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Consequences of late referral on patient outcomes

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Abstract There is growing awareness of a need not only to identify patients with chronic renal failure (CRF) at an earlier stage in the disease process, but also to initiate treatment strategies earlier, in order to delay both progression of CRF and co-morbid diseases and to define the optimal time required to prepare CRF patients for renal replacement therapy (RRT). These three strategies are linked, and rely on appropriate identification of patients at risk of renal disease. The challenge currently facing nephrologists is both how to minimize the consequences of late referral and how to improve the timeliness of referral.

Published studies support the notion that outcomes are poor in patients who access specialized nephrology care late in the course of their renal disease (just prior to the need for dialysis). A National Institute of Health consensus publication recommends early referral to a multidisciplinary renal care team, and the recent Canadian Society of Nephrology guidelines recommend that at least 12 months are needed prior to initiation of dialysis for adequate medical and psychological preparation for RRT. Despite these recommendations, a substantial proportion (20–50%) of patients starts dialysis without prior exposure to nephrologists.

Limited data exist on current referral patterns to nephrologists. Diabetes and/or hypertension cause renal disease in up to 40% of patients requiring dialysis. These patients are presumably being monitored by internists, endocrinologists or cardiologists, and many referrals come from these physicians; other patients may be referred by general practitioners.

Data regarding disease status at the time of referral are also limited. Substantial cardiovascular disease and risk factors are evident at the time of referral. Most of the literature describes data for those starting dialysis (i.e. late referral) rather than a broader spectrum of all patients with renal insufficiency referred to nephrologists. Reasons for late referral include insensitivity of current screening tools. Serum creatinine is well known to be an inaccurate marker of renal dysfunction, and too insensitive to identify patients with *very* early stages of disease, thus contributing to the prevalence of late referrals. Physician and patient attitudes are other barriers to early referral and need to be studied more fully.

The consequences of late referrals include increased morbidity, mortality, and resource utilization. There is also an impact on patients' quality of life and missed opportunities for pre-emptive transplantation. Late referral also limits therapeutic options, and these limitations have consequences on long-term outcomes once patients are on dialysis.

It is clear that late referral of patients with CRF obviates the opportunity for significant delay of disease progression and institution of proactive strategies to reduce the overall burden of illness in the population. There is ample evidence that strategies to delay progression of renal disease are effective, as are strategies to reduce cardiovascular disease. Anaemia and a fall in haemoglobin concentration have been associated with left ventricular hypertrophy and with growth of the left ventricle. A combined approach is necessary for best nephrological clinical practice, with a clear definition of early renal insufficiency; this will involve the development of tools to permit early identification of patients with early renal insufficiency, and the implementation of strategies to optimize treatments aimed at both delaying progression and preparing patients for RRT.

Key words: dialysis; early renal insufficiency; renal disease; screening; serum creatinine

Introduction

Morbidity and mortality remain high among patients on dialysis, despite advances in technology and improved understanding of treatment strategies. Factors that are present at the initiation of dialysis, as well as those that exist before its commencement, have an impact on patient outcomes. If long-term patient outcomes are to be improved, then there is a need for earlier identification of, and intervention in, patients with renal disease. Strategies have been described that delay the progression of both renal and comorbid diseases. Optimal treatment of patients before initiation

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of dialysis is contingent on an accurate definition of the population categorized as 'pre-dialysis' patients. However, the term 'pre-dialysis' is still used to define a heterogeneous group of patients, including those who are referred both 'early' and 'late' in the clinical course of their renal disease. Once accurate definitions and terminology are established, it will be important to determine the barriers to timely referral so that they can be systematically addressed. Finally, it is important to establish goals for the treatment of patients with chronic or progressive renal failure, and strategies by which to achieve those goals. This paper addresses issues related to late referral to nephrologists, focusing on current referral patterns and their consequences, the current burden of illness in the renal population, both prior to and at initiation of dialysis, and the known consequences of late referral.

