucasian dialysis patient, it may be considered high for a female Asian patient or low for a male African American patient, as recently showed in a 54,000 hemodialysis patient cohort (55). Asian American dialysis patients tend to have increased mortality with BMI > 25 kg/m² (55–57), whereas Caucasian and African American patients have greater survival (58,59). Similarly, the so-called lipid paradox (higher mortality with lower serum cholesterol) does not hold in African American hemodialysis patients. In these latter individuals, a LDL-cholesterol >70 mg/dL is indeed associated with twofold increase in cardiovascular death risk, whereas for other races the opposite association has been found (60).

Reduced intake and reduced levels of antioxidant vitamins have been observed in maintenance patients (61), likely due to imposed dietary restriction of fresh fruits and vegetables to avoid hyperkalemia (61,62) and also to lower intake of foods high in phosphorus and calcium (63–65). Hypoalbuminemia and decreased protein intake is strongly associated with mortality in patients with CKD (66), and restricting protein intake, a common approach to lower dietary phosphorus, appears associated with higher death risk in dialysis patients (63,67). Economically and socially disadvantaged dialysis patients may be less compliant with such dietary protein restrictions. We feel that it is time to raise such provocative question as to whether a higher intake of dietary protein (despite high phosphorus burden) and other biologically valuable foods (despite higher potassium content) among minorities in both United States and Israel may play a role in their greater survival. Some foods may contain nutraceuticals that may modulate inflammatory or oxidative mediators or enhance their gene expressions (68–70). Hence, we hypothesize that certain dietary habits in certain racial/ethnic groups may modulate such dyslipidemic, proinflammatory, and prothromboembolic conditions leading to differences in survival across the ethnic and racial groups (Fig. 6) (71).

MBD and CKD Disparities

Virtually, all maintenance dialysis patients have some degree of MBD including secondary hyperparathyroidism, vitamin D deficiency, mineral disarrays, renal osteodystrophy, and vascular calcification (72–75). Strong associations between surrogates of CKD–MBD such as high parathyroid hormone (PTH) level or hyperphosphatemia and survival are reported (76–78). Administration of vitamin D receptor activators (VDRA) is associated with improved CKD survival (79–81). Across different racial and ethnic groups of dialysis patients, however, African Americans have higher PTH and lower vitamin D levels (44–46). A recent study showed that only African American maintenance hemodialysis patients who received VDRA (44) or even higher doses of VDRA (45) had greater survival than whites. Whereas it is less likely that the administration of a single medication explain the 3-decade-old CKD racial survival disparities, close links may exist between protein intake and impact of MBD on mortality in dialysis patients (63), suggesting that low PTH may be another facet of PEW (76). We are not aware of any data related to potential differences in MBD profile between Israeli Arab and Jewish dialysis patients.

Psychosocial and Cultural Factors and Mental Health

Significant differences in psychosocial and cultural factors exist among US dialysis patients (82–84). Whereas some of these differences may be related to socioeconomic status, race, and ethnicity are important independent determinants of diversity in psychosocial characteristics (85,86). Some studies have indicated that African Americans generally prefer more aggressive treatment at the end of life than whites (87). Strong religiosity or spirituality of African Americans may play a role (88). However, it is not clear whether the African Americans' perception of life influences their better survival when they undergo

dialysis treatment (89). To the best of our knowledge, there are no data to examine such differences between Israeli Arab and Jewish maintenance dialysis patients, although differences in culture and perception of life should exist.

A recent study examined the role of ethnicity and spiritual coping in cancer patients' end-of-life treatment preferences and reported that African Americans were more likely to desire life-sustaining measures than the Caucasians (90). In another study, 51 African American patients expressed varied levels of psychosocial and spiritual well-being, a characteristic associated with life-sustaining treatment preferences (85). Health-related quality of life measures via SF36 are strong predictors of survival and hospitalization in patients with CKD (91) and correlate with their nutritional status (92,93). Sexual dysfunction, which affects the perception of well-being in dialysis patients, has significant variation across race (94). Patients with CKD from underserved socioeconomic background may not fully adhere to treatment regimens (89,95,96), but nonadherence and its impact on survival is still not well understood. Previous studies have tended to neglect the study of phenomenological perceptions and psychosocial influences on nonadherence behavior as well as issues unique to culturally diverse populations.

