Late referral: loss of chance for the patient, loss of money for society

Paul Jungers

Department of Nephrology, Necker Hospital, Paris, France

Introduction

Despite all efforts to alert the medical community about its multiple detrimental consequences, late nephrological referral of renal patients still remains a frequent problem in all countries. Recent studies show that up to 40% of patients suffering from chronic renal insufficiency (CRI) begin renal replacement therapy (RRT) less than 6 months after being referred to a renal unit, without having benefited from early nephrological care in the predialysis period [1–11]. This situation is most unfortunate as substantial advances have been made in the management of CRI patients. Late referred patients do not benefit from such progress, especially from the renoprotective and cardioprotective strategies that constitute the basis of optimal therapy of CRI patients today [12–16].

Renoprotection (i.e. use of dietary and pharmacological measures aimed at halting or at least slowing progression of renal failure), is currently considered a fundamental goal in the treatment of CRI patients, but it can be fully effective only if implemented from the early stage of renal failure [12,14,17]. Cardioprotection has more recently emerged as another fundamental goal of the treatment of CRI patients in the predialysis phase. Because risk factors for accelerated atherosclerosis, left ventricular hypertrophy and myocardial fibrosis, the main causes of cardiovascular (CV) disease in uraemic patients, develop from an early stage in CRI, cardioprotective therapy should be implemented as early as possible in the course of renal failure to effectively prevent the development of CV disease and reduce the excess CV morbi-mortality that affects uraemic patients [18–20]. In addition, optimal treatment of CRI patients includes prevention of metabolic disorders, prevention of malnutrition, preservation of quality of life, and adequate preparation for RRT.

In concrete terms, tight blood pressure control, use of angiotensin II inhibitory drugs, statins, calcium and iron supplements, and phosphate binders, vitamin supplementation, timely use of recombinant erythropoietin, dietary counselling, preservation of nutritional status assessed by serum albumin level, and in-time creation of arteriovenous native fistula are parts of the integrated therapeutic strategy to be offered to predialysis CRI patients [14,18,21,22]. Such management of predialysis CRI patients is complex and requires guidance by a specialist to achieve optimal efficacy and safety. Only early, regular management by a dedicated nephrological team, in close cooperation with other involved physicians, may give the patient his best chances of avoiding, or at least substantially delaying end-stage renal disease (ESRD), and preventing or at least attenuating, uraemic complications. Late referred patients are unfairly deprived of such benefits. Moreover, late referral results in considerable extra cost for the health care system.

Loss of chance for the patient

The aspects of the loss of chance of late referred patients are multiple and have to be considered from the incipient stage of renal disease, well before the stage of established, irreversible renal function impairment.

Loss of chance of avoiding ESRD and the need for RRT

A major interest of having nephrological advice as soon as any sign of renal disease is detected is to
establish an opportunity for a preventive intervention, at a stage when renal disease may respond to aetiologic therapy. Rapidly identifying and treating renal diseases such as obstructive or infectious nephropathies, analgesic or non-steroid anti-inflammatory drugs (NSAIDS) nephropathy, or renal artery stenosis, for instance, may stop or reverse the development of CRI, thus avoiding further progression to ESRD. Rapid diagnosis and aggressive treatment of systemic or glomerular diseases responsive to corticosteroids and/or immunomodulating drugs may limit renal lesions and prevent progression toward ESRD. Thus, immediate diagnosis of potentially curable renal diseases is of primary importance, as only early intervention in the form of aetiological treatment or withdrawal of an offending drug may prevent, or halt the development of progressive renal failure. Very few studies have examined the proportion of patients who reached ESRD due to such potentially curable causes, when diagnosed at a late stage or left untreated. In our experience, nearly 5% of patients who started maintenance dialysis at Necker Hospital over the past 12 years had ESRD resulting from such causes, in whom the need for RRT could have been avoided, had the patients been referred earlier to a nephrologist.

Loss of chance of benefiting from optimal renoprotective treatment

Renoprotection involves a multifactorial approach, the cornerstone of which is stringent blood pressure control and the use of drugs that inhibit the systemic effects of angiotensin II (AII), either angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor antagonists (ARAs), associated with moderation of protein intake. AII inhibitors are used because of their effects on systemic blood pressure and glomerular haemodynamics, and their antiproteinuric and antifibrotic action. Optimal blood pressure levels to achieve according to the degree of proteinuria are well defined, and usually require a combination of several antihypertensive agents.

