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Protective effect of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor antagonists (ARBs) on microalbuminuria in diabetic patients

ABSTRACT

This review assesses the protective effect of ACEIs and ARBs on microalbuminuria in diabetic patients and identifying the preferred type based on their beneficial effects in addition to their blood pressure-reducing effect in diabetic patients with microalbuminuria and adverse drug reaction profile. In this review, articles published between 2001 and 2019 are included and MEDLINE search was used with key words such as diabetes, microalbuminuria, angiotensin II receptor antagonists, and ACEIs. ARBs reduced the risks of end stage renal disease (ESRD) and two-fold rise in the serum creatinine level; ACEIs did not reduce the risks of ESRD in an analysis of studies including both type 1 and type 2 diabetic patients. However, a meta-analytical review or study needs to be conducted to evaluate the comparative effects of ARBs and ACEIs in either type 1 or type 2 diabetic patients. Early treatment with ACEIs or ARBs decreased the risk of microalbuminuria in patients with type 2 diabetes. Telmisartan is found to be beneficial in microalbuminuria or diabetic nephropathy. Long-term therapy with higher dose of irbesartan resulted in consistent protective effects on the renal functions even after its withdrawal. ACEIs or ARBs are consideredas the 1st line therapy in both type 1 and 2 diabetic patients with microalbuminuria. ARBs are definitely preferred for patients who cannot tolerate ACE inhibitors. ARBs may be preferred over ACEIs due to their predominant renal protective effects in addition to their beneficial effect of improving blood pressure in type 2 diabetes mellitus. However, the comparative effects of ARBs and ACEIs in either type 1 or type 2 diabetic patients with microalbuminuria needs to be further evaluated in a randomized controlled study. (Clin Diabetol 2020; 9)

Key words: angiotensin, enzyme inhibitors, receptor blockers, microalbuminuria, diabetes, renal, protective effects

Introduction

Albuminuria is developed in 1/3rd of the diabetic patients. There is higher risk of all-cause mortality and end-stage renal disease (ESRD) in diabetic patients with albuminuria. Cardiovascular disease and mortality can be predicted on the basis of microalbuminuria as it is an indicator of endothelial dysfunction. Microalbuminuria is also reported in cases with hypertension, dyslipidaemia, renal malfunction, obesity, and smoking; all these are contributors to the development of atherosclerosis. Hyperactivity of renin–angiotensin system leads to the development of cardiovascular events in diabetic patients with microalbuminuria [1–3].

It has been reported in studies that angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor antagonists (ARBs) lead to a reduction in the cardiovascular mortality rate and an improvement in glomerular filtration rate in hypertensive diabetic

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patients with microalbuminuria, macroalbuminuria, or normoalbuminuria [1, 4, 5].

This review is carried out to assess the protective effect of ACEIs and ARBs on microalbuminuria in diabetic patients and to identify the preferred ACEIs and ARBs based on their beneficial effects in addition to their blood pressure-reducing effect in diabetic patients with microalbuminuria and adverse drug reaction profile. The safety aspects of ACEIs and ARBs are also discussed.

Methodology

This review includes articles published between 2001 and 2019. A MEDLINE search was used for it. The following words were used while searching articles: diabetes, microalbuminuria, angiotensin II Receptor antagonists, angiotensin-converting enzyme inhibitors. Articles on clinical trials, meta-analysis reports, guidelines and past reviews are included. Thus, human clinical studies in relation to the effect of ACEIs and ARBs including ramipril, perindopril, olmesartan, losartan, irbesartan, telmisartan etc. especially on microalbuminuria in diabetic patients are considered. Non-renal parameter-related clinical studies and preclinical studies were excluded for this review. Possible mechanisms in the protective effect of ACEIs and ARBs in diabetic patients with microalbuminuria are also discussed in this review.

Microalbuminuria in diabetes

A review article by Satchell et al. [6] indicates the following: microalbuminuria is a predominant risk factor for CV (cardiovascular) disease and advancement in renal impairment, especially in diabetic population, though it seems to be valid in non-diabetic individuals as well; it is well-known that the diabetic population has the tendency to develop renal complications. It is essential to know the pathological and physiological mechanisms behind the development of microalbuminuria to strategize therapies needed to prevent and treat microalbuminuria [6].

