Is Population-Wide Diuretic Use Directly Associated With the Incidence of End-Stage Renal Disease in the United States?

A Hypothesis

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Background: We introduce the hypothesis that population-wide use of diuretics might be associated with acceleration of the incidence of end-stage renal disease (ESRD).

Methods: Based on the technique of data fusion, pooled-data trends in disease incidence and antihypertensive medication use were examined to determine whether changes in drug use patterns are predictive of disease emergence in the United States. National databases for all-cause cardiovascular disease (CVD) mortality and stroke mortality from the National Vital Statistics Registry, renal failure data obtained from the United States Renal Data Service, and drug information obtained from IMS Health (Fairfield, CT) were examined.

Results: A statistically significant inverse relationship was observed between all-cause CVD mortality rates and ESRD incidence rates for the period 1980 to 1998 ($r = -0.98948; P < .0001$). A statistically significant direct time-lagged relationship was found between both annual changes in diuretic distribution and total diuretic expenditure to annual changes in the ESRD growth rate ($r = 0.754, P = .03, r^2 = 0.568, 95\% CI for slope = 0.08975 to 1.3010$).

Conclusions: Increasing annual diuretic distribution in the US is directly associated with accelerated time-lagged growth rates of ESRD incidence. One potential explanation is that diuretic therapy could promote ESRD expression. A large-scale, randomized, controlled trial to investigate acceleration of ESRD by diuretics would be justifiable. The data invites the hypothesis that reliance on nondiuretic antihypertensive therapies such as calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers might attenuate the epidemic rise of ESRD that is prevalent in the United States.

Age-adjusted cardiovascular mortality rates have been declining worldwide for more than 30 years. Numerous factors have been suggested as being responsible for this decline, including treatment of systemic arterial hypertension. During the 1970s and 1980s, when most of the decline occurred, the treatment of hypertension was achieved primarily with diuretic-based treatment regimens.

It is curious that, concurrent with the consistent annual decline in cardiovascular disease (CVD) mortality, a simultaneous annual increment in the incidence rate of end-stage renal disease (ESRD), as defined by the United States Renal Data Service (USRDS), has been reported since the initiation of the USRDS database in 1980. This observation has led us to hypothesize the existence of some variable that contributes to the reduction of cardiovascular mortality rates and simultaneously permits accelerated ESRD rates. Another obvious consideration is that improved cardiovascular care generally has resulted in expansion of the ESRD population due to survival of patients with chronic kidney diseases, who in the past would not have survived co-morbid vascular disease, to subsequently incur end-stage renal failure. The observation of changing disease prevalence behaviors could be explained by patient survival bias.

Methods

This article analyzes correlations among national databases describing various American health status measures.
The National Vital Statistics databases are available online and describe mortality rates from stroke and CVD from 1970 to 1998. The USRDS publishes an annual data report describing incidence, prevalence, morbidity, mortality, and treatment modality trends in renal disease. The USRDS database has compiled data since 1980. A commercial database, owned by IMS Health (Fairfield, CT), has compiled information on prescription drug manufacture, distribution and consumption by drug category within the US and has archives of data for the previous 12 years.

To test the hypothesis that antihypertensive drug use might be associated with the incidence of end-stage renal failure, we obtained from the USRDS a customized data search identifying the incidence rate per million for all-cause end-stage renal failure and for hypertension-related end-stage renal failure for the years 1980 through to 1999. The data for year 2000 was taken from the USRDS annual data report for 2000, published in 2002. From IMS Health, we obtained a proprietary database describing dollar value sales of all cardiovascular drug products distributed from manufacturers to distributors in the US from 1990 to 2001 and the annual percentage change in supply from 1991 to 2001. We make the assumption that drug supply from manufacturers reflects population consumption of that drug for any given year. This assumption allows use of the IMS Health database to reflect the annual percentage change in population-wide exposure to various categories of cardiovascular medications.

Data for diuretic therapy includes the overall value for all diuretic therapy prescribed in the US for all indications including hypertension, congestive heart failure, and other indications for diuretic therapy. Review of the IMS Health “Top 200 Prescribed Drug List” for each of 1999 and 2000 shows that for the diuretic category, hydrochlorothiazide represented the majority (54% of overall prescribed diuretic volume and 55% of new diuretic prescriptions written) and that furosemide accounted for the bulk of the remainder. Chlorthalidone, metolazone, indapamide, and spironolactone are not represented at all in the Top 200 listings for 1999 or 2000. The term “diuretic therapy” used in this article therefore refers predominantly to therapy with hydrochlorothiazide (HCTZ) and furosemide.