The benefits of renoprotective therapy in terms of antiproteinuric action and the slowing of renal failure progression are well documented in diabetic nephropathy, the leading cause of ESRD in most countries. Aggressive blood pressure control with ACEIs together with optimal glycaemic control has been shown to delay or reverse the onset of microalbuminuria, and slow the progression of both albuminuria and renal failure in type 1 diabetes, as well as in type 2 diabetes. Intervention at the early stage of diabetic nephropathy is possible in patients who benefit from regular joint care by a diabetologist and a nephrologist, and may be expected to allow a substantial retardation of ESRD. However, unfortunately, pre-dialysis care of most diabetic patients is often sub-optimal, especially in type 2 diabetes, with a high proportion of patients lacking prescription of AII inhibitors even at the stage of proteinuria and overt nephropathy, and a number referred to the nephrologist at the advanced stage of renal failure, thus losing the chance of delaying ESRD. As an example, the rate of decline of GFR in type 1 or 2 diabetics with macroalbuminuria is about 10 ml/min/year on average, thus leading to ESRD within about 7 years. If the rate of decline in GFR is reduced to 5 ml/min/year thanks to a well coordinated renoprotective strategy, then one may expect the time until ESRD to be doubled, a very substantial gain of several years.

The same considerations apply to non-diabetic nephropathies. In proteinuric glomerular diseases, AII inhibitors have been shown to reduce proteinuria and slow the rate of decline of GFR or even halt the progression in patients in whom proteinuria was suppressed. In addition, diabetic or older patients often have underlying atheromatous renal artery stenosis. Early diagnosis and treatment of this localization will help to preserve the function of the affected kidney(s).

To summarize, the lack of early renoprotective treatment deprives the patient of the benefit of having avoided, or substantially delayed ESRD and the need for RRT.

Loss of chance of benefiting from adequate cardioprotective treatment

The impact of CV disease on the morbi-mortality of dialysis patients is well established, and there is a direct relationship between the prevalence of CV disease at start of dialysis and the subsequent mortality on dialysis. Several studies have shown that CV disease develops over years during the predialysis period, because risk factors for accelerated atherosclerosis (e.g. hypertension, dyslipidaemia, hyperhomocysteinaemia), left ventricular hypertrophy (hypertension, anaemia and fluid overload), interstitial myocardial fibrosis (e.g. secondary hyperparathyroidism), and arteriosclerosis are present from an early stage of CRI. Such cardioprotective measures should be initiated as early as possible in the course of CRI to exert preventive effects. Cardioprotective strategy relies on a plurifactorial approach, according to the recommendations of the National Kidney Foundation Task Force, including optimal blood pressure control, correction of anaemia, smoking cessation, prevention of fluid overload, treatment of dyslipidaemia and hyperhomocysteinaemia, and detection of coronary artery disease. Such complex therapy requires guidance by a specialist and, again, late referred patients are deprived of the benefits of early, well coordinated management. One may thus hypothesize that late referred patients, in the absence of early implemented cardioprotective measures, will experience a higher prevalence of CV disease when reaching ESRD than patients who benefited from early nephrological care, and subsequently suffer a higher CV mortality while on dialysis.
Several studies showed that late referred patients receive suboptimal treatment of hypertension and anaemia during the predialysis period, and exhibit a higher prevalence of CV disease, hypoalbuminaemia and anaemia at the start of dialysis than early referred patients [1,8,13–16,36–38]. However, no evidence has been provided that the duration of regular predialysis nephrological care could influence the development of CV disease and the length of survival after start of dialysis. Interestingly, two recent studies from France afford data that strongly suggest a beneficial effect of a long duration of predialysis nephrological care in terms of cardioprotection. In a prospective epidemiological study recording all incident patients who began maintenance dialysis in the Ile-de-France area in 1998, prevalence of severe CV comorbidity was nearly twice as high in ERSD patients who had been referred less than 6 months before the start of dialysis than in those who received nephrological care for at least 3 years [37]. In the other study, the authors analysed data from 1057 patients living in the Paris area who began maintenance dialysis at the Necker Hospital between 1989 and 1998 [39]. They observed that the prevalence of severe CV disease was about two times higher in patients who were referred less than 6 months, and even 6–35 months prior to start of dialysis than in those who had received regular nephrological care for at least 3 years before reaching ESRD (about 38% \(\text{vs}\) 22%, a very significant difference). Moreover, 5-year mortality on dialysis was about twice as low in patients followed for 3 years or more than in the other two groups, although the mean age of patients at the start of dialysis did not differ between the three groups. Such findings suggest that prolonged nephrological predialysis care is associated with better preserved CV condition, resulting in lower CV mortality on dialysis, although one cannot exclude that in some of late referred patients severely altered CV condition was the cause, rather than the consequence, of late referral. Importantly, they also suggest that a much longer duration of specialized care than that conventionally defining late referral (i.e. 1–6 months) is needed to observe significant cardioprotective effects. Indeed, predialysis care duration of only some months, even if sufficient to restore the clinical condition of the patient, is clearly insufficient to prevent the development of uraemia-related CV disease. If confirmed by other groups, these data will constitute a strong additional argument favouring early referral and regular nephrological care of CRI patients.

