



Combined diabetes-renal multifactorial intervention in patients with advanced diabetic nephropathy: Proof-of-concept

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ABSTRACT

Aims: To evaluate efficacy of a multifactorial-multidisciplinary approach in delaying CKD 3–4 progression to ESRD.

Methods: Two-year proof-of-concept stratified randomized control trial conducted in an outpatient clinic of a large public hospital system. This intervention, led by a team of endocrinologists, nephrologists, nurse practitioners, and registered dietitians, integrated intensive diabetes-renal care with behavioral/dietary and pharmacological interventions. 120 low-income adults with T2DM and CKD 3–4 enrolled; 58% male, 55% African American, 23% Hispanic.

Results: Primary outcome was progression rate from CKD 3–4 to ESRD. Fewer intervention (13%) than control (28%) developed ESRD, $p < 0.05$. Intervention had greater albumin/creatinine ratio (ACR) decrease (62% vs. 42%, $p < 0.05$) and A1C $< 7\%$ attainment (50% vs. 30%, $p < 0.05$) and trended toward better lipid/blood pressure control ($p = \text{NS}$). Significant differences between 25 ESRD and 95 ESRD-free patients were baseline eGFR (28 vs. 40 ml/min/1.73m²), annual eGFR decline (15 vs. 3 ml/min/year), baseline ACR (2362 vs. 1139 mg/g), final ACR (2896 vs. 1201 mg/g), and final A1C (6.9 vs. 7.8%). In multivariate Cox analysis, receiving the intervention reduced hazard ratio to develop ESRD (0.125, CI 0.029–0.54) as did higher baseline eGFR (0.69, CI 0.59–0.80). Greater annual eGFR decline increased hazard ratio (1.59, CI 1.34–1.87).

Conclusions: The intervention delayed ESRD. Improved A1C and ACR plus not-yet-identified variables may have influenced better outcomes. Multifactorial-multidisciplinary care may serve as a CKD 3–4 treatment paradigm.

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1. Introduction

Advanced diabetic nephropathy, defined as chronic kidney disease stages 3–4 (CKD 3–4), is the leading cause of end-stage renal disease (ESRD) resulting in renal replacement therapy (USRDS, 2013). Annually, 44% of new ESRD cases have a primary diagnosis of diabetes (USRDS, 2013). Once patients develop ESRD, mortality in the dialysis population is ten times greater than among Medicare patients of similar age without kidney disease, and treatment costs are \$49.3 billion annually (USRDS, 2013).

Current treatments have had limited success in abating progression toward ESRD in CKD 3–4. Treatments addressed separately individual risk factors associated with progression such as uncontrolled glycemia, blood pressure, and albuminuria. Use of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) slows CKD progression; however, most patients in these studies were not in the CKD 3–4 categories (Brenner et al., 2001; Lewis et al., 2001). Better albuminuria control and its effect on CKD 3–4 progression may be controversial. In the ACCORD study, controlled hypertension resulted in improved albuminuria but also worsening of renal function (Cushman et al., 2010). Neither glycemic nor lipid control in CKD 3–4 stages was extensively studied.

Multifactorial approaches, such as in STENO-2 (Gæde et al., 2003; Gæde, Lund-Andersen, Parving, & Pedersen, 2008), have shown more powerful multiplier effects on diabetes and cardiovascular outcomes than those focused on individual risk factors. One study that targeted several factors simultaneously in non-advanced nephropathy with

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mean estimated glomerular filtration (eGFR) rate of 55 ± 17 ml/min/1.73m² showed lower monthly eGFR decline (Joss et al., 2004). Yet no multifactorial interventions have been documented for treatment of CKD 3–4 with the intent of delaying progression toward ESRD.

We designed a one-institution proof-of-concept stratified randomized control trial to evaluate the effect on the progression of CKD 3–4 of an intensive multifactorial-multidisciplinary intervention composed of both behavioral/dietary and pharmacological strategies in a team setting aimed at several modifiable risk factors in patients with T2DM and CKD 3–4 compared to conventional care.

2. Materials and methods

2.1. Design overview

The study protocol focused on measuring the cumulative effect of integrating in a multidisciplinary fashion previously proven CKD 3–4 treatment modalities for delaying or preventing ESRD. The protocol was approved by the Institutional Review Board, Cook County Health & Hospitals System (CCHHS). All enrolled patients provided written informed consent. The study was registered at ClinicalTrials.gov (NCT00708981).

The two-year study was a stratified randomized control trial. Patients were randomized into eGFR strata based on baseline estimated eGFRs, calculated using MDRD equation (Levey et al., 2006). The three strata were CKD 3a (eGFR 46–59 ml/min/1.73m²), CKD 3b (eGFR 30–45 ml/min/1.73m²), and CKD 4 (eGFR 15–29 ml/min/1.73m²). Consented patients were randomized into the multifactorial-multidisciplinary intervention and control as follows: 20, 20 into CKD 3a, 20, 20 into CKD 3b, and 20, 20 into CKD 4 for a total of 60 in intervention and 60 in control (see consort chart in Supplementary materials). The study site was the Fantus outpatient clinic, the primary CCHHS outpatient clinic in Chicago, IL.