Damage to the endothelial glycocalyx is an essential feature. Various mediators are involved in the damage process, such as reactive oxygen species (ROS), vascular endothelial growth factor (VEGF) and proinflammatory cytokines. Impairment in the pathway of the endothelium cell and podocyte leads to endothelial damage and aggravates the impairment. Impairment in glomerular podocyte and its loss is involved during a damaging process of advancement of microalbuminuria to overt nephropathy (macroalbuminuria) [6].

It is reported that damage to the endothelial glycocalyx is predominantly involved in microalbuminuria and generalised endothelial dysfunction, and in microvascular and macrovascular complications. Therefore, treatments targeting the endothelial glycocalyx could be beneficial in microalbuminuria in the diabetic population. A decrease in microalbuminuria could help improve endothelial dysfunction and may be beneficial in reducing the risk of cardiovascular diseases [6].

The American Diabetes Association suggests the evaluation of albuminuria in type 2 diabetes population initially at the time of diagnosis of diabetes and every year afterwards [7].

Another review by Basiet al. [8] indicates that ACE inhibitor or ARB therapy is recommended for patients with microalbuminuria or obvious proteinuria. Maximization of the dosages of ACE inhibitor or ARB therapy is useful during the management of albuminuria with regular monitoring. ACE inhibitor or ARB therapy is useful to reduce hypertension. But, if the blood pressure is not controlled, add-on therapy with other antihypertensives could be beneficial to maintain the blood pressure. Other therapies, such as statins, renin inhibitors, and glycosaminoglycans, have also been found to be effective in reducing urinary albumin excretion [8].

Clinical efficacy of ACEIs and ARBs on microalbuminuria in diabetic patients

As per a systematic review and meta-analysis by Wang et al. [1] ACEIs and ARBs result in similar improvement in microalbuminuria in patients with diabetes and albuminuria. It was noted that ARBs led to a significant reduction of the risk of end-stage renal disease (ESRD) in patients with diabetes and albuminuria. Most importantly, ACEIs did not show this reno-protective effect of reducing the risk of ESRD. This was a meta-analysis of twenty-six randomized controlled clinical studies including a big population of nearly ten thousand patients. ACEIs and ARBs also showed reduction in the risk of two-fold increase in the serum creatinine level. The improvement in microalbuminuria was similar with ACEIs and ARBs. It can be concluded from this meta-analysis that ARBs might be the preferred therapy over ACEIs due to their beneficial effect on renal functions. However, the researchers incorporated both type 1 and type 2 diabetic patients with albuminuria in this meta-analysis. Therefore, there could be the risk of bias. Thus, a meta-analytical study needs to be conducted to evaluate the comparative effects of ARBs and ACEIs especially in either type 1 or type 2 diabetic patients [1].

Persson et al. [4] evaluated the impact of ACEIs or ARBs on the prevention of microalbuminuria in patients with type 2 diabetes and normoalbuminuria. They concluded that the risk of microalbuminuria for patients with type 2 diabetes and normoalbuminuria is significantly lower with ACEIs or ARBs. The conclusion was

reached based on the meta-analysis of six randomized controlled clinical trials on nearly seventeen thousand patients with type 2 diabetes and normoalbuminuria. Unlike the meta-analysis report by Wang et al. [1], all-cause mortality was reduced to a certain extent with both ACEIs and ARBs by Persson et al. Studies on the following ACEIs or ARBs were considered for this review: enalapril, ramipril, trandolapril, candesartan, perindopril and olmesartan [4].

Uzuet al. [3] reported in their study that both ARBs and aliskiren, a direct renin inhibitor (DRI), reduced albuminuria significantly in hypertensive patients with type 2 diabetes. Moreover, albuminuria decreased significantly with ARBs in patients with high-normal albuminuria and DRI did not reduce albuminuria in similar patients. ARBs showed similar effectiveness to that of DRI in reducing urinary excretion of albumin, angiotensinogen, urinary albumin-to-creatinine ratio, and systolic and diastolic blood pressure. Thus, it indicates that DRI is not superior to ARBs. Patients were treated with the following ARBs in this study: valsartan, telmisartan, olmesartan, candesartan, losartan, irbesartan, azilsartan [3].

A choice of ACEIs and ARBs in diabetic patients with microalbuminuria

The following are the results from different studies for individual ACEIs and ARBs to conclude a choice of ACEIs and ARBs in diabetic patients with microalbuminuria.

