Increased urinary albumin excretion (UAE) has been shown to be associated with increased cardiovascular mortality in patients with type 2 diabetes. This study evaluated whether the association between UAE and cardiovascular mortality in 880 patients with type 2 diabetes was related to an increase in left ventricular mass (LVM). LVM was estimated by electrocardiographic index, namely adjusted Cornell voltage. LVM was significantly different between the stages of albuminuria (8.17 ± 0.12 in normoalbuminuric, 9.05 ± 0.21 in microalbuminuric, and 10.30 ± 0.30 in overt albuminuric patients; \( P < 0.001 \)). There also was a positive correlation between log UAE and LVM independent of BP. During 5yr of follow-up, survivors had significantly lower LVM (8.62 ± 0.11 \textit{versus} 9.88 ± 0.45; \( P = 0.0140 \)) and lower UAE (154.60 ± 16.53 \textit{versus} 446.62 ± 114.11; \( P = 0.0003 \)) than nonsurvivors. The results indicate that patients with type 2 diabetes and increased UAE should be evaluated for increased LVM as an important and potentially reversible cardiovascular risk factor.


Materials and Methods

A total of 880 patients with type 2 diabetes from the Appropriate Blood Pressure Control in Diabetes (ABCD) trial population were included in our study. The design of the ABCD trial has been described previously, and the results have been reported (4–7). Type 2 diabetes was diagnosed according to the criteria based on the World Health Organization report of 1985 (8), which followed the National Diabetes Group criteria of 1979 (9).

Three BP measurements were taken at 2-min intervals in the sitting position by trained nurses who used a standard mercury sphygmomanometer. UAE was measured for individual patients on three separate occasions and consisted of one 24-h urine collection and two overnight collections. The median value then was used to determine the UAE stage: Normoalbuminuria (<20 \( \mu \)g/min), microalbuminuria (20 to 200 \( \mu \)g/min) to overt diabetic nephropathy (>200 \( \mu \)g/min) (2). Although increased UAE has been proposed to be an indicator of diffuse vascular disease in type 2 diabetes (3), the exact pathway for the associated increased cardiovascular mortality is not clear.

An increase in left ventricular mass (LVM) is known to be a risk factor for cardiovascular mortality, but the relationship among mortality and increased UAE and LVM in a large group of patients with type 2 diabetes is in need of investigation. In this study, we used adjusted Cornell voltage criteria by electrocardiography to evaluate the relationship among UAE, LVM, and mortality in 880 patients with type 2 diabetes and a mean body mass index (BMI) of 32 kg/m\(^2\).

Statistical Analyses

Data were analyzed using SAS 9.1 (SAS Institute, Cary, NC). Numerical data are presented as means and SE or geometric mean and confidence interval. \( P < 0.05 \) was considered as statistically significant. A log transformation was applied to UAE because of a skewed distribution. Wilcoxon rank sum and Kruskal-Wallis tests were used for tests of differences between means. Pearson correlation coefficients were used to test the relationship between adjusted Cornell voltage and
Results and Discussion

In our study, the characteristics of the 880 patients with type 2 diabetes reflect those that generally are observed in urban-dwelling patients in the United States (Table 1). They averaged 59 yr of age and were obese with suboptimal control of blood glucose, lipids, or BP according to current recommendations for patients with type 2 diabetes. The mean UAE was at the early microalbuminuric stage, and renal function, as assessed by creatinine clearance, was reasonably well preserved at 85 ml/min. The study evaluated the relationship between UAE and LVM by adjusted Cornell voltage with all-cause mortality and cardiac deaths in the patients with type 2 diabetes. As shown in Figure 1, the adjusted Cornell voltage, as an index of LVM, was found to be significantly different between the stages of albuminuria (8.17 ± 0.12 in normoalbuminuric, 9.05 ± 0.21 in microalbuminuric, and 10.30 ± 0.30 in overt albuminuric patients; P < 0.0001).

There was a positive correlation between log UAE and adjusted Cornell voltage (r = 0.27, P < 0.0001). This relationship remained significant after adjustment for systolic and diastolic BP (P < 0.0001). These results support the findings in a Japanese study in patients with type 2 diabetes in which LVM also was found to increase in proportion to the progression of diabetic nephropathy (11). Other publications also have demonstrated a relationship between microalbuminuria and left ventricular hypertrophy (LVH) in patients with type 2 diabetes (12). In the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study, reduced urine albumin/creatinine ratio as well as regression of LVH was associated with a lower incidence of cardiovascular events in hypertensive patients without diabetes (13,14).

In our 5-yr prospective study, the relationship among UAE, LVM, and mortality was examined in 880 patients with type 2 diabetes. An increase in LVM has been shown to be a major cardiovascular risk factor. Specifically, systolic and diastolic dysfunction, cardiac arrhythmias, ischemic heart disease, and sudden death are known to be associated with increased LVM. A diminished capillary-to-cardiac myocyte ratio is a feature of increased LVM and thus predisposes to these cardiovascular complications (15). There also is an increase in cardiovascular mortality as UAE increases in type 2 diabetes from normoalbuminuria to microalbuminuria to overt albuminuria (16,17). The mechanism for this relationship, however, is not known. It has been hypothesized that the microvascular injury and increased permeability in the glomerulus, which lead to increased UAE, also are occurring in the vasculature of the heart (18). The increase in LVM therefore may be a compensatory response to areas of cardiac ischemia. In this regard, patients with diabetes can have a cardiomyopathy and increased LVM independent of hypertension and large vessel coronary artery atherosclerosis. Increased LVM and UAE therefore could have a common pathogenesis, thus providing an important link among albuminuria, LVM, and increased mortality. Our study investigated this possibility.

