Diabetic Nephropathy: Impact of Comorbidity

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Throughout the industrialized world, diabetes mellitus is the leading cause of end-stage renal disease (ESRD), surpassing glomerulonephritis and hypertension. Both the incidence and the prevalence of ESRD caused by diabetes have risen each year over the past decade, according to reports from European, Japanese, and North American registries of patients with renal failure. Illustrating the dominance of diabetes in ESRD is the 1997 report of the United States Renal Data System (USRDS), which noted that of 257,266 patients receiving either dialytic therapy or a kidney transplant in 1995 in the United States, 80,667 had diabetes [1], a prevalence rate of 31.4%. Also, during 1995 (the most recent year for which summative data are available), of 71,875 new (incident) cases of ESRD, 28,740 (40%) patients were listed as having diabetes.

In America, Europe, and Japan, the form of diabetes is predominantly type II; fewer than 8% of diabetic Americans are insulinopenic, C-peptide-negative persons with type I disease. It follows that ESRD in diabetic persons reflects the demographics of diabetes per se [2]: 1) The incidence is higher in women [3], blacks [4], Hispanics [5], and native Americans [6]. 2) The peak incidence of ESRD occurs from the fifth to the seventh decade. Consistent with these attack rates is the fact that blacks older than the age of 65 face a seven times greater risk of diabetes-related renal failure than do whites. Within our Brooklyn and New York State hospital ambulatory hemodialysis units in October 1997, 97% of patients had type II diabetes. Despite widespread thinking to the contrary, vasculopathic complications of diabetes, including hypertension, are at least as severe in type II as in type I diabetes [7,8]. When carefully followed over a decade or longer, cohorts of type I and type II diabetic individuals have equivalent rates of proteinuria, azotemia, and ultimately ESRD. Both types of diabetes show strong similarities in their rate of renal functional deterioration [9] and onset of comorbid complications. Initial nephromegaly as well as both glomerular hyperfiltration and microalbuminuria (previously thought to be limited to type I) is now recognized as equally in type II [10].
Diabetic neuropathy topics. People with diabetes and progressive kidney disease are more difficult to manage than age- and gender-matched nondiabetic persons because of extensive, often life-threatening extrarenal (comorbid) disease. Diabetic patients manifesting end-stage renal disease (ESRD) suffer a higher death rate than do nondiabetic patients with ESRD owing to greater incidence rates for cardiac decompensation, stroke, sepsis, and pulmonary disease. Concurrent extrarenal disease—especially blindness, limb amputations, and cardiac disease—limits and may preempt their rehabilitation. For most diabetic patients with ESRD, the difference between rehabilitation and heartbreaking invalidism hinges on attaining a renal transplant as well as comprehensive attention to comorbid conditions.

Gradually, over a quarter century, understanding of the impact of diabetes on the kidney has followed elucidation of the epidemiology, clinical course, and options in therapy available for diabetic individuals who progress to ESRD. For each of the discussion points listed, improvement in patient outcome has been contingent on a simple counting (point prevalence) of the number of individuals under consideration. For example, previously the large number of diabetic patients with ESRD were excluded from therapy owing to the belief that no benefit would result. A reexamination of exactly why dialytic therapy or kidney transplantation failed in diabetes, however, was stimulated. IDDM—insulin-dependent diabetes mellitus; NIDDM—non–insulin-dependent diabetes mellitus.
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FIGURE 1-3
Statistical increase in diabetes. In the past 20 years, since the diabetic patient with end-stage renal disease (ESRD) is no longer excluded from dialytic therapy or kidney transplantation, there has been a steady increase in the proportion of all patients with ESRD who have diabetes. In the United States, according to the 1997 report of the United States Renal Data System (USRDS) for the year 1995, more than 40% of all newly treated (incident) patients with ESRD have diabetes. For perspective, the USRDS does not list the actual incidence of a renal disease but rather tabulates those individuals who have been enrolled in federally reimbursed renal programs. The distinction may be important in that a relaxation in policy for referral of diabetic kidney patients would be indistinguishable from a true increase in incidence.

FIGURE 1-4
Prevalence of diabetes mellitus in minority populations. Attack rates (incidence) for diabetes are higher in nonwhite populations than in whites. Type II diabetes accounts for more than 90% of all patients with end-stage renal disease (ESRD) with diabetes. As studied by Carter and colleagues [13], the effect of improved nutrition on expression of diabetes is remarkable. The American diet not only induces an increase in body mass but also may more than double the expressed rate of diabetes, especially in Asians. (From Carter and coworkers [13]; with permission.)

PERCENTAGE OF PATIENTS WITH END-STAGE RENAL DISEASE WITH TYPE II DIABETES

<table>
<thead>
<tr>
<th>Country</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>99</td>
</tr>
<tr>
<td>Germany</td>
<td>90</td>
</tr>
<tr>
<td>United States Pima Indians</td>
<td>95</td>
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</tbody>
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FIGURE 1-5
Percent of diabetic ESRD. Noted first in United States inner-city dialysis programs, type II diabetes is the predominant variety noted in those individuals undergoing maintenance hemodialysis. Our recent survey of hemodialysis units in Brooklyn, New York, found that 97% of the mainly African-American patients had type II diabetes. Thus, there has been a reversal of the previously held impression that uremia was primarily a late manifestation of type I diabetes. (From Ritz and Stefanski [14] and Nelson and coworkers [15]; with permission.)

FIGURE 1-6
Thrifty gene. In addition to the artificial increase in incident patients with end-stage renal disease (ESRD) and diabetes that followed relaxation of acceptance criteria, industrialized nations have experienced a real increase in type II diabetes that correlates with an increase in body mass attributed to overfeeding. Formerly termed non-insulin-dependent diabetes mellitus (NIDDM) or maturity-onset diabetes, the variety of diabetes observed in industrialized overfed populations is now classified as type II disease. According to the Thrifty Gene hypothesis, the ability to survive extended fasts in prehistoric populations that hunted to survive selected genes that in time of excess caloric intake are expressed as hyperglycemia, insulin resistance, and hyperlipidemia (type II diabetes). A study by Ravussin and colleagues of American and Mexican Pima Indian tribes illustrates the effect of overfeeding on a genetic predisposition to type II diabetes. Separated about 200 years ago, Indians with the same genetic makeup began living in different areas with different lifestyles and diets. In the Arizona branch of the Pimas, who were fed surplus food and restrained to a reservation that restricted hunting and other activities, the prevalence of type II diabetes progressively increased to 37% in women and 54% in men. In contrast, Pimas living in Mexico with shorter stature, lower body mass, and lower cholesterol had a lower prevalence of type II diabetes (11% in women and 6% in men). (From Shafrir [16] and Schalin-Jantti [17]; with permission.)