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Original Investigation

Dental Health and Mortality in People With End-Stage Kidney Disease Treated With Hemodialysis: A Multinational Cohort Study

*Suetonia C. Palmer, PhD,[1] Marinella Ruospo, MSc,[2,3] Germaine Wong, PhD,[4] Jonathan C. Craig, PhD,[4] Massimo Petruzzi, PhD,[5] Michele De Benedittis, PhD,[6] Pauline Ford, PhD,[7] David W. Johnson, PhD,[7,8] Marcello Tonelli, MD,[9] Patrizia Natale, MSc,[2] Valeria Saglimbene, MSc,[2] Fabio Pellegrini, MSc,[10] Eduardo Celia, MD,[2] Ruben Gelfman, MD,[2] Miguel R. Leal, MD,[2] Marietta Torok, MD,[2] Paul Stroumza, MD,[2] Anna Bednarek-Skublewska, MD,[2,11] Jan Dulawa, MD,[2,12] Luc Frantzen, MD,[2] Juan Nin Ferrari, MD,[2] Domingo del Castillo, MD,[2] Amparo G. Bernat, MD,[2] Jorgen Hegbrant, PhD,[2] Charlotta Wollheim, MSc,[2] Letizia Gargano, MSc,[2] Casper P. Bots, PhD,[13] and Giovanni F.M. Strippoli, PhD,[2,4,5,14] on behalf of the ORAL-D Study Investigators**

Background: Dental disease is more extensive in adults with chronic kidney disease, but whether dental health and behaviors are associated with survival in the setting of hemodialysis is unknown.

Study Design: Prospective multinational cohort.

Setting & Participants: 4,205 adults treated with long-term hemodialysis, 2010 to 2012 (Oral Diseases in Hemodialysis [ORAL-D] Study).

Predictors: Dental health as assessed by a standardized dental examination using World Health Organization guidelines and personal oral care, including edentulousness; decayed, missing, and filled teeth index; teeth brushing and flossing; and dental health consultation.

Outcomes: All-cause and cardiovascular mortality at 12 months after dental assessment.

Measurements: Multivariable-adjusted Cox proportional hazards regression models fitted with shared frailty to account for clustering of mortality risk within countries.

Results: During a mean follow-up of 22.1 months, 942 deaths occurred, including 477 cardiovascular deaths. Edentulousness (adjusted HR, 1.29; 95% CI, 1.10-1.51) and decayed, missing, or filled teeth score $\geq$ 14 (adjusted HR, 1.70; 95% CI, 1.33-2.17) were associated with early all-cause mortality, while dental flossing, using mouthwash, brushing teeth daily, spending at least 2 minutes on oral hygiene daily, changing a toothbrush at least every 3 months, and visiting a dentist within the past 6 months (adjusted HRs of 0.52 [95% CI, 0.32-0.85], 0.79 [95% CI, 0.64-0.97], 0.76 [95% CI, 0.58-0.99], 0.84 [95% CI, 0.71-0.99], 0.79 [95% CI, 0.65-0.95], and 0.79 [95% CI, 0.65-0.96], respectively) were associated with better survival. Results for cardiovascular mortality were similar.

Limitations: Convenience sample of clinics.

Conclusions: In adults treated with hemodialysis, poorer dental health was associated with early death, whereas preventive dental health practices were associated with longer survival.

INDEX WORDS: Renal failure; end-stage kidney disease; hemodialysis; oral health; oral hygeine; dental disease; all-cause mortality; cardiovascular mortality; modifiable risk factor; ORAL-D (Oral Diseases in Hemodialysis) Study.

From the [1]University of Otago, Christchurch, New Zealand; [2]Diaverum Medical Scientific Office, Lund, Sweden; [3]Amedeo Avogadro University of Eastern Piedmont, Novara, Italy; [4]University of Sydney, Sydney, Australia; [5]University of Bari, Bari; [6]Universita' del Piemonte Orientale, Vercelli, Italy; [7]University of Queensland; [8]Translational Research Institute, Brisbane, Australia; [9]University of Calgary, Calgary, Canada; [10]Global Medical Biogen Idec, Cambridge, MA; [11]Medical University of Lublin, Lublin; [12]Medical University of Silesia, Silesia, Poland; [13]Academic Centre for Dentistry Amsterdam (ACTA), Oral Biochemistry, Amsterdam, the Netherlands; and [14]Diaverum Academy, Lund, Sweden.

[*]A list of the ORAL-D (Oral Diseases in Hemodialysis) Study Investigators appears in the Acknowledgements.

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Address correspondence to Giovanni Strippoli, MD, PhD, Department of Emergency and Organ Transplantation, University of Bari, Piazza Giulio Cesare, 70124 Bari, Italy. E-mail: gfmstrippoli@gmail.com

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Chronic kidney disease (CKD) is responsible for approximately 12 billion years of life lost to premature mortality or lived with disability each year.[1] Patients with end-stage kidney disease treated with dialysis have a particularly heavy burden of severe symptoms[2] and can expect to live for only 4 to 5 years on average.[3,4] Despite decades of research, no treatment strategies have been shown to improve critical health outcomes, such as mortality, in people with end-stage kidney disease.

