Prevention of Type 2 Diabetic Nephropathy

Introduction
Diabetes Mellitus is a major health problem in the most of world countries. In Northern America the population with type II diabetes will exceed 300 millions in the next 25 years. In Iran, overall prevalence of diabetes mellitus is between 3.07% and 6% in rural and urban regions, respectively. Prevalence of nephropathy among diabetic patients is 10% and 22.4% of dialysis cases is related to diabetes2–3. Proteinuria increases the cardiovascular death by 10 folds in subjects with type 1 diabetes. Similarly in type 2 diabetes, microalbuminuria is a risk factor for CHD by its association with both endothelial damage and nephropathy. Studies have suggested that prevention of the progression of diabetic nephropathy is associated with lower risk of cardiovascular death. Control of the modifiable risk factors such as blood glucose level, hyperlipidemia, hypertension, diet, smoking and proteinuria is necessary to prevent the disabilities and severe consequences of diabetes. This discussion is based on all available prospective studies to intervene contributing factors for prevention. It was tried to include EVIDENCE BASED MEDICINE, grade A1 and A2 as explained separately.4–5

Microalbuminuria (MA)
MA is elevated urinary albumin excretion to 30–300 mg/D in 24 hours urine collection or 20 to 200 g/min or g/ml in urine samples. Some studies advise to collect urinary albumin in spot urine creatinine concentration (albumin / Creatinine ratio 2.5 to 25 mg albumin / mmole Creatinine). Because of albumin excretion shows highly daily variation (30%), MA should be assessed in different days. Tests should be positive in the absence of fever, physical exercise, urinary tract infection, uncontrolled hypertension, hyperglycemia, or congestive heart failure. The Microalbuminuria preceded which usually lasted 5–10 years in type 1 diabetes6. There is evidence that the period of impaired glucose tolerance may have already resulted in renal and tubular damage. About 80% of type 2 diabetic patients with MA, have hypertension. Other risk factor of renal damage, most commonly systolic hypertension may contribute to increased urinary albumin excretion. In recent histological studies6, injury resulting from severe renal damage in type 2 diabetic patients with MA was found to be associated more than type 1 diabetic patients with MA, typical structural damage to the diabetic kidney or atypical pattern of renal injury such as glomerular sclerosis. All patients with proliferative retinopathy had typical glomerulopathy, and none of the patients without retinopathy had typical lesions. This may explain why many
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MA patients with type 2 diabetes never develop definitive diabetic renal damage. Albuminuria worsens the HTN and there is relentless decline in GFR and progression to ESRD. Pathogenesis of MA consists of Podocyte structural changes. One study showed changes in structure and density of podocyte occurring in early diabetes and might contribute to increasing albuminuria in type 2 diabetes. In another study, nephrin appears to play a key role in pathogenesis of proteinuria. Nephrin molecules function as a barrier with adjacent podocyte form a zipper like lattice structure in the slit diaphragm. The effect of ACE inhibitor for reduction of proteinuria can be explained by up regulation of nephrin gene expression in diabetic nephropathy and appear to be coupled with inhibition of angiotensin II synthesis contribute to reduced albuminuria and not only reduction of blood pressure. MA is not only the predictor of future nephropathy but the evidence of existing nephropathy. For patients with advanced renal lesions MA is not a predictor, but simply a sign of established nephropathy. The rate of progression of MA to overt proteinuria is 30-45% reported recently. The known correlation of MA to cardiovascular events may be explained by the facts that the generalized microvascular complication in type 2 diabetes are also found in the kidney, making MA a mirror of the generalized vascular pathology. The importance of MA as a marker of perm selectiveness of MA as a marker of perm selectivity is under question and recently it was showed that MA is due to abnormality of proximal tubular reabsorption of albumin and changes in lysosomal enzymes mediated degradation of albumin.

Prevention of MA

Treatment strategies include: primary prevention that is treatment modalities applied to any normalbuminuric diabetic patient at risk. Secondary prevention, that is treatment modalities for high risk patients (for example, Microalbuminuria) for development of diabetic nephropathy; and finally tertiary prevention, that is treatment of overt diabetic nephropathy aimed at preventing or delaying the development of ESRD, that develops in 20% of type 2 diabetic subjects after onset of overt proteinuria.