Data were analyzed using MODSTAT statistical software (MODSTAT developed by Dr. Robert C. Knodt, ©1993 to 2002, all rights reserved), using the Pearson correlation for comparison of trends. Two-tailed t tests were used as appropriate. Outcomes with a $P$ value < .05 were defined as statistically significant.

This report is an ecological study using correlations of pooled cross-sectional data derived from contemporaneously constructed databases. This technique is inspired by a data analysis technique known as data fusion (also known as information fusion), and we will refer to this methodology as data fusion hereafter. Data fusion refers to the combination or integration of more than one data set measuring the same physical event, experimental subjects, or population to obtain better information than that from any single set of data. The National Library of Medicine PubMed database identifies 51 instances of publications making reference to data fusion since 1993, and a peer-reviewed scientific journal is now dedicated to articles using this methodology (Information Fusion, ©2004 Elsevier B.V.).

In this study, the annual data from the USRDS and IMS Health databases were fused as though they had been obtained concurrently by one observer for the purposes of analysis. Pearson correlations were done on the resulting database information and simple linear correlations were evaluated for significance.

Results

Figure 1 demonstrates that a highly significant inverse relationship exists between the decline in age-adjusted CVD mortality in the US taken from the National Vital Statistics Registry and the concurrent rise in ESRD taken from the USRDS annual data reports for the period from 1980 to 1998.

Figure 2 shows the annual percentage change in the cost of diuretics distributed in the US from 1991 to 1998 and the annual percentage change in incidence rate for ESRD from 1993 to 2000, shown together on the same graphic scale, with the data for ESRD time-lagged 2 years following the changes in diuretic distribution changes. The data shown in Fig. 2 were the inciting data for the hypothesis as presented. The assumption was that diuretic use could be shown to be directly associated with ESRD incidence in a time-lagged fashion of unknown duration.

![FIG. 1. Inverse relationship between cardiovascular disease (CVD) mortality and end-stage renal disease (ESRD) incidence, 1980 to 1998. ESRD incidence rate per million, $r = -0.98948, P < .0001.$](https://academic.oup.com/ajh/article-abstract/18/6/744/120037/18019)
This analysis was the earliest example that we identified of such an association actually existing. The likelihood that this relationship, or one more extreme, exists by chance alone is defined by the $P$ value, which in this instance is $0.0078125$, or odds of $1:128$ that the relationship exists by chance alone. This relationship was identified by post hoc analysis and raises the possibility of “data dredging bias” diminishing the value of this single analysis. It is readily apparent, however, that for all eight data pairs, annual increases in diuretic distribution were invariably associated with increases in ESRD incidence rate growth 2 years later, whereas decreases in diuretic distribution were invariably associated with attenuations of ESRD incidence growth 2 years later.

The relationship shown in Fig. 2 allows generation of the hypothesis that diuretic distribution changes are directly associated with and precede ESRD growth rate changes. Figure 3 is a demonstration of a simple linear equation that would describe such a relationship and that shows a statistically significant direct linear association between changes in diuretic distribution and time-lagged changes in the growth rate of ESRD. For the purposes of this equation, ESRD growth rate changes were defined to be the actual mathematical difference between the percentage growth rate increments observed from 1 year to the next. For example, if the ESRD incidence rate grew by $3\%$ in 1 year and then grew by $1\%$ the following year, the change in growth rate would be reflected as $-2\%$. The significance of the relationship ($P = .03$) exceeds the stated pretest level of significance ($P < .05$) to show that a direct relationship exists between population-wide diuretic exposure and subsequent delayed ESRD behavior measured by population based incidence rate changes.

The third National Health and Nutrition Examination Survey (NHANES III) identified that, among the hypertensive population, $10.6\%$ are treated with diuretic monotherapy. Assuming that 50 million patients in the US have hypertension ($>140/90$ mm Hg), this would represent 5.3 million patients on diuretic monotherapy for hypertension. The relationship in Fig. 3 suggests that, for every $1\%$ change in diuretic therapy, we would expect to see $0.7\%$ increase in the ESRD growth rate later. In 2002, the USRDS showed an incident population of new ESRD patient of 100,000. In this context, assuming that the linear relationship holds true, for every increase of $1\%$ in diuretic use (+53,000 hypertensive patients), we would expect to see a $0.7\%$ attributable increase in ESRD (+700 patients) annually; this would be one case for every 76 hypertensive patients newly exposed to diuretic monotherapy.