Current referral patterns

Current referral patterns can be classified into three major categories: early, late, and not referred (Figure 1). For patients with renal insufficiency, the consequence of never being referred to a nephrologist is death; the extent to which this currently occurs is not known. Alternatively, if patients are referred early in the course of their renal disease, opportunities to intervene exist that may delay or halt the progression of the renal disease process and/or of associated car diovascular, metabolic and bone diseases [1–4]. Furthermore, with early referral, adequate physical, social, and psychological preparation for renal replacement therapy (dialysis or transplantation) is possible. If patients are referred late in the course of their renal disease, opportunities for proactive intervention are lost, as is adequate time to prepare for arteriovenous access or living donor transplantation. Optimal therapy for patients with renal disease, therefore, includes timely referral to a nephrology team.

'Timely referral', however, remains a poorly defined term. The National Institute of Health (NIH) Consensus Conference Statement, published in 1994 [5], described the need to refer patients to a nephrology team at least 4 months before initiation of dialysis. In a 1999 Canadian Society of Nephrology publication 'timely referral' is defined as being at least 12 months prior to dialysis initiation [6]. Both definitions of timeliness presuppose that general practitioners, internists, and other specialists are able to predict when dialysis will be necessary in any given patient—a difficult skill even for trained nephrologists. Problems therefore will be encountered in defining timeliness, as a knowledge of future events is required. It has been suggested that timely referral to a nephrologist should apply to any patient who has evidence of renal impairment, or to those within high-risk groups (e.g., patients with hypertension, diabetes, or cardiovascular disease) who have abnormalities of renal function or urine sediment. For the purposes of this article, however, 'late referral' is defined as those persons commencing dialysis therapy within 4 months of being known to a nephrologist.

It is estimated that 20–50% of patients starting dialysis are late referrals [7]. The variation in reported prevalence rates is explained by differences in defining the group of patients for whom there was an opportunity for earlier referral. Approximately 20–25% of patients starting dialysis were previously known to a physician, but were not referred to a nephrologist in a 'timely' manner. The other 25% of patients classified as 'referred late' were not referred earlier for a number of reasons: the patients either had acute renal failure that did not resolve, or rapidly progressive glomerulonephritis, or were non-compliant or asymptomatic, or were unknown to a physician.

Magnitude of the problem of renal insufficiency

To view the current problem of late referral in context, it is useful to review population data that define patients at risk, or patients who have early renal disease. Data from the National Health and Nutrition

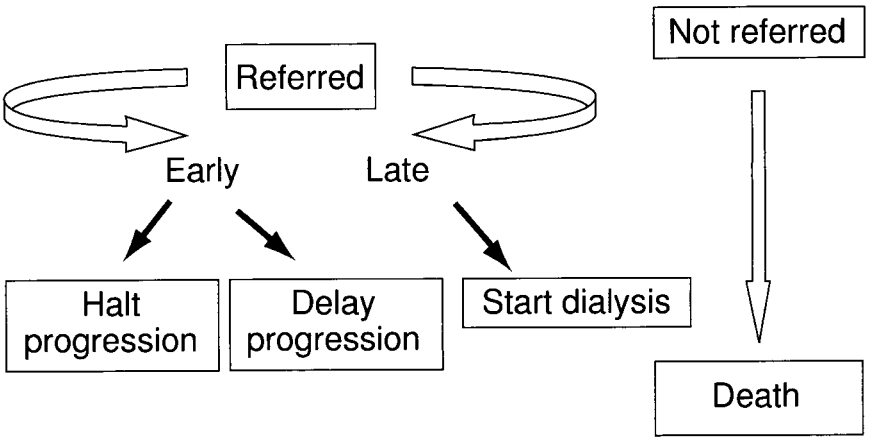

Fig. 1. Referral patterns for patients with renal insufficiency.

Examination Survey (NHANES III) of 12 000 people in the United States has estimated the prevalence of early renal insufficiency (ERI) to be between 10.9 million and 0.8 million, depending on the definition of 'early' renal disease (i.e. serum creatinine concentrations >1.5 g/dl or >2.0 g/dl) [8]. In the UK, Khan *et al.* [9] estimated the annual incidence in the population of serum creatinine concentrations greater than 300 μmol/l to be approximately 600 per million population. If individuals over the age of 85 years and individuals with malignancy are excluded, the incidence of serum creatinine is still impressive at approximately 450 per million [9]. The proportion of the population, therefore, who ought to be referred to a nephrologist is huge and potentially beyond the current capabilities of most national nephrology communities. If prevention or delay of renal disease progression does lead to improved patient outcomes, then planning for increased workload and strategies is essential.