Clinical efficacy of ramipril

As per the DIABHYCAR study (2004), no beneficial effect was found on ESRD or two-fold rise in serum creatinine with the ACE inhibitor ramipril. The same study indicates no beneficial effect with low dose (1.25 mg) ramipril once daily on cardiovascular and renal outcomes of patients with type 2 diabetes and albuminuria, although a slight reduction in blood pressure and urinary albumin was observed [9].

Clinical efficacy of perindopril

In a placebo-controlled clinical trial conducted by Yao et al. on Asian patients, perindopril reduced urinary albumin excretion rate (AER) significantly in patients with initial stage of diabetic nephropathy with normal blood pressure and microalbuminuria during the one-and-half-year treatment [10].

Jerums et al. [11] reported the following results in a placebo-controlled i.e. six-year follow-up study with perindopril, maintenance of albumin excretion rate (AER), reduction in GFR in Australian type 2 diabetic patients with normal blood pressure and microalbuminuria. The blood pressure remained normal in 83% of patients with perindopril. A significantly smaller number of patients developed macroalbuminuria [11].

Another double-blind study conducted by Kopf et al. concluded that urinary albumin excretion rate was maintained by perindopril in patients with insulin-dependent diabetes mellitus and mild-to-moderate hypertension and stable microalbuminuria, and perindopril therapy was found to be safe as well [12].

Clinical efficacy of olmesartan

In a study conducted by Raff et al. [13] it was found that olmesartan (OLM) prolonged the onset of the development of microalbuminuria in type 2 diabetic patients. Moreover, OLM prolonged the development of ECG signs of cardiac structural adaptation and left ventricular remodelling in type 2 diabetic patients [13].

Clinical efficacy of losartan

The RENAAL study seems to be a landmark work to show the following benefits with losartan therapy in patients with type 2 diabetes and nephropathy: reduction in the incidence of ESRD and two-fold rise in the serum creatinine level, 35% showed reduction in the level of proteinuria and good tolerance were documented with this drug. However, this study did not report the effect of the therapy on microalbuminuria. Moreover, there was no impact of losartan on the rate of death [14, 15].

A review of a clinical study by Ruilope et al. [16] indicates that losartan appears to be an essential therapy in type 2 diabetic patients with nephropathy in addition to dietary therapy for proteinuria and diabetes. In addition to blood pressure lowering effect, a renal protective benefit of losartan helps delay the initiation of dialysis or kidney transplantation [16].

According to a study conducted by Woo et al., losartan leads to an effective reduction in the urinary excretion of transforming growth factor (TGF)-beta and albumin in type 2 DM patients with microalbuminuria during a six-month therapy in addition to its property of effective reduction in arterial blood pressure [17].

A long-term randomized clinical study conducted by Weil et al. [18] indicated that losartan therapy reduced the mesangial fractional volume in type 2 diabetic American-Indian patients with microalbuminuria. Thus, losartan therapy helped preserve the kidney structure in these patients [18].

A randomized controlled-study by Agha et al. [19] concluded that losartan demonstrated a significant reduction in proteinuria in patients with normotensive type 2 diabetes mellitus (T2DM) patients with early nephropathy. This study indicates that the effect

of losartan seems to be beyond its blood pressure reducing effect. This was a ten-month study on 361 patients. Eighty percent of the patients reported significant reduction in albuminuria by more than 30%. The anti-albuminuric effect of losartan was a reversible impact [19].

A similar beneficial effect of losartan on the urinary excretion of albumin was demonstrated in a multicentric randomized, double-blind, placebo-controlled clinical study conducted by Zandbergen et al. [20]. A 25–30% relative reduction was observed in this study with two different dosages through a ten-week therapy. This reemphasizes the effect of losartan on proteinuria possibly not associated with blood pressure reducing effect. Additionally, the safety of losartan was established with normotensive patients [20].

Clinical efficacy of irbesartan

In a double-blind placebo-controlled randomized study, Andersen et al. [21] reported a persistent reduction of microalbuminuria after withdrawal of a two-year high-dose (300 mg, once daily) irbesartan treatment on hypertensive type 2 diabetic patients with persistent microalbuminuria. This indicates a long-term renal protective effect of high-dose irbesartan treatment. This study also concluded that placebo and irbesartan 150-mg groups demonstrated increase in urinary albumin excretion. Most importantly, it was decreased persistently and significantly by 47% in the high-dose irbesartan group [21].