Oral health represents a potential determinant of health outcomes in people with end-stage kidney disease. Dental conditions such as caries, tooth loss, and poor oral hygiene are nearly universal worldwide, particularly affecting disadvantaged populations,[5,6] and are associated with excess mortality, including cardiovascular and cancer-related deaths.[7-9] Adults who have CKD have more severe oral disease than the general adult population,[10] yet infrequently use dental services.[11] Oral disease is associated with inflammation and malnutrition, which may accelerate cardiovascular disease in the setting of dialysis treatment, and therefore represents a putative etiology for cardiovascular events in the context of kidney failure.[12,13]

To our knowledge, the Oral Diseases in Hemodialysis (ORAL-D) Study[14] is the first cohort study to investigate whether oral disease using standardized assessments of dental disease and preventative dental health practices are associated with early death independent of existing cardiovascular disease and other sociodemographic factors.

METHODS

Study Population and Data Source

The ORAL-D Study included consecutive adults 18 years or older who had been treated with long-term hemodialysis within a convenience sample of clinics operated by a single dialysis provider in Europe (France, Hungary, Italy, Poland, Portugal, and Spain) and South America (Argentina).[14] We enrolled participants from July 2010 to February 2012. Patients were not enrolled if they had cognitive impairment sufficient to preclude consent or they preferred not to participate.

Demographic, clinical, laboratory, and dialysis-related data were obtained from linked databases using a unique identification code. All participants underwent a standardized oral examination by a dentist trained in periodontology, according to World Health Organization (WHO) guidelines.[15] All dentists participated in a teleconference to calibrate the protocol before examining patients. All participants anonymously completed questionnaires about self-reported dental care practices.[16] The exposures in analyses were edentulousness (complete absence of teeth), extent of dental disease (decayed, missing, or filled teeth), brushing teeth, dental flossing, use of mouthwash, frequency of changing toothbrush, time spent each day on oral hygiene, age of first visit to a dental practitioner, and time elapsed since the most recent dental visit.

Data for total and cause-specific mortality were obtained from a centralized database in which changes to patient status were updated by managing clinicians on a monthly basis. Cardiovascular death was adjudicated by participants' treating clinicians, who were unaware of dental exposures. Deaths were classified as due to cardiovascular causes when they were a sudden death or death attributed to acute myocardial infarction, pericarditis, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest, valvular heart disease, pulmonary edema, congestive cardiac failure, or cerebrovascular accident, including intracranial hemorrhage, ischemic brain damage including anoxic encephalopathy, or mesenteric infarction or ischemia of the bowel. The primary outcome defined a priori was all-cause mortality and the secondary outcome was death due to cardiovascular causes. Patients who withdrew from the study, underwent kidney transplantation, were lost to follow-up, or survived were censored.

Ethics Approval

We received ethics approval for the ORAL-D Study from the following responsible local human research ethics committees: Comitè de Protection des Personnes Sud-Mediterranèe II (France), Komisja Bioetyczna, Slaskiego Uniwersytetu Medycznego W Katowicach (Poland), CE da Diaverum Portugal (Portugal), Comite Etico de Investigacion Clinica (CEIC) de la Fundaction Puigvert and Agencia Valenciana de Salud, Departament de Salut Valencia (Spain), and Szegedi Tudomanyegyetem, Szent-Gyorgyi albert klinikai kozpont, and Regionalis human orvosbiologiai kutatasetikai bizottsaga (Hungary). Ethics approval was not required in Italy or Argentina. The study was performed in accordance with the Declaration of Helsinki.

Statistical Analysis

All statistical analyses were performed using SAS, version 9.3 (SAS Institute Inc). $P < 0.05$ was considered statistically significant.

Dental disease characteristics and health care practices were considered as time-fixed binary variables throughout the follow-up period. In all participants, we did analyses for extent of edentulousness and the decayed, missing, or filled teeth index; in dentate participants, we did analyses for brushing teeth, using mouthwash or dental floss, frequency of changing a toothbrush, time spent on oral hygiene, age of starting dental care, and time elapsed since last dental checkup. We also considered analyses for the number of decayed, missing, or filled teeth as a categorical variable according to the WHO classification and as a continuous exposure variable. In survival analyses, we included participants who had complete data for all oral health exposure variables (n = 4,054 participants overall, including n = 3,243 dentate participants).

Event rates for study outcomes were calculated for each dental exposure category, reporting Kaplan-Meier estimates. Time-to-event cumulative incidence Kaplan-Meier curves were plotted across dental exposure variables. Because there was heterogeneity in risks of survival (all-cause and cardiovascular mortality) among countries ($P < 0.001$), we then applied random-effects Cox proportional hazard models fitted using shared frailty to account for within-country clustering of mortality risk to estimate associations among dental status, oral hygiene and dental care variables, and risk of early all-cause and cardiovascular mortality. We used a lognormal distribution in the frailty model. In multivariable-adjusted models, we controlled for the following baseline factors: age, sex, race, smoking history, self-reported family income, prior myocardial infarction, diabetes, dialysis vintage, and mean arterial blood pressure, hemoglobin, and serum phosphorus values. The proportional hazards assumption in all Cox models was assessed by fitting log (time)-dependent covariates in the multivariable model and checking graphically by plotting Schoenfeld residuals, but no variable violated the proportionality assumption. We did not impute missing data.

In sensitivity analyses, we considered competing risks for death attributable to cardiovascular causes from other causes of death.