This article presents naturopathic treatments for diabetic kidney disease, also known as diabetic nephropathy. From the outset, it should be emphasized that controlling blood sugar and hypertension are the two most important and indispensable strategies in treating diabetic nephropathy. Because there are many resources available covering naturopathic treatments for hyperglycemia and hypertension, they will not be covered here. Instead, this article will focus on specific dietary, lifestyle, and supplement regimens that have been shown to reduce morbidity and mortality in diabetic nephropathy.

Background
Diabetic nephropathy is a common complication in type 1 and type 2 diabetes (20-40% incidence among diabetics) and is one of the leading causes of end-stage renal disease (ESRD) in the US. It is estimated that 50% of type 1 diabetics with overt nephropathy will have ESRD in seven to ten years, and the time course may be shorter among type 2 diabetics. ESRD, when untreated with dialysis or a kidney transplant, has a high mortality rate.

The earliest clinical sign of nephropathy is the detection of albumin in the urine (>30 mg/day but <300 mg/day); this is the microalbuminuria stage. Overt nephropathy typically happens five to ten years after the onset of microalbuminuria and is characterized by persistent presence of albumin in the urine of >300 mg/day and decline in kidney function as measured by glomerular filtration rate (GFR). Diabetic retinopathy is highly associated with nephropathy (60-90% rate of comorbidity), and the absence of the former should increase suspicion that the nephropathy may have other causes.

The key change in diabetic nephropathy is an increase in extracellular material, such as thickening of the glomerular basement membrane, expansion of the mesangium, and signs of glomerular fibrosis. Although the exact causes are unknown, elevated blood glucose is associated with glomerular basement membrane thickening, while glomerular hypertension is associated with sclerosis. Inflammatory cytokines such as transformation growth factor beta (TGF-b) and NF-KappaB also play a role by upregulating cellular hypertrophy and fibrinogenesis.

Allopathically, the mainstays of treatment include the following: (1) blood sugar control; and (2) blood pressure control, preferably with ACE inhibitors and/or angiotensin II receptor antagonists. In terms of diet, the recommendation is protein restriction to 0.8-1.0 g/kg/d. (Note that patients on dialysis may have higher protein requirements.)

Prevention
It is best to treat nephropathy during the microalbuminuria stage. Once overt nephropathy sets in, the pathologic changes in the glomerulus are most likely irreversible. Three tests for microalbuminuria screening are available: (1) random spot urinary albumin-to-creatinine ratio (preferred method); (2) 24-hour urine microalbuminuria test; (3) other timed — e.g., four-hour or overnight — urine collection.

The American Diabetes Association (ADA) recommends annual screening for microalbuminuria among type 1 diabetics starting at five years after initial diabetes diagnosis. All type 2 diabetics should be screened yearly, starting at diagnosis, and during pregnancy. Additionally, serum creatinine should be measured at least yearly to estimate GFR in all adults with diabetes whether or not there is albuminuria.
Diet & Lifestyle Interventions

A carbohydrate-restricted, low-dietary-iron, polyphenol-enriched diet (CR-LIPE) has been shown to (1) reduce death or renal transplant by nearly 50%; and (2) reduce doubling of serum creatinine by half (Table 1). This is based on a controlled study done by Faccini & Saylor in 2002, where subjects were type 2 diabetics with confirmed renal disease (N=191) and mean follow-up time was 3.9 years.

<table>
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<tr>
<th>CR-LIPE Diet</th>
<th>Control Diet</th>
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<td>Kidney transplant or death</td>
<td>20%</td>
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<tr>
<td>Percentage who doubled creatinine</td>
<td>21%</td>
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Features of the CR-LIPE diet include the following:

- A 50% reduction of carbohydrates from the previous level of intake
- Replacement of iron rich red meats (beef and pork) with iron poor white meats (poultry and fish) and with protein-enriched food items known to inhibit iron absorption, e.g., dairy, eggs, and soy
- Elimination of all beverages except tea, water, red wine, and milk
- Tea was highly recommended. Red wine was not to exceed 150 ml with lunch and 150 ml with dinner. Milk was recommended for breakfast. Outside mealtimes, water was the only approved beverage.
- Exclusive use of polyphenol-enriched extra-virgin olive oil for both dressing and frying
- Except for carbohydrate restriction, this diet was fed ad libitum (up to the discretion of subjects)

The control group ate a standard protein restricted (0.8g/kg/d) diet, iso-caloric for ideal body weight maintenance. When the macronutrient profiles of the CR-LIPE vs. control diet were analyzed, it was shown that the CR-LIPE diet resulted in significantly less carbohydrates (35% vs. 65%), more protein (25-30% vs. 10%), and slightly more fat (30% vs. 25%).