Screening for renal disease

Interestingly, the estimates of populations who potentially require renal replacement services are based on defining renal dysfunction according to serum creatinine concentrations, unadjusted for body size or gender. The true prevalence of individuals with impaired renal function is likely to be much higher if renal function, not just serum creatinine concentration, is used to define renal dysfunction. The recent Modification of Diet in Renal Disease (MDRD) formula, and older formulae, such as Cockcroft–Gault, have been used to improve estimates of renal function from simple laboratory parameters [10,11]. In a large urban population, Duncan *et al.* [12] recently surveyed all patients attending a centralized municipal set of laboratories and applied the conservative, simple Cockcroft–Gault formula to all patients whose serum creatinine was measured. Using a creatinine clearance cut-off of less than 50% to define abnormal, it was demonstrated that of 15% those patients with normal serum creatinine concentrations according to laboratory criteria had abnormal renal function when the Cockcroft–Gault formula was applied. These results identified a group of patients who were at risk but were not easily identified by non-nephrologists. Recently, Couchoud and colleagues [13] proposed that a set of sex- and age-corrected serum creatinine cut-off concentrations should be implemented to appreciate differences in renal function not reflected by serum creatinine. The first step in ensuring timely referral of patients to nephrologists is the implementation of sensitive screening tools.

In a recent editorial in this journal, Jungers [14] addressed the utility and feasibility of screening for renal insufficiency. He concluded that since the 'principles of preventative therapy are now well established, and the evidence that appropriate drug intervention is effective in halting or at least slowing renal insufficiency', strategies to improve early identification and care of renal patients are essential [14]. However, current patterns of 'late referral' may reflect, at least in part, difficulties with today's screening tools. Strategies that serve to educate both patients and physicians about the meaning of specific tests of renal function may be useful. Examples of similar campaigns to educate patients and physicians can be found in the field of cardiovascular disease, with respect to cholesterol screening [15,16].

At present, nephrologists should focus on those renal patients who are known to the medical system but who have not yet been referred to the kidney disease specialist. Reasons for non-referral to nephrologists, therefore, need to be examined. These reasons include non-recognition of ERI (see above), and non-nephrologist attitudes towards (i) the utility of dialysis, (ii) the role of nephrologists, and (iii), in some health care systems or cases, physician concerns about loss of income. It is beyond the scope of this paper to review each of these in depth, but it is important to acknowledge that the problems of non-referral and delayed or late referral are related both to issues of identification of renal dysfunction and to attitudes towards referral.

Physician factors

Attitudes towards referral by non-nephrologists have been studied by only a few investigators. Mendelssohn *et al.* [17] demonstrated that 84.3% of general practitioners in Ontario, Canada, would not refer patients with serum creatinine concentrations between 120 and 150 μmol/l (which reflects at least 50% loss of renal function), and that almost 30% would not even refer patients with serum creatinine concentrations of 151–300 μmol/l. Similar attitudes have been documented in other countries including the USA, the UK, and France.

Other reasons for delayed referral include the perceived futility of dialysis for older, diabetic patients and the perceived non-utility of nephrology care prior to the actual start of dialysis. Specifically, many specialists perceive nephrologists only as providers of dialysis therapy. A problem of delayed referral even at low levels of renal dysfunction may be due to a lack of appreciation of the meaning of serum creatinine concentrations in relation to renal function, or a lack of appreciation of the utility of nephrological care during early stages of renal insufficiency. Ultimately, late referral translates into lost opportunities for intervention, and therefore contributes to the poor outcomes seen in patients who are 'referred late'. Interestingly, there is a dearth of publications in general medical journals describing the impact of nephrology care on patient outcomes. The few studies that have specifically addressed nephrological care and patient outcomes have been published in nephrology journals [1,18–22].

Consequences of delayed referral

The consequences of late referral have been well documented by numerous investigators since as early as 1972 [11,23–27]. Morbidity and mortality among patients 'referred late' is worse than among those referred in a timely manner. The cost to the health care system in terms of hospitalizations and procedures is also higher.