Primary prevention

Risk factors and makers for progression from normo to micro and to macroalbuminuria in type 2 diabetes have been identified. Some randomized controlled trials in diabetes have suggested a beneficial effect of ACE inhibitors on development of MA. In contrast, this literature contains two new studies comparing the effect of ACE inhibitors versus a long acting dihydropyridine CCB or B-blocker.

In 2 years randomized placebo controlled trial, lisinopril was administered in normotensive patients with normo or microalbuminuria. At the end of study, lisinopril decreased the progression of renal disease in normotensive IDDM against little or no effect in normoalbuminuric patients.

Another randomized double blinded placebo controlled cross over study, 64 microalbuminuria hypertensive type 2 diabetic and 60 normoalbuminurics included in study. Each group were divided in two subgroups receiving either irbesartan (150 mg orally bid) or placebo. In both groups, irbesartan reduced 24 hours mean systolic and diastolic pressure and albumin excretion rate (AER) in microalbuminuria hypertensive patients, and AER in normotensive microalbuminuric subjects.

Secondary prevention

Ravid et al, originally described the beneficial of ACE inhibition in normoalbuminuria patients with type 2 diabetes by demonstrating that only 12% of the patients developed nephropathy with ACE inhibitors, compared with 42% in placebo group.

As shown in another study Irbesartan in Diabetic Nephropathy Trial (IDNT) 1715 patients randomly assigned to irbesartan (300 mg orally), Amlodipine (10 mg daily), or placebo. The mean duration of follow-up was 2.6 years, and the risk of doubling the serum creatinine was 33% lower in irbesartan group than the placebo and 37% lower than the Amlodipine...
group. The risk of ESRD was 23% lower than the other groups. There was no change in blood pressure control between the three groups. The cardiovascular event has no differences.

Later studies have supported these findings. Long term studies in hypertensive type 2 diabetes with MA have revealed a similar beneficial effect of ACE inhibition and long acting dihydropyridine calcium antagonist agents and in progression to overt nephropathy.

Tertiary Prevention
Arterial hypertension, albuminuria, and poor glycemic control are the most important risk factors for progressive decline in GFR in diabetic nephropathy. Once nephropathy is present (proteinuria more than 500 mg/day), and arterial hypertension more than 130/85, and serum creatinine more than 1.2 mg/dl in female and 1.4 mg/dl in male, as De Jong et al emphasized the importance of utilization of ACE inhibitors with titration of dosage to lower the level of proteinuria as far as possible. The antiproteinuric effect of ACE inhibitors is well documented. ACE inhibitor reduces the level of angiotensin II formation and increased the level of bradykinin accumulation. The effect of ACE inhibitor on glomerular hemodynamic or glomerular barrier function could also help to explain the possible Reno-Protective effect (the beneficial effect on kidney function beyond the expected from blood pressure lowering effect alone), which is still a controversial issue. In a double blinded randomized cross over study comparing an angiotensin II type 1 receptor antagonist Losartan with Enalapril in diabetes type 1, showed both groups have similar result for reducing proteinuria and blood pressure control. The dosage of Losartan should be 100 mg/day for optimum effect. Losartan can reduce the abnormally elevated size selective property of the glomerular membrane in diabetic nephropathy.

In HOPE study as mentioned before Ramipril was beneficial for prevention of cardiovascular and overt nephropathy and this effect was greater than that attribute to the decrease in blood pressure. In RENAAAL (Reduction of Endpoints in Non-insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan) study, have shown Losartan 50-100 mg significantly reduced the incidence of doubling of serum creatinine level 25% (P=0.006), ESRD by 28% (P=0.002), or death (P=0.01) compared with placebo in 1513 patients with type 2 diabetes mellitus and proteinuria.

In Irbesartan Diabetic Trial 1715 hypertensive patients with overt nephropathy due to type 2 diabetes received irbesartan 300 mg, amlopidine 10 mg or placebo once daily with conventional antihypertensive agents other than ACE inhibitors, ARB, CCB. After follow-up 2.6 years, the risk of doubling the serum creatinine concentration in Irbesartan group was 33% and 37% lower than in placebo and amlopidine group respectively. The death rate and cardiovascular mortality was the same in all three treatment groups.

Glycemic Control
Primary Prevention
As shown in Diabetic Control and Complication Trail (DCCT), intensified therapy in type 1 diabetes reduced the occurrence of microalbuminuria by 39% and that albuminuria by 54% when two cohorts analyzed together. So it seems that additional treatments modalities needed to reduce or avoid the increasing burden of diabetic nephropathy.