CR-LIPE captures the combined effects of various dietary and bio-chemical interventions, i.e., macronutrient changes, high polyphenol intake, and decrease in oxidative stress via iron reduction.

The authors postulate that the key mechanism explaining these life-saving benefits is the fivefold reduction in serum ferritin (as a measure of body iron stores) due to reduced iron intake, absorption inhibition by milk, polyphenols, and tannins in tea. Iron in high amounts has been linked with oxidative stress, while iron depletion is linked with insulin sensitization. Low carbohydrate intake is also associated with a reduction in risk factors for morbidity associated with diabetes such as decreasing hyperlipidemia, insulinemia, and glycemia.

This CR-LIPE diet differs widely from the ADA's recommendation of protein restriction. The former diet results in approximately 25-30% of daily intake from protein, while the ADA's recommendation of 0.8g/kg/d results in approximately ten percent of daily intake from protein. Reviewing the bibliography of ADA's position statement, the advice to decrease protein intake is based on the following:

(1) A randomized control trial with N=121, with follow up at six and 12 months shows that protein restriction decreased albuminuria by 28% and 18%, respectively. The author's conclusion of this study is that, "Substantial protein restriction in primary care, type 2 diabetic patients with no nephropathy is barely feasible. However, even a small reduction has a substantial and potentially beneficial effect on albuminuria." 

(2) A meta-analysis with a pooled N=108, and follow-up times ranging from nine to 33 months showing that protein restriction among insulin-dependent diabetics reduced the decline in GFR or urinary albumin excretion or creatinine clearance.

(3) A randomized control trial with N=82, with follow up of four years shows a ten-percent incidence of ESRD or death in the protein restriction of 0.6 g/kg/d group vs. 27% in the "usual protein intake" group of about 1.02 g/kg/d.

The ADA's protein restriction recommendation is based on evidence level "B.”

The CR-LIPE study directly compared the effects of a CR-LIPE diet vs. standard protein restriction of 0.8/kg/d and concluded that CR-LIPE is superior to standard protein restriction in terms of improving overall survival rates. CR-LIPE captures the combined effects of various dietary and bio-chemical interventions, i.e., macronutrient changes, high polyphenol intake, and decrease in oxidative stress via iron reduction. The CR-LIPE study, published in 2002, has not been repeated to date and will need more corroborating evidence before it may be widely adopted. Also, it should be noted that the CR-LIPE diet has not yet been studied in the setting of ESRD or dialysis.

A few small pilot crossover-designed studies indicate that a soy-based protein diet may be beneficial to individuals with diabetic nephropathy. A small (N=14), seven-month crossover study in male type 2 diabetics with nephropathy found that a soy-based diet significantly reduced
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urinary albumin excretion. Similar results were found in another small (N=14), seven-week crossover study, which showed that replacement of portions of animal protein with soy and vegetable proteins, in a setting of a low protein diet, reduced albuminuria and urinary urea nitrogen. A small (N=12) 20-week crossover study of type 1 diabetics found that a soy-based diet significantly reduced GFR compared to control. Larger scale studies are needed to more clearly elucidate the role of soy protein in the setting of diabetic nephropathy.

Lifestyle Intervention

Smoking Cessation

Cigarette smoking is associated with proteinurinia and quicker progression of all types of chronic kidney diseases. Furthermore, cigarette smoke condensate worsened experimental renal injury and increased proteinuria.

Biologically Based Interventions

Antioxidant Therapy

Studies have shown that diabetes and diabetic complications are associated with greater oxidative stress and reduced levels of antioxidants. Recently, a unifying mechanism has been proposed suggesting that both macrovascular and microvascular (including nephropathy) diabetic complications are all mediated via an intracellular increase in reactive oxygen species. This link between oxidative stress and progression to diabetic nephropathy is supported by at least one subsequent study. A recent review article, specifically written to assist clinical nephrologists in the treatment of glomerular proteinuria, lists antioxidants such as d-alpha-tocopherol, alpha-lipoic acid, selenium, and vitamin C as potential anti-proteinuric agents.

Several clinical studies demonstrate that antioxidant supplementation can help improve kidney function among individuals with diabetic nephropathy. Treatment with vitamins C (200 mg QD) and E (100 iu QD) for 12 weeks, or vitamins C (1,250 mg QD) and E (680 iu QD) for four weeks, or vitamin E (1,200 iu QD) for four months, or vitamin C (500 mg BID) for nine months have all been shown to significantly reduce urinary albumin excretion ratio among diabetics. The addition of zinc (30 mg QD) and magnesium (200 mg QD) to vitamins C and E therapy resulted in a synergistic reduction of urinary albumin excretion.

