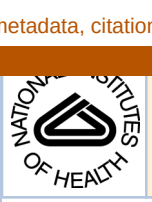

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Can existing drugs approved for other indications retard renal function decline in patients with type 1 diabetes and nephropathy?

Alessandro Doria[1,2], **Monika A. Niewczas**[1,2], and **Paolo Fiorina**[2,3,4]

[1]Section on Genetics and Epidemiology, Joslin Diabetes Center, Boston

[2]Harvard Medical School, Boston, USA

[3]Transplantation Research Center (TRC), Nephrology Division, Children's Hospital and Brigham and Women's Hospital

[4]San Raffaele Scientific Institute, Milan, Italy

Abstract

Mounting evidence from human, animal, and *in vitro* studies indicates that existing drugs, developed to treat other disorders, might also be effective in preventing or slowing the progression of diabetic nephropathy to end stage renal disease. Examples of such drugs include the urate-lowering agent allopurinol, the anti-TNF agents etanercept and infliximab, and the immuno-modulating drug abatacept. Since some these medications are already on the market and have been used for a number of years for other indications, they can be immediately tested in humans for a beneficial effect on renal function in diabetes. Special emphasis should be placed on evaluating the use of these drugs early in the course of diabetic nephropathy when renal damage is most likely to be reversible and interventions can yield the greatest delay to end stage renal disease.

Keywords

diabetic nephropathy; uric acid; inflammation; immune system; novel therapeutics

Introduction

Diabetic nephropathy is the long-term complication of diabetes that imposes the highest social and economic burden, being one of the main causes of end stage renal disease (ESRD).[1] Despite improvements in glycemic and blood pressure control, and the introduction of renin–angiotensin system (RAS) blockers, the overall risk of diabetic

Address for correspondence: Alessandro Doria, MD, PhD, MPH, Section on Genetics and Epidemiology, Joslin Diabetes Center, One Joslin Place, Boston, 02215, MA, USA, Tel: 617-309-2406, Fax: 617-309-2667, alessandro.doria@joslin.harvard.edu, or, **Paolo Fiorina, MD PhD**, Transplantation Research Center, Nephrology Division, Children's Hospital, Harvard Medical School, 300 Longwood Ave., Enders 5th floor, Room En530, Boston, 02215, MA, USA, Tel: 617-919-2624, Fax: 617-732-5254, paolo.fiorina@childrens.harvard.edu.

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nephropathy in the population is not declining.[2–4] Thus, novel therapeutic approaches are urgently needed to complement glycemic control and RAS inhibition.

One approach is to identify novel drug targets by gaining a better understanding of the pathogenesis of diabetic nephropathy at the molecular level, as discussed by other articles in this issue[5–7]. However, going from the identification of a drug target to the development of a clinically effective intervention is a long and costly process and only a small number of compounds that enter the development pipeline end up being approved for clinical use. The process is further complicated in the case of diabetic nephropathy by the lack of good animal models, as discussed by Breyer in this issue[8].

A complementary strategy is to investigate whether existing drugs, developed and approved for other indications, may have as yet unknown therapeutic effects on diabetic nephropathy. The most obvious advantage of this approach is that clinical trials of these drugs, if justified, can be started at once. Other benefits include the extensive postmarketing surveillance conducted for many of these compounds, reducing the possibility of unknown side effects, and the fact that some of these drugs are inexpensive owing to their long presence on the market and their availability as generic preparations.

Some examples of existing drugs that could be tested for a beneficial effect on diabetic nephropathy are reported in Table 1. Below we examine the evidence suggesting that these medications might be effective in preventing or slowing down kidney damage in diabetes and discuss how clinical trials of these drugs should be designed in order to maximize their probabilities of success.

Drugs targeting metabolic pathways

One possible strategy is to target metabolic pathways that are not involved in the etiology of diabetic nephropathy, but modulate the susceptibility of the kidney to the deleterious effects of hyperglycemia. Existing interventions in this category that have been investigated in clinical trials include B-vitamins, to decrease homocystinemia[9–11], and statins, to decrease cholesterolemia[12,13]. While neither of these treatments has yielded the expected benefits[14–17], new hope for such adjuvant therapies has recently come from the finding of a link between uric acid and progression of kidney damage in diabetes.