In conclusion, intensive glycemic control by multiple insulin injection therapy can delay onset and progression of the diabetic retinopathy, nephropathy and neuropathy. In practice optimum glycemic control is demanding, difficult to achieve and frequently associated with problems (hypoglycemic and weight gain). Thus a target glycated haemoglobin value should be selected for each individual patient that provides an appropriate balance between risks and benefits.

Secondary Prevention
Once the stage of microalbuminuria is reached there is little evidence for an impact of good
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glycemic control on the progression of Microalbuminuria. In the type 2 diabetes patients, intensive glycemic control had no significant impact for reduction of progression of MA to overt nephropathy in the large UKPDS study. Only one study in Japan showed some beneficial effects for intensive therapy. However, the current guidelines recommend improved glycemic control in all diabetic patients with MA as this will reduce the risk of development and progression of retinopathy.

Tertiary prevention

The role of glucose control is relatively less important than the blood pressure control for reducing CV events and slowing renal disease progression. For many years, it was believed that intensive glycemic control does not have significant effect on renal function over nephropathy. For people with type 2 diabetes, glucose control has been shown to reduce CV events, but with right blood pressure control. Therefore, it is recommended to best possible glycemic control in all patients with overt nephropathy this also help to prevent and delay the progression of other microvascular complication. Most oral agent particularly chlorpropamide, glibenclamide, tobutamide and metformin are metabolized or excreted by kidneys, therefore accumulate in renal failure increasing the risk of hypoglycaemic. Lactic acidosis which is a serious consequence may occur when serum creatinine more than 1.5 mg/dl.

Blood pressure control

Primary prevention

In older patients with the prevalent phenomenon of isolated systolic hypertension, the initial goal of treatment is to lower systolic blood pressure cautiously without inappropriately decreasing diastolic blood pressure. The ABCD study randomly assigned patients to intensive treatment (target diastolic blood pressure, 75 mmHg) or moderate control (target diastolic blood pressure 80 to 89 mmHg). After 5 years of follow-up there was no difference between the group in progression of nephropathy, retinopathy or neuropathy. Total mortality rate was 5.5% in the intensive group, but 10.7% in the moderate group. There was no difference in cardiovascular mortality in both groups. It is important to control diastolic BP lower than 80 mmHg is beneficial. The systolic target not reached in randomized trial, but shown as 10 point reduction in systolic blood pressure, from 154 to 144 mmHg, led to substantial decreases in mortality and end points. Thus while the optimal of control for systolic blood pressure has not been clearly established, it may be responsible for target of 130 to 135 mmHg based on the level attained in ABCD trial.

Secondary Prevention

The definition of hypertension in MA is not universally agreed upon, but generally a blood pressure level of B.P. more than or equal to 130/85 mmHg is considered elevated. Recently, it has been recommended that the intervention, initially non-pharmacological therapy started first. When the blood pressure reached to more than 140/90 mmHg with the aim to lower to 130/85, and if tolerated a further careful lowering to 120/60 suggested. Early treatment with ACE inhibitor normalizes intraglomerular pressure and prevents glomerulosclerosis and proteinuria in diabetic animals. Type 2 diabetes with MA are hypertensive and will benefit from intensive blood pressure control that will help slow down the progression to overt nephropathy and also reduce the cardiovascular risk profile. In normotensive patients with MA type 2 diabetes the same effect of ACE inhibitors as in type 1 diabetes has been shown. A follow-up after seven years of treatment confirmed the renoprotective effect of ACE inhibition in this cohort study. It appears that intensive treatment of type 2 diabetes with MA is worthwhile to delay the progression of microvascular and possibly macrovascular complications and is without severe side effects.

Tertiary Prevention
in Losartan administration for Endpoint reduction in hypertension (LIFE)\textsuperscript{19}, 1195 hypertensive diabetic patients (age 55-80 years), were treated for four years with losartan or atenolol, often in addition to antihypertensive drugs other than ACE inhibitor or ARBs or B-blocker. Losartan reduced mortality by 39% compared with atenolol. Albuminuria was reduced significantly less frequently with losartan than with atenolol treatment (7% versus 13%; P=0.002).

**Effects of different antihypertensive drugs**

In FACET study\textsuperscript{25}, patients assigned to losinopril or amlopidine. Systolic blood pressure control was better in amlopidine group than losinopril, while diastolic blood pressure was similar. In losinopril group there was same cardiovascular events.