In type 1 and type 2 diabetics, treatment with alpha lipoic acid...
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(600 mg QD) for 18 months halted progression of urinary albumin concentration (UAC), compared to controls whose UAC nearly doubled. This dose of alpha lipoic acid has been shown to exert significant antioxidant activity even in the setting of poor glycemic control and a wide range of albuminuria.

A three-month trial comparing alpha lipoic acid (600 mg QD) or selenium (100 mcg QD) or D-alpha-tocopherol (1200 iu QD) to a control group found significantly diminished urinary excretion rates in each of the three antioxidant groups.

Phytotherapy

Plant-based treatments for diabetic nephropathy are supported by human and animal research models. Several studies examining phytotherapy interventions for diabetic nephropathy have been conducted in China. Injections of Ginkgo Biloba extracts combined with conventional Western medical interventions have been found to decrease urinary albumin excretion in early stages of diabetic nephropathy. A three-month study found administration of Fructus Arctii and Radix Astragalus led to significantly reduced urinary albumin excretion in individuals with diabetic nephropathy. A decoction of Radix Astragalus and Rhizoma Ligustici Chuanxiong (150ml QD) for six months significantly decreased urinary albumin excretion in type 2 diabetic individuals with microalbuminuria. A Traditional Chinese Medicine formulation combined with conventional Western medical interventions led to significant improvement in urinary albumin excretion, total 24 hr. protein excretion, and renal function. Animal model studies have shown the following: polyphenols have been shown to reduce transforming growth factor-beta and prevent fibrosis and deterioration of renal function, as well as reduce uremic toxic products in renal failure. Quercetin and turmeric have been shown to attenuate the severity of nephropathy, most likely through their antioxidant properties.

Polyunsaturated Fatty Acids

Several clinical studies have shown that the use of eicosapentaenoic omega 3 fatty acids (EPA) have been able to improve urinary albumin excretion ratios for type 2 diabetics at 900mg/day and 1,800 mg/day doses. A seven-year, multi-center (N=192), prospective study has shown that diabetic nephropathy regression (reversal of microalbuminuria to normoalbuminuria, or macroalbuminuria to micro- or normoalbuminuria) is associated with a reversal of that same ratio. Specifically, one type 1 diabetic patient and four type 2 diabetic patients regressed from macroalbuminuria to microalbuminuria, and one type 2 diabetic patient regressed from macroalbuminuria to normoalbuminuria. These results are particularly interesting as they are inconsistent with the conventionally held belief that overt nephropathy is irreversible. Further research is needed to explore if there are circumstances that may allow for reversal of overt nephropathy.

While outside the scope of this article to discuss in detail, it should be noted that several of the...
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Interventions listed above have other known benefits in altering the pathophysiology and co-morbidities associated with diabetes, e.g., diabetic neuropathy and alpha-lipoic-acid. Therefore, the benefits of supplementing with the above biologically based interventions may extend beyond diabetic nephropathy.

Clinical Context
A comprehensive naturopathic approach to diabetic nephropathy treats the whole person by identifying causative and contributing factors that may exist in the physical, psychoemotional, and spiritual planes. These factors can be addressed by utilizing a wide range of treatment modalities including, but not limited to, homeopathy, constitutional hydrotherapy, glandular therapy, counseling, and environmental medicine. The complexity involved in implementing these modalities in clinical practice precludes their inclusion in the present discussion and will be left for a separate paper.

Conclusion
Diabetic nephropathy is a major complication of diabetes and can result in significant morbidity and mortality if untreated. Control of blood sugar and hypertension are the two established basic clinical problems that need to be addressed in treating diabetic nephropathy.

In this article, we have highlighted and presented the evidence for other interventions:

1. Prevention through yearly screening for microalbuminuria and possibly through early adoption of treatment interventions discussed in this article is important, given the prevailing opinion that glomerular changes are irreversible once overt nephropathy sets in.

2. Diet has a major impact on mortality rates. The current standard recommendation is protein restriction. There is also emerging evidence that a more multi-faceted diet, incorporating carbohydrate restriction, iron depletion, and polyphenol supplementation, may be superior. The study that supports this needs to be corroborated on a larger scale before widespread adoption.

3. Smoking cessation is a major lifestyle intervention. This includes exposure to second-hand smoke.

4. Supplementation with antioxidants, certain phytotherapeutics, and omega-3 fatty acids is important.

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acids have been shown to reduce urinary albumin excretion. Although the exact mechanisms are unknown, there is evidence it might be through mediation of oxidative stress.

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Notes
3. Ibid. 1999.
4. Ibid.
15. Ibid.
21. Supportive evidence from well-conducted cohort studies and/or supportive evidence from a well-conducted case-control study.
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