Ethnicity and renal disease: questions and challenges

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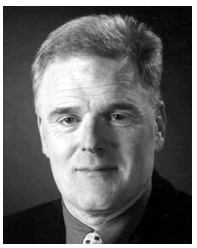

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ABSTRACT – There are significant ethnic variations in the incidence of end-stage renal disease (ESRD). In the UK, the incidence of ESRD in South Asians and African Caribbeans is three times higher than in White Caucasians. This is partly explained by a high prevalence of diabetic nephropathy, but also by susceptibility to a wide range of other renal diseases. The relative contributions of genetic and environmental factors to this susceptibility are not yet well understood. The age structure of the population indicates that the prevalence of ESRD in ethnic minority populations will continue to increase more rapidly than in the White Caucasian population. Additional resources are required for renal replacement therapy in areas with substantial ethnic minority populations, taking into account the increased waiting times for cadaveric renal transplantation in these populations. Early intervention programmes to delay or prevent renal failure must be targeted to these high-risk populations.

KEY WORDS: African Caribbean, diabetic nephropathy, dialysis, renal replacement therapy, renal transplantation, South Asian, type 2 diabetes

Increased susceptibility to renal disease among populations of non-European origin is recognised throughout the world. The rapid immigration of ethnic minority populations to the UK in the last half-century continues to accelerate. Their high susceptibility to renal disease has major public health implications for the UK because of the high cost of renal replacement therapy (RRT).

Key Points

- South Asians and African Caribbeans in the UK have increased susceptibility to renal disease
- Diabetic nephropathy is not the only cause of renal failure increased in these populations
- The interactions of genotype and environment in the pathogenesis of this susceptibility to renal disease are not yet understood
- Increased resources to treat renal failure are required in areas of the UK with substantial ethnic minority populations
- Early intervention programmes to delay or prevent renal failure must be targeted to these high-risk populations

Population changes in the UK

In the UK the two predominant ethnic minority populations are African Caribbean, whose migration started in the 1950s, and South Asian, whose migration gained pace in the 1970s. Some migrants came directly from India, Pakistan and Bangladesh; and a rapid migration occurred in the early 1970s from sub-Saharan Africa. More recently, immigration to the UK has been from a broader range of populations, especially from Africa.

The South Asian population in the UK continues to grow. In the 1991 Census, South Asians comprised 22% of those living within the city boundary of Leicester. By the time of the 2001 Census, more than 50% of those living within the Leicester city boundary were of South Asian origin. In the UK South Asian populations have significant differences from White Caucasians in incidences of common diseases, including coronary heart disease as well as diabetes and renal disease.[1]

Causes of renal failure in ethnic minority populations

Type 2 diabetes

The increasing incidence of type 2 diabetes is one major cause of an excess of renal disease in African Caribbeans and South Asians. In Leicester, for example, 25% of the South Asian population aged over 65 years now have type 2 diabetes. Similar increases are seen in other populations around the world, particularly when they are urbanised. This includes Australian Aboriginals, Pacific Islanders, Hispanics, and Native Americans. Current predictions suggest a 30–50% increase in the prevalence of type 2 diabetes in the developed world by the year 2025. But this is slight compared to predictions of two- to three-fold increases in prevalence in developing countries during the same period.

In Leicester in the early 1990s among new patients starting on RRT for end-stage renal disease (ESRD), 20% of those of European origin were diabetic, compared to 40% of South Asians. This reflects not just the increased prevalence of type 2 diabetes but an

increased risk of renal failure among type 2 diabetics. Using commencement of RRT as an inclusion criterion, we observed that the relative risk of a South Asian diabetic developing ESRD compared to a White diabetic was increased more than 13-fold.[2] This figure is close to the documented risk of developing ESRD among Pima Indians (a Native American population with marked susceptibility to type 2 diabetes) which is 14 times that of the US White population.[3] However, using RRT as a criterion may overestimate diabetic nephropathy as a cause of renal failure (since people with diabetes may have other renal pathologies, particularly renovascular disease) or may underestimate the burden of renal failure if there is under-referral.