In the Second Joslin Kidney Study (JKS), elevated baseline serum uric acid was one of the strongest independent predictors of early GFR in diabetes[18]. In this prospective study, including 355 Joslin patients with micro- or high-normoalbuminuria and estimated GFR ≥ 60 ml/min at baseline, a direct dose-response relationship was observed between baseline serum uric acid levels and subsequent risk of early increased GFR loss, defined as a rate of GFR decline above the 97.5th percentile of the distribution in the general population (Figure 1). The unadjusted odds ratio was 1.5 (95% CI 1.3–1.9, p=0.0002) for each mg/dl increase in serum uric acid, which translates into a ~2-fold increase in the risk of early GFR loss for a serum uric acid levels ≥ 5 mg/dl as compared to levels <5 mg/dl. The magnitude of this effect did not significantly change after adjustment for urinary AER, gender, HbA1c, or, importantly, baseline GFR. Serum uric acid also predicted the transition from normoalbuminuria to micro- or macro-albuminuria in the Coronary Artery Calcification in Type 1 Diabetes Study[19,20]. As in the JKS, the effect of uric acid was not influenced by adjustment for other baseline variables. Similarly, in a study from Denmark, the uric acid level shortly after the onset of type 1 diabetes was a significant independent predictor of macroalbuminuria 18 years later[21].

The prospective nature of these findings and their robustness to adjustment for potential confounders strongly suggest that moderately elevated serum uric acid may play a causal

role by favoring the deterioration of kidney function caused by the diabetic milieu. Alterations of nitric oxide (NO) pathways and induction of pro-inflammatory cytokines[22,23], and increased oxidative stress resulting from the generation of uric acid by xanthine oxidase[24,25] could be responsible for this effect. Two small clinical trials have recently provided proof of concept data for translating these findings into a novel intervention. One of these study was from Hong-Kong and included 51 subjects (25% of whom with diabetes) having CKD Stage 3 or higher, who were treated with allopurinol for 12 months[26]. At the end of the intervention, about 20% of individuals in the allopurinol group had had a significant increase in serum creatinine as opposed to about 70% in the placebo group. The other study was from Spain and included 113 subjects with CKD stage 3 or higher, who were treated with allopurinol for 24 months[27]. About 15% of the participants had diabetes. During the trial, GFR increased by 1 ml/min in the allopurinol group as compared to a 3 ml/min loss in the placebo group. A beneficial effect of urate-lowering drugs on the progression of kidney disease has also been observed in animal models[28].

The availability of a safe and inexpensive uric acid-lowering drug such as allopurinol makes this intervention especially attractive. Allopurinol is an inhibitor of xanthine oxidase, which is responsible for the conversion of hypoxanthine to xanthine and of xanthine to uric acid. It has been on the market since 1964 as the main drug for the prevention of gout in hyperuricemic subjects and the prevention of acute urate nephropathy and gout in patients receiving chemotherapy for cancer. At the average dosage (300 mg/day), allopurinol causes a 30–40% reduction in serum UA[29–31], but up to a 60% reduction can be obtained using the maximum dosage of 600 mg.[32] Skin rashes, usually maculopapular, are the most commonly reported adverse effect. Rashes may be followed by more severe hypersensitivity reactions such as exfoliative lesions and the Stevens-Johnson syndrome, but such occurrence is very rare, in the order of 1 in 10,000[33]. Other potential adverse effects include gout flares (if there is a history of gout), hepatotoxicity, and, rarely, bone marrow depression. A new uric acid-lowering drug (febuxostat) that does not have the skin side effects of allopurinol has become recently available[30], although its cardiovascular safety is still being investigated (NCT01101035).

Drug targeting inflammatory pathways

Inflammation, as indicated by the presence of inflammatory cells in the tubulointerstitium, has been known for many years to occur in the diabetic kidneys. Indeed, a number of studies have shown that in diabetic subjects the degree of tubulointerstitial injury correlates better with the impairment of renal function than the degree of glomerular damage[34–36]. In agreement with these findings, prospective studies have shown that increase urinary levels of tubular and inflammatory markers such as kidney injury molecule-1 (KIM1) and monocyte chemotactic protein-1 (MCP-1) accompany the progression of diabetic nephropathy[37,38]. The demonstration in animal models that lymphocytes are not essential for these changes points to a key role of innate immunity in this process[39] and suggests that drugs targeting these pathways could exert a beneficial effect in preserving renal function in diabetes.

