Autosomal dominant polycystic kidney disease: neoplasia in disguise?

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Genetic diseases are unique because the underlying defect (the mutated gene/protein) can be identified and studied even if the pathophysiology of the disorder is not understood. In this way our knowledge of autosomal dominant polycystic kidney disease (ADPKD) has greatly increased over the last couple of years. The major gene, PKD1 (accounting for 85% of ADPKD cases) was identified in 1994 [1] and fully characterized in the following year [2,3]. Over the past 12 months the rate of progress has continued with the identification of a second gene, PKD2 (responsible for most of the remaining cases), clues to the mechanism of disease revealed, and localization of the PKD1 protein, polycystin.

PKD2 was identified on chromosome 4 by the, now traditional, positional cloning approach [4]; a major clue to the identity of the gene came from a significant region of homology to PKD1. Despite this region of similarity, the PKD2 protein is quite different from polycystin (which has a large extracellular region and a suggested role in cell–cell or cell–matrix interactions [3]); the PKD2 protein is less than one quarter of the size of its counterpart with no large extracellular component. However, like PKD1 it is thought to be membrane associated, this time with six predicted transmembrane domains and cytoplasmic N and C termini. Its closest sequence similarity (apart from polycystin) is with a subunit of voltage-activated Ca\(^{2+}\) or Na\(^{+}\) channels, suggesting a role in ion transport [4]. The notion that ADPKD proteins may be associated with ionic regulation is supported by the recent finding of significant homology between 17% of polycystin and 50% of a sea urchin sperm membrane glycoprotein [5]. This protein acts as a receptor for egg jelly (REJ) triggering the acrosome reaction, a key stage in the fertilization process involving binding of sperm to egg. The REJ protein mediates this process via the regulation of ion channels, suggesting that polycystin may also play a role in ion transport.

Several studies have now investigated the location of polycystin in foetal, adult, and cystic renal tissue using monoclonal [6] or polyclonal antibodies [7–10]. Considerable variation is seen in these studies, presumably reflecting the specificities of the antibodies and the preservation, fixation and pre-treatment of tissue. However, some consensus is evident with higher expression generally seen in foetal than in adult tissue. In the foetus tubular epithelial cells stain L, with evidence of expression also in the ureteric bud and the S and comma shaped bodies of the developing nephron. Staining of regions of the Bowman’s capsule has also been described with some studies showing tuft glomerular staining [7,10]. In the adult expression is probably more localized to the collecting duct with less staining of proximal tubules. The subcellular localization of polycystin is less clear. Some staining studies show largely a membrane location, predominantly in the apical regions of cells [9] or on all plasma membrane fractions [9]. Although expression of polycystin appears low in normal adult tissue there is clear agreement on the high level of expression in cystic epithelia [6–10]. However, it seems unlikely that this increased expression is a primary event in cyst formation, since high level expression from the normal allele has also been demonstrated [6]. More likely this strong expression reflects the de-differentiated state of cystic epithelia and suggests possible autoregulation of polycystin expression.

A central question in ADPKD is the mutational mechanism and why only a small function of nephrons (estimated <1%) become cystic if all contain a mutant allele. Few PKD1 mutations have been described so far because of the large size of the mRNA and the complex duplicated area encoding the gene [1]. The available data shows that most are stop or frameshift changes which may inactivate the molecule [11]; the effect of complete absence of a PKD1 allele is seen in one group of patients with large deletions of PKD1 and the adjacent tuberous sclerosis gene, TSC2, resulting in tuberous sclerosis and severe polycystic kidney disease [12]. There is striking phenotypic variation of ADPKD, for example in fraternal twins with the same mutation, one had large renal cyst development evident in utero.
whereas the other had apparently normal kidneys when last examined at 5 years [13]. Any theory of pathogenesis must take account of this variability of disease expression.

Two recent studies suggest that PKD1 is recessive at the cellular level (similar to many inherited cancer predisposing syndromes) with cysts forming in patients with a germline mutation only after somatic mutation of the normal allele. These analyses show that the epithelia in a single cyst is usually clonal, being derived from a single cell [14], but with somatic loss of heterozygosity (LOH) (or in one case a point mutation) evident in up to 24% of cysts [14,15], inactivating the cells normal polycystin allele.

Although this two hit mechanism may explain the focal nature of disease and the wide phenotypic variation, it appears at odds with the evidence of strong polycystin staining in cystic tissue. Using a C terminal antibody (as most studies have) the expectation would be for loss of signal in cystic tissue if somatic (and germline) changes result in termination or loss of the protein. Although loss of polycystin staining has been described in up to 10% of cysts [9] this proportion appears too low unless the majority of somatic changes are missense; a question which needs investigation. Alternatively, it is possible that somatic mutation at PKD1 is reflecting a high level of genomic change within cystic tissue similar to that seen during tumour development. Analogous with neoplasia these somatic changes, although not a requirement for cyst formation, may promote cyst expansion. In this case the stimulus for cyst growth may be the result of somatic mutation of other genes—for example, TSC2, which would be lost in some of the described LOH [15], is a known tumour suppressor gene. Further analysis of the extent of somatic change in cystic epithelia is clearly required.

The accumulating evidence is edging us closer to understanding the normal role of ADPKD proteins. Data on the mechanism of disease appears conflicting, but has importantly focused our attention on events within cystic epithelia. Whether the described somatic changes are essential for cyst formation or may later play a role in cyst development has not yet been resolved. Either way we must now consider cystogenesis a multistep process and Jared Grantham’s statement that PKD is ‘Neoplasia in Disguise’ [16] seems more true than ever.

References
Nephrotoxicity of ifosfamide—moving towards understanding the molecular mechanisms

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Ifosfamide may induce renal Fanconi syndrome (FS). Approximately 60 case reports, predominantly from paediatric populations, have been published. Incidence ranges between 1.4 and 5% of ifosfamide-treated patients, another 15% of patients develop a severe, but subclinical tubular dysfunction. This FS is typically observed months or even years following cessation of chemotherapy. Only few patients develop symptoms while still on treatment. For the majority of patients the proximal tubular damage leading to the clinical picture of renal FS does not resolve over time. On the other hand, terminal renal failure in these patients has not been observed as yet. Reversibility of renal damage has been demonstrated in few patients only.

