Relationship Between Urinary Sodium Excretion Over Time and Mortality in Type 2 Diabetes

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It remains unclear whether dietary salt intake over years (not just at baseline) influences hard outcomes. We have previously demonstrated an increased risk of mortality in patients with type 2 diabetes (T2D) and low baseline 24-h urinary sodium excretion ($24hU_{Na}$) (1). Based on the same cohort of patients, the aim of the current study was to examine the relationship among serial measurements of $24hU_{Na}$, estimated glomerular filtration rate (eGFR), and all-cause mortality, adjusting for covariates associated with $24hU_{Na}$ and eGFR.

This was a prospective cohort study of patients with T2D attending a single tertiary hospital diabetes clinic, initiated in mid-2000 with follow-up completed in 2010 (1). Serial $24hU_{Na}$ (mmol/24 h) and eGFR (mL/min/1.73 m^2) measurements were performed at regular intervals. The impact of $24hU_{Na}$ and eGFR over time on all-cause mortality was determined by a joint model of longitudinal (linear-mixed model) and time-to-event (Weibull parametric survival model) data.

Follow-up $24hU_{Na}$ and eGFR data from 588 patients were used in the current analysis. There were 152 deaths (26%) after a median follow-up of 9 years. Significant predictors of eGFR in the linear-mixed model were baseline eGFR and BMI, age, sex, follow-up time (years), and $24hU_{Na}$ and albumin excretion rate over time. Survival model predictors were sex, $24hU_{Na}$, and eGFR over time; baseline eGFR; diastolic blood pressure; presence of congestive heart failure and/or atrial fibrillation; and duration of diabetes.

The relationship between all-cause mortality and $24hU_{Na}$ (adjusted for covariates) is demonstrated in Fig. 1, where an increase in all-cause mortality was evident in those with lower $24hU_{Na}$. Predicted survival at 9.5 years ranged from 94% ($24hU_{Na}$ = 264 mmol/24 h; 90th percentile) to 77.5% ($24hU_{Na}$ = 96 mmol/24 h; 10th percentile).

Low $24hU_{Na}$ was associated with increased all-cause mortality, allowing for changes in $24hU_{Na}$ and eGFR over time, consistent with the original study findings (1).

Limitations are recognized. Observational data presented here are restricted to patients with long-standing T2D and our analysis is hypothesis-generating rather than identifying a direct causal relationship. Furthermore, observational studies may be subject to confounding.

The strengths are the use of multiple $24hU_{Na}$ measurements to estimate dietary salt intake over time in each individual and the use of a joint model for statistical analysis (2,3). Joint modeling has not been previously used to predict mortality in cohort studies of dietary salt intake and has the advantage that over time repeated measurements can reduce measurement error and overcome the effect of treatment of covariates (4).

Low $24hU_{Na}$ excretion over time was associated with increased mortality in people with T2D. The study findings are in line with the Institute of Medicine report (5) no longer recommending lowering sodium intake to $\leq$65 mmol/24 h in patients with diabetes. These findings call for research on the effects of habitual low salt intake on markers of renin-angiotensin-aldosterone system activity, endothelial function, and sympathetic nervous system activity in people with diabetes. Studies, now in progress, should help to resolve the question of whether low dietary salt intake is a pathogenetic factor, as opposed to a marker, for cardiovascular or renal events in diabetes.

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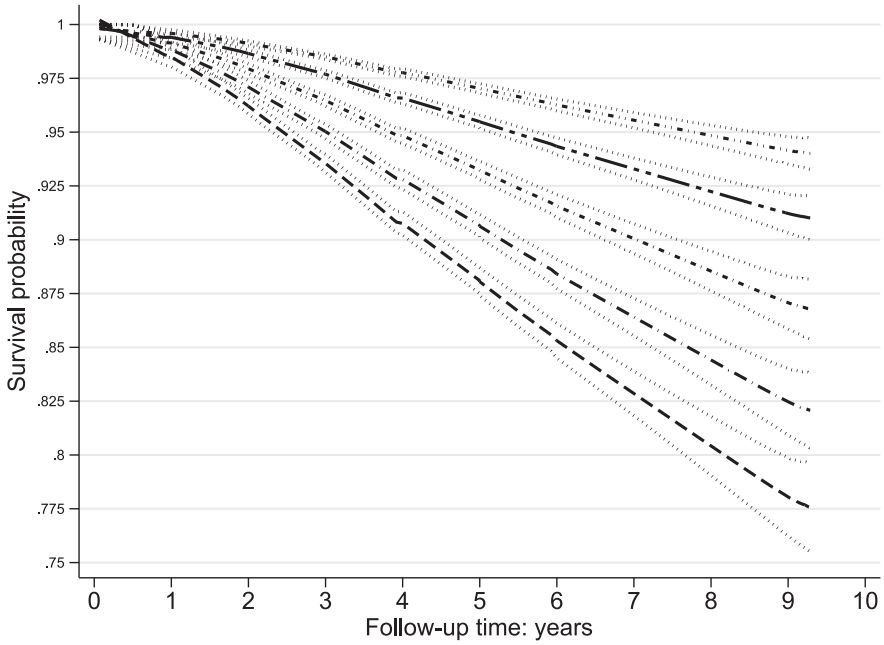

Figure 1—All-cause mortality across percentiles of 24hU_{Na} (mmol/24 h), averaged over covariate effect. All-cause mortality: effect of percentiles of 24hU_{Na} (mmol/24 h), taking into account longitudinal measurements of 24hU_{Na} and eGFR throughout the study period. Survival by percentiles of 24hU_{Na}: other predictors held at mean value. Joint model of longitudinal (eGFR) and survival (all-cause mortality) data (95% CI). 10th percentile (96 mmol/24 h) is represented by – – – –; 25th percentile (128 mmol/24 h), –. – . – . –; 50th percentile (168 mmol/24 h), -.-.-.-.-.-.-.; 75th percentile (216 mmol/24 h), — - - —; and 90th percentile (264 mmol/24 h), - . . - . . - . . -.

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