

Pandemic ESRD Due to Diabetes: Can Anything Be Done?

Amy L. Friedman and Eli A. Friedman

Diabetes mellitus is a complex illness. It combines—in its several disease forms—insulin resistance, insulin deficiency, and other metabolic defects on carbohydrate and lipid digestion. The result is an increased concentration of glucose in the blood, which can corrupt vital organ systems, especially blood vessels and nerves. Worldwide, approximately 150 million people have diabetes mellitus, with an anticipated doubling in prevalence by 2025. In developed nations, diabetes mainly afflicts those ages 65 years or more, while in developing countries the peak incidence is among 45-64 year olds.

The family of diseases classified as diabetes includes Type 1 diabetes (formerly “insulin-dependent”) in which beta cells in the pancreatic Islets of Langerhans fail to produce insulin, and Type 2 diabetes (“non-insulin-dependent”) due to the inability to utilize insulin. Both diabetes types are complex, with only partially understood associations to gene mutations and environmental factors. Type 2 diabetes is typically managed by diet modification and oral medications. Although one-third of those with Type 2 diabetes ultimately are insulin treated. In America and Europe, diabetes is overwhelmingly Type 2. Less than 7% of diabetic Americans are insulinopenic (low insulin concentration), with C-peptide negative (inflammatory protein in plasma) persons defining their disorder as Type 1 diabetes. End-stage renal disease (ESRD) in diabetic persons reflects the demographics of diabetes per se in that: 1) the incidence is higher in women, blacks, Hispanics, and native Americans, and 2) the peak incidence of ESRD in diabetes occurs from the 5th to the 7th decade. Inferred from these relative attack rates is the reality that blacks over the age of 65 face a seven times greater risk of diabetes-related renal failure than do whites. In the urban U.S., it is not surprising,

Amy L. Friedman, MD is an associate professor of surgery at the Yale University School of Medicine in New Haven, CT.

Eli A. Friedman, MD is a distinguished teaching professor of medicine at the Downstate Medical Center in Brooklyn, NY.

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| <ol style="list-style-type: none"> 1. No Specific Uremia Intervention = Passive Suicide 2. Peritoneal Dialysis <ul style="list-style-type: none"> • Intermittent Peritoneal Dialysis (IPD) • Continuous Ambulatory Peritoneal Dialysis (CAPD) • Continuous Cyclic Peritoneal Dialysis (CCPD) 3. Hemodialysis <ul style="list-style-type: none"> • Facility Hemodialysis • Home Hemodialysis • Daily Hemodialysis (Nocturnal) 4. Renal Transplantation <ul style="list-style-type: none"> • Cadaver Donor Kidney • Living Donor Kidney 5. Pancreas plus Kidney Transplantation <ul style="list-style-type: none"> • Type 1 • Type 2 (Application Increasing) |
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Table 1. Options in uremia therapy for diabetic ESRD patients.

therefore, that ESRD associated with diabetes is mainly a disease of poor, elderly blacks.

As tabulated in the U.S. Renal Data System (USRDS) Report (2005), diabetes mellitus leads the causes of ESRD in the United States, Japan, and most nations in industrialized Europe. Of 102,567 patients begun on therapy for ESRD during 2003, 46,330 (45.2%) had diabetes, an incidence rate of 148 per million population. Reflecting their relatively higher death rate compared to other causes of ESRD, the prevalence of U.S. diabetic ESRD patients on December 31, 2003, was 36.5% (165,113 of 452,957 patients). Both glomerulonephritis and hypertensive renal disease rank below diabetes in frequency of diagnosis among new ESRD patients, substantiating the contention that “diabetes is the most important cause of ESRD in the Western world.”

According to the 2003 National Diabetes Fact Sheet issued by the U.S. Centers for Disease Control and Prevention, 18.2 million people in the U.S. have diabetes—5.2 million of whom are unaware of their disorder.

1. Retinopathy, glaucoma, cataracts.
2. Coronary artery disease. Cardiomyopathy.
3. Cerebrovascular disease.
4. Peripheral vascular disease: limb amputation.
5. Motor neuropathy. Sensory neuropathy.
6. Autonomic dysfunction: diarrhea, dysfunction, hypotension.
7. Myopathy.
8. Depression.