Non-diabetic renal failure

In Leicester and West London in the 1980s, we also established that the non-diabetic South Asian population had a more than three-fold higher risk of developing ESRD.[2,4] Data from the Thames region in the early 1990s confirmed that the non-diabetic South Asian population had an age-adjusted relative risk of developing ESRD of 3.5 compared to the white European population, and the African Caribbean population had an increased risk of 3.2.[5] In the African Caribbean population, hypertension and type 2 diabetes are the dominant causes of ESRD, with an additional important influence of sickle cell disease. In South Asians, not only are there significant increases in diabetic nephropathy, but also of most types of glomerulonephritis (confirmed by renal biopsy) as well as reflux nephropathy. Furthermore, there is an excess of individuals in whom the cause of renal disease is not identified since at presentation there is already advanced renal impairment with a bland urine sediment and smooth shrunken kidneys on renal imaging, making them unsuitable for renal biopsy. A recent renal biopsy study reports increases in most patterns of parenchymal renal disease, including chronic interstitial nephritis of undetermined cause.[6] There is a marked excess of tuberculosis among South Asians with renal failure; anecdotal evidence suggests tuberculosis as a possible aetiological agent for this non-specific chronic renal disease, with occasional impressive improvements in renal function in response to anti-tuberculous therapy even in the absence of positive microbiological evidence or characteristic renal histology. But cause and effect have not been systematically confirmed.

These findings have close parallels in ethnic populations elsewhere in the world. In the USA, ESRD among African Americans is approximately four-fold higher than in Whites, and among type 2 diabetics the risk of ESRD is 12 times greater for African Americans.

But the most striking increase yet reported is among Australian Aboriginals. One carefully studied population in Tiwi Island, Northern Territories, has the unenviable reputation of being among the least healthy people in the world.[7] Obesity and type 2 diabetes are endemic and the incidence of ESRD is more than 2,000 per million population per year (pmp), compared to the median figure among Whites in the UK of 100 pmp, and South Asians and African Caribbeans of ~300 pmp. This is associated with a standardised mortality ratio more than four times that of Whites living in the same area and a six-fold increase in cardiovascular deaths. This is a potent reminder that ESRD carries with it more risks than merely those of requiring lifelong RRT. Accelerated cardiovascular disease is the major cause of death in all ESRD populations. Proteinuria, even if it has not resulted in renal failure, is an independent risk factor for such cardiovascular mortality in all populations that have been studied.

Renal disease not causing renal failure

The increased susceptibility to renal disease is not restricted in South Asians to those conditions which consistently result in ESRD. For example, there is evidence of an increased prevalence of renal involvement from systemic lupus in South Asians.[8] There is also evidence from both Leicester and Birmingham that steroid responsive nephrotic syndrome in childhood (a condition not usually associated with progressive renal failure) is more common in South Asian than in White populations.[9,10]

Susceptibility to renal disease

Genetics

There is a significant increase in the incidence of renal disease among African Americans when a first-degree relative has renal disease, whatever the cause. There is a similar increased risk of familial renal disease in South Asians, even when the confounding variable of high rates of consanguinity in some Asian communities is taken into account.

There are some interesting parallels in other populations. The Pima Indians are the archetypal group with genetic susceptibility to diabetic nephropathy which accounts almost entirely for the marked increase in ESRD incidence in that population. By contrast, the Zuni Indians, also from south-west USA, have the same high incidence of ESRD as the Pima Indians but only about a quarter of this is due to diabetic nephropathy, with glomerulonephritis being the dominant other cause.[11]

As yet these genetic susceptibilities remain speculative. No genes linked with susceptibility to renal disease have been consistently identified in the South Asian or African Caribbean populations, nor have genetic studies of sufficient size and power yet been established.

Environment

Genetic and environmental factors are difficult to dissociate, and may coincide. The effects of urbanisation are well documented in a number of these susceptible populations – rapid increases in the incidence of obesity, type 2 diabetes, and hypertension have been seen in the Pima Indians, Australian Aboriginals, African Americans and South Asians in the UK among others. Two perspectives on these observations have been discussed. One proposal is that there is a 'thrifty genotype', rapid insulin release promoting fat storage and reduced calorie wastage, which would confer survival advantage during times of

fasting but during prolonged feasting (urbanisation) would confer risk of insulin resistance, central obesity and diabetes.[12] The alternative view is that there is a 'thrifty phenotype' – populations have had to adapt to poorer nutritional environments with a phenotype characterised by intrauterine growth retardation and lower birth weight. When a more favourable environment allows catch-up growth in childhood and adolescence, renal and vascular systems programmed for smaller growth respond with earlier glucose intolerance and hypertension.[13]