Clinical efficacy of telmisartan

Furat et al. [2] reported in a controlled study that telmisartan was beneficial for decreasing systemic inflammation and levels of urinary albumin excretion in patients who had type 2 diabetes mellitus and had undergone coronary artery bypass surgery. Microalbuminuria levels between the groups differed significantly in the pre-operative period, first hour postoperatively and fifth day post-operatively. C-reactive protein levels between the groups differed significantly on the fifth day post-operatively [2].

A review by Schmieder et al. [22] demonstrated that the effect of telmisartan on kidney function benefits in patients with microalbuminuria or overt diabetic nephropathy. They reported that telmisartan offers benefits at all the stages of the renal abnormalities in patients with type 2 diabetes. Telmisartan delays the progression to overt nephropathy in patients with microalbuminuria. The effectiveness of telmisartan is similar to angiotensin-converting enzyme inhibitors, but with a greater tolerance than angiotensin-converting enzyme inhibitors. The effect of telmisartan on protein excretion in diabetic nephropathy appears to be better than that of losartan and equivalent to that of valsartan. In the ONTARGET study, telmisartan offered a comparable cardiovascular protection to ramipril in diabetic patients [22].

Clinical efficacy of ACEIs plus ARBs

In a study conducted by Joshi et al. [23] it was found that the fixed dose combination of losartan and ramipril demonstrated a good to excellent efficacy in approximately 98% patients and accomplished a target blood pressure in nearly 79% patients with a 12 week--therapy. The combination offered a reduction in the urinary albumin excretion in most of the patients with microalbuminuria and proteinuria. This was an open, non-comparative, multicentric clinical study conducted on Indian patients. All the patients were treated with combination of losartan + ramipril in two fixed doses. Nearly 21% patients obtained normoalbuminuria with this therapy [23].

However, a study conducted by Tütüncü et al. concluded that ACE inhibitors and angiotensin II receptor blockers lead to comparable efficacy in treating diabetic microalbuminuria, and the combination of the two drugs did not add any further benefit. In this prospective, randomized clinical trial, the efficacy of treatment with enalapril or losartan, or both enalapril and losartan, was compared in patients with microalbuminuria [24].

Moreover, a review by Mercier et al. [5] indicated that dual RAAS inhibition with ACE inhibitors, ARBs or ACE inhibitors, and direct renin inhibitors failed to improve cardiovascular or renal outcomes and predisposed patients to adverse events. Thus, more studies need to be conducted to assess the efficacy and safety of the ACEI plus ARB therapy [5].

Based on the reno-protective effects demonstrated above, ARBs (losartan, telmisartan high-dose irbesartan) may be preferred for diabetic patients with albuminuria.

Guidelines on the role of ACEIs and ARBs on microalbuminuria in diabetic patients

American Diabetes Association (ADA) Guidelines

ADA recommends the following: "An ACE inhibitor or ARB, at the maximum tolerated dose is indicated for blood pressure treatment as first-line treatment for hypertension in patients with diabetes and urinary albumin-to-creatinine ratio (UACR) ≥ 300 mg/g creatinine or 30–299 mg/g creatinine. If one class is not tolerated, then it should be replaced with the other" [25] (Figure 1).