Table 2. *Diabetic complications which persist and/or progress during ESRD.*

der. Among U.S. adults, the prevalence of diagnosed diabetes increased 49% from 1990 to 2000. Healthcare expenditures for diabetes in the U.S. amount to a minimum of \$132 billion, including direct medical costs of \$92 billion and indirect costs of \$40 billion (disability, work loss, and premature mortality).

Diabetic ESRD patients are managed similarly to nondiabetic ESRD patients (Table 1) with two exceptions: 1) simultaneous pancreas and kidney transplantation is a diabetes-specific therapy that, when successful, establishes normal glucose metabolism while correcting kidney failure; and 2) opting for no treatment, meaning electing passive suicide, is the choice more often selected for and by diabetic than by nondiabetic individuals (Table 1). No prospective, controlled trials of dialytic therapy—of any type—versus kidney transplantation have been reported or are likely to be initiated.

Coincident vasculopathic and neuropathic complications of diabetes including heart and peripheral vascular disease, retinopathy, and nervous system malfunction limit rehabilitation and often dominate the patient striving to continue or return to pre-ESRD life activities (Table 2). It follows that comprehensive management of the diabetic dialysis or transplant patient depends on a collaborating team in close communication striving to prevent blindness, limb amputation, cardiovascular disease, and stroke (Table 3). Successful coordination of the multiple collaborators has been affected by several specialties but is most often placed under the responsibility of a nephrologist.

Strategies to reduce the rapidly expanding impact of diabetic nephropathy center on elucidating the biochemical and pathophysiologic impact of a high blood glucose concentration. Clarifying how a high blood glucose concentration induces tissue injury in diabetes suggests paths to potential interventional therapies. In health, protein

alteration resulting from a nonenzymatic reaction between ambient glucose and primary amino groups on proteins to form glycosylated residues called Amadori products is termed the Maillard reaction. After a series of dehydration and fragmentation reactions, Amadori products are transformed to stable covalent adducts called advanced glycosylation endproducts (AGEs). In diabetes, accelerated synthesis and tissue deposition of AGEs is proposed as a contributing mechanism in the pathogenesis of clinical complications. Accumulation of AGEs in the human body is implicated in aging and in complications of renal failure and diabetes. AGEs are bound to a cell surface receptor inducing expression of multiple cytokines that in sum promote oxidative stress, local, and system-wide tissue injury.

Pharmacologic prevention of AGE formation is an attractive means of preempting diabetic microvascular complications because it bypasses the necessity of having to attain euglycemia (normal glucose concentration), an often unattainable goal. Pimagidine (aminoguanidine) interferes with non-enzymatic glycosylation and reduces measured AGE levels leading to its investigation as a potential treatment. Pimagidine treatment in rats made diabetic with streptozotocin preempts complications viewed as surrogates for human diabetic complications. Representative examples from a rapidly expanding literature detailing potential application of aminoguanidine (2270 Library of Medicine citations as of September 2005) include:

- 1) Preventing development of cataracts in rats 90 days after being made “moderately diabetic” by treatment with aminoguanidine.
- 2) Blocking AGE accumulation in rats 32 weeks after induction of diabetes.
- 3) Reducing severity of experimental diabetic retinopathy in spontaneous hypertensive rats.
- 4) Ameliorating slowing of sciatic nerve conduction velocity in diabetic rats.
- 5) Preventing development of the “stiff myocardium” that is a main component of diabetic cardiomyopathy.

Separate multicenter trials of aminoguanidine (Pimagidine) were conducted in adults with Type 1 and Type 2 diabetes and documented, fixed proteinuria of at least 500 mg/day, and a plasma creatinine concentration of <1.0 mg/dL (88 μ mol/L) in women or <1.3 mg/dL (115 μ mol/L) in men randomly assigned to treatment with aminoguanidine or placebo for four years. In the Type 1 trial, reported in abstract, 56 sites enrolled 69 subjects