Others have emphasised the potential association between the fetal environment and subsequent susceptibility to hypertension and renal disease,[14] postulating that intrauterine growth retardation is associated with reduced nephron number which in turn may predispose to the development of hypertension, and perhaps also to renal failure. The kidney would certainly be particularly susceptible to fetal malnutrition since 60% of nephrons are formed in the third trimester. There is also some evidence based on estimation of renal mass by ultrasound scanning, that kidney size is disproportionately reduced in babies who are small for gestational age rather than those born prematurely.[15] In addition, there are autopsy data indicating that the number of glomeruli decreases proportionately with birth weight below 3 kg,[16] and also that glomerular volume increases in proportion to this reduction in glomerular number.[16] The latter observation is particularly important since there is increasing evidence that increased glomerular size predisposes to glomerular scarring. In the Tiwi Island Aboriginal population, in whom 25% have a birth weight less than 2,500 g, there is also a direct association between lower birth weight and increasing risk of adult proteinuria which predicts not only risk of renal failure, but also cardiovascular risk.[17]

There is as yet little evidence to link these observations directly to the increased susceptibility to ESRD among UK ethnic populations. Although birth weights are lower in South Asians than in Whites in Leicester, a wide range of environmental factors may be responsible for this. The birth weights of those South Asians who presently have ESRD are largely unknown, as the majority were born abroad.

The size of the public health challenge

End-stage renal disease relentlessly increases with age and the UK South Asian population, for example, has an age distribution significantly skewed to younger adults, reflecting the patterns of migration and variations in birth rates. Thus the ageing of the South Asian population will produce additional increases in the prevalence of ESRD. Therefore ethnicity and age must be included in the models which are used to predict population needs for RRT in the UK.

Estimates of need are built on the presumption that current acceptance rates are a true reflection of demand. There may be concern amongst some ethnic minority populations that this is not yet the case. Demand may be underestimated if there is inequity of access to healthcare at primary care level or in onward referral to renal units. Timing of referral is also of significance since there is very good evidence that late referral, particularly first presentation as a uraemic emergency, is associated with significant increases in morbidity and mortality. Although access to healthcare is well organised in established migrant communities, the situation may be less favourable among more recent migrant communities where language and cultural difficulties diminish opportunities for equal access.

Outcome of renal replacement therapy in ethnic minority populations

The effectiveness of RRT for ethnic minority populations has to be assessed across a broad range of issues, including mortality, morbidity, and quality of life, and requires review if care is to be optimised. We have undertaken a series of unpublished studies in Leicester over the last 20 years, making retrospective reviews of outcome in successive cohorts, using postcode matching as a means to minimise the impact of geographical and socioeconomic factors.

We found no difference between South Asians and Whites in terms of mortality of all causes on RRT when corrected for the three predominant variables – age, vascular disease and diabetes. We also found that ethnicity had no impact on complication-free technique survival on haemodialysis, or on problems related to vascular access on haemodialysis, or on hospital admission rates.

On continuous ambulatory peritoneal dialysis (CAPD), however, we did find in the 1980s that complication-free technique survival was significantly worse among non-English speaking South Asians, chiefly due to a greater risk of CAPD peritonitis. Over the last 20 years, we successively introduced a range of improvements in dialysis-related care, including information days specifically designed for South Asians, the provision of multilingual written information and increasing recruitment of staff with relevant language skills, as well as individualised training programmes. A further evaluation in the 1990s showed that there was no longer inequality, and the complication-free technique survival or infection rates on CAPD did not differ among the South Asian population, whether they spoke English or not. This improvement required sustained use of additional resources, particularly the time of a range of health professionals, a factor which must be taken into account by healthcare planners.

To date no specific studies have focused on outcome of RRT in African Caribbean populations in the UK.

Renal transplantation in South Asians

Experience in Leicester of cadaveric renal transplantation has shown no significant difference in patient or graft survival between South Asians and Whites. The same degree of human leukocyte antigen-D related (HLA DR) matching was achieved in the two populations but only at the price of a significant increase in time on the transplant waiting list for South Asians (median 36 months) compared to Whites (median 14 months). Inequality of access to cadaveric transplantation is an issue for minority populations, and it is important that South Asians on

the transplant waiting list who are never offered a cadaveric kidney are not forgotten. Equivalent HLA matching will always be difficult to achieve and this is particularly aggravated in the UK since the rate of cadaveric organ donation among South Asians and African Caribbeans is significantly lower than among White Caucasians. The complex cultural and social background to this low rate has been examined in a number of UK centres over the last decade. Engagement with leaders from the major religious groups represented in these communities has confirmed that there are no absolute barriers to donation from their perspectives. It is expected that there will be a gradual improvement in organ donation rates from these populations as time goes by and next-of-kin permission for donation increasingly involves those born and educated in the UK. This situation makes it particularly important that the opportunity to use living donors for renal transplantation is maximised in these communities.

