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Review Article

Internal Medicine Section

Olmesartan in Management of Proteinuria

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ABSTRACT

Proteinuria is a marker and predictor of cardiovascular morbidity and mortality. Blockade of angiotensin receptor might result in reduction in proteinuria. Olmesartan, an Angiotensin Receptor Blocker (ARB) which is approved for the treatment of hypertension is believed to produce antiproteinuric effects through different mechanisms. The objective of this review is to assess the cause, duration and degree of proteinuria and understand the current place of olmesartan in management of proteinuria associated with Cardiovascular Disease(CVD) and hypertension. We performed a comprehensive search of MEDLINE, PubMed and Google Scholar databases for articles related to Olmesartan and proteinuria (till June 2017).

Angiotensin-II induces transforming growth factor-β upregulation and increase transcapillary pressure. AT-I receptor blocked by olmesartan result in reduction in proteinuria. Olmesartan significantly reduces Blood Pressure (BP) and delays the onset of Chronic Kidney Disease (CKD), it also delayed the risk of onset of microalbuminuria. Olmesartan have nephroprotective, antioxidant, antifibrotic activities and proteinuria reducing effects which can be beneficial in patients with hypertension. Olmesartanis believed to produce antiproteinuric effects through different mechanisms. It is indicated for treatment of hypertension to reduce the risk of fatal and non fatal CV events which may or may not be associated with proteinuria.

Keywords: Angiotensin II, Angiotensin receptor blocker, Chronic kidney disease

INTRODUCTION

Proteinuria is