Apart from the cumulative ifosfamide dose, platinum derivatives and a reduction of kidney mass, i.e. unilateral nephrectomy, have been identified as risk factors. By contrast, methotrexate and gentamicin—given between chemotherapy cycles—as well as young age, are no risk factors in ifosfamide-induced nephrotoxicity [1]. The identification of patients at risk of developing severe nephrotoxicity has not been possible, since investigation of renal function during ongoing therapy with increasing cumulative doses of ifosfamide has so far failed to identify any specific predictor of increasing ifosfamide-induced renal toxicity.

Skinner et al. [2] first pointed out that beside overt renal FS most patients treated with high cumulative ifosfamide doses develop subclinical renal impairment, primarily located at the proximal tubular site. Distal tubular as well as glomerular dysfunction are secondary to the primary proximal tubular damage. Impairment of tubular amino acid transport is the leading renal symptom of ifosfamide-induced renal damage. Clinically, the most important manifestation of tubular dysfunction is renal phosphate wasting which is seen in approximately 30% of patients and which determines the extent of hypophosphataemia and the resulting metabolic bone disease. The affected patients may develop rickets, growth failure, fluid and electrolyte loss as well as renal tubular acidosis [1].

Few patients have undergone renal biopsies; in these patients, proximal tubular atrophy was the predominant finding, while interstitial nephritis was only reported in a single patient.

Ifosfamide thus induces toxic proximal tubular damage which may lead to overt FS in some patients.

Unlike other toxin-induced FSs, which resolve following discontinuation of toxin exposure, ifosfamide-induced tubular damage is longlasting and potentially progressive.

The pathogenesis of FS is not fully understood. In some metabolic diseases like Lowe’s syndrome or mitochondrial myopathy, associated FS has been related to a defective energy production within the proximal tubular cells.

Ifosfamide and cyclophosphamide are isomeric compounds. Neither FS nor proximal tubular damage of the above-mentioned type have, however, been reported following cyclophosphamide.

A direct hint for a differential toxicity of the two drugs comes from studies using cultured proximal tubular cells and measuring membrane voltage and conductance: incubation of these cells with ifosfamide induced a significant reversible depolarization and a decrease in conductance, whereas cyclophosphamide did not induce any change [3]. The authors conclude that these differences in acute effects may be involved in differences in long-term toxicity.

Both ifosfamide and cyclophosphamide have to undergo hepatic metabolism to form the cytostatically active mustards [4]. Along this pathway, acrolein is generated. It is toxic to epithelial cells and responsible for the urotoxicity seen after both drugs. Binding of acrolein by mesna is highly effective in reducing haemorrhagic cystitis. Consequently, ifosfamide as well as cyclophosphamide treatment is always combined with mesna therapy.

Differences in the metabolism of the two parent drugs concern side-chain oxidation, which is of minor importance in cyclophosphamide metabolism. Consequently the products of this side-chain oxidation—especially chloroacetaldehyde—have been speculated to be responsible for the ifosfamide-induced nephrotoxicity. Since this difference in metabolism is merely a quantitative difference, at least some extent of proximal tubular damage should be expected following high doses of cyclophosphamide: this, however, is not the case. Hence, differences in side-chain oxidation are probably not responsible for the differences in nephrotoxicity.

Both parent drugs are metabolized by the cytochrome P-450 system, especially its isoenzymes IIB and IIA [5]. These enzymes are also expressed in the proximal tubular system, so that local metabolism is possible. In comparison to the cyclophosphamide mustard, the ifosfamide mustard alkylates DNA with a...
higher affinity and is effective over a prolonged time [6]. This allows differential toxicity of the two mustards to different cells. Following local tubular metabolism of ifosfamide, a specific damage to proximal tubular DNA—either nucleic or mitochondrial—could possibly explain the long-lasting regenerative inability and failure of the energy-dependent functions of these cells.

The ifosfamide–mesna combination induces glutathione depletion in both plasma [7] and—in a rat model—renal tubular cells [8]. Glutathione is a ubiquitous detoxifying system. Its depletion renders any cell susceptible to oxidative stress by free radicals.

The amount of mesna given with ifosfamide is much higher compared to the dose given with cyclophosphamide treatment. Since mesna forms an adduct with plasma cysteine, mesna alone will cause glutathione depletion via cysteine depletion. Consequently, the high mesna doses given together with ifosfamide will contribute to a profound loss of the intracellular redox potential. Since the proximal tubular cell is able to reabsorb mesna from the proximal tubule, mesna will recirculate through these cells. As a consequence, glutathione depletion will be especially severe in proximal tubular cells. This fact may thus be crucial for the toxicity at this site.

In a rat model of ifosfamide-induced tubular damage, induced FS was attenuated by pretreatment with glycine [9]. Glycine depletion alone predisposes proximal tubular cells to necrotic damage. A protection against this effect is thought to be mediated by membrane stabilization. Following ifosfamide exposure, intracellular glutathione and the redox potential were reduced. In spite of effective protection by glycine, however, these levels did not return to normal. Instead, intracellular ATP as well as inorganic phosphate levels decreased. The authors conclude that primary toxicity must be distal to toxin uptake and must affect phospholipid synthesis and energy production.

A second possibly protective principle against ifosfamide-induced tubular damage was again described in a rat model by Schlenzig and co-workers [10]: ifosfamide treatment induced a severe decrease in the urinary excretion of tricarboxylic acid cycle intermediates; this indicates impaired cellular energy supply. This decrease could almost completely be prevented by supplementation of carnitine to these animals. Carnitine detoxifies CoA-bound moieties. One of these, chloroacetyl-CoA, is generated from chloroacetaldehyde during side-chain oxidation of ifosfamide. This metabolite is then bound to carnitine and excreted in the urine as an acylcarnitine derivative; this process will ultimately result in carnitine depletion. Since carnitine is, however, necessary to transport acyl-CoA groups into the mitochondria to start the energy production, its urinary loss will result in a decrease of intracellular ATP and finally in energetic failure.

In summary, ifosfamide may induce irreversible and potentially progressive renal tubular damage resulting in clinically apparent FS, which is not seen after cyclophosphamide treatment. The pathophysiology of this side-effect may be related to direct toxicity of ifosfamide to proximal tubular cells or to specific binding of the ifosfamide mustard to proximal tubular DNA, either nuclear or mitochondrial; this could affect the regenerative capacity and energy production of affected cells. It may then be related to glutathione depletion of ifosfamide–mesna therapy. This depletion is more profound in ifosfamide–mesna treatment due to the higher mesna doses used. In addition it is possibly most effective in proximal tubular cells, because mesna recirculates through these cells. Decreases of renal tubular toxicity following glycine and carnitine supplementation in rat models again point to interaction with the intracellular glutathione pool and to a defective energy production within the proximal tubular cells. Ifosfamide-induced FS—like FS in the context of mitochondrial myopathies—might thus be related to mitochondrial damage in proximal tubular cells.