Numerous clinical, haematological, hormonal and metabolic abnormalities have been documented in patients at the time of dialysis initiation, including anaemia, malnutrition, hyperparathyroidism, hyperphosphataemia, hypocalcaemia, acidaemia, hypertension, and congestive heart failure. The presence of low albumin, anaemia, left ventricular hypertrophy (LVH), and congestive heart failure at dialysis initiation have been linked to poor dialysis outcomes [28–31]. Each of these parameters is potentially modifiable. Although no data exist yet to link changes in these factors to changes in patient outcomes, it would seem rational that attention to these abnormalities before dialysis initiation would have a positive impact on longer-term patient outcomes. However, large prospective studies are needed to confirm such a positive impact on patient outcomes.

A very direct consequence of later referral is the lack of permanent vascular access, and the precipitous commencement of dialysis in unstable patients. Studies have shown that late referral leads to an increase in infection, morbidity, and even mortality [19,21,32]. Furthermore, modality selection may be influenced by the timing of referral: those patients who are referred to nephrology teams early in the course of their disease are more likely to choose peritoneal dialysis rather than haemodialysis [33,34]. Delayed referral therefore has major direct consequences for patients and for health care systems.

Publications to date have described the status of patients at the time of dialysis initiation relative to the time of referral. Problems with these analyses include the retrospective nature of the studies, the lack of reasons given for early *vs* late referral, and non-uniform definitions of 'early' *vs* 'late' referral. Despite these shortcomings, the data are remarkably similar irrespective of the country or health care system from which they are derived. Patients who are referred to a nephrologist early (usually defined as more than 4 months prior to beginning of renal replacement therapy) are younger, and have higher albumin, bicarbonate, and haemoglobin concentrations than those who are referred late; in addition, patients referred early are more likely to have a permanent access and to have chosen peritoneal dialysis as an initial modality. Many of the publications pre-date the NIH Consensus guideline recommendations. Curtis *et al.* therefore examined current practice in a recent Canadian survey [manuscript in preparation]. Table 1 shows that similar referral patterns are evident, even in the current era (1998–1999). Approximately 30% of patients commencing dialysis in Canada were known to nephrologists for less than 3 months prior to starting dialysis; these patients were older, more likely to have diabetes, had started haemodialysis through a temporary line, and had lower albumin and haemoglobin concentrations at the initiation of dialysis.

Table 1. Patterns of referral to a nephrologist (recent Canadian survey: 15 centres/7 provinces: 1-month sample)

	All (238)	Known (157)	Not known (84)	p-value
Age (years)	59	57	62.5	0.01
Diabetes (%)	38	35	36	0.54
HD (%)	67	68	65	0.64
Temp. line (%)	52.5	41	75	0.001
Albumin (g/l)	31	33	29*	0.002
Hb (g/dl)	9.2	9.4	8.9	0.051
CCr	10.9	11	10.8	0.057

*Significant difference.

There is substantial evidence to show that late referral of patients to nephrologists results in poorer clinical status at the time of dialysis initiation. Given that the factors known to adversely affect long-term dialysis outcomes are present in late-referred patients, a proportion of the morbidity and mortality of patients on dialysis may therefore be attributed to the failure to refer patients to a nephrologist and institute appropriate treatments in a timely manner prior to dialysis initiation.

Data available from the Canadian Multicentre Cohort Study of Patients with Early Renal Insufficiency (funded by the Kidney Foundation of Canada) allows some documentation as to the status of patients seen by nephrologists. A total of 446 patients seen by nephrologists in eight centres across Canada were entered. The mean creatinine clearance of the group was 36 ml/min (mean serum creatinine concentration of 263 μmol/l), indicating substantial, although not end-stage, renal impairment. Interestingly, almost 25% of the group had a creatinine clearance of less than 25% [35]. At study entry, this group of patients demonstrated a high prevalence of cardiovascular diseases and risk factors for cardiovascular disease. Specifically, the prevalence of LVH was 36% overall, and 48% in the group with a calculated creatinine clearance of less than 25 ml/min (i.e. the group most likely to commence dialysis). In this population, as in the dialysis population, anaemia and a fall in haemoglobin concentration were associated with LVH and with growth of the left ventricle. Cardiac symptoms, according to New York Heart Association and Canadian Cardiovascular Society classifications, as well as hospitalizations, are associated with lower haemoglobin concentrations, lower renal function values, faster rates of renal decline, and growth of the left ventricle. In identifying modifiable risk factors, this study highlighted the opportunities for intervention that exist in the renal population prior to dialysis.

