Review

NON-RENAL REPLACEMENT MODALITIES IN TREATMENT OF DIABETIC NEPHROPATHY: A SHORT CLINICAL PERSPECTIVE

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ABSTRACT

Diabetic nephropathy accounts for a significant burden in patients with microvascular complications. Recent insights into possible mechanisms of the disease permit us to take a fresh look at possible modalities of treatment, besides lowering blood glucose. We have now well established thresholds for glycemic control, and HbA_{1c} as well as blood pressure goals. There is enough evidence to use pre-emptive treatments such as ACE-inhibitors or even beta-blockers to bring down the blood pressure into the desirable range. Newer treatments are likely in the future, based on pathobiology delineated through astute observations and intense bench research. This perspective touches upon new areas of understanding, while underscoring the relevance of past observations.

KEY WORDS: Diabetes; Hypertension; Nephropathy; Proteinuria; Angiotensin; Angiotensin converting enzyme; TGFβ.

INTRODUCTION

In the last two decades there has been a steady increase in the incidence of end stage renal disease (ESRD) in patients with diabetes, world wide (1). Most investigators agree that the progression to end stage renal disease is similar in both type-1 and type-2 diabetes (2). The enormity of its impact can be gauged by the fact that diabetes accounts for almost 40% of patients with ESRD. When present, diabetic nephropathy is associated with: a) Decreased quality of life, b) Significant retinopathy, c) Increased cardiovascular morbidity and mortality.

CLASSIFICATION

Diabetic nephropathy can be insidious and unrelenting, if ignored. It is now well recognized that evolution of nephropathy proceeds along predictable lines, allowing for the development of a classification:

Stage 1: Hyperfiltration [Glomerular hypertrophy]

Stage 2: Hyperfiltration [Mesangial expansion / basement membrane thickening]

Stage 3: Microalbuminuria [Mesangial sclerosis]

Stage 4: Overt proteinuria [Progressive sclerosis] Hypertension

Stage 5: ESRD [Fibrosis/sclerosis]

Based on the above classification, renal preservation measures can be undertaken much before progression to stage 5. At this stage, the only remedy available would be renal replacement by transplantation, or less efficiently by dialysis.

Based on convincing evidence from DCCT (3), Kumamoto study (4), and the UKPDS (5), it is quite clear that controlling hyperglycemia offers significant risk reduction in the areas of retinopathy, neuropathy and nephropathy. However, hyperglycemia alone can not be considered as the sole factor responsible for nephropathy.

GENETICS

Variable prevalence in certain ethnic groups (native Americans, African Americans, Hispanics), and familial clustering strongly favors involvement of genetic factors in the pathogenesis of nephropathy (6). However, at the present time we do not have clinically useful markers of increased susceptibility. Several candidates have been implicated and these include the ACE gene (7), renin gene (8), angiotensin gene (9), aldose reductase gene (10), angiotensinogen II receptor gene (11), PC-1 gene (12), insulin receptor gene (13) and Apo E polymorphism (14).

However, it might be added, that considerable contradictions exist in the literature to be able to identify a common genetic defect, across different ethnic groups. Even if a genetic loci were to be well defined across ethnic barriers, treatments
do not exist at the present time to overcome these defects. Genetic counseling might become available in future, once a consensus is reached.

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TARGETS FOR PREVENTION/THERAPY

In order to implement preventive/pre-emptive strategies, non-genetic factors must be targeted and these include hyperglycemia (3-5), hypertension (15,16), proteinuria/microalbuminuria (17,18), smoking (19), dyslipidemia (20), high protein intake (21) and hyperuricemia.

Benefits have been proven beyond doubt, with interventions which were aimed at the first three targets. As for the last three targets, there is evidence of possible benefit. Smoking cessation clearly is associated with benefit. It must be noted that microalbuminuria defines a 24 hour urinary albumin excretion between 30-300mgs. Patients must be routinely screened for nephropathy by yearly evaluation of 24 hour urine albumin excretion.