References
Ageing and the renin–angiotensin system

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Introduction

Normal ageing is characterized by changes in the activity or responsiveness of a number of hormonal systems, altering homeostatic mechanisms in the elderly. One such system is the renin–angiotensin system (RAS), which has classically been considered to be suppressed in ageing. Altered activity of the active products of this cascade, angiotensin II (Ang II), and aldosterone, contribute to the increased incidence of certain fluid and electrolyte disorders in the elderly. In recent years it has become apparent that in addition to the well-known circulating (plasma) RAS, there are a number of independent, locally regulated tissue renin–angiotensin systems, whose activity may not necessarily parallel that in the systemic circulation. Much less is known of these tissue systems in ageing, though preliminary evidence suggests that further exploration of the systems is warranted.

The systemic RAS in ageing

It has long been recognized that plasma renin and aldosterone levels fall with advancing age [1]. The mechanisms of RAS suppression are not yet well defined. Hall and co-workers [2] have postulated that these age-related changes result from the loss of nephrons: compensatory hyperfiltration in the remaining nephrons leads to increased sodium chloride delivery to the macula densa, with suppression of renin synthesis and release, and therefore reduced formation of Ang II and aldosterone. Studies in ageing animals indicate that both renal renin formation and release are reduced, and that both contribute to the observed fall in plasma renin concentration [3]. Few studies have attempted measurement of Ang II levels in the elderly. Preliminary studies in animals are conflicting as to whether plasma Ang II levels fall in parallel with plasma renin levels. In humans, one study found an insignificant decline in plasma Ang II levels with ageing [4], though those subjects were neither numerous nor very old.

These abnormalities lead to suppression of renin and aldosterone levels at baseline, but also to impaired ability to mount appropriate responses to RAS stimuli. In ageing animals renal renin release in response to acute volume depletion is impaired compared to responses in younger animals [3]. In the elderly population a similar impairment in plasma renin response to sodium restriction has been noted [1,2]. The tubular response to administration of aldosterone is blunted [5], as is the plasma aldosterone response to potassium infusion [6].

The changing RAS activity also leads to altered responsiveness to blockade of the system. Suppression of the RAS is considered to be a mechanism underlying the lesser effectiveness of ACE (angiotensin-converting enzyme) inhibitors as antihypertensives in elderly patients. As discussed below, the salutary effects of ACE inhibitors on renal function and proteinuria may be blunted in the ageing animal as well [7,8]. Conversely, ageing animals appear to be more sensitive to the renal vasoconstrictor effects of Ang II [9,10], demonstrating impaired natriuresis and augmented kaliuresis with this manoeuvre [9].

The renal RAS in ageing

Deterioration of renal structure and function is part of normal ageing. By itself, age-related loss of renal function poses little danger. However, this functional loss may be greatly accelerated when functioning nephron number is further reduced by acute renal failure. Though mechanisms of age-related renal disease remain poorly understood, there is evidence implicating haemodynamic forces in this process. Ageing Munich–Wistar rats are normotensive, yet develop an age-related reduction in afferent arteriolar resistance. The resultant enhanced pressure transmission allows an increase in glomerular capillary pressure [8]. This glomerular capillary hypertension is reminiscent of other renal diseases, in which it is linked to stimulation of sclerosing mediators and subsequent injury.

Studies in diverse renal diseases have implicated the RAS as an effector of glomerular and tubular injury. In ageing rats, ACE inhibitors (whether started early or late in life) slowed proteinuria and glomerular injury [8]. Similar findings have recently been reported in other ageing models [11,12]. Though benefit is apparent, the data indirectly suggest that this manoeuvre may be slightly less effective in the ageing kidney, than in the younger one.

This benefit might not have been predicted, given the age-related fall in plasma renin. However, emerging data suggest that the falling plasma renin concentration

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does not necessarily reveal the intrarenal changes with ageing. Optimal methods for assessing the intrarenal (tissue) RAS remain controversial and elusive. However, one could postulate that the ‘renal’ RAS should, in fact, be considered as two distinct systems. According to this construct the vascular RAS consists of the circulating components and the RAS in the renal vasculature (including glomeruli), while the tubular (or tubulointerstitial) RAS consists of the proximal tubules and interstitium. Functional, biochemical, and preliminary molecular biological data are most consistent with downregulation of the vascular RAS. Both PRC and plasma Ang II fall with ageing [1,12]. Both decreased renal renin formation (assessed by renin mRNA) and sluggish renal renin release (at least to acute stimuli) contribute to the age-related fall in PRC. In addition, ACE activity in the renal vasculature and glomeruli is suppressed in ageing animals [3]. As a result, the renal vasoconstriction in response to exogenous Ang II is enhanced in the ageing kidney [9,10], most probably due to upregulation of the Ang II (AT1) receptor. Such a scenario would pose little problem in a healthy state, but renal vascular hypersensitivity to Ang II could be harmful when the elderly kidney is exposed to an RAS stimulus (hypotension, Na restriction).

In contrast to the vascular RAS, there is some evidence that the tubulointerstitial RAS may not be equivalently suppressed in the ageing kidney. Though proximal tubular ACE is suppressed in middle-aged rats [3], a preliminary report suggests that in very old age, the renal Ang II levels (which probably reflect the tubulointerstitial compartments) are substantially elevated [13]. Though preliminary, these reports indicate the potential for a pathogenetically important dissociation between the plasma and the intrarenal renin–angiotensin systems in advancing age.

The RAS and age-related renal injury

ACE inhibitors slow the progression of a number of experimental and clinical renal diseases. Recently these drugs have been shown to slow the development of glomerular, vascular, and tubulointerstitial injury in ageing rats [7,13] and mice [11], suggesting specific beneficial effects on the kidney. At this point, little is known about mechanisms of Ang II-induced injury in the ageing kidney. However, in other models Ang II has been shown to stimulate the formation or release of a number of cytokine mediators of sclerosis, such as osteopontin, platelet-derived growth factor, and transforming growth factor-β1. Conceivably, ACE inhibitors protect the ageing kidney by interfering with the actions of one or more of these disease mediators.