Previous studies have used both echocardiography and electrocardiography to assess LVM (19,20). It has been shown in individuals without diabetes that LVM, as assessed by either technique, is associated with increased mortality (21). Approximately 50% of the patients with diabetes in our study did not have readable echocardiograms because of obesity. ECG with adjusted Cornell voltage therefore was used to assess LVM, because it has been recommended for obese patients (10). The prognostic value of electrocardiographic criteria to measure LVM has been shown in recent studies (22,23). Another study also demonstrated in healthy subjects that 12-lead ECG with Cornell voltage is strongly correlated with measured LVM by magnetic resonance imaging (24).

Most important, our study examined whether this relationship between increased UAE and increased LVM was associated with increased all-cause mortality and cardiac death. During 5 yr of follow-up, 66 deaths occurred in the study population. The 814 survivors had significantly lower LVM (8.62 ± 0.11 versus 9.88 ± 0.45; P = 0.0140; Figure 2) and lower UAE (154.60 ± 16.53 versus 446.62 ± 114.11; P = 0.0003) in comparison with the 66 who died during study period. Of the 66 deaths, 35 were documented to be cardiovascular related.

**Table 1.** Baseline characteristics of the study population (N = 880)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SE</th>
</tr>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>58.6 ± 0.28</td>
</tr>
<tr>
<td>UAE (µg/min)</td>
<td>176.50 ± 17.69</td>
</tr>
<tr>
<td>Adjusted Cornell voltage</td>
<td>8.72 ± 0.11</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>145.28 ± 0.58</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>90.93 ± 0.28</td>
</tr>
<tr>
<td>Duration of diabetes (yr)</td>
<td>8.85 ± 0.24</td>
</tr>
<tr>
<td>Duration of hypertension (yr)</td>
<td>5.71 ± 0.31</td>
</tr>
<tr>
<td>Glycohemoglobin (%)</td>
<td>11.60 ± 0.11</td>
</tr>
<tr>
<td>Serum triglyceride (mg/dl)</td>
<td>283.33 ± 13.89</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>31.49 ± 0.19</td>
</tr>
<tr>
<td>Serum creatinine (ml/min)</td>
<td>1.11 ± 0.25</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>84.51 ± 1.07</td>
</tr>
</tbody>
</table>
converting enzyme inhibitors may decrease both UAE and LVM, this intervention may not only decrease progression of renal disease but also diminish cardiovascular mortality.

Acknowledgments
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References

Figure 2. Survivors of all-cause mortality had lower adjusted Cornell voltage than nonsurvivors (P = 0.0140). Those who experienced cardiac-related death had higher adjusted Cornell voltage than survivors (P = 0.0039).

The 845 individuals who did not die of a documented fatal cardiac event also had a significantly lower LVM (8.64 ± 0.11 versus 10.57 ± 0.64; P = 0.0039; Figure 2) and lower UAE (157.96 ± 16.21 versus 624.04 ± 199.13; P = 0.0049) than the 38 individuals who experienced a fatal cardiac event. With logistic regression analysis, both UAE (odds ratio 1.252; P = 0.0087) and adjusted Cornell voltage (odds ratio 1.141; P = 0.0094) increased the risk for a fatal cardiac event independent of the specific antihypertensive agent used.

In our study, adjusted Cornell voltage also correlated positively with systolic (r = 0.24, P < 0.0001) and diastolic (r = 0.28, P < 0.0001) BP and serum creatinine level (r = 0.23, P < 0.0001). In this regard, 24-h ambulatory systolic and diastolic BP in patients with type 2 diabetes has been found to correlate with LVM (25), and treatment of hypertension has been shown to reduce LVM and concentric left ventricular remodeling in patients without diabetes (26). Increased LVM also has been found to be frequent in normoalbuminuric patients who have type 2 diabetes and are not receiving antihypertensive treatment (27). Moreover, in another study, patients with type 2 diabetes were found to have increased concentric LVM independent of any increase in ambulatory BP (28). In the study by Andersen et al. (12), diastolic dysfunction was closely related to increased UAE. In hypertensive patients with type 2 diabetes, an elevated UAE was associated with an increased LVM, a higher prevalence of a concentric LVH, depressed midwall systolic performance, and impaired diastolic function (29). The insulin resistance that accompanies obesity in patients with type 2 diabetes is another factor that may contribute to an increase in LVM, because insulin is known to possess mitogenic properties (30).

Conclusion
Increased UAE in patients with type 2 diabetes correlates not only with progression of nephropathy but also with increased cardiovascular mortality. Using the adjusted Cornell voltage technique, our results implicate an increase in LVM as a contributor to the association between UAE and increased all-cause and cardiac mortality in type 2 diabetes. Because angiotensin-


The relationship between urinary albumin excretion and left ventricular mass to mortality in type 2 diabetes is applicable to the November *JASN* Frontiers in Nephrology papers by Abbate et al. (pp. 2974–2984) and Rüster and Wolf (pp. 2985–2991), which discuss the mechanisms by which proteinuria causes renal damage and how the renin-angiotensin system leads to progressive renal disease. Interference with these critical pathways is important in preventing progressive renal disease and mortality. In addition, the Basic Science article by Ye et al. (pp. 3067–3075) and THE editorial by Ingelfinger (pp. 2957–2959) in the same issue of *JASN* discuss the new possibilities of inhibiting ACE2 for reduction of albuminuria in a murine model of diabetes. Another murine model in a *JASN* article by Sung et al. (pp. 3093–3104) shows that blockade of VEGF signaling also reduces albuminuria in diabetes.