Typically screening is recommended to begin at puberty or five years after diagnosis in patients with type-1 diabetes, and at the time of initial diagnosis and annually thereafter in those with type2 diabetes. Given the daily marked variability in albumin excretion, at least two separate 24-hour collections must be evaluated. Urinary albumin excretion is elevated after exercise, uncontrolled hypertension, congestive heart failure (CHF), acute febnle sickness and urinary infection. Ouantitation of proteinuria can be carried out by using protein to creatinine ratio, in a single urine specimen.

Similar benefits from divergent therapeutic agents would implicate a common pathway that responds to a variety of stimuli. It is pertinent to recall factors that are strongly linked to renal pathology (22-33)

1. Alteration in renal hemodynamics
2. Change in tissue metalloproteinases and proteinase inhibitors (TIMP)
3. Oxidative stress
4. Endothelial dysfunction
5. Glucotoxicity
6. Advanced glycation end products (AGE)
7. Protein kinase-C (PKC) activation
8. Growth hormone
9. Altered cell cycle regulation
10. GLUT-1 gene polymorphism
11. Mesangial expansion
12. Renal fibrosis

Review of current literature reveals several features that are common to all inducers of renal injury such as up-regulation of a sclerosing cytokine -TGFβ1. It is a chemoattractant which recruits monocytes to produce IL-1 and other cytokines. It induces angiogenesis and tissue proliferation, besides increasing extra cellular matrix deposition. TGFβ1 gene has a glucose response element in its promoter region. Angiotensin-II has also been shown to cause transcriptional activation of TGFβ1. Furthermore oxidized LDL is reported to stimulate production of proinflammatory cytokines, thereby enhancing glomerular damage. Additionally there is evidence of NF-κβ (nuclear factor- κβ in resident renal cells leading to its direct involvement in human renal disease. High glucose itself can promote mesangial cell proliferation possibly through PKC-NF- κβ pathways (34-43) Even more intriguing is the stretch activation of certain protein kinases. Taken together, it is not difficult to envision a positive response to a variety of divergent modalities, since the ultimate mediators of damage appear to be common.

This realization further underscores the fact that greater benefit might accrue with multiple interventions, applied together (correcting dysglycemia. treating hypertension, correcting dyslipidemia, use of antioxidants, aspirin etc).

THERAPEUTIC CHOICES/AGENTS CURRENTLY AVAILABLE

At present treatments are directed towards targets in sight. In a diabetic patient these would include:

1. Antihyperglycemic agents
2. Aritihypertensive agents
3. Reducing proteinuria
4. Lipid lowering agents
5. Dietary modification (protein restriction ?)
6. Smoking cessation
7. Aspirin

Antihypergylcemic Agents

Antihypergylcemic agents that can be used relatively safely in patients with diabetic nephropathy are:

a) Insulin(s)

b) Non-sulfonylurea insulin secretagogues
   1) Megltinide – Repaglinide
   2) D-phenylalanine - Nateglanide

c) Second generation sulfonylureas
   1) Glyburide/Glybenclamide
   2) Glipizide
   3) Glimeperide
   4) Gliclazide

d) Thiozolidinediones
   1) Rosiglitazone
   2) Pioglitazone

Treatment with alpha glucosidase inhibitors is not recommended in patients with renal impairment. Use of biguanides (Metformin) is contraindicated in renal impairment. It is important to enforce strict glycemic control [Fasting plasma glucose < 120 mg/dl; Postprandial < 180 mg/dl and bed time plasma glucose 100 - 140 mg/dl. HbA1c < 7%].

It must be emphasized that intensive glycemic control, using various insulin regimens, have yielded the best results so far. However, many patients will experience more frequent hypoglycemic episodes, limiting the use of such intensified regimens. In a more recent study, intensive diabetes management decreased Na-Li counter transport in young subjects with type 1 diabetes and enlarged kidneys (44).

