

Early Nephrology Referral for the Chronic Kidney Disease Patient: Seeing the Light or Groping in the Dark?

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Chronic kidney disease and end-stage renal disease are worldwide public health problems associated with high morbidity and a substantial expenditure on health care resources [1]. In Israel, at the end of 2013 the number of patients undergoing chronic dialysis was approximately 6000 and the annual direct cost of dialysis care approximately 5% of the total health budget (estimated 1.25 billion of 26 billion Israeli shekels; 0.26 billion of 7.46 billion U.S. dollars, respectively) [2].

CKD and ESRD patients suffer from low quality of life, and high rates of comorbidities, hospitalization, morbidity and mortality [1]. As reported in the United States Renal Data System summary for 2013, once renal replacement therapy is initiated the expected remaining life span is approximately 8 years (varying with race) for dialysis patients aged 40 to 44, and 4.5 years for those 60 to 64 years of age [1]. In fact, the life expectancy of dialysis patients is only one-third to one-sixth that in the general population and, in older dialysis patients, only slightly better than that in patients with lung cancer. However, recent evidence suggests that mortality rates among incident dialysis patients have decreased over the last few

years [1]. For example, between 2003 and 2010, first-year death rates in the U.S. fell by more than 16%, while second-year death rates declined by 21% between 2002 and 2009 [1].

Substantial clinical data indicate that many of the clinical features and outcomes observed among patients with ESRD are already evident in those with earlier stages of CKD, with the risk of hospitalization and cardiovascular events in CKD patients progressively increasing as glomerular filtration rate declines [3,4]. This finding suggests that the comorbidities and complications observed in ESRD manifest themselves well before the onset of ESRD and, therefore, appropriate CKD care might have a significant impact on subsequent morbidity and mortality of patients after initiation of dialysis. In light of this evidence, several important questions come to mind. Is early CKD (eGFR < 60 ml/min/1.73 m²) care provided by primary care physicians or internists sufficient, or should these patients be referred to a nephrologist for specialist care? What evidence is there in favor of a potential added value of nephrology care over standard care and, if there is a significant benefit, when is the ideal time for the CKD patient to be referred for specialist care? What are the possible causes of late referral worldwide and specifically in Israel? Finally, is there any impact of guideline-driven pre-dialysis nephrology care on survival of CKD patients?

During the last decade, a succession of observational studies that included thousands of CKD patients from France, USA, Australia, Canada, Korea, Holland

and many other countries has shown a striking benefit of early nephrology referral on subsequent survival following commencement of dialysis [5–12]. This benefit appears to be time-dependent: those who received nephrology care for more than 3 months have better outcomes than those with less than 3 months follow-up. Even more impressive, nephrology care for longer than one year before dialysis initiation was associated with the greatest survival benefit. A recent meta-analysis summarized currently available data from 27 longitudinal cohort studies, providing information on 17,646 participants, 11,734 of whom were referred early and 5912 (33%) referred late [12]. A highly significant reduction in mortality for patients who were referred early was evident 3 months after dialysis initiation (odds ratio 0.51, 95% confidence interval 0.44–0.59, $P < 0.00001$) and the effect persisted at 5 years (OR 0.45, 95%CI 0.38–0.53). Similarly favorable effects were seen for hospitalization. Differences in mortality and hospitalization data were not explained by differences in prevalence of diabetes mellitus, previous coronary artery disease, blood pressure control, serum phosphate or serum albumin.

It should be emphasized that this evidence comes from large-scale cohort studies. Ideally, randomized controlled trials comparing outcomes of early vs. late referral should be performed to verify the advantage of early referral. However, since enrolment to such studies would be ethically and scientifically challenging given the inevitable biases of participating physicians and the inability to blind patients and

CKD = chronic kidney disease
ESRD = end-stage renal disease

eGFR = estimated glomerular filtration rate

OR = odds ratio
CI = confidence interval

physicians to the treatment arms, we have to accept the current level of evidence as the best possible.