Quality of life on renal replacement therapy

While it is encouraging that ethnic minority populations with renal disease are not disadvantaged when quantitative assessments of morbidity and mortality on RRT are made, it is much more difficult to make adequate assessments of quality of care. Clearly there is a very wide range of issues where language and cultural influences may affect attitudes of patients and their carers to chronic renal disease. Many of these have considerable subtlety and may be particularly challenging if health professionals caring for these patients are predominantly of White European background. These issues include, for example, acceptance of the concept of a chronic disease, attitudes to the goals of therapy, self-recognition of complications and emergencies, and both the practical and symbolic aspects of dietary care.

There have been few evaluations of quality of life in ethnic minority populations on RRT. One questionnaire-based study in Coventry reported that quality of life was poorer in South Asian patients than in Whites on both peritoneal dialysis and haemodialysis, and following renal transplantation.[18] This important work has some limitations: the questionnaire was administered in English, and assistance in completing the questionnaire came from the research nurse or from a close family member. To maximise the efficacy of a quality of life instrument it is important not only to ensure that it is disease specific, but also that it is translated into relevant languages. Even with translation it must be appreciated that the written word may not provide accessibility. Studies in Leicester indicate that 25% of South Asian elders (over 65 years old) cannot read or write English or their first language. Furthermore, in certain circumstances responses may be less than frank if a third party, whether family member or health professional, assists with the response.

Screening and early intervention

General population screening for renal disease has never been advocated in the UK. Although the costs and implications of renal failure are very high, its relative rarity does not justify population-wide screening. In high-risk ethnic minority populations, however, the case for screening among both diabetics and non-diabetics is strong, especially if directed towards older people.[19]

The prime justification for screening is that earlier intervention can delay or prevent the onset of renal failure. There is now substantial evidence that lifestyle and dietary interventions can have a significant impact on the incidence of type 2 diabetes, and that, once diabetes is established, tight glycaemic control minimises the development of diabetic nephropathy. In diabetic and non-diabetic renal disease, tight blood pressure control and inhibition of the rennin–angiotensin system are now proven strategies for delaying progressive renal failure. Furthermore, these same approaches significantly protect against the attendant increase in cardiovascular risk which is a dominant cause of morbidity and mortality in these patients.

Blood pressure targets have been progressively lowered over the last decade in the light of growing evidence. A target blood pressure of 130/85 is now recommended for all patients with chronic renal disease, and should be lowered to 125/75 if the patient has proteinuria >1 g/24 hours.[20] The evidence for these targets is based on patients studied all over the world and there is no reason to suppose that this strategy is less successful in any ethnic population. Meeting such targets is likely to prove extremely challenging in clinical practice; but encouraging data indicate that progression of renal disease can be slowed in African Americans provided blood pressure is lowered sufficiently.

Direct evidence that such interventions are effective in ethnic minority populations is also becoming available from the very high-risk Australian Aboriginal population in Tiwi Island,[21] where high-risk patients were identified by blood pressure >140/90 mmHg, diabetes with microalbuminuria, or overt proteinuria without diabetes. Although not a randomised control trial, the intervention was a community education programme emphasising strategies to reduce obesity and improve diabetic control, with the introduction of an angiotensin-converting enzyme inhibitor. The outcome of this intervention was striking: within three years there was measurable benefit in improved blood pressure control, significant decrease in proteinuria, and reductions in the incidence of ESRD and overall mortality. This is, of course, an extremely high-risk population with an incidence of ESRD five times that of the high-risk South Asian and African Caribbean populations in the UK. Nevertheless, it provides an encouraging pointer for possible future approaches in the UK, which will need to be culturally sensitive and acceptable if they are to maximise benefit.

Action now in the UK

An epidemic of ESRD in ethnic minority populations in the UK is already upon us. This has major implications for the commissioning of renal services in parts of the country where there are large ethnic minority populations. The very high demand for RRT must be met and this will require a disproportionate emphasis on dialysis facilities, given the low renal transplant rates in these populations. Furthermore, the problem will grow

predictably in the short to middle term because of the predominance of middle aged and young populations whose ageing will create an increasing incidence of ESRD. Public health planning must take this into account and provide realistic levels of resource to enable appropriate delivery of care for ESRD to continue.

Additional initiatives are also required if the magnitude of this problem in the future is to be contained: genetic mechanisms underlying this susceptibility to renal disease will need to be explored; epidemiological studies will have to be conducted to define further populations at risk and to agree the most appropriate approaches to screening. The success of any initiatives will depend crucially on raising public and community awareness, on better understanding of different cultural health beliefs, and on empowering patients.