randomized to receive 150 or 300 mg of aminoguanidine orally bis in die (b.i.d., or twice a day) versus a placebo with a mean treatment exposure of 2.5 years. Throughout the study, more than 90% of subjects in both treatment and placebo groups were concurrently treated with either an angiotensin converting enzyme inhibitor or receptor blocker. Compared with the placebo group, the aminoguanidine group evinced a significant (<0.05) reduction in doubling of serum creatinine concentration in those who had proteinuria >2g/24h. There was a nonsignificant “trend” toward slowing the creatinine rise in the entire group. Simultaneously, protection against diabetic retinopathy and a decrease in hyperlipidemia was noted in the treated group. Side effects in the aminoguanidine group included a transient flu-like syndrome, worsening anemia, and development of antinuclear autoantibodies (ANA). A similar study in 599 subjects with Type 2 diabetes enrolled in 84 centers in Canada and the U.S. was interrupted because of liver function abnormalities in the aminoguanidine treated group. Other adverse effects of aminoguanidine treatment included myocardial infarction, congestive heart failure, atrial fibrillation, anemia, ANA titre conversion, and upper GI symptoms.

Other drugs with promising activity against AGEs under evaluation include desferrioxamine, D-penicillamine, pentoxifylline, pioglitazone, metformin, and nifedipine. Because AGE-induced nephrotoxicity in diabetes is linked to activation of protein kinase C (PKC) isoforms (PKC may regulate the production and action of cytokines involved in many metabolic processes) that promote oxidative stress, ruboxistaurin mesylate, an inhibitor of PKC beta isoforms, has attracted interest. In the diabetic rat, ruboxistaurin normalized glomerular hyperfiltration, decreased urinary albumin excretion, and reduced glomerular transforming growth factor-beta1 and extracellular matrix protein production. Additionally, ruboxistaurin treatment significantly attenuated fibrosis and impaired cardiac function following experimental myocardial infarction in rats. Clinical trials of ruboxistaurin are now in progress.

While medical approaches to amelioration of diabetes are currently limited to external administration of insulin or other agents to normalize glucose, or interference with the production or interactions of the AGEs, surgical

Specialist	Frequency of Evaluation
• Nephrologist (Team Coordinator)	• Monthly or More Frequently as Required
• Endocrinologist	• As Determined by Team Coordinator
• Cardiology	• Annually or More Frequently as Required
• Ophthalmology	• Annually or More Frequently as Required
• Dentist	• Semiannually or More Frequently as Required
• Podiatry	• Monthly or More Frequently as Required
• Nurse Educator	• Monthly or More Frequently as Required
• Nutritionist	• As Determined by Team Coordinator
• Transplant Surgeon	• Pre-ESRD, then per Team Coordinator
• Vascular Surgeon (As Required)	• As Determined by Team Coordinator (Gastroenterologist, Geriatrician, Urologist, Gynecologist, Neurologist)
• Immunizations	• Pneumovax, Influenza annually, Hepatitis B, Tetanus

Table 3. Collaborative team management of diabetic kidney disease.

interventions target an earlier step in the chain of consequences of this disease by direct restoration of the normal insulin/glucose axis through transplantation of insulin producing cells. Living beta cells that regulate their own production and secretion of insulin in response to circulating glucose levels are located within the roughly five to 15 million Islets of Langerhans distributed throughout a single human pancreas. Successful transplantation of a new supply of beta cells, islets containing beta cells or a pancreas bearing islets and beta cells, restores continuous glucose sensing and appropriate insulin release and obviates the need for artificial methods of doing so. As shown in Table 4, multiple obstacles must be overcome in order to successfully transplant islets.

The ideal source to fuel islet transplantation remains problematic in 2006. Consistent with other organ and tissue transplants that depend on live cells, the dream of abrogating the rejection of xenogeneic islets (non-human donors) has not yet been realized. Until this goal is achieved and an unlimited supply through tolerance of tissue from bred animals becomes feasible, clinical islet transplantation will depend on the availability of human pancreases, either from living or deceased donors. Auto-transplantation of islets isolated from an individual’s own organ has been successfully performed in rare circumstances that require extirpation of the entire gland for pain relief in chronic pancreatitis. Despite this in vivo proof of principle of the technical ability to procure func-