Conclusion

Ageing is known to disrupt many hormonal systems, and the RAS is no exception. However, the rapid advances in our understanding of the relative roles of the plasma vs independent tissue renin–angiotensin systems have only just begun to be applied to the study of ageing. Though the plasma RAS appears to be suppressed with normal ageing, intervention studies in animals have shown that ACE inhibition may slow age-related deterioration in organ systems, such as the kidney [8,11,13] and the heart [14]. Further investigations are warranted to understand the role of these changes, in hopes of their eventual clinical application.

References

Antihypertensive treatment in nephropathy of type II diabetes: role of the pharmacological blockade of the renin–angiotensin system

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Type II diabetic nephropathy is a leading diagnosis of patients entering ESRD programmes in most of the world [1]. Nephropathy is a dreaded complication that affects a variable proportion of diabetic patients, which shortens the life expectancy of the individual while costing billions of dollars to society. The thrust of research in nephropathy has been targeted toward the patient with type I diabetes. This has led to one of the great success stories in clinical nephrology, the use of angiotensin-converting enzyme inhibitors (ACEi) to slow or arrest the progression of diabetic renal disease [2–6]. The salutary effects of these agents has been termed ‘renoprotection’, referring to the specific protection of renal function that these agents provide independent of their effect on blood pressure. There are several large multicentred, prospective, double-blind, placebo-controlled trials demonstrating renoprotection from ACEi in both incipient and overt type I diabetic nephropathy [4–6]. This has resulted in captopril being the first pharmaceutical agent approved by the United States Federal Drug Administration (FDA) specifically for renoprotection. In animals, where the majority of the experimental work has been done with ACEi and diabetic renal disease, ACEi lower systemic blood pressure, intraglomerular pressure, and proteinuria. Angiotensin II has growth factor and profibrogenic peptide properties that increase messenger RNA expression for extracellular matrix components. Some of this effect may be mediated by transforming growth factor beta (TGF-β). ACE inhibitors block these non-haemodynamic effects of angiotensin II in addition to the previously described haemodynamic effects, and renoprotection may be a result of the inhibition of both of these diverse mechanisms. That renal function can be preserved by mechanisms that are independent of the level of blood pressure (renoprotection) does not mean that the level of blood pressure can or should be ignored. The earliest data on slowing progression of renal failure in type I diabetes was a result of lowering blood pressure without the use of ACEi. This work, done over a decade ago, used hypertensive type I patients in which overt nephropathy was present and enough time had elapsed to determine a rate of loss of renal function. A subsequent lowering of blood pressure slowed the rate of deterioration in renal function [7]. Reports such as these are not available for the type II population, nor are they likely to appear since it would now be unethical to not treat hypertension in a population of patients with such a high risk of cardiovascular disease. Still, it should be apparent if not obvious that blood pressure control must remain an integral part of the management of type II diabetic renal disease.

Although the FDA labelling for captopril specifies type I diabetes, many clinicians are extrapolating the results of these studies to treat patients with type II diabetes. Are there experimental and clinical data to support this move? There are dissimilarities between type I and II diabetic nephropathy in regard to the presentation, clinical course and histology; however, these are not two independent diseases [8]. In fact in many aspects they appear identical and might indicate that the salutary effects of ACEi apply to the type II population. Predictions in this regard have been hampered by the fact that the majority of the experimental models have used insulinopenic animals and may not mimic the hyperinsulinaemic metabolic state of type II diabetes.

The salutary effects of ACEi have been extensively demonstrated in type I patients with both incipient (microalbuminuria) and overt nephropathy [4–6]. Data in patients with type II diabetes is more limited. In the study by Ravid et al. [9] 94 type II diabetic patients with microalbuminuria were prospectively treated with either the ACEi enalapril or placebo for 5 years. Study end-points were albuminuria and reciprocal serum creatinine. Patients receiving enalapril had an improved clinical course for both end-points. In the patients receiving enalapril, the mean patient 24-h albuminuria was stable over the 5-year study period: 143 mg/24 h at study initiation and 140 mg/24 h at study end. Patients receiving placebo had an increase in albuminuria from 123 mg/24 h to 310 mg/24 h. The reciprocal creatinine fell by 13% in the placebo group as compared to a minimal decrease (1%) in the enalapril group. The mean arterial blood pressure (MAP) was about 3 mmHg lower in the enalapril-treated group over the course of the study. This approached but did not reach statistical significance (P = 0.08). Therefore renoprotection appears to be evidenced by this study in type II patients with microalbuminuria.

A similar but smaller study was reported by Lebovitz et al. [10,11] which included type II patients with microalbuminuria (n = 38) and overt nephropathy (n = 46). Patients received either the ACEi enalapril or placebo for 3 years. In the microalbuminuric patients treatment with enalapril was associated with a slower rate of loss of glomerular filtration rate (GFR) by the urinary clearance of 125I-iothalamate; however, this

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was in the setting of statistically significant differences in blood pressure (MAP 101 mmHg placebo vs 96 mmHg enalapril), making it difficult to determine if renoprotection was responsible for the improved prognosis. There was no difference in the rate of loss of GFR in the overt nephropathy patients receiving either enalapril or placebo.

Nielsen et al. [12] treated 35 patients with type II diabetes and overt nephropathy with either the ACEi lisinopril or the beta blocker atenolol for 1 year. Endpoints were GFR determined by plasma clearance of \([\text{Cr}]\) EDTA and proteinuria. The blood pressures were similar in both treatment groups. Although the lisinopril group had a greater reduction in proteinuria compared to the atenolol group (49 vs 12%), there was no difference in rate of loss of GFR (11.7 vs 11.6 ml/min/year).

Bakris et al. [13] compared the ACEi lisinopril to the non-dihydropyridine calcium channel blockers (CCB) verapamil and diltiazem, and to the beta blocker (BB) atenolol in 52 patients with type II diabetes and proteinuria. Patients were treated for approximately 5 years and blood pressures were similar in each of the three groups during the course of the trial. The rate of loss of renal function (the slope of a patient’s creatinine clearance over time) between the ACEi group was slightly better than that of the CCB group (−1.0 vs −1.4 ml/min/year); however, this did not reach statistical significance (P = 0.11). Both of these treatment groups, however, had better preservation of renal function than the BB-treatment group, which lost renal function at a rate of −3.5 ml/min/year (P < 0.005). This is the first study to demonstrate renoprotection in the overt stage of type II diabetic nephropathy, and has done so with both ACEi and the non-dihydropyridine CCBs. There is a suggestion from this study that ACEi are more renoprotective than CCBs; however, this needs to be confirmed with larger trials.