2.2. Multifactorial-multidisciplinary intervention

The multifactorial-multidisciplinary intervention combined coordinated medical care with tight control of known renal risk factors including blood pressure, glycemia, lipid control, and albuminuria. The multifactorial-multidisciplinary intervention began with group diet instruction based on the guidelines for managing diabetes and dyslipidemia (American Diabetes Association, 2007) and renal disease (KDOQI, 2007) followed by individual visits with the entire study staff (an endocrinologist, nephrologist, nurse practitioners, certified diabetes educator/dietitian, and research coordinator). The purpose of having all the specialty practitioners at the same appointment was to improve coordination of care and to better integrate each patient's various treatment protocols impacting the underlying CKD 3–4 including glycemia, blood pressure, albuminuria, hyperlipidemia, hyperkalemia, hyperphosphatemia, and hyperparathyroidism. In addition to study visits, case management and additional follow-ups were instituted as clinically necessary to promote target achievement.

The specific targets for the intervention were A1C <7%, BP <130/80 mmHg, and reduction of proteinuria <0.5 g/day (American Diabetes Association, 2007) using a protocol that included ACE-I, ARB or their combination (MacKinnon et al., 2006; Rossing, Jacobsen, Pietraszek, & Parving, 2003), LDL <100 mg/dl, triglycerides <150 mg/dl, and HDL >40 and 50 mg/dl for males and females.

No drug therapies beyond the usual formulary available to all CCHHS providers were introduced. Visit frequency allowed for more intensive diabetes management including, when warranted, basal bolus multiple injections regimens and more complex hypertensive drug therapies using well-defined escalation and safety protocols (see Supplementary materials). For dyslipidemia, conventional statin, fibrate, and niacin, medications were used.

Intervention visit frequency was monthly for the first 6 months and bimonthly for the next 18 months for a planned total of 15 clinic visits over two years. These visits replaced their separate usual care visits to the diabetes and renal clinics, which were typically quarterly or 16 visits over two years. In addition, patients may have unscheduled visits as deemed clinically necessary. Patients assessed as needing more intensive follow-up were also case managed with frequent phone contact by a study staff member.

Control patients received usual care, which included visits with their primary care physicians and, for most of them, visits with board certified specialists in separate diabetes and renal clinics with visit frequency determined by physicians in the relevant clinics. CCHHS system-wide treatment protocols based on current at-the-time treatment guidelines (American Diabetes Association, 2007; KDOQI, 2007), available via Intranet and EMR, guided physician care for diabetes, hypertension, and hyperlipidemia.

2.3. Participants

Patients were included in the study if they had T2DM, were between the ages of 18 and 70, had cognitive functioning that allowed for T2DM self-management, and had documented CKD 3–4. Patients were recruited from the existing patient population in the CCHHS general medicine clinic and specialty diabetes and renal clinics. Study design did not allow for blinding. Documentation of CKD 3–4 was defined as eGFR (Levey et al., 2006) corresponding to CKD stages 3–4 (moderate–severe i.e. eGFR >15 ml/min/1.73m² and <60 ml/min/1.73m²) and presence of proteinuria or albuminuria as follows: current macroalbuminuria, current microalbuminuria, and documentation of previous macroalbuminuria, or current microalbuminuria and documentation of diabetic retinopathy or laser therapy. If patient had only microalbuminuria, then renal ultrasound was used to demonstrate normal-sized kidneys. The exclusion criteria are included in the Supplementary materials.

2.4. Outcomes and follow-up

The primary efficacy endpoint was the development of ESRD defined as eGFR <15 ml/min/1.73m² that persists in subsequent tests.

Determination of the time of reaching ESRD was based on readily available laboratory and clinical data in the electronic medical record (EMR) in addition to data collected during the 6-month interval visits.

Secondary objectives included achievement of individual risk factor treatment targets of blood pressure, glycemia, lipids, and albuminuria; others were safety measures of hypoglycemia and hyperkalemia.

At six-month intervals during this 2-year study, laboratory data were collected and physical exams performed on both intervention and control patients and included vitals and history taking (adverse events, review and adherence to medications, and use of contraindicated medications and supplements). Patients who reached the ESRD endpoint did not continue the study. For study dropouts, last observation data points were included and carried forward in data analysis.

2.5. Statistical analysis

As a proof-of-concept study, the sample size was driven by the need to recruit effectively sufficient number of patients from one institution and by the fact that there are no data on the effect of multifactorial intervention on ESRD development. Previous data available from studies with monofactorial therapy and in patients with less advanced kidney failure showed a risk reduction ranging from 28% to 33% (Brenner et al., 2001; Lewis et al., 2001). Since our patient population with more advanced nephropathy was at higher risk of developing ESRD than that in previous studies, we made an empirical assumption that 25% patients in control would reach ESRD.

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