Macrophages are the major inflammatory cells infiltrating the kidney in diabetic nephropathy[40]. Accumulation and activation of these cells have been described in the kidneys of db/db mice with proteinuria, their extent being correlated with hyperglycemia, HbA1c levels, albuminuria, elevated plasma creatinine, glomerular and tubular damage, renal fibrosis, and kidney expression of macrophage chemokines[41]. Interestingly, some of the beneficial effects of drugs commonly used in diabetes appear to result from their capacity to interfere with macrophage functions. For instance, angiotensin II receptor blockers and ACE inhibitors reduce macrophage-mediated injury in diabetic nephropathy by

down-regulating macrophage NF-kB signaling[42]. Other agents that interfere with macrophage functions could be similarly useful to prevent diabetic nephropathy. An example is MMF – an immunosuppressant that was shown to inhibit kidney macrophage accumulation and diabetic nephropathy severity in Zucker rats[43]. An especially attractive target is MCP-1 - a chemokine having potent chemoattractive effects on macrophages. Inhibition of MCP-1 or its receptor reduces interstitial inflammation and macrophage accumulation in experimental models of diabetes[44–46]. An MCP-1 inhibitor – Bindarit - has been demonstrated to reduce albuminuria in active lupus nephritis[47] and a phase II study of this drug in albuminuric subjects with type 2 diabetes has just been completed (NCT01109212), although results have not been made public yet.

Another strategy is to use drugs acting on the development of interstitial fibrosis, the sequela of inflammation that is in the end responsible for the loss of kidney function. One such drug is pirfenidone – an inhibitor of TGF-β production that has been shown to decrease matrix deposition in experimental models of kidney disease[48]. In a small, exploratory study, this compound had beneficial effects on GFR decline in both type 1 and type 2 diabetic subjects with advanced diabetic nephropathy, but these findings must be validated in larger studies[49].

Additional suggestions about possible targets are expected from epidemiological studies. In this regard, a recent cohort study including over a thousand patients with both types of diabetes attending the Joslin Clinic has shown that elevated circulating levels of TNF receptors 1 and 2 are strong, independent predictors of subsequent kidney function loss[50,51]. The predictive power of these two inflammatory markers was much stronger than that of other markers of endothelial dysfunction and inflammation or other components of the TNF pathway including TNFα itself. The role of TNFα is well recognized in the etiology of rheumatoid arthritis and TNFα inhibitors, such as etanercept or infliximab, are routinely used in the treatment of this disease[52]. There is also a body of literature supporting a role of TNFα in the etiology of diabetic nephropathy[53]. However, the findings from the Joslin study raise the question as of whether interventions in diabetic nephropathy should be specifically focused on TNF receptors rather than on the TNF pathway in general. In support of this hypothesis, *in vitro* exposure of human kidney cells to soluble TNF receptors triggers cell death even in the absence of TNF α in the medium[54]. Furthermore, TNFR1 and TNFR2 knockout mice show a delay in the fibrotic response in experimental models of tubulointerstitial fibrosis[55]. A new antagonist of TNF receptors (progranulin), inhibiting the interaction between TNFα and TNFRs in a dose-dependent manner, has been recently identified through a global genetic screening[56]. This molecule and its engineered derivative Atsttrin have been shown to delay the course of rheumatoid arthritis in animal studies[57]. Thus, one can hypothesize that TNFR inhibition may become an attractive therapeutic tool to evaluate for the prevention of ESRD in diabetes in the near future.

Drug targeting immunological mechanisms

While diabetic nephropathy has never been considered an immunological disease, several reports in the literature have recently raised the possibility that immune-related mechanisms may be involved in its pathogenesis[58,59].

T-cells have been found in the kidneys of animal models of diabetic nephropathy[60], probably recruited into this organ by the overexpression of MCP-1, CX3CL1, and ICAM-1 by inflamed endothelial cells[61]. Since T-cell depletion affects the development and the natural history of renal damage in animal models[62], drugs that target these cells (e.g., anti-CD3 mAb or ATG) or abrogate their proliferation/activation may have a use for diabetic nephropathy, even though they should probably be reserved to high risk patients (e.g.; fast decliners) given the potential for severe adverse events[63]. Interventions targeting B-cells are

also available, but the evidence for a role of these cells in diabetic nephropathy is not as clear cut as for T-cells.