Patients referred at a very late stage do not benefit from such adequate preparation for dialysis [1,11,15,40,41]. Most of them have to start dialysis in emergency conditions, using central vein catheterization, and subsequently the permanent access is often an AV graft which requires a shorter maturation time, but has a high incidence of complications and vascular access failure, resulting in repeated hospitalizations [40,42,43]. In addition, late referral does not allow a true choice of dialysis method, thus often excluding the patient from benefiting from out-centre haemodialysis or peritoneal dialysis [1,6,13].

Last but not least, late referral is the cause of severe emotional distress for the patient, due to the sudden announcement of irreversible loss of renal function and need for indefinite RRT, together with decreased incomes and risk of loss of employment resulting from prolonged hospitalization [13]. These multiple human and socioeconomic consequences result in a severe alteration of the quality of life of patients.

**Loss of money for the society**

Late referral results in a considerable wastage of medical resources that apparently is not sufficiently appreciated. One has to consider not only direct overcosts, but also indirect overcosts, the importance of which has not been highlighted.

**Direct overcosts**

The most apparent overcost results from the prolonged hospitalizations that are usually required in late referred patients. In our experience, the mean duration of hospital stay at initiation of dialysis was about 30 days in late referred patients, compared to about 8 days in patients who had been referred at least 6 months prior to dialysis [37], resulting in an over-cost of nearly 30 000 Euros per patient. Scandinavian authors recently reported very similar figures, with the average duration of hospital stay at start of dialysis being 31 days in late referred patients, compared to only 7 days in early referred ones [11]. Important other overcosts result from rehospitalizations related to vascular access problems, especially with AV grafts, the initial permanent access currently used in more than half of patients in the USA [14,40]. In this country, it is estimated that as much as one-quarter of the total cost of ESRD is spent on the maintenance of vascular access in haemodialysis patients [40]. In addition, the loss of working days during hospitalizations, the compensation for which depends on the insurance system in the various countries, represents a wastage of resources for the society.

Specific studies to quantify the total direct overcosts resulting from late referral are still lacking. Such studies certainly should lead to a better awareness of the undesirable wastage of resources resulting from late referral. It may be estimated that direct overcosts probably account for at least 5–10% of the expenses.
consumed in connection with initiation of dialysis in incident patients.

Indirect overcosts

Indirect overcosts are much more difficult to quantify, although they probably represent an even more important detriment than direct excess costs themselves. They derive from the above mentioned considerations about the loss of chance of avoiding or delaying ESRD in late referred patients [23, 24]. This is the case in patients with potentially preventable or reversible renal disease who could have avoided ESRD and the need for RRT, had they be seen by the nephrologist soon after renal disease was suspected. This is also the case in patients with incipient CRI whose progression toward ESRD should have been halted, or at least substantially slowed, had they received renoprotective therapy from an early stage. Such a situation is especially frequent in diabetics, who are often referred late to the nephrologist [30].

If optimal renoprotective therapy may delay the need for dialysis by several years, then considerable savings may be expected, because diabetic nephropathy is the main cause of ESRD in most countries, and this is probably true also of non-diabetic renal diseases. Even if optimal management of predialysis patients requires frequent visits, this will be cost-effective. Indeed, thanks to frequent clinical controls, most complications may be anticipated and prevented, thus avoiding a number of hospitalizations, the cost of which is considerably greater than that of out-patient visits. On the other hand, the cost of predialysis drug treatments, including the most expensive ones (e.g. AII inhibitors and erythropoietin) is at least ten times lower than that of hospitalizations or of dialysis procedure for the same duration. Specific studies comparing the duration of renal autonomy in early vs late referred patients, especially diabetics, are also lacking, and probably difficult to implement. Such studies would, however, be of great interest to quantify the unnecessary years of dialysis resulting from late referral.

When considering together the direct and indirect overcosts that result from late referral, it may well be possible that more than 10% of the sums annually spent for maintenance dialysis could be spared with better predialysis management of patients. This corresponds to considerable savings, in the order of magnitude of more than one billion dollars per year in a country like the USA.

Conclusion

Late referral of renal patients appears to have many more deleterious consequences than commonly thought, both in terms of human and clinical consequences for the patients, and wastage of money for the society. Late referral should not be considered only from the narrow point of view of its immediate or short-term effects resulting from lack of preparation to dialysis. A more pertinent concept is to consider the duration of predialysis regular nephrological care, and its consequences in the long term on the length and quality of life of ESRD patients. Only a sufficiently long duration of predialysis nephrological management, several years in our experience, may allow renal patients to fully benefit from the effects of a well integrated reno- and cardioprotective strategy. Such optimal management should not induce increased costs, but instead should result in substantial savings, another not negligible consideration. Human and economical benefits of early referral are universally acknowledged, but, unfairly, are not shared by all patients. An intelligent policy for all public health systems should be to actively encourage early referral of all renal patients, and better cooperation between nephrologists and other physicians.

References

5. Ellis PA, Reddy V, Bari N, Cairns HS. Late referral of end-stage renal failure. QJM 1998; 91: 727–732