The greater beneficial effect of combination therapy on albuminuria may be exclusively explained by better control of hypertension.

The Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT) is the largest trial of blood pressure lowering to date\textsuperscript{29}. This trial compared the efficacy of ACE inhibitor (lisinopril), to a calcium channel blocker (amilodipine) and a thiazide diuretic (chlorthalidone) as first line therapy for mild to moderate hypertensive. The primary outcome was combined fatal coronary mortality, stroke, coronary heart disease, and peripheral arterial diseases. The result showed difference between treatment in primary outcome and all cause of mortality, the amlopidine group had a higher failure than the chlorthalidone group. Cholesterol, hypokalemia and incidence of new diabetes were higher in the chlorthalidone group than in the other group after 2 and 4 years of follow-up. However these differences caused an increased cardiovascular events or higher mortality rates. For the diabetic patients' lisinopril appeared to have no particular advantage for most of cardiovascular and renal outcomes. On the average 405 of patients did not reach to goal blood pressure of 140/90 mmHg or less.

In summary, up to 80% patients with type 2 diabetes will develop or die of macrovascular disease. Hypertension is a significant risk factor for cardiovascular diseases and also contribute to the development on nephropathy and retinopathy. The clinical trials of blood pressure control in diabetes have shown a consistent and dramatic effect in preventing clinical outcome, including cardiovascular mortality and morbidity and even possibly benefits in preventing microvascular complications. As shown in HOT study, a four point difference in diastolic blood pressure cause 50% decrease in cardiovascular events. And in UKPDS study a 10 points difference in systolic blood pressure from 154 to 144 mmHg led to a substantial decrease in mortality and end points. Thus the optimum systolic blood pressure of 130-135/80 should be attained. In ALLHAT, no difference was shown in cardiovascular events or renal outcome between diuretics and ACE inhibitor therapy for the diabetic subgroups. Thiazides especially decreased the rate of stroke and heart failure in black patients, so combination of ACE inhibitors and diuretics should be the first line of therapy in black patients. The result of life study suggest that ARBs could also be considered the first line therapy in patients with diabetes and left ventricular hypertrophy, but it remains to be seen whether these results are applicable to the entire groups of diabetic patients or not. While calcium channel blockers compared favourably with placebo, they fared poorly compared with ACE inhibitors. Thus they are best reserved as the second and third line agents in patients with diabetes. Calcium channel blockers should be used in patients with diabetes who have recent coronary events. Also some dihydropyridine CCB such as nifedipine, amlopidine or felodipine may worsen urinary albumin excretion and can accelerate the progression of diabetic nephropathy in other diabetic patients despite significant blood pressure reduction, at least in comparison with ACE inhibitors and ARBS. It is worthwhile to mention that dihydropyridine group will antagonize the tubuloglomerular feedback system, and will propagate the systemic blood pressure to renal microcirculation.
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Lipid lowering treatment
Patients with diabetes type 2 have a complex lipid pattern, and even more pronounced when nephropathy develops, usually elevated triglyceride, decreased HDL concentration of LDL cholesterol not different from non-diabetic patients. Nevertheless, there is an excess of small dense LDL particles that are highly atherogenic. In contrast to type 1 diabetes, optimal treatment of hyperglycemia does not normalize the dyslipidemia, due to a part of metabolic syndrome in pre-diabetic patients.

In MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high risk individual that were randomly assigned reduced 12.9% versus 14.7%, (P=0.0003). There were highly significant reduction of 18% in the coronary death rate. There were highly significant reduction of about one quarter in the first events rate for non fatal myocardial infarction or coronary death (8.7% versus 11.8%, P<0.0001). For the first occurrence of any event there was 24% reduction in simvastatin group after the first year. The annual risk of myopathy with simvastatin was 0.01%. The benefit of statin therapy appeared to be largely independent of and hence additional to cardio protective drugs such as aspirin, β-blocker, and ACE inhibitors. It has been suggested that there is a threshold of cholesterol at about 125 mg/dl, below which it would not lower the risk, but in contrast, this study has demonstrated that LDL below 77 mg/dl reduce vascular risk by about 25%. The adult Treatment Panel of the US National Cholesterol Education Program recently recommended that the Cholesterol LDL concentration should be below 100 mg/dl.27

Protein intake
Dietary protein restriction retards the progression of renal disease in animal model tested. By the major observational studies over individuals with diabetes failed to show an impact of dietary protein restriction on the rate of GFR decline. Short term, non randomized cross over study and self control studies, methods and insufficient adjustment for the other promoters, including antihypertensive treatments with ACE-inhibitors, have weakened the strength of these conclusion. In MDRD, in which only 3% of the patients had type 2 diabetes and none had type 1 diabetes, failed to show a clear benefit of protein restriction. The general consensus is to prescribe a protein intake of adult Recommended Dietary Allowance (RDA) of 0.8 Gms/Kg in the patient with overt nephropathy. However it has been suggested that once GFR begins to fall further restriction to 0.6 Gms/Kg may prove useful in slowing the decline in some patients.