In addition to immune cells infiltrating the kidney, a variety of immune-related molecules have been found to be expressed by non-immune cells such as podocytes, mesangial cells, and tubular cells and to be upregulated in response to high-glucose or other stresses. For instance, Gutwein et al. found that cytokines such as IFN-γ and TNF-α induce podocyte expression of CXCL16 and ADAM10, which may in turn chemoattract T-cells[64]. Also, Huber et al. demonstrated that human podocytes, either grown in culture or isolated from biopsies, express many chemokines' receptors, including CCR4, CCR8, CCR9, CCR10, CXCR1, CXCR3, CXCR4, and CXCR5[65]. Podocytes also express CD80 (B7.1) in response to LPS and other types of stress, and lack of this molecule significantly reduces LPS-mediated podocyte injury[66]. Studies are underway to determine whether podocytes respond in a similar way to high glucose. If this is the case, one could hypothesize the use of CTLA4-Ig (Abatacept) – a molecule that binds and blocks B7.1 on podocytes – as a therapeutic approach to diabetic nephropathy. This drug has been safely tested in patients with new onset type 1 diabetes in a study aimed at delaying C-peptide loss[67]. In this multicenter trial, patients with recently diagnosed type 1 diabetes were randomly assigned to abatacept (10 mg/kg) or placebo administered intravenously on days 1, 14, 28, and monthly for a total of 27 infusions over 2 years. Abatacept-treated subjects experienced few infusion-related adverse events (22% in patients on abatacept and 17% in those on placebo) and did no show any increase in the risk of infections (42% vs. 43% in the abatacept vs. the placebo group, respectively) or neutropenia (9% vs. 14%). Thus, abatacept seems to be as safe as placebo when used in mono-therapy. In view of these findings and the extensive clinical trials of Abatacept for immune-related kidney diseases (Table 2) and Belatacept (which differs from Abatacept by only 2 aminoacids and binds both CD80/B7.1 and CD86/B7.2) in kidney-transplanted patients, these drugs appear as the most attractive immuno-modulatory interventions for diabetic nephropathy. Of note, B7.1/CD80 and CD86/B7.2 are also expressed on human tubular cells during inflammation where they may interact with their ligand CD28, either soluble or expressed by T-cells, and lead to the loss or damage of tubular cells[68]. Thus, blockage of B7.1 and of B7.2 may also have a benefit at this level in addition to that on podocytes.

Clinical trials to test the efficacy of existing drugs

Since many of the drugs discussed above have been already approved for other indications, their effect on diabetic nephropathy can be readily tested in randomized clinical trials. It is crucial, however, that these trials are properly designed in order to maximize power and to exploit the full potential of these drugs to prevent or retard renal function loss.

Target population

One important aspect concerns the selection of the individuals to whom these interventions should be applied. As illustrated in detail in the introductory issue of this article[69], the rate of renal function decline varies widely among the diabetic subjects who progress to ESRD, suggesting heterogeneity in the underlying mechanisms of kidney damage. It is also likely that the molecular pathways involved in the etiology of kidney damage undergo changes as the renal function declines from norml to ESRD. Thus, candidate drugs should be tested in specific groups of diabetic subjects defined on the basis of their rate of kidney function loss (e.g., rapid progressors vs. slow progressors) and their stage of renal function loss (e.g., early vs. late). For each drug, the group of patients to be targeted should be decided on the basis of the evidence from human and animal studies concerning the role of the drug target in the progression of kidney disease.

Interventions that may be effective at the early stages of renal fucntion loss are especially attractive since these can yield the greatest delay to ESRD. If a diabetic patient loses GFR at a constant rate of 4 ml/min per year, a 50% reduction in that rate of decline will delay reaching ESRD (GFR ≤ 15 ml/min) by 20 years if the intervention is started when the GFR is 90 ml/min, as opposed to a delay of only 8 years if the intervention is started when the GFR is 45 ml/min. For young type 1 diabetic patients with kidney complications, such as that depicted in Figure 2, this may make the difference between developing ESRD in their 70s as opposed to their 50s. A potential argument against early interventions is that a good proportion of the diabetic patients with mild to moderately decreased GFR may be "slow progressors" who will never reach ESRD. Thus, one may need to treat a large number of them to prevent ESRD in the relatively small proportion at risk. However, biomarkers, such as serum uric acid in the case of allopurinol[18] or TNF receptors for drugs targeting the TNF system[50,51], are often available to identify individuals who are at greater risk of loosing GFR and would specifically benefit from the interventions under consideration. This is in addition to increased albuminuria, which can also be used to select higher risk candidates for early interventions.

