Better Oral Health May Reduce Mortality Risk for Patients with End Stage Renal Disease

Better dental hygiene and oral health can lead to better overall outcomes for patients with end stage renal disease (ESRD). Researchers saw the effect regardless of the age at which patients initiated oral hygiene practices.

Poor oral health is a risk factor for cardiovascular and all-cause death among patients with chronic kidney disease (CKD). Compared to the general population, dialysis patients have more severe oral disease, and their uptake of dental health services is very low. But questions remain whether improving oral health would result in better outcomes.

No drug or other intervention appears to work very well to lower the elevated mortality risk of hemodialysis patients, so other interventions need to be examined, according to Giovanni Strippoli, MD, PhD, MPH, of the University of Bari, Italy, and Senior Vice President and Scientific Director of Diaverum, a global provider of renal services.

Therefore, Strippoli and colleagues undertook the prospective multinational ORAL Diseases in hemodialysis (ORAL-D) study involving 4320 consecutive adult hemodialysis patients recruited from randomly selected clinics in the Diaverum dialysis network in Europe and South America between July 2010 and February 2012. Patients had a mean age of 61.7 years, 58 percent were men, and 23 percent lacked teeth.

The study assessed the relationship between periodontal, dental, salivary, and mucosal health and mortality. At baseline, patients underwent a standardized oral examination and were surveyed about their dental health practices, other behavioral health risks, thirst, co-morbidities, and demographic factors.

Presenting the ORAL-D results at the the ERA-EDTA conference in Amsterdam, Strippoli reported that at a median follow-up of 22.1 months (12 months minimum), 650 participants died from any cause, and of those, 325 died from a cardiovascular event.

After adjusting for age, sex, income, smoking, cardiovascular disease, blood pressure, time on dialysis, and serum phosphorus level, the researchers saw a 27 percent increased risk of death (hazard ratio, HR = 1.27) among participants without teeth. Even worse, the risk of death in people with teeth (dentate) was elevated by 46 percent (HR = 1.46) for individuals with more than 12 decayed, missing, or filled teeth.

In the dentate population, oral hygiene practices were associated with a reduced risk of death by a statistically significant amount. Brushing teeth was associated with a 26 percent reduced risk of all-cause death, flossing 51 percent, changing a toothbrush at least every 3 months 21 percent, and spending 2 minutes or more on oral hygiene daily 19 percent. However, the age of starting dental care did not matter. The risk of death from cardiovascular causes followed a similar pattern. For people older than 60 years, the association between decayed, missing, and filled teeth and the risk of death was not as strong as for younger participants but was still statistically significant (31 percent greater; HR = 1.31).

The authors concluded that these results show an independent association between poor dental health and mortality for adult hemodialysis patients. Oral hygiene practices were associated with lower mortality.

A previously published meta-analysis by Strippoli and co-workers (*Nephrol Dial Transplant* 2014; 29: 364–375) comprising 11,340 adults with CKD in 88 studies supports the present findings. In that paper, they found that one in five people with stage 5D disease (therefore on dialysis) lacked any teeth, and 57 percent had periodontitis compared to 32 percent with less severe CKD. Among the stage 5D patients, 26 percent reported never brushing their teeth, only 11 percent flossed, 19 percent reported oral pain, and about half reported dry mouth.

Although a causal link between poor oral hygiene and all-cause or cardiovascular mortality cannot be drawn from observational data, and common pathways may be at play leading to oral problems and cardiovascular events, the authors did cite research showing that intensive periodontal treatment was associated with improved endothelial function. Furthermore, poor, painful, or absent dentition may be a factor in malnourishment.

Strippoli said the study findings strongly suggest that good dental care and dental hygiene should be urged for anyone with ESRD.

Novel Disease-Modifying Agent for Diabetic Nephropathy

A novel compound in development, emapticap pegol (emapticap; NOX-E36, Noxxon Pharma), a drug with anti-inflammatory properties, may be the first disease-modifying drug for the nephropathy in type 2 diabetes mellitus (T2DM). In a presentation at the European Renal Association—European Dialysis and Transplant Association conference in Amsterdam in June, researchers presented evidence that emapticap had positive effects on the kidney that persisted for several weeks after the drug was stopped.

Emapticap specifically binds and inhibits the pro-inflammatory chemokine CCL2 (also called monocyte chemotactic protein 1, MCP-1). Phase 1 studies showed it to be safe and well tolerated, and there were hints of renoprotective effects. These signals have now been followed up in a study involving 75 T2DM patients with albuminuria.

At the conference, Hermann Haller, MD, director of the department of nephrology and hypertension at the Hannover Medical School in Hannover, Germany, presented results of that randomized, double-blind, placebo-controlled, phase 2a study conducted at sites in five European countries.

Patients in the trial were on stable antidiabetic therapy and on drugs to block the renin-angiotensin system (e.g., ACE inhibitors or angiotensin receptor blockers). They had an albumin-to-creatinine ratio (ACR) >100 mg/g, an estimated glomerular filtration rate (eGFR) >25 mL/min/1.73 m^2, and a glycated hemoglobin (HbA_{1c}) between 6.0 percent and 10.5 percent. Patients received emapticap or placebo subcutaneously twice a week for 12 weeks and were followed for an additional 12 weeks without drug or placebo.

Haller reported that the drug reached pharmacologically active levels at the dose given and had the expected effect of reducing the number of monocytes bearing receptors for CCL2. Preclinical work had shown that this effect prevented the migration of inflammatory cells into the kidney, thereby preserving its structure and function, according to a news release from the company developing the drug.

Compared to placebo, emapticap reduced the mean ACR by 32 percent ($p = 0.014$) in the group of 49 patients deemed to be most relevant for future studies for this indication (i.e., censoring patients with kidney disease not from diabetes). Thirty-one percent of patients receiving the active drug had a 50 percent or greater reduction in ACR, compared to only 6 percent of patients receiving placebo. No differences were seen in blood pressure or eGFR between the emapticap and placebo groups, so the effect on ACR occurred independently of changes in blood pressure or eGFR and were thus presumably working through a different mechanism.

The patients on emapticap continued to receive benefit even after the drug was stopped and throughout the second 12-week (off-drug) period. The maximum decrease in ACR was seen 8 weeks after the last dose and was a mean 39 percent lower than for the placebo group ($p = 0.01$). At the end of the initial 12-week period, HbA_{1c} trended downward with emapticap compared to placebo (an absolute change from baseline of -0.32 percent vs. +0.06 percent, respectively; $p = 0.096$). This difference became statistically significant 4 weeks after the last dose ($p = 0.036$).

The researchers concluded that the drug is safe, well tolerated, and effective in reducing ACR and HbA_{1c} with prolonged administration in patients with T2DM and albuminuria. They noted that the renoprotective effect independent of blood pressure reduction distinguishes this compound from other drugs and is a novel approach.

Haller noted that the residual beneficial effect after the drug is stopped may indicate that emapticap ameliorates the underlying pathophysiology of the disease and "may hence be the first disease-modifying drug for this indication." The research group suggests further clinical studies to assess the potential of the drug to stave off end stage renal disease and cardiovascular events.

Aside from the renal effects, the reduction in HbA_{1c} suggests that emapticap also can benefit glycemic control.

In light of positive early results but then failure of some drugs in larger trials, confirmation of these phase 2 results is clearly warranted. Bardoxolone, a compound that reduced inflammation and oxidative stress, looked good in increasing eGFR among T2DM patients in phase 2b but failed in phase 3 because of higher cardiovascular mortality in the group receiving the drug.