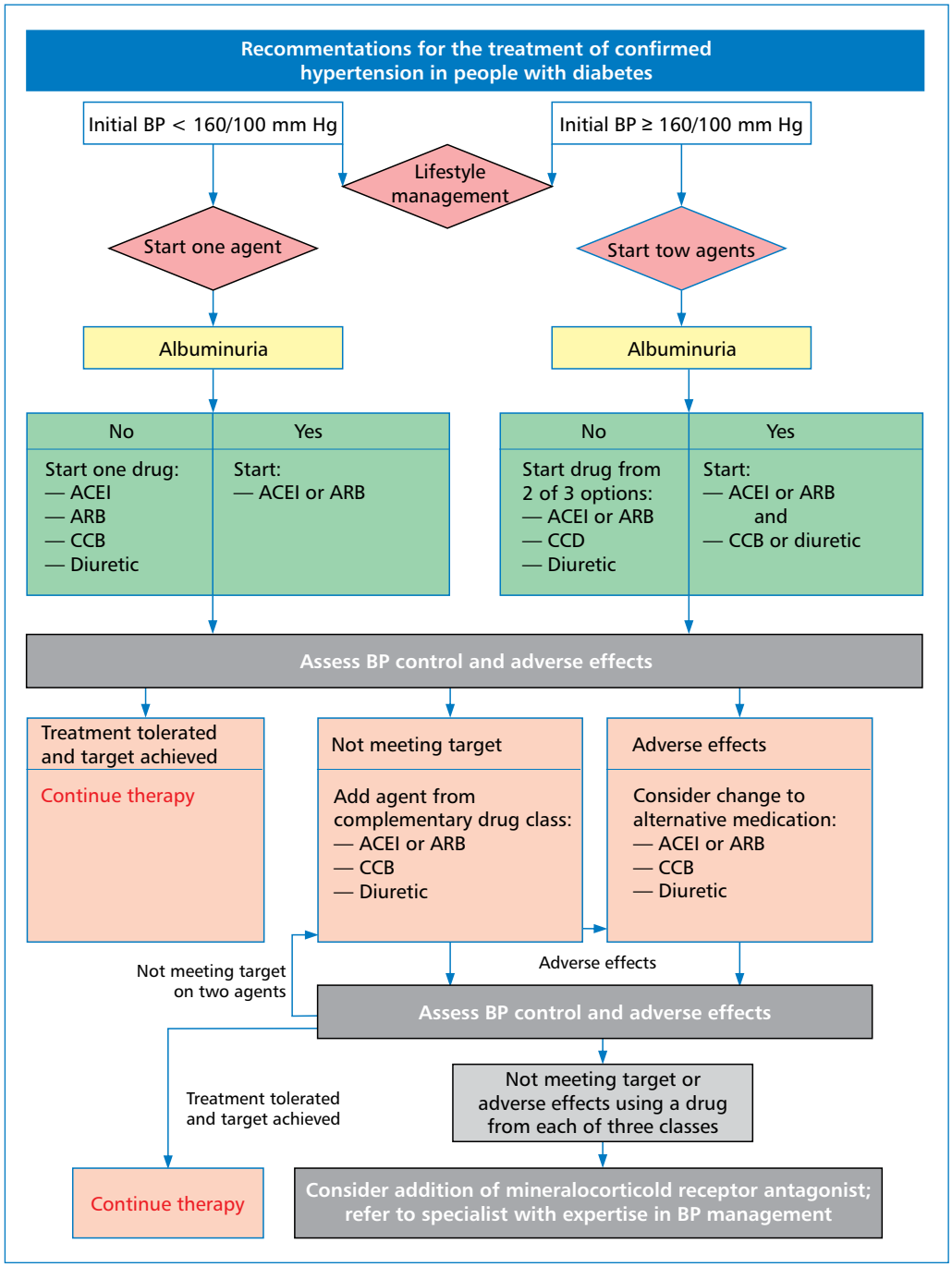

Figure 1. Recommendations by ADA for the treatment of confirmed hypertension in people with diabetes

NICE guideline recommendations

Type 1 diabetes:

— "ACE inhibitors should be initiated with the usual precautions and titrate to the maximum dose in all adults with diagnosed nephropathy (including those with microalbuminuria alone) and type 1 diabetes".

— "If ACE inhibitors are not tolerated, then it should be replaced with angiotensin II receptor antagonists. The combination therapy is not recommended".

Type 2 diabetes:

— "Initiate ACE inhibitors with the usual precautions and titrate to the maximum dose in all individuals with confirmed raised albumin excretion rate (> 2.5 mg/mmol for men, > 3.5 mg/mmol for women)".

— "Replace an angiotensin II-receptor antagonist for an ACE inhibitor for a person with an abnormal albumin:creatinine ratio if an ACE inhibitor is poorly tolerated" [26].

Guidelines from National Institute for Health and Care Excellence (NICE) 2014 and Kidney Disease Outcomes Quality Initiative (KDOQI) 2012

— "Use an ACE inhibitor or an ARB in patients with diabetes and albuminuria, even for subjects with microalbuminuria and normal blood pressure" [27, 28].

Results and discussions

It is cited in the ADA guidelines that to reduce the risk of aggravation of kidney disease, treatment needs to be initiated with ACEIs or ARBs on patients with albuminuria (urine albumin-to-creatinine ratio ≥ 30 mg/g) [25].