Antihypertensive Agents

The U.S. National Kidney Foundation (16) has published an elegant summary of antihypertensive drug treatment for preservation of renal function in diabetes. It is well known that patients with hypertension and diabetes have a five to six fold greater risk of developing ESRD, compared to people with hypertension, without accompanying diabetes.

Agents known to reduce proteinuria and cardiovascular events in high-risk groups include:

a) ACE inhibitors
b) Beta blockers
c) Alpha-beta blockers (Carvedilol)
d) Calcium channel blockers (CCB)*
e) Combination of ACE inhibitor and an α receptor blocker (45)
f) Diuretic

(*Nondihydropyridine CCB's are best used in combination with an ACE inhibitor).

It is obvious that achieving the lower goal blood pressures is impossible with monotherapy. Multiple anti-hypertensives may have to be used to achieve these lower blood pressures. Clinicians must realize that there are barriers to achieving desired goals and these have to do with affordability, education and attitude. ACE inhibitors have effects beyond simple lowering of blood pressure. ACE inhibitors have been shown to reduce TGF-β1 levels (46).
National Kidney Foundation consensus report recommends lowering the blood pressure of patients with diabetes to <130/80 mm Hg, and cite the recommendations from one large prospective study, to lower pressure to less than 125/75 mm Hg for people who have proteinuria of greater than 1 gram per day and renal insufficiency regardless of etiology (47).

Treating Dyslipidemia

Several studies point to the benefits of treating hyperlipidemia in patients with renal disease. Such treatment has been shown to reduce proteinuria. A recent meta-analysis also revealed a favorable effect of treatment on protein/albumin excretion. At present we recommend treating patients with statins (HMG CoA reductase inhibitors) to affect reduction in lipids. Recent studies implicate lipids and lipoproteins in intracellular signal transduction. In particular, oxidized LDL and lysophosphatidyl-choline (LPC a major constituent of oxidized LDL) have been shown to stimulate phosphoinositide turnover with resultant activation of PKC. Cholesterol metabolites have been shown to inhibit expression of inhibitory large G proteins in several models. Native and atherogenic LDL can activate MAP kinase pathway involved in mesangial proliferation (48). Thus a rationale exists to correct dyslipidemia, as one of the key measures to prevent/retard the decline in renal function (49). Incidentally, using hypolipidemic therapy (Pravastatin), investigators in the West of Scotland Coronary Prevention Study (WOSCOP), demonstrated a 30% reduction in the hazard of becoming a diabetic (50).

Treating Proteinuria

Data have become available from several clinical trials, where reductions in proteinuria of more than 30% from baseline, correlated with marked reductions in renal disease progression. Recently PARADE (Proteinuria, Albuminuria, Risk Assessment Detection Elimination) task force recommended that therapies used to treat hypertension, should also target proteinuria reduction (51). Proteinuria itself may be a contributor to renal injury (52,53).

Dietary Protein Restriction

Dietary protein restriction reduces rate of progression of renal disease (54). At present it is generally recommended that the daily protein intake ought to be around 0.8 g/kg/day. It must be stated that in general, gains have been mild at the best. This must be used as ancillary modality.

Smoking Cessation: Smoking represents an important factor associated with progression of nephropathy and it is only prudent to recommend smoking cessation (55).

Use Of Aspirin: Aspirin is recommended as a primary prevention strategy in high risk men and women with type 2 diabetes (56).

FUTURE DIRECTIONS

1. Tissue specific inhibition of TGFβ1 transcriptional activation
2. Tissue specific repression of protein kinase-C activation
3. Targeted suppression of .NF-κβ
4. Tissue specific inhibition of AGE induced damage
5. Identification of reliable markers to identify people at risk
6. Octreotide (57)
7. Decorin - the leucine rich proteoglycan to inhibit TGF-β1
8. Thiozolidinediones
9. C-peptide

Many of these are speculative, however, there is enough reason to believe that these could be the future drug targets for prevention of renal disease and offer alternatives to the devastating renal replacement therapies. When the technology of pancreas transplant becomes widely available, it will be yet another effective treatment to prevent, retard or reverse renal disease.

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