- Islet Source
 - Deceased donor human (single or multiple)
 - Living donor human (segmental)
 - Auto-transplant (human)
 - Animal (\pm genetic engineering)
- Isolation, Purification, Modification
 - Fresh
 - Cultured
 - Frozen
 - Gene Therapy
 - Ultraviolet Irradiation
 - Micro-encapsulation
- Engraftment
 - Liver (portal vein infusion)
 - Intra-Thymic
- Prevention of Allo- and Auto-Immune Responses
 - Pharmacologic Immunosuppression
 - Thrombin inhibition
 - Micro-encapsulation

Table 4. Key requirements for successful islet transplantation.

tional islets from a live donor, use of an alternate live islet source (i.e., from a non-autologous source) from a healthy person to a recipient with diabetes, is controversial. In this setting, a segmental pancreas resection is performed to procure the islets. The donor is left with a portion of a gland without regenerative potential and assumes an increased risk of developing diabetes. Combined with the immediate technical risks of surgery, the potential development of diabetes dissuades most transplant teams from offering this approach. Thus, deceased donors currently represent the only source of clinically transplantable islets.

Unfortunately, as for all tissues and organs, deceased donors of islets are scarce and have proven to be the rate limiting step to clinical transplantation. This restriction is made particularly relevant by the frequent need for islets procured from two or more separate pancreases in order to achieve insulin independence, the best definition of a desirable outcome. As this is written (October, 2005), a fresh approach to islet transplantation by Shapiro's Edmonton Group has gained attention because of the protocol's avoidance of steroids that is credited with the multiple successes in inducing freedom from insulin in Type 1 diabetes. But these encouraging results, now also reproduced at other centers, have depended thus far on islets harvested from more than one donor (as many as four pancreases per recipient). Clearly, the current availability of human islets will never suffice even for all potential recip-

ients with Type 1 diabetes. Not far down the road, however, growth of immortalized Beta cells and humanized porcine pancreata and islets may solve the supply dilemma just as insertion of the insulin gene into yeast cells ended worry over an insufficient supply of insulin.

If islet transplants are still so rare and are only now becoming truly successful, why have so many resources been enthusiastically expended in clinical pursuit of this technology? The answer lies within the reports of long term successes of whole organ pancreas transplantation, now reaching 90% one-year graft survival for simultaneous kidney and pancreas allografts. In this approach, an intact, vascularized gland is permanently anastomosed to the diabetic recipient's vessels, permitting the resident islets to sense glucose levels and release appropriate amounts of insulin into their new host's blood stream. The exocrine component of the pancreas is not needed, but also functions with the release of digestive enzymes that are drained into the recipient's bladder or intestinal tract. Though this approach bears substantial surgical risks, including reoperation for complications in as many as 25% of recipients, when it works well, it is spectacular. To date, reports have demonstrated more normal hemoglobin A1C levels than any other replacement technique without the risk of intermittent and symptomatic hypoglycemia. As hoped, the survival of the pancreatic allograft also prolongs life expectancy for the recipient. Furthermore, prolonged pancreas allograft function is credited with stabilization of end organ diabetic consequences of diabetic retinopathy and autonomic neuropathy. Even more dramatic is the demonstration of the pancreatic allograft in preventing the recurrence of diabetic nephropathy in kidney transplants. Thus, the stabilization and, in some circumstances, improvement of the microangiopathic complications of hyperglycemia and AGEs are attributed to the functioning islets contained within a viable pancreatic allograft. Islet transplantation would be considered an ideal means of garnering the benefits of pancreatic transplantation without the need to assume the surgical risks of this procedure. Unfortunately, the disproportionately lesser results of islet transplants compared to pancreas transplants imply that the intact organ affords the islets a protective effect, preventing both alloimmune and autoimmune destruction. These ill-defined processes remain an as yet unmet long-term challenge in this field.

With the tantalizing successes of pancreas transplantation presently at hand, and the promise of islet transplan-

tation more real than ever before, why not consider these modalities to achieve euglycemia in all diabetics, thereby avoiding development of end organ damage from AGEs?