Epilogue

Notwithstanding the racial and ethnic differences in CKD rates, there are some less discouraging facts pertaining to interaction of health outcomes and race/ethnicity. Even though two-thirds of all US dialysis patients die within 5 years of initiating maintenance dialysis treatment, African American and other minorities have consistently greater survival over the past several decades than whites who need dialysis therapy. A similar survival disparity model appears to exist in the crude rates of Israeli Arab and Jewish patients with ESRD. Discovering the factors responsible for survival advantages of minority dialysis patients in these two nations and other areas in the world may have major clinical and public health implications. Improving health delivery and outcomes in patients with CKD in the United States and across the globe may be reinforced by studying different health systems in other nations and comparing their similarities and distinctions. Examining the regulated solid organ purchase in Iran (97), a country with distinct CKD disparities (98), has contributed to heightened discussion among US nephrologists to this end. Similarly, studying the survival and ethnic disparities among Israeli dialysis patients and their similarities and distinction compared to US CKD population may lead to approaches for improving clinical outcomes in all dialysis patients as well as in populations with other chronic disease states associated with poor survival (8).

We hypothesize that independent of access to care, such factors as dietary and/or inflammatory status, better bone and mineral disorder profile, and/or better mental health and coping capabilities may play a role in engendering the observed CKD survival differences; however, robust data to support these hypotheses are yet to be fully developed. A healthier nutritional status and dietary intake as a result of less restrictive dietary habits may be a cause of the survival advantages of minority dialysis patients, notwithstanding that this might mean to modify or even liberalize at least some of the strict dietary restrictions imposed upon maintenance dialysis patients to control phosphorus, potassium, water and salt. Prospective observational studies and trials of nutritional interventions are warranted to examine whether longevity can be improved in patients with CKD across the globe and other populations with chronic disease states. Additional models among dialysis patients in other countries with racial/ethnic minorities (99) or among other medical conditions and chronic disease states should be examined to learn from distinctions and similarities and advance novel and biologically plausible hypotheses. We face the urgency for immediate

action and the unique opportunity to discover the mechanisms responsible for these disparities and to module them to improve clinical outcomes of all patients.

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Fig. 1. Comparing mortality in the general population of African Americans and Caucasians in the United States (US Census Bureau Vital Statistics, 2010). The y-axis is mortality rate.

Fig. 2.
Crude annual mortality US dialysis patients: African Americans vs. whites (USRDS data 2009).

Fig. 3.
Rise in the incidence of end-stage renal disease in Israel in both Arabs and Jews (39).

Fig. 4. Kaplan–Meier survival graphs comparing the survival rates from the time of first dialysis treatment in Israeli dialysis patients between Arabs and Jews (39).

Fig. 5. Rise in the prevalence of patients with a functioning kidney transplant in Israel in both Arabs and Jews (39).

Fig. 6.
Potential mechanisms leading to survival disparities of African American dialysis patients.

Table 1
Comparison between African Americans and Israeli Arabs with regard to end-stage renal disease (ESRD)

Type	Characteristics	African Americans in the United States	Israeli Arabs
GP	Type of base population	Highly industrialized nation, mostly white European	Moderately to highly industrialized, white
GP	Minority population proportion *	14%	19%
GP	Socioeconomic status and education level	Different income and education level	Different income and education level
GP	Life expectancy *	Lower than whites	Slightly lower than Jews
GP	Retention of cultural heritage	Highly acculturated	Cultural heritage mostly maintained
GP	Recent period of enslavement	Yes	No
GP	Physical (phenotypic) distinction	Substantial	Less dramatic
GP	Genotypic distinction	Major distinction	Some distinction
CKD	Burden of ESRD in the minority	Three (3) times higher than white non-Hispanic Americans	1.2 times higher than Jewish Israelis
CKD	Age at the start of ESRD	Younger than non-Hispanic whites	Younger than Jewish Israelis
CKD	Causes of ESRD in minority	Higher prevalence of hypertension and diabetes	Higher prevalence of diabetes
CKD	ESRD survival of the minority	Greater survival	Greater survival
CKD	Kidney transplant rate	Lower than the majority	Same or slightly higher
CKD	Access to dialysis therapy	Same as majority	Same as majority
CKD	Dietary profile	Higher protein intake? Less compliance with diet restrictions?	No clear data but anecdotally higher dairy protein intake
CKD	Nutrition inflammation	Larger muscle mass, higher serum creatinine	Likely larger lean body and muscle mass
CKD	MBD profile	Higher PTH, lower 25-D level, higher likelihood of VDRA (with higher doses)	No data
CKD	Mental health and coping	Likely better coping capabilities with ESRD	No data

CKD, chronic kidney disease; VDRA, vitamin D receptor activators.

* GP: General population, pertains to the non-CKD population.