The use of ACEi has been well tolerated in these studies. Whether or not this will hold true in a large population of patients with type II diabetes and overt nephropathy is unknown. Hyporeninaemic hypaldosteronism is common in these patients, and hyperkalaemia may be exacerbated by ACEi. With the high incidence of micro- and macrovascular disease present in patients with type II diabetes, acute renal failure secondary to functional or structural renal artery stenosis may also be expected in some patients. Therefore, although it may seem appropriate to treat type II patients demonstrating any evidence of nephropathy with an ACEi, this should be done under close observation, at least until more data is available concerning their efficacy and safety.

Angiotensin II antagonists are now available for clinical use and study. ACEi prevent the enzymatic breakdown of bradykinin and therefore have side-effect profiles (particularly cough) that differ from that of angiotensin II antagonists. On the other hand, the preservation of bradykinin and its dilatory effect on the efferent arteriole may be responsible for some of the salutary effects of ACE inhibition, although the effect of bradykinin on renal haemodynamics appears to be species dependent [14,15]. The lack of cough alone may lead to the eventual replacement of ACEi with angiotensin II antagonists. Before this occurs, however, efficacy must be demonstrated with angiotensin II antagonists similar to that which has been shown with ACEi for the diverse conditions that these remarkable agents are applied to. In that regard, the Collaborative Study Group is now evaluating the angiotensin II antagonist irbesartan in type II overt diabetic nephropathy. This multicentred, international trial is the largest diabetic nephropathy study to date. With the patients in the three arms of the trial receiving either the angiotensin II antagonist irbesartan, the CCB amlopidine, or placebo in the setting of equivalent blood pressures, the role of angiotensin II antagonists and the question of renoprotection in overt type II diabetic nephropathy should hopefully be defined.

References
I/D polymorphism of the angiotensin converting enzyme gene: a clue to the heterogeneity in the progression of renal disease and in the renal response to therapy?

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Introduction

For nephrologists consideration of genetic aspects has long been limited to hereditary disorders due to mutations in a single gene such as Alport syndrome or polycystic kidney disease. Nevertheless a more extensive role for genetic risk in renal disease was since long suggested by familial clustering of, for instance, diabetic nephropathy and by racial predisposition to end-stage renal disease. Moreover, the rate of long-term renal function loss displays a considerable interindividual variability even for patients with the same diagnosis, whereas the individual rate of long-term renal function loss is often remarkably constant [1]. This well-known phenomenon may reflect differences in the severity of renal damage, but genetic determinants of progression rate might provide an additional explanation.

Recent developments in molecular genetic techniques afforded new insight into the role of genetic risk in common, and presumably polygenic disorders such as cardiovascular and renal disease. Several polymorphisms of genes coding for components of the renin-angiotensin-aldosterone system (RAAS) have been identified. The I/D polymorphism of the ACE gene has drawn a lot of interest as the DD genotype appeared to be an independent risk factor for myocardial infarction and left ventricular hypertrophy, in particular in patients without other cardiac risk factors, such as those with normal cholesterol, non-smokers, and women [2]. Concomitant polymorphism of the AT₁ receptor potentiates the cardiac risk [3], providing evidence for gene–gene interaction. As DD homozygotes have elevated serum [4] and tissue ACE [5], increased vascular conversion of angiotensin I [6] and an increased pressor response to angiotensin I [7], it was hypothesized that increased angiotensin II formation is involved in the increased cardiac risk.

The RAAS is not only involved in cardiovascular disease but also in renal pathophysiology. Not surprisingly, therefore, the number of studies on the role of ACE genotype in renal disease expands rapidly. There is increasing evidence that the DD genotype is a renal risk factor as well. Here we will briefly review this evidence, with particular focus on a trend emerging from the current data that could guide further research to unravel the mechanisms underlying this increased renal risk and thus to develop more effective therapeutic strategies for patients at risk.

ACE genotype and the prevalence of renal disease

Early case-control studies in diabetic patients found an overrepresentation of the D allele in patients with nephropathy compared to those without nephropathy. Subsequent large studies, however, did not confirm these findings, either in IDDM [8], or in NIDDM [9,10], suggesting that the D allele does not affect the susceptibility to develop nephropathy. Similar observations were made in IgA nephropathy [11–13]. Whereas the picture is still far from complete, current evidence seems to indicate that ACE genotype does not affect the susceptibility to acquire renal parenchymal disease. Renovascular disease, on the other hand, was found to be associated with the D allele [14], which may reflect its primary vascular genesis.

ACE genotype and the progression of renal disease

Interestingly, prospective studies showed an increased rate of renal function loss in DD homozygotes in patients with renal disorders of mixed origin [15] (which was confirmed by a large retrospective study [16]), in nephropathy in IDDM [17], and in IgA nephropathy [11]. Moreover, in IgA nephropathy the D allele was overrepresented in patients with renal function deterioration [12,13], an association more prominent in patients without proteinuria or hypertension [12], suggesting that, as in cardiac disease, in renal disease the D allele may act as an independent risk factor. Renal survival was found to be worse in DD homozygotes in NIDDM [18], and in polycystic kidney disease [19].

Thus the D allele is associated with an increased rate of renal function loss. Remarkably, this was found in a spectrum of renal disorders, although it is still unclear whether the risk imposed by the D allele is similar for all types of renal disease [16]. In accord with this increased progression rate the D allele was
overrepresented in haemodialysis patients [16]. Yet a normal genotype distribution in patients with end-stage renal disease has also been reported [20,21]. The latter findings may seem discrepant with the above studies. It should be remembered, however, that results from association studies can easily be affected by selection bias, for instance due to excess cardiac mortality in DD homozygotes.