Response/outcome variable

Past clinical trials of therapies for diabetic nephropathy have often used albuminuria as the response variable. However, prospective studies have shown that, in a substantial proportion of type 1 diabetes patients, there may be a dissociation between natural history of renal function and that of albuminuria.[70–72] Since it is the loss of renal function that drives the increased morbidity and mortality associated with diabetic nephropathy, it seems obvious that this, rather than albuminuria, should be the outcome on which the efficacy of an intervention is measured. If the goal is to intervene early, as we have argued in the previous paragraph, the most effective response variable would be the GFR at the end of the intervention considered on a continuous scale after adjustment for the baseline value. This approach is equivalent to comparing pre- to post-treatment changes in GFR between treatment arms, but yields greater power when the correlation between pre- and post-treatment values is only moderate[73]. A related approach is to measure the GFR at different time points in order to estimate the slope of GFR decline during the intervention period. The problem with this strategy, however, is that GFR slopes may be unduly influenced by transitory changes in the GFR early in the course of treatment as discussed by Stevens et al.[74]. Furthermore, the methods for comparing slopes are more complex, since they involve the analysis of time × treatment interactions. Such complexity may offset the gain in power provided by the multiple GFR measures. Survival analyses based on hard endpoints, such as ESRD or serum creatinine doubling, are not useful for the study of interventions on early GFR loss since an extremely long trial duration and large sample size would be required in order to have enough events for a meaningful comparison between treatment arms. For instance, an untreated patients having a baseline GFR of 80 ml/min and losing GFR at a constant rate of 4 ml/min/year would need 12 years to experience a doubling of serum creatinine and 17 years to reach ESRD. It should be added that it is not strictly necessary to demonstrate efficacy on hard endpoints in the case of drugs that are already on the market and for which there is no interest in applying to the FDA for a new indication. If such evidence is needed, as in the case of a new drug, one approach can be to restrict the study population to subjects who have a GFR closer to the end-point and are at especially high risk of losing renal function based their previous clinical history or biomarker profile.

Time frame

Another important aspect concerns the optimal duration of the trial. Many of the trials conducted thus far have been relatively short, mostly being less than two year long, in order to minimize attrition and contain financial and human costs. However, it is critical that trials

are long enough to go beyond functional, short-term effects that drugs may have on GFR[74]. Even more importantly, the longer is the trial, the larger are the differences in GFR that can be attained between treatment arms, increasing the power of the study for any given sample size.

Summary and conclusions

Despite the progress that has occurred during the pat 20 years, preventing end stage renal disease in diabetes is still an unmet need. While research is ongoing to develop new medications, several drugs that are already on the market for the treatment of metabolic, inflammatory, and immunological disorders can be hypothesized to have beneficial effects on diabetic nephropathy based on the known links between their molecular targets and kidney damage in diabetes. Given their known safety profile, some of these drugs could and should be immediately tested for a beneficial effect on kidney function in humans. In doing so, we should take the opportunity to rethink the design of diabetic nephropathy clinical trials in order to increase power and maximize the impact of interventions on the natural history of kidney disease in diabetes.