Figure 4 demonstrates the relationship between total diuretic expenditures in the US for all indications and the change in incidence rate of ESRD 4 years later. The data fusion methodology that we have used has identified a 4-year time lag as providing the strongest correlation coefficients for all comparisons, as well as being biologically more sensible than a 2-year time lag. The 4-year time lag is now used in our analyses as the a priori hypothesis for data testing, eliminating “data dredging bias” for this and future data analyses. Increasing expenditure upon diuretics for population-wide use in the US appears to be correlated with subsequent increases in ESRD incidence within the population exposed 4 years later. This does not mean that ESRD evolves within a 4-year duration but, rather, suggests that diuretic use may provide an environment, which accelerates ESRD expression in a population at prior risk.

Figure 5 shows the rising median age of ESRD incidence has slowed by nearly $50\%$ during the 1990s compared with previous years. The regression lines show that the slope of median age of dialysis incidence in the pre-1990s is twice as steep as that seen in the post-1990 time frame.

Figure 6 is derived from the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) published data, showing the significant difference between chlorothalidone (diuretic) and amlodipine
(calcium channel blocker [CCB]) of the study with regard to change in glomerular filtration rate (GFR) over the 4 years of follow-up.

Discussion

The data confirm inversely related trends in CVD mortality and ESRD incidence. Because CVD and ESRD share multiple risk factors in common, it is curious to observe divergent rather than parallel trends. To explain the divergence, many hypothesize survival bias as previously mentioned. Alternatively, beneficial interventions directed to patients with CVD are either permissive of nephrotoxicity or are directly nephrotoxic. Because diuretics act pharmacologically in the kidney, it is conceivable that diuretics promote both cardiovascular mortality benefit and nephrotoxicity. Some suggest that, with individuals surviving longer with previously fatal chronic diseases, ESRD has increased as a consequence of prolonged survival. However, that explanation alone is insufficient to explain the magnitude of growth in ESRD incidence.

Figure 1 identifies a 40% decline in CV disease mortality over two decades and a concurrent 400% increase in ESRD incidence. The USRDS 2003 Annual Data Report identifies no change in the prevalence from 1995 to 2002 of all CVD, ischemic heart disease, peripheral vascular disease, or congestive heart failure among new ESRD patients overall at the time of dialysis initiation. If “survival bias” were the only explanation due to improved CVD care, we should see an increase in the proportion of comorbid CVD among patients who survive to start dialysis (ie, increased comorbid survival, the necessary precursor to define survival bias). The data shows no increase; in other words, the ESRD incident population has no more comorbid CV disease in 2002 than was present in 1995.

Age is an independent risk marker for both CV disease and renal disease in the population. Because the median age of patients starting dialysis has been steadily rising, this clearly implies that increased survival must be involved in the increasing incidence rate of ESRD and that the CV risk of those surviving to start dialysis is also increasing. However, because the rate of rise of the median age to start dialysis has decelerated (Fig. 5), it demonstrates that age and survival are playing a lesser role in ESRD incidence than in the past, and raises the potential that other factors such as treatment related variables might contribute a relatively greater role in ESRD incidence than they did in the past. This is the essence of our hypothesis.

Treatment of hypertension reduces the incidence of cardiovascular mortality, reflected by reduced stroke and heart failure mortality and to a lesser extent ischemic heart disease–related deaths. Diuretic-based therapy is also protective against cardiovascular mortality and stroke-related mortality, although the reduction in mortality related to ischemic heart disease is less than what would be predicted for the observed blood pressure reduction. Published large-scale hypertension trials and surveys, the European Working Party on High Blood Pressure in the Elderly EWPHE, the Swedish Trial in Old Patients with Hypertension (STOP), NHANES III, the Systolic Hypertension in Europe trial (Syst-Eur), the Systolic Hypertension in the Elderly Program (SHEP), the Intervention as a Goal in Hypertension Treatment (INSIGHT) trial and ALLHAT have independently demonstrated that diuretic-based therapy is either detrimental to renal function or is at least permissive of significantly quantifiable renal impairment.