The National Kidney Research Fund's ABLE (A Better Life) initiative has in the last two years led the way in bringing ethnic minority renal disease to government, public and community attention,[22] and is supporting programmes in West London and Leicester to improve case recognition, to develop appropriate models for public and community awareness, and to educate and empower the primary care health professionals who are crucial to the implementation of effective preventive programmes.

References

1 Feehally J, Burden AC, Mayberry JF, Probert CSJ *et al*. Disease variations in Asians in Leicester. *QJM* 1993;**86**:263–9.

2 Burden AC, McNally PG, Feehally J, Walls J. Increased incidence of end-stage renal failure secondary to diabetes mellitus in Asian ethnic groups in the United Kingdom. *Diabet Med* 1992;**9**:641–5.

3 Nelson RG, Newman JM, Knowler WC, Sievers ML *et al*. Incidence of end-stage renal disease in Type 2 (non-insulin-dependent) diabetes mellitus in Pima Indians. *Diabetologia* 1988;**31**:730–6.

4 Lightstone L, Rees AJ, Tomson C, Walls J *et al*. High incidence of end-stage renal disease in Indo-Asians in the UK. *QJM* 1995;**88**:191–5.

5 Roderick PJ, Raleigh VS, Hallam L, Mallick NP. The need and demand for renal replacement therapy in ethnic minorities in England. *J Epidemiol Community Health* 1996;**50**:334–9.

6 Ball S, Lloyd J, Cairns T, Cook T *et al*. Why is there so much end-stage renal failure of undetermined cause in UK Indo-Asians? *QJM* 2001;**94**:187–93.

7 Hoy W. Renal disease in Australian Aborigines. *Nephrol Dial Transplant* 2000;**15**:1293–7.

8 Samanta A, Feehally J, Roy S, Nichol FE *et al*. High prevalence of systemic disease and mortality in Asian subjects with systemic lupus erythematosus. *Ann Rheum Dis* 1991;**50**:490–2.

9 Feehally J, Kendell NP, Swift PG, Walls J. High incidence of minimal change nephrotic syndrome in Asians. *Arch Dis Child* 1985;**60**:1018–20.

10 Sharples PM, Poulton J, White RH. Steroid responsive nephrotic syndrome is more common in Asians. *Arch Dis Child* 1985;**60**:1014–7.

11 Shah VO, Scavini M, Stidley CA, Tentori F *et al*. Epidemic of diabetic and non-diabetic renal disease among the Zuni Indians: the Zuni Kidney Project. *J Am Soc Nephrol* 2003;**14**:1320–9.

12 Neel JV, Julius S. Type II diabetes, essential hypertension, and obesity as 'syndromes of impaired genetic homeostasis': the 'thrifty genotype' hypothesis enters the 21st century. *Perspect Biol Med* 1998;**42**:44–74.

13 Barker DJP, Hales CN, Fall CHD, Osmond C *et al*. Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. *Diabetologia* 1993;**36**:62–7.

14 Mackenzie HS, Brenner BM. Fewer nephrons at birth: a missing link in the etiology of essential hypertension? *Am J Kidney Dis* 1995;**26**:91–8.

15 Konje JC, Bell SC, Morton JJ, DeChazal R, Taylor DJ. Human fetal kidney morphometry during gestation and the relationship between weight, kidney morphometry and plasma active renin concentration at birth. *Clin Sci* 1996;**91**:169–75.

16 Hughson M, Farris AB, Douglas-Denton R, Hoy WE, Bertram JF. Glomerular number and size in autopsy kidneys: The relationship to birth weight. *Kidney Int* 2003;**63**:2113–22.

17 Hoy WE, Wang Z, VanBuynder P, Baker PR *et al.* The natural history of renal disease in Australian Aborigines. Part 2. Albuminuria predicts natural death and renal failure. *Kidney Int* 2001;**60**:249–56.

18 Bakewell A, Higgins R, Edmunds ME. Does ethnicity influence perceived quality of life of patients on dialysis and following renal transplant? *Nephrol Dial Transplant* 2001;**16**:1395–401.

19 Ellis P, Cairns H. Renal impairment in elderly patients with hypertension and diabetes. *QJM* 2001;**94**:261–5.

20 National Health and Nutritional Examination Survey. The Sixth Report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure. *Arch Intern Med* 1997;**157**:2413–15.

21 Hoy WE, Baker PR, Kelly AM, Wang Z. Reducing premature death and renal failure in Australian aboriginals. A community-based cardiovascular and renal protective program. *Med J Aust* 2000;**172**:473–8.

22 Lightstone L. *Preventing kidney disease: the ethnic challenge*. Peterborough: National Kidney Research Fund, 2001.