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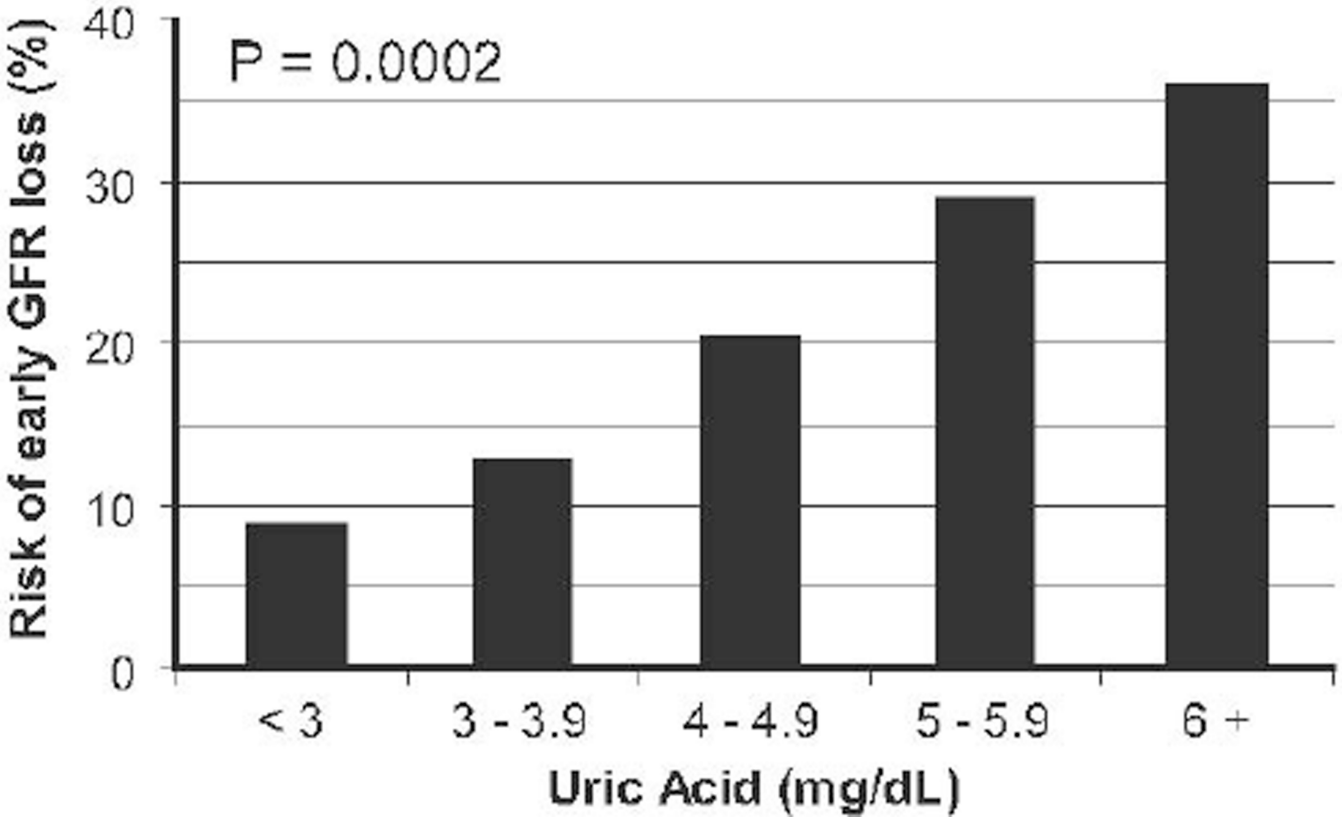

Figure 1.
Risk of early GFR loss in the JKS during 4–6 years of follow-up according to baseline serum UA levels (from Ficociello et al.)