In EWPHE, a significant excess incidence rate was found in the active diuretic treatment group compared with placebo for impaired renal function, a serum creatinine level >2.0 mg/dL. In a logistic analysis of NHANES III, the presence of elevated creatinine level was positively associated with the prescription of diuretics (odds ratio = 1.7, 95% CI = 1.4 to 2.2). In Syst-Eur, serum creatinine concentration did not change in the population of patients who received monotherapy with nitrendipine, whereas it increased by 6.73 mmol/L (P < .001) in the population of patients who received HCTZ alone or in combination with other study medication. In SHEP, the actively treated diuretic population had small but statistically significant increases in serum creatinine levels compared with controls (2.8 mmol/L, P < .001). The INSIGHT trial showed statistically significant increases in the frequency of impaired renal function observed and withdrawal from therapy due to renal function impairment for the diuretic-treated group compared with the nifedipine-treated group. Secondary analysis of ALLHAT shows a statsi-
tically significantly faster rate of decline in GFR in patients randomized to diuretic therapy than either angiotensin-converting enzyme (ACE) inhibitor or CCB therapy.16

The present analysis is an ecological study that epidemiologically describes the relationship between increased diuretic use in the US and the subsequent growth in the incidence rate of ESRD in a directly associated time-lagged fashion. The observation of time-lagged correlation between exposure to an agent and disease incidence is not new in epidemiology. An illustrative example of such a correlation is the relationship between asbestos exposure and the incidence of mesothelioma decades later. The discovery of such an etiologic relationship is not amenable to a double-blind, randomized-control study design but is demonstrable with population statistics. We suggest that diuretic exposure resulting in accelerated ESRD behavior in the population may have a similar etiologic relationship.

Previous publications suggest possible mechanisms for renal injury inherent with chronic diuretic therapy. Glomerulosclerosis in general is associated with several anatomic–pathologic correlations, including glomerular capillary hypertension, mesangial matrix expansion, mesangial hypercellularity, and dyslipidemia. Animal models of progressive renal disease have demonstrated that diuretic-based therapy has adverse effects on each of the factors known or hypothesized to affect glomerulosclerosis.17–21

NHANES III has demonstrated that the prevalence of elevated creatinine in patients being treated for hypertension is higher among patients receiving diuretics than among patients receiving any other medication category.12 Diuretic therapy was identified as the only antihypertensive medication category to be an independent risk predictor of elevated serum creatinine level among treated hypertensive patients. NHANES III failed to identify an association between ACE inhibitor use and elevated creatinine levels, implying that factors other than volume changes or glomerular hemodynamics are responsible for the observations. Another small, 2-year, randomized trial22 of indapamide compared with HCTZ identified that HCTZ did not prevent GFR decline in a population of patients with mild renal insufficiency even while controlling blood pressure effectively, and that indapamide improved GFR in a similar population while controlling blood pressure to an equal extent. This implies that volume contraction is not the factor responsible for creatinine rise observed with HCTZ use, inasmuch as indapamide produces equal volume contraction.

Diuretic distribution in the US has had three apparent peaks in the 1990s. The first peak appeared in 1992, concurrent with the publication of the SHEP23 and Medical Research Council (MRC)24 studies of diuretic therapies for isolated systolic hypertension. The second peak occurred during 1994 to 1995, concurrent with reports25 of increased cardiac deaths purportedly associated with short-acting CCB. The final peak appeared in 1998, concurrent with the publication in November 1997 of the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VI).6 This suggests that diuretic consumption patterns seem to be responsive to contemporary medical literature.

This article is not the first to suggest thiazide diuretics as potentially harmful agents. Exposure to thiazide diuretics has been epidemiologically linked to an increased risk for the development of renal cell carcinoma.26 Recent reports in patients with congestive heart failure also suggest that increased mortality is associated with chronic diuretic use in both heart failure patients with renal insufficiency and in those with earlier stages of renal disease.27 Thiazide diuretics are also implicated in promoting the emergence of new-onset type 2 diabetes in several recent studies.28–30

This is an observational ecological study of pooled-data collected over time by government-funded and private agencies. A time-lagged correlation between drug use and disease behavior is observable, and serves as the basis for our hypothesis. The time-lagged relationships described emerge from the data and have not been prespecified by us. The methodology is clearly limited, as there is no individual specific information, nor is there any indication of specific agent used, dose, or exposure time for affected individuals. This analysis does not differentiate between diuretic use as monotherapy or as part of combination therapy. The data are further limited by cost expenditure as a surrogate for actual units of medication consumed. Notwithstanding these limitations, significant correlations appear between the parameters described that could have plausible physiologic explanations and implications.

We wish to emphasize that this analysis cannot, and does not, prove causation between diuretic use and subsequent ESRD incidence. However, until a randomized clinical trial designed to examine this hypothesis is undertaken, the data imply that diuretics appear to permit, induce, or possibly accelerate renal disease in a small but significant proportion of diuretic-treated patients. On the other hand, other equally rational first-choice drugs such as CCB, ACE inhibitors, and angiotensin receptor blockers do not show this tendency, while having the same overall beneficial profiles for mortality prevention as demonstrated in recent large clinical trials.

References