Lifestyle intervention
Lifestyle intervention reduces progression from impaired glucose tolerance overt nephropathy. However it has been suggested that once GFR begins to fall, further restriction to 0.6 Gms/Kg may prove useful in slowing the decline in some patients.

Lifestyle intervention
Lifestyle intervention reduces progression from impaired glucose tolerance to type 2 diabetes and can improve the metabolic control and prevent microvascular outcome in established type 2 diabetes. In a randomized controlled clinical trials of 56 patients with type 2 diabetes managed by systemic group education and 56 control patients managed by individual consultation and education and followed for four years showed that, glycated haemoglobin increased in control groups but not in Index group that BMI decreased (P<0.001) and HDL increased. Quality of life, knowledge of diabetes and health behaviors improved with group care (P<0.009). Diastolic blood pressure and relative cardiovascular risk decreased from baseline in group care and control group alike.20 The same result obtained in Swedish study with seven years follow up29 and Chinese study (non randomized), that failed to show a difference in outcome between the diet or exercise intervention.17

In the diabetes prevention program and its Global Implication study, 27 centers participated
in this study and they randomly 3234 subjects assigned to three interventions, metformin 850 mg twice daily, placebo twice daily and intensive program of lifestyle intervention to achieve and maintain a weight reduction of at least 7% of initial weight with low calorie diet, low fat and physical activity such as brisk walking for at least 150 min/wk. The mean of the participant's age was 651 years and the mean body mass index was 34 kg/m². 68% were women, and 45% were non-Caucasian. The average follow-up was 2.8 years. The incidence of diabetes was 11, 7.8 and 4.8 cases per 100 person-years in the placebo, metformin and lifestyle groups. The lifestyle intervention reduced the incidence of diabetes by 31% (CI 95%; 17 to 43%), compared with placebo; the lifestyle intervention group was significantly more effective than metformin. Because the lifestyle intervention changes prevented one case per seven persons treated for three years and worked equally in all racial and ethnic groups in the Diabetes Prevention Program (DPP), they should be applicable to all high risk population worldwide and may be able to reduce the projected progressive rise in the incidence of diabetes and the expected increase in ESRD³⁶.

Low dose aspirin and stopping smoking

Treatment with low dose aspirin has beneficial effect on cardiovascular events and is recommended as a primary prevention strategy. In type 2 diabetes patients. This recommended from the American Diabetes Association. In microalbuminuric patients, renal synthesis of vasodilating prostaglandins has been reported and high dose indometacin reduced the albumin excretion rate by 58%. Its role in primary and secondary prevention mentioned by reducing the cardiovascular events but has no impact on rate of albumin excretion in type 2 diabetes³¹.

Smoking was an independent risk factor for the initiation of diabetic glomerulopathy in type 1 diabetes. In addition some studies suggest that smoking act as promoter in diabetes. Issues are somewhat more complex in type 2 diabetes since smoking also increases the risk of subjects to develop type 2 diabetes, possibly because it increases resistance. Nevertheless the risk of smokers to develop microalbuminuria and acceleration of the progression of nephropathy has been equally well documented in type 2 diabetes³².

New Horizon

Although the renal risk in diabetic nephropathy can be reduced, but there are other studies still experimental or done in small number of patients that worths to mention.

Some of these are as follows:

Hyperglycemia and hypertension in addition to renin angiotensin axis are important in progression of diabetic nephropathy. Hypertension and hyperglycemia induce changes in cellular function by common intracellular signalling pathways. Hyperglycemia and advanced glycation end product in addition to glucose independent pathways such as hypertension and activation of RAS induce activation of protein kinase C. So inhibition of protein Kinase C may be beneficial in prevention of diabetic nephropathy as shown in rat model by reducing albuminuria, structural injury, and TGF-B expression, despite continued hypertension and hyperglycemia³³.

References
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