ACE genotype and the response to intervention therapy

The finding of elevated serum and tissue ACE and of increased conversion of angiotensin I in DD homozygotes elicited the hypothesis that these patients might particularly benefit from ACE inhibitor therapy. Data on ACE genotype as a determinant of the response to ACE inhibition in renal patients, however, are conflicting. The blood-pressure response to ACE inhibition in DD homozygotes was either similar [22] or impaired [23] in comparison to II and ID genotype. As to the antiproteinuric response—a predictor of progression of renal disease—ACE inhibition reduced proteinuria only patients with the DD genotype. In another study from Japan, in proteinuria of diverse origin [24], the I allele was associated with a poor antiproteinuric response to ACE inhibition as well. In several studies from Europe, however, the antiproteinuric response to ACE inhibition in patients with the II/ID genotype was similar [22] or better [23] than in DD homozygotes, in non-diabetic and in diabetic patients [25,26]. Differences in patient selection, study design, and treatment regimen (e.g. dosage of the ACE inhibitor and dietary sodium intake) may account for the above discrepancies. In addition, differences in genetic background between Caucasian and Japanese subjects should be considered. D allele frequency and the relationship between ACE genotype and RAAS phenotype depend on ethnic factors [27]. As the interaction between ethnic factors and ACE genotype awaits clarification it would be prudent for the moment not to extrapolate observations from one particular population to another.

As to long-term renoprotection it is remarkable that the prospective observations of an increased progression rate in DD homozygotes were made despite adequate blood pressure control with either beta blockade or ACE inhibition in the non-diabetic patients [15] and with ACE inhibition in the diabetic patients [17], that is, during regimens of proven renoprotective potential. Thus, long-term renoprotection by intervention therapy is harder to achieve in patients with the DD genotype.

A study in essential hypertension suggests that ACE genotype may affect hormonal and tissue responsiveness to different antihypertensives. During ACE inhibition angiotensin II levels fell only in DD homozygotes. In this study an increased AT₁ receptor expression on mononuclear leukocytes was found in DD homozygotes, that was corrected by ACE inhibition. In II homozygotes, on the other hand, AT₁ receptor expression decreased during calcium-channel blockade but not during ACE inhibition [28]. The relevance of these findings for therapeutic efficacy and its impact for renal patients, however, remain to be established.

How could ACE genotype affect the progression of renal disease?

In spite of the increased cardiac and renal risk in DD homozygotes, remarkably, the D allele is overrepresented among healthy centenarians [29]. This strongly suggests that the D allele as such does not necessarily increase morbidity, but that additional factors (genetic or environmental) are required for the D allele to affect risk profile.

Once renal damage is present ACE genotype can apparently act as a genetic modifier of the progression of renal disease. What mechanisms could be involved? First, we wish to note that it is unclear whether the DD genotype mediates progression of renal disease or is rather a progression marker. Be this as it may, the D allele is associated with progressive renal function loss in diverse renal disorders. We therefore suggest that the mechanism of increased renal risk in DD homozygotes entails effects on common denominator(s) of renal function loss. A common pathway is assumed to account for progressive renal function loss regardless the type of initial renal damage. As in this pathway the RAAS plays an important role, it is tempting to speculate that ACE genotype affects progression rate by effects on RAAS phenotype implicated in this common pathway (e.g. tissue action of angiotensin II). Such a hypothesis is all the more attractive because this putative mechanism of action might also be involved in the increased cardiac morbidity in DD homozygotes, thus providing a unifying hypothesis for the increased renal and cardiac risk.

Directions for the future

The DD genotype is associated with progressive renal function loss in many populations, and moreover, renoprotection is hard to obtain in these patients. How could the present knowledge be turned into therapeutic benefit? First, it is important to better identify individuals in whom the D allele is likely to exert a deleterious effect. Considering the polygenic nature of renal and cardiovascular disease, the evidence for gene–gene interaction and the growing number of candidate genes (e.g. eNOS, endothelin, IL-1 receptor, and TNF-α) this would require studies in large and well-defined populations. We wish to emphasize, furthermore, the need for truly prospective studies, i.e. studies where patients are randomized not only according to manifestations of disease and treatment, but also according to genotype. Of note, current knowledge on the effects of ACE genotype is derived from studies
where patients were recruited for other purposes and from association studies. This may introduce selection bias even if the studied population is in Hardy–Weinberg equilibrium with respect to ACE genotype. Selection bias as to other, unidentified, risk modifiers may in fact explain some of the above-mentioned conflicting results.

Several issues should be clarified in order to improve renoprotective treatment for patients at risk. These include the mechanisms underlying the increased rate of renal function loss in DD homozygotes, the role of RAAS phenotype, the interaction with other renal risk factors, and the effect on therapy responsiveness. If indeed RAAS phenotype is involved, it might be worthwhile to investigate the therapeutic efficacy of AT1 receptor blockers, high-dose ACE inhibition, or the combination. Considering the parallel between increased renal and cardiac risk, it seems reasonable to focus pathophysiological studies on putative mechanisms common to renal and cardiac damage.

Conclusions

The progress in molecular genetic techniques provided great potential for the search for genetic risk factors in complex and presumably polygenic disorders such as renal disease. As a result ACE genotype could be identified as a genetic risk factor for progressive renal function loss. Other candidate genes are under investigation and it is likely that additional genetic risk factors will be found in the near future. To turn such knowledge into therapeutic benefit, integration of the new genetic knowledge with pathophysiological and clinical studies is crucial. Elucidation of the mechanisms of risk modification, and its interaction with other risk factors by prospective studies in well-defined populations will not only allow to identify individuals in whom the D allele is likely to act as a risk factor, but hopefully also to develop more effective treatment for these patients.

References

Pancreas transplantation: where do we stand in Europe in 1997?

Burckhardt Ringe and Felix Braun
Georg-August-Universität Göttingen, Germany

Patients suffering from terminal renal failure due to diabetes mellitus are not good candidates for either renal allotransplantation or chronic haemodialysis because they suffer from a systemic disease which is not corrected by either procedure. Patients afflicted with diabetes mellitus of juvenile onset, where there is usually an absolute lack of insulin accompanied with terminal renal failure, are justifiably candidates for renal and pancreatic allotransplantation, since there is presently nothing else to offer them.

These are the introductory remarks to the original publication of William Kelly and Richard Lillehei from Minneapolis about the first human kidney and pancreas transplant performed 30 years ago [1]. The key message of this historical article—outlining the whole scenario, but also expressing desperation and hope at the same time—is still a reality today. The 'International Symposium on Organ Transplantation in Diabetics' held in The Hague in 1983 was certainly a milestone in the further evolution of this issue, and gave the first major and comprehensive survey. Since then, the prognosis of diabetic patients has changed significantly—mainly due to better understanding of pathophysiology and course of this metabolic disease as well as the overall improvement of diagnostic and therapeutic management.