Obrador *et al.* [36] reported that even in those

patients seen by nephrologists, sub-optimal care is being delivered. Their recent study reviewed patients seen in different nephrology settings over a 2-year period; their data show that almost 60% of patients seen by nephrologists commence dialysis with albumin concentrations below 35 g/l, and that only 25% of anaemic patients receive epoetin. Patients who were older, female, Caucasian, and had private medical insurance were more likely to receive epoetin [36]. These findings demonstrate that care may not be optimal even in current nephrology practice. As nephrologists attempting to increase the numbers of patients referred earlier in the course of disease, it is important that improved outcomes at both dialysis initiation and in the long term are demonstrated by further studies. Levin *et al*. [19] have previously established that when patients attend a multidisciplinary clinic, the patient's clinical status is improved at dialysis initiation and over the first 6 months of dialysis. However, the optimal timing and the extent and type of interventions necessary to improve renal patient outcomes still need to be defined.

Conclusion

The consequences of late referral to nephrologists on patient outcomes are profound and far reaching. Effective strategies currently exist to prevent or delay both the progression of renal disease and the serious co-morbidities that exist in the population with renal insufficiency. The most serious consequence of late referral to a nephrologist is that it is too late to apply these known strategies to patients who may have benefited had they been referred earlier. Equally serious is the inability to study systematically the impact of different strategies in patients with chronic renal insufficiency. As a result, clinicians and researchers are unable to reduce the burden of illness in the renal patient population, and the subsequent impact of that burden of illness on health care systems. Obvious strategies to improve this situation include clearly defining chronic renal insufficiency populations for both nephrologists and non-nephrologists, identifying better tools for screening, screening of high-risk populations, and educating both patients and physicians as to the utility of screening and early implementation of treatment strategies, such as preventing a fall in haemoglobin concentration. The implications of implementing these strategies and improving patient outcomes are obvious; however, both human and fiscal resources will be required.