Unfortunately, the risks of the requisite pharmacologic immunosuppression remain so substantial that the theoretical benefits of glucose normalization are not sufficient justification in those diabetics who will not develop ESRD or the life-threatening complications seen in Table 2. Other than the great expense of using them, (approximating \$20,000 per year), these drugs increase the risks of life threatening infections and malignancies, among other consequences. Without a means of identifying in advance which patients will subsequently develop nephropathy and therefore might benefit from preemptive replacement of intrinsic glucose homeostasis, transplantation would be inappropriate. Currently, consideration of either pancreas or islet transplantation is restricted to 1) diabetics with ESRD, in whom immunosuppression will already be required for renal transplantation, 2) those with life threat from autonomic neuropathy that prevents the awareness of hypoglycemia, or, rarely, for 3) those with progression

of other types of neuropathy. In all of these patients, a minimum life expectancy of five years is present, as it is not until at least five years that the beneficial effects of pancreas transplantation have been demonstrated.


If pancreas or islet transplantation achieves optimal glucose regulation and avoidance of ongoing AGE-induced damage for the insulinopenic Type 1 diabetic, albeit at substantial technical and pharmacologically-induced risk, the benefits for the patient with Type 2 diabetes are far less clear. Exactly how the primary restoration of an intrinsic insulin source may obviate the complications in a patient who already has resistance to insulin is not apparent. Nevertheless, nearly 7% of all pancreas transplants have been performed in Type 2 diabetics, with results that match those in Type 1 diabetics. Yet, these startling results must not be viewed as indication for considering these very specialized techniques appropriate for the majority of Type 2 diabetics who have relatively more advanced age and greater obesity than Type 1 patients. It may be prudent to consider referral of only a limited group of young and lean Type 2 diabetics for these proce-

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dures. Yet, often the patient characteristics that are typical of Type 2 diabetes are contraindications to these procedures. For example, diabetes typically develops at a later age in Type 1 versus Type 2 diabetes, and consequently, the onset of ESRD is also later. With candidacy for pancreas or islet transplantation linked to life expectancy, it is clear that older patients, or those with Type 2 diabetes, are less likely to be found suitable. Similarly, obesity is a typical attribute of the ESRD patient with Type 2 diabetes. Although the presence of significant obesity is considered by many centers to be a strong relative contraindication to kidney transplantation, it is an absolute one for pancreas transplantation at most programs. Thus, for most ESRD patients with Type 2 diabetes, who are older and more obese than the similar cohort with Type 1 diabetes, pancreas and islet transplantation are not realistic options.

Although not yet successfully applied in humans, diabetes mellitus has long been targeted for curative therapy by gene therapy. Until the past three years, the main obstacles have not only been vector-related toxicity but also the lack of physiological regulation of the expressed

insulin. As championed by L. Chan at Baylor University's Molecular Biology Institute, substantive recent advances in understanding the developmental biology of β cells and the transcriptional cascade that drives it have enabled both in vivo and ex vivo gene therapy combined with cell therapy to be used in rat and primate models of diabetes with success. Concurrent developments in grasping stem cell biology and immunology have opened up further opportunities for gene therapy to be applied to target autoimmune diabetes (Type 1 diabetes in humans).

The future of therapy for Type 1 diabetes is bright, due to resources, talents, and energy of many, with the promise of averting or comprehensively treating the metabolic consequences of this disease. However, the same cannot yet be said for Type 2 diabetes. New approaches, including some applied lessons from successful strategies in Type 1 disease, need to be developed. Until this happens, efforts to more tightly control hyperglycemia, coupled with limited applications of surgical techniques and a focus on reversible medical conditions such as obesity and physical inactivity, will remain mainstay therapies. ■



The advertisement features a central image of a beige medical chair with a side table, set against a green circular background. The text "Medical Clinic Environment" is arched above the chair, and "Nephrology", "Dialysis", and "Oncology" are written vertically on the left, right, and bottom of the circle respectively. Below the chair, it says "J7P Model" and "Model Color: Mushroom". To the right of the chair is the KAG logo, which consists of stylized letters "KAG" in red and white, with "Chairs" written in a small font above the "G". Below the logo, it reads "Dialysis & Pheresis Technologies, Inc.", "Color Palette Available", and "1.800.359.1651". At the bottom right, the slogan "We Build it FOR COMFORT & SAFETY" is displayed in large, bold letters, with "A Clear leader in chair comfort." underneath. At the very bottom, contact information is provided: "visit our website: www.kagind.com" and "email: jomoya@jomoya.com".