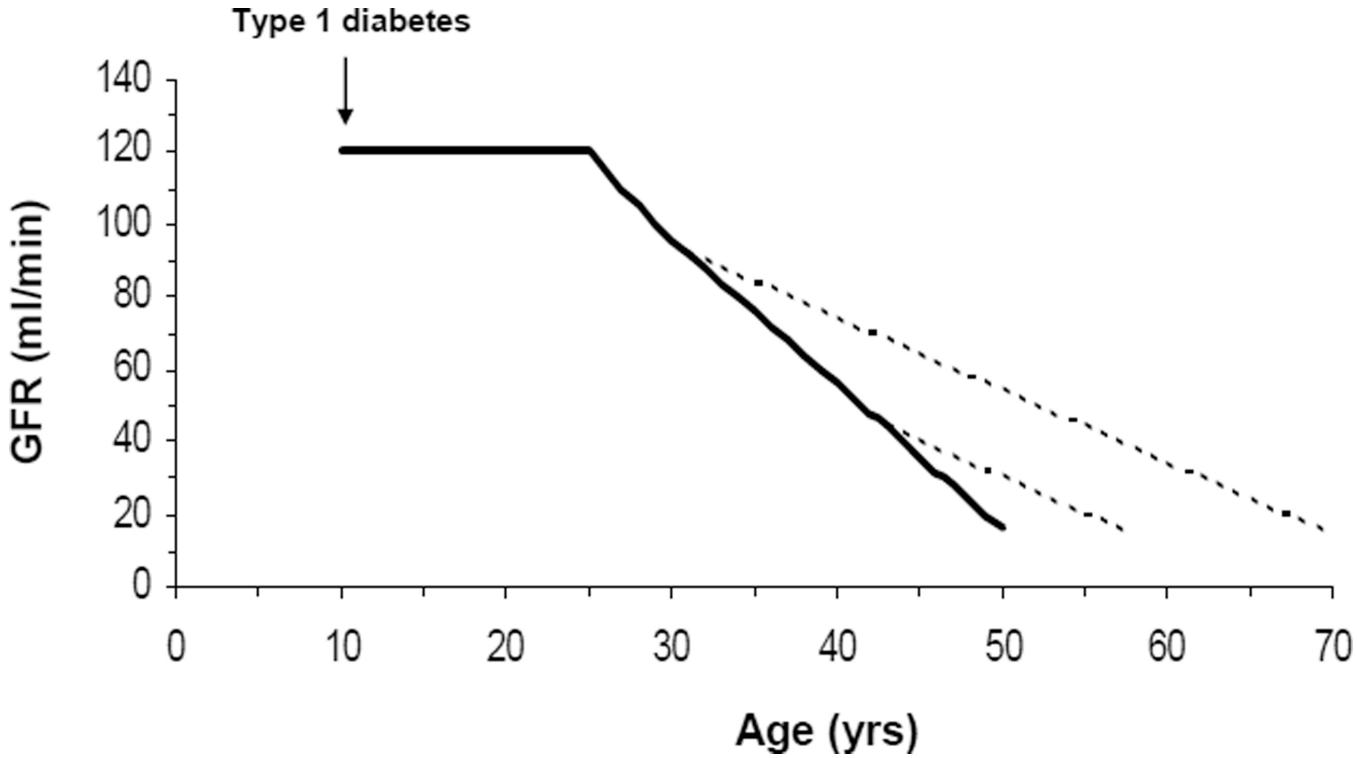

Figure 2.
GFR trajectory of a hypothetical type 1 diabetes patients who developed diabetes at age 10 and started to lose renal function at age 25 at a constant rate of 4 ml/min per year. The solid line represents the GFR trajectory without treatment, the dotted lines are the trajectories with an intervention that reduce GFR decline from 4 to 2 ml/min/year and is started at a GFR of 90 ml/min or at a GFR of 45/ml/min.

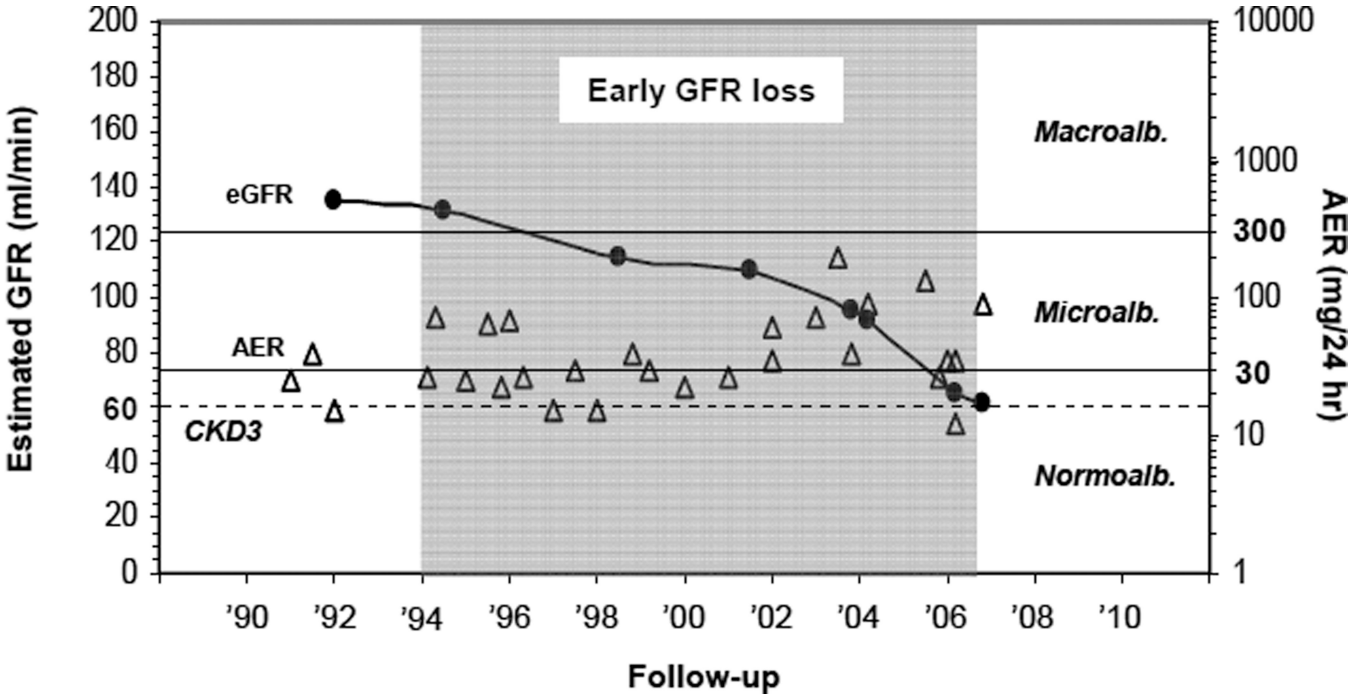

Figure 3.
Course of urinary albumin excretion (triangles) and renal function (circles) over the 14 years preceding the onset of CKD3 in a Joslin type 1 diabetic patient.