Therapeutic options in the diabetic patient with uremia

Nevertheless, diabetes mellitus—type I of juvenile onset or type II in adults, also classified as insulin-dependent (IDDM) and noninsulin-dependent diabetes mellitus (NIDDM), respectively—remains a challenge. It is one of the most common diseases worldwide, which is characterized by the development of serious microvascular complications resulting from hyperglycaemia, and finally multiple organ system failure. Diabetic nephropathy has become the leading cause of end-stage renal disease [2].

Therapeutic options available are conservative management including exogenous insulin administration, peritoneal or haemodialysis, kidney transplantation (KTx) from cadaveric or living donors, isolated or combined pancreas transplantation (PTx), and cell transplantation (ITx). The objectives of treatment are complete normalization of glucose metabolism, and prevention, amelioration, or reversal of secondary complications. Pancreatic transplantation is presently the only therapy to fulfill this goal, and to cure diabetes [3].

What is the current experience with pancreas transplantation?

In order to elucidate the role of pancreas transplantation in 1997 large International Registry and selected single centre reports were reviewed, and are briefly summarized in Table 1, also with respect to other treatment modalities [4–12]. Worldwide, 8845 pancreas transplants have been reported to the International Pancreas Transplant Registry (IPTR) until November 30, 1996, ~1000 new cases every year. In the USA, 6500 pancreas transplants were performed and 2345 were performed elsewhere, including Europe. Therefore, most of the results and thoughts presented here will necessarily be based on the American experience, with an attempt to include some of the European centres.

Surgical aspects of pancreas transplantation

Widespread clinical application of pancreas transplantation was hampered for a long time by technical imperfection and thus a high rate of surgical complications, together with uncontrollable immune reactions leading to graft failure. Since pancreatic transplantation is not a life-saving procedure—unlike replacement of vital organs such as heart or liver—the calculation of risk versus benefit always played a dominant role.
Table 1. Treatment and prognosis of patients with diabetes mellitus: selected comparative data of registry and single center reports

<table>
<thead>
<tr>
<th>Treatment group characteristics, period</th>
<th>No</th>
<th>1 year</th>
<th>5 year</th>
<th>10 year</th>
<th>Source author, year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conservative therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDDM adults normoalbuminuria overt nephropathy</td>
<td>593</td>
<td>85</td>
<td>65</td>
<td>Rossing, 1996</td>
<td></td>
</tr>
<tr>
<td>Hemodialysis (HD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987–1993</td>
<td>31</td>
<td>78</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Kidney transplantation (KTx)</strong></td>
<td></td>
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<tr>
<td>type I diabetes</td>
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<td></td>
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<tr>
<td>type II diabetes</td>
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<tr>
<td><strong>IDDM</strong></td>
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<tr>
<td>isolated pancreas transplantation (PTx)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA bladder drainage PTx alone</td>
<td>229</td>
<td>91 (57)</td>
<td>81 (33)</td>
<td>IPTR 1997, pers. com.</td>
<td></td>
</tr>
<tr>
<td>PTx after KTx</td>
<td>374</td>
<td>92 (60)</td>
<td>74 (28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Simultaneous pancreas + kidney transplantation (P + KTx)</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>World total 5 year survivors 12.66–05.90</td>
<td>504</td>
<td>94 (K 71, P 67)</td>
<td>89 (K 69, P 64)</td>
<td>Sutherland, 1995</td>
<td></td>
</tr>
<tr>
<td>IDDM bladder drainage</td>
<td>67</td>
<td>92 (K 96, P 68)</td>
<td>84 (K 76, P 56)</td>
<td>Ringers, 1996</td>
<td></td>
</tr>
<tr>
<td>IDDM segmental</td>
<td>26</td>
<td>92 (K 93, P 82)</td>
<td>91 (K 93, P 82)</td>
<td>Secchi, 1996</td>
<td></td>
</tr>
<tr>
<td>total, bladder drainage</td>
<td>53</td>
<td>96 (K 95, P 85)</td>
<td>91 (K 93, P 82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Islet transplantation (ITx)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adult allografts 1893–1995</td>
<td>305</td>
<td>24 patients insulin independent for at least 7 days</td>
<td>14 patients insulin independent at 1 year</td>
<td>ITR, 1996</td>
<td></td>
</tr>
<tr>
<td>type I diabetes 1974–1995</td>
<td>270</td>
<td>(25% basal C-peptide &gt; 1 ng/ml, 7% insulin independent &gt; 7 days)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>C-peptide negative 1990–1994</td>
<td>96</td>
<td>95</td>
<td>95</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Diabetes mellitus: indications and rationale of transplantation

**Kidney transplantation (KTx)**

*standard:* first-line treatment to be considered in all uremic patients with diabetes when starting on peritoneal or haemodialysis only few contraindications (e.g. advanced diabetic complications).

acceptable to good long term results, especially with living donor organ, good rehabilitation, better cost effectiveness as compared to maintenance dialysis.

**Isolated pancreas transplantation (PTx)**

*exceptional:* in non-uremic patients with hyperlabile/instable type I diabetes (e.g. control of metabolic problems such as hypoglycemic unawareness) or the presence of two or more diabetic complications defined as: proliferative retinopathy, early nephropathy (GFR > 70 ml/min and proteinuria 150–3000 g/24 h), overt peripheral or autonomic neuropathy, and vasculopathy with accelerated atherosclerosis prerequisite: minimal HL-A mismatch, effective immunosuppression

accepted: in post-uremic patients with type I diabetes after previous kidney transplant from living or cadaveric donor with stable graft function (serum creatinine < 2 mg/dl or GFR > 40 ml/min) inferior long term results due to HL-A non-identity of kidney and pancreas.

**Simultaneous pancreas and kidney transplantation (P + KTx)**

accepted: in carefully selected, and especially young (20–40 year-old) pre-uremic patients with type I diabetes (GFR < 40 ml/min) performed routinely in specialized centers (‘pre-emptive’ transplantation)

optimal: treatment of choice in most uremic patients with type I diabetes pancreas and kidney graft from the same cadaveric donor

contraindications mainly in case of serious cardiovascular complications (e.g. non-correctable coronary artery disease, significant cardiomyopathy or recent myocardial infarction) best chance of patient and graft survival (kidney and pancreas) as well as quality of life only curative therapy of diabetes.