Assuming that early referral is truly advantageous, are there specific underlying factors that could explain the benefit of pre-dialysis nephrology care? Few studies have assessed this question and it appears likely that multiple factors can be invoked. An obvious and perhaps most powerful factor is avoidance of the dangers associated with acute complications of uremia necessitating emergency dialysis and hospital admission, as well as the need for central venous catheters for vascular access in this situation [5,6,13,14]. Additional established benefits of prolonged nephrology care are better blood pressure control, slower progression of CKD, avoidance of potentially nephrotoxic medications, and treatment of CKD-specific complications that are also cardiovascular risk factors. These include anemia (erythropoiesis-stimulating agents and iron), hyperlipidemia (statins), low serum albumin (dietary modification), vitamin D deficiency (supplementation), metabolic acidosis (bicarbonate supplementation), abnormal mineral metabolism (correction of calcium, phosphate, parathyroid hormone), as well as psychosocial disturbances (referral to psychiatrist and social worker). In addition, education regarding the options available for RRT allows for informed patient choice, leading to better uptake of home peritoneal dialysis, earlier placement of an arteriovenous fistula for hemodialysis, and early assessment for preemptive kidney transplantation [1,6,12-14]. Obviously, this list does not imply that all aspects will always be covered adequately by all nephrologists. Rather, nephrologists are challenged to implement these tasks according to the standards of the profession. Indeed, in light of the above mentioned evidence, it is reasonable to believe that nephrologists will perform these tasks more fully and efficiently than non-nephrologists.

Against the background of the above discussion, the article by Berar Yanay et

al. in this issue of *IMAJ* [16] is to be welcomed; it is the first Israeli study to assess the impact of the timing of nephrology referral on outcome of CKD patients after initiation of dialysis [15]. The study analyzed 200 incident dialysis patients; 41% were referred late (dialysis required less than 3 months after their first nephrology consultation). The early and late referral groups were similar in mean age, gender distribution, prevalence of diabetes, hemoglobin and albumin levels at dialysis initiation. All patients in the late referral group started dialysis with central venous catheters. The 4 year survival rate was 41.1% in the early and 18.7% in the late referral group ($P < 0.0001$). Multivariate analysis demonstrated a powerful impact of late referral on mortality rate (hazard ratio 1.873, 95% CI 1.133–3.094), with the effect being most prominent in patients < 70 years old, females and diabetics. Unfortunately, apart from the probably greater use of permanent vascular hemodialysis access in the early referral group, the specific factors responsible for the benefit, and the possible reasons for the greater benefit in specific subgroups, cannot be determined based on the data presented in this article. Nevertheless, the findings by Berar Yanay and co-authors that pre-dialysis nephrology care in the Israeli CKD population improves survival after the initiation of RRT support current evidence from other countries. Moreover, the current work demonstrates an unacceptably high prevalence of late nephrology referral in Israel, irrespective of the underlying causes that could not be explored due to insufficient data.

Multiple causes of late referral have been identified worldwide. These include factors that are difficult to correct, such as referral bias of physicians; refusal, non-compliance and socioeconomic status of the patient; and the structure of the health care system within a given country [12,14]. Referral depends upon practice patterns, which are not uniform across health care systems or geographic regions. As a result, there is a variety of recommendations regarding the indications for refer-

ral to nephrologists, but none has been universally adopted [16-18]. Obviously, based on the current evidence, patients should be referred at least one year before dialysis is required. However, this time-dependent definition presupposes that the primary care physician, internist or other physician is able to predict when dialysis will be necessary in any given patient – an absolutely unrealistic expectation. Based on the overall data available, we suggest that the eGFR be the primary determinant of referral, and that patients with stage 3 CKD (eGFR 30–59 ml/min per 1.73 m²) should be seen by a nephrologist, who would then co-manage the patient with the primary care physician. Additional factors that should influence the decision to refer are: resistant hypertension, prominent proteinuria, hematuria, presumed hereditary kidney disease, inability to identify a presumed cause of CKD, eGFR decline of more than 30% in less than 4 months without an obvious explanation, and difficult-to-manage complications of CKD, as described earlier.

Ideally, a collaborative multicenter national study should be performed to address the subject of timely referral of CKD patients to nephrologists in Israel. However, given the challenges in organizing such a trial, we suggest, in the meantime, appropriate training of primary care physicians with regard to guidelines on timing and indications for referral, and understanding of the potential consequences of late referral. These initiatives will help promote better communication among nephrologists, referring physicians and other specialists, thereby paving the way towards improved outcomes following the commencement of RRT.

In summary, based on current evidence, we suggest that timely referral of CKD patients to a nephrologist is a simple strategy that can favorably impact on survival of these patients in Israel as well as globally.

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