Table 1

Examples of existing drugs that could have an application in preventing or halting the progression of diabetic nephropathy.

Drugs	Target	Current indication	Generic available
Allopurinol	Uric Acid	Gout, chemotherapy-induced hyperuriciema	Yes
Febuxostat	Uric Acid	Gout, chemotherapy-induced hyperuriciema	No
Etanercept	TNFα	Rheumatoid and psoriatic arthritis, plaque psoriasis, ankylosing spondylitis	No
Infliximab	TFNα	Rheumatoid and psoriatic arthritis, plaque psoriasis, ankylosing spondylitis, Crohn's disease, ulcerative colitis	No
Atsttrin	TNFα receptors	Human experimentation in progress.	No
Sirolimus	mTor pathway	Prevention of transplant rejection	Yes (Canada)
Basiliximab	CD25	Prevention of transplant rejection	No
Mycophenolate mofetil (MMF)	IMPDH (purine biosynthesis)	Antoimmune disorders, prevention of transplant rejection	No
Abatacept	CD80/B7.1	Rheumatoid arthritis	No
Belatacept	CD80/B7.1 and CD86/B7.2	Prevention of transplant rejection	No

Table 2

Clinical Trial with CTLA4-Ig (Abatacept) in kidney/immunological diseases. Abatacept (marketed as Orencia) is a fusion protien generated with an immunoglobulin fused to the extracellular domain of CTLA4 and capable of stable binding to B7.1/CD80, thus blocking its activation.

Study/Identifier	Purpose	Status/PI
Efficacy and Safety Study of Abatacept to Treat Lupus Nephritis NCT00430677	The purpose of this clinical research study is to learn if abatacept treatment of patients with active lupus nephritis who are also taking mycophenolate mofetil (MMF) and steroid as part of this study will control the nephritis despite a protocol-defined steroid taper; the endpoint is "confirmed complete renal response", a composite including stabilization or improvement of renal function, improvement of proteinuria, and improvement of urinary sediment. The safety of this treatment will also be studied	Ongoing Bristol-Myers Squibb
Abatacept and Cyclophosphamide Combination Therapy for Lupus Nephritis (ACCESS) NCT00774852	This study is for people with lupus who have developed complications in their kidneys, or lupus nephritis. The study will determine whether adding the experimental medication abatacept to standard cyclophosphamide therapy is more effective in improving lupus nephritis than standard cyclophosphamide therapy by itself	Ongoing David wofsy,, University of California, San Francisco Betty Diamond, MDFeinstein Institute
Abatacept in Treating Adults With Mild Relapsing Wegener's Granulomatosis NCT00468208	Wegener's granulomatosis (WG) is a rare disease that causes inflammation of blood vessele, or vasculitis. It may involve many different parts of the body, but typically affects the upper and lower respiratory tract and kidneys. The purpose of this study is to determine the safety and effectiveness of the medication abatacept in treating adults with mild relapsing WG	Ongoing Carol A. Langford, The Cleveland Clinic Peter A. Merkel, Boston University
Abatacept in ANCA Associated Vasculitis (ABAVAS) NCT00482066	The purpose of this study is to investigate whether abatacept can prevent relapse in patients with ANCA associated vasculitis(AAV). This is a randomised double blined placebo controlled trial	Terminated Alan Salama Imperial College London
Intravenous CTLA4-Ig Treatment in Recent Onset Type 1 Diabetes Mellitus NCT00505375	The purpose of this study is to determine whether treatment with CTLA4-Ig (Abatacept) in individuals with new onset T1DM will improve insulin secretion (C-peptide production) compared to placebo	Ongoing Tihamer Orban, joslin Diabetes Center
Islet Transplantation Using Abatacept NCT00276250	Islet transplantation in type 1 diabetices with hypoglycemic unawareness using abatacept as a part of a novel calcineurin-inhibitor-sparing immunosuppressive regimen.	Ongoing Christian P Larsen/Thomas C Pearson Emory University