**Islet transplantation (ITx)**

ideal: in principle, but still experimental procedure with limited clinical experience, so far, only very few recipients with long term insulin independence major problems: insufficient islet cell mass, control of immune reactions, drug toxicity.

Several surgical techniques have been used in the past to manage the exocrine secretions including duct occlusion, intestinalization, enteric or urinary drainage. Also, questions of extra- or intraperitoneal, even paratopic placement as well as portal and systemic venous drainage of the graft were investigated.

Currently, pancreaticoduodenal transplantation—the entire pancreas together with a duodenal segment, which is Anastomosed side-to-side to the urinary bladder, seems to be the procedure of choice. This technique is associated with a relatively low complication rate, and has the additional advantage of continuous monitoring of graft function. Introduction of effective immunosuppressive protocols, recently including FK 506, has also reduced the incidence and severity of acute rejection.

At present, recipients of simultaneous pancreas and kidney transplants represent the largest series. Their actuarial patient and graft survival rates are 92 and 79% at 1 year, and 81 and 67% at 5 years, respectively. These results compare favourably with kidney replacement, and especially with pancreas transplantation alone (Table 1). The major impact on quality of life is insulin-independence per se, together with establishment of an euglycaemic state. According to several studies the majority of patients stated that dialysis-free management of immunosuppression was easier than managing diabetes and dialysis.

**What is the clinical benefit of pancreas transplantation?**

One of the crucial questions, of course, is the effect of pancreas transplantation on secondary diabetic complications. Apart from better renal graft survival rates—when combined with a pancreas, recurrence of diabetic nephropathy will be prevented. The other sequelae, retin-, neuro-, and vasculopathy may more or less improve or at least stabilize, depending on the degree of damage. Recurrence of diabetes (isletitis) due to autoimmune processes has been observed in segmental pancreatic grafts only, and seems to be effectively preventable by adequate immunosuppression.

A synopsis, reflecting the current views about indication and timing of transplantation in diabetes mellitus is given in Table 2. There is little doubt that all diabetic patients with end-stage nephropathy should get the same opportunity and standard of therapy as compared to patients with other causes of renal failure, i.e. maintenance dialysis and kidney transplantation. In principle, patients with IDDM or type I diabetes can be considered as potential candidates for pancreas transplantation, depending on careful selection as well as the status of renal function. Since reversal of secondary complications is less predictable than prevention, ideally pancreas transplantation should be performed early in the course of diabetes.

In practice, however, isolated pancreas transplantation is still an exception in individual patients with normal or only slightly impaired renal function, when metabolic control of diabetes or progression of secondary complications become a problem. Well accepted are patients with a previous renal transplant or in a pre-uremic state. Simultaneous pancreas and kidney transplantation is regarded as optimal, and even the treatment of choice in uremic patients with type I diabetes in an increasing number of centres including Europe. This recommendation is strongly supported by the fact that diabetes can be cured. Islet cell transplantation, ideal in principle, is still in a developmental phase with limited long term success rates.

**Table 2.** Diabetes mellitus: indications and rationale of transplantation

<table>
<thead>
<tr>
<th>Type of Transplantation</th>
<th>Indications and Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kidney Transplantation (KTx)</strong></td>
<td>Standard: first-line treatment to be considered in all uremic patients with diabetes when starting on peritoneal or haemodialysis. Only few contraindications (e.g. advanced diabetic complications). Acceptable to good long term results, especially with living donor organ, good rehabilitation, better cost effectiveness as compared to maintenance dialysis.</td>
</tr>
<tr>
<td><strong>Isolated Pancreas Transplantation (PTx)</strong></td>
<td>Exceptional: In non-uremic patients with hyperlabile/instable type I diabetes (e.g. control of metabolic problems such as hypoglycemic unawareness) or the presence of two or more diabetic complications defined as: proliferative retinopathy, early nephropathy (GFR &gt; 70 ml/min and proteinuria 150–3000 g/24 h), overt peripheral or autonomic neuropathy, and vasculopathy with accelerated atherosclerosis. Prerequisite: minimal HL-A mismatch, effective immunosuppression. Accepted: In post-uremic patients with type I diabetes after previous kidney transplant from living or cadaveric donor with stable graft function (serum creatinine &lt; 2 mg/dl or GFR &gt; 40 ml/min). Inferior long term results due to HL-A non-identity of kidney and pancreas.</td>
</tr>
<tr>
<td><strong>Simultaneous Pancreas and Kidney Transplantation (P + KTx)</strong></td>
<td>Accepted: In carefully selected, and especially young (20–40 year-old) pre-uremic patients with type I diabetes (GFR &lt; 40 ml/min). Performed routinely in specialized centers ('pre-emptive' transplantation). Optimal: Treatment of choice in most uremic patients with type I diabetes. Pancreas and kidney graft from the same cadaveric donor. Contraindications mainly in case of serious cardiovascular complications (e.g. non-correctable coronary artery disease, significant cardiomyopathy or recent myocardial infarction). Best chance of patient and graft survival (kidney and pancreas) as well as quality of life. Only curative therapy of diabetes.</td>
</tr>
<tr>
<td><strong>Islet Transplantation (ITx)</strong></td>
<td>Ideal: In principle, but still experimental procedure with limited clinical experience. So far, only very few recipients with long term insulin independence. Major problems: insufficient islet cell mass, control of immune reactions, drug toxicity.</td>
</tr>
</tbody>
</table>
What will the future hold?

As we have learned from the evolution of other types of organ transplantation, e.g. the liver, it is to be expected that the future perspectives of pancreas transplantation will be bright. There is still enough room for improvement, especially regarding organ procurement and specific immunomodulation, but also investigating alternatives such as islet cell transplantation from xenogenic origin or gene transfer, to cure or even prevent diabetes mellitus. At present, and even cautiously valued, it seems justified to gradually adopt and share the great enthusiasm of David Sutherland and John Najarian from the University of Minneapolis, the centre with the longest and largest transplant experience in diabetic patients.

The triopathy of complications associated with diabetes (retinopathy, neuropathy, nephropathy) can not only be stopped but in many instances, reversed—if caught early enough with a successful pancreas transplant.

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