References

1. Hood S, Sondheimer J. Impact of pre-ESRD management on dialysis outcomes: a review. *Semin Dial* 1998; 11: 175–180
2. Klahr S, Levey AS, Beck GJ *et al.* The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. *N Engl J. Med.* 1994; 330: 877–884
3. Modification of Diet in Renal Disease Study Group (prepared by Kopple JD *et al.*). Nutritional status of patients with different levels of chronic renal failure. *Kidney Int* 1989; 36 [Suppl 27]: 184–194
4. Fournier A, Aparicio M. Recommendations for clinical practice concerning the prevention of renal osteodystrophy before extra-renal purification. *Nephrologie* 1998; 19: 129–130
5. Morbidity and mortality of renal dialysis. NIH Consensus Statement. *Ann Intern Med* 1994; 121: 62–70
6. Mendelssohn D, Barrett B, Brownscombe L *et al.* Elevated levels of serum creatinine: recommendations for management and referral. *Can Med Assoc J* 1999; 161: 413–417
7. Arora P, Obrador GT, Ruthazer R *et al.* Prevalence, predictors, and consequences of late nephrology referral at a tertiary care center. *J Am Soc Nephrol* 1999; 10: 1281–1286
8. Jones CA, McQuillan GM, Kusek JW *et al.* Serum creatinine levels in the US population: third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 1998; 32: 992–999
9. Khan IH, Catto GRD, Edward N, Macleod AM. Chronic renal failure: factors influencing nephrology referral. *QJM* 1994; 87: 559–564
10. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med.* 1999; 130: 461–470
11. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16: 31–41
12. Duncan L, Heathcote J, Djurdjev O, Levin A. Screening for renal disease with serum creatinine: who are we missing? *J Am Soc Nephrol* 1998; 9: 153A
13. Couchoud C, Pozet N, Labeeuw M, Pouteil-Nobel C. Screening early renal failure: cut-off values for serum creatinine as an indicator of renal impairment. *Kidney Int* 1999; 55: 1878–1884
14. Jungers P. Screening for renal insufficiency: is it worthwhile? Is it feasible? *Nephrol Dial Transplant* 1999; 14: 2082–2084
15. Summary of the second report of the National Cholesterol Educational Program (NCEP). Expert panel on detection evaluation and treatment of high blood cholesterol in adults. *J Am Med Assoc* 1993; 269: 3015–3023
16. Harris DE, Record NB, Gipson GW, Pearson TA. Lipid lowering in a multidisciplinary clinic compared with primary physician management. *Am J Cardiol* 1998; 81: 929–933
17. Mendelssohn DC, Kua BT, Singer PA. Referral for dialysis in Ontario. *Arch Intern Med.* 1995; 155: 2473–2478
18. Ifudu O, Dawood M, Homel P, Friedman EA. Excess morbidity in patients starting uremia therapy without prior care by a nephrologist. *Am J Kidney Dis* 1996; 28: 841–845
19. Levin A, Lewis M, Mortiboy P *et al.* Multidisciplinary predialysis programs: quantification and limitations of their impact on patient outcomes in two Canadian settings. *Am J Kidney Dis* 1997; 29: 533–540
20. Obrador GT, Pereira BJ. Early referral to the nephrologist and timely initiation of renal replacement therapy: a paradigm shift in the management of patients with chronic renal failure. *Am J Kidney Dis* 1998; 1: 398–417
21. Innes A, Rowe PA, Burden RP, Morgan AG. Early deaths on renal replacement therapy: the need for early nephrological referral. *Nephrol Dial Transplant* 1992; 7: 467–471.
22. Ismail N, Neyra R, Hakim R. The medical and economical advantages of early referral of chronic renal failure patients to renal specialists [editorial]. *Nephrol Dial Transplant* 1998; 13: 246–250
23. Bonomini V, Baldrati L, Stefoni S. Comparative cost/benefit analysis in early and late dialysis. *Nephron* 1983; 33: 1–4
24. Eadington DW, Craig KJ, Winney RJ. Comorbidity and biochemical indices modulate the impact of late referral on survival on RRT (abstract). *Nephrol Dial Transplant* 1994; 9: 960
25. Ratcliffe PJ, Phillips RE, Oliver DO. Late referral for maintenance dialysis. *BMJ* 1984; 288: 441–443
26. Schmidt RJ, Domico JR, Sorkin MI, Hobbs G. Early referral and its impact on emergent first dialyses, health care costs, and outcome. *Am J Kidney Dis* 1998; 32: 278–283
27. Sesso R, Belasco AG. Late diagnosis of chronic renal failure and mortality on maintenance dialysis. *Nephrol Dial Transplant* 1996; 11: 2417–2420

28. Hakim R, Levin N. Malnutrition in hemodialysis patients. *Am J Kidney Dis* 1993; 21: 125–137
29. Lowrie EG, Huang WH, Lew NL. Death risk predictors among peritoneal dialysis and hemodialysis patients: a preliminary comparison. *Am J Kidney Dis* 1995; 26: 220–228
30. Madore F, Lowrie EG, Brugnara C *et al.* Anemia in hemodialysis patients: variables affecting this outcome predictor. *J Am Soc Nephrol* 1997; 8: 1921–1929
31. Foley RN, Parfrey PS, Harnett JD *et al.* Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int* 1995; 47: 186–192
32. Jungers P, Zingraff J, Page B, Albouze G, Hannedouche T, Man NK. Detrimental effects of late referral in patients with chronic renal failure: a case control study. *Kidney Int* 1993; 41 [Suppl]: S170–173
33. Nissenson A, Prichard S, Cheng I. Non-medical factors that impact on ESRD modality selection. *Kidney Int* 1993; 40 [Suppl]: S120–127
34. Lameire N, Van Biesen W, Dombros N *et al.* The referral pattern of patients with ESRD is a determinant in the choice of dialysis modality. *Perit Dial Int* 1997; 17 [Suppl 2]: S161–166
35. Levin A, Thompson C, Ethier J. *et al.* Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis* 1999; 34: 125–134
36. Obrador GT, Ruthazer R, Arora P, Kausz A, Pereira JB. Prevalence of and factors associated with suboptimal care before initiation of dialysis in the United States. *J Am Soc Nephrol* 1999; 10: 1793–1800