A systematic review and meta-analysis by Wang et al. [1] showed that ARBs significantly reduced the risks of ESRD by approximately 26% and doubling of the serum creatinine level by nearly 25% [1].

As per a meta-analysis of 28 studies by Vejakama et al., ACEI/ARB lead to persistent protective effect on renal functions over other antihypertensive drugs, predominantly CCBs, and placebo in patients with type 2 diabetes. This reno-protective benefit seems to be beyond antihypertensive effect as there was no difference in reduction in the blood pressure between ACEI/ARB and active comparators. In this study ACEI/ /ARB demonstrated significant reduction in the risk of two-fold rise in serum creatinine, macroalbuminuria, and albuminuria compared to other antihypertensive drugs [29].

An inhibition of the renin–angiotensin II system (RAS) seems to be very important in preventing or delaying albuminuria in diabetic patients. It is reported that the mechanism behind a decrease in albuminuria in diabetic nephropathy with ARBs, e.g. olmesartan, obstructs the podocyte apoptosis in the kidney [30]. An animal study showed a rise in p27 (Kip1) mRNA and protein expression in diabetic glomeruli and podocytes. An ARB therapy reduces p27 (Kip1) expression; this therapy helps reduce renal hypertrophy [31]. A preclinical study illustrated a reduction in albuminuria and advancement in glomerulosclerosis type 2 diabetes with valsartan by decreasing podocyte injury, oxidative stress and inflammation in renal tissues [32].

A pilot study by Esmatjes et al. demonstrated reduction in TGF-beta1 plasma level and urinary albumin excretion with losartan on hypertensive type 2 diabetes mellitus patients with microalbuminuria. The researchers suggested TGF-β_1 as an indicator of beneficial reno-protective effect with inhibition of the renin–angiotensin system. Such a mechanism of decrease in the synthesis of TGF-β for a beneficial reno-protective effect with the use of losartan was further substantiated by Houlihan et al. through a study on hypertensive type 2 diabetic patients with elevated albumin excretion [33, 34].

ACEIs are also beneficial in blocking increased expression of TGF-β type II receptor in diabetic nephropathy [35]. ACEIs also appeared to be responsible for an alteration in matrix degradation pathways and that may reduce matrix accumulation in diabetic nephropathy [36].

Based on an animal study, Bonnet et al. suggested prevention of renal gene and protein expression of nephrin as a possible mechanism for the beneficial effect of ARBs in reducing proteinuria in hypertensive diabetics. The researchers used irbesartan in this study [37].

A preclinical study by Ertürküner et al. [38] indicates that perindopril helps prevent impairment in renal corpuscle (Mesangial matrix and podocyte) diabetic rats [38].

Cordonnier et al. projected another mechanism of inhibition for interstitial cell growth ARBs. Researchers found out that perindopril reduces excessive interstitial cell growth in patients with diabetic glomerulopathy suffering from hypertension [39].

Low-dose irbesartan therapy seems to be inadequate to protect the kidney due to inadequate inhibition of the RAAS in patients with type 2 diabetes and microalbuminuria. This inadequate inhibition of the RAAS was demonstrated by dose-dependent rise in plasma renin levels. Researchers also suggested evaluation of a 300 mg dose of irbesartan. Implementation of high-dose irbesartan treatment offers a consistent decrease in microalbuminuria may be due to reversal of renal structural and/or biochemical anomalies that contribute to long-term renal protective effects [21].

A systematic review and meta-analysis of twelve randomized controlled trials done by Caldeira et al. leads to the conclusion that treatment with ARBs should be implemented in patients who cannot tolerate ACE inhibitors. The researchers noticed that ARBs lead to minimal incidences of cough and angioedema, which are common side effects of ACE inhibitors [40].

Conclusion

ACEIs or ARBs are considered to be the 1st line of therapy for both type 1 and 2 diabetic patients with microalbuminuria. ARBs are preferred for patients who cannot tolerate ACE inhibitors. ARBs (e.g. losartan or telmisartan or higher dose of irbesartan) may be preferred over ACEIs due to their predominant renal protective effect in addition to their blood pressure improving beneficial effects of improving blood pressure in type 2 diabetic patients. However, the comparative

effects of ARBs and ACEIs in either type 1 or type 2 diabetic patients with microalbuminuria need to be further evaluated.

Conflict of interest

The authors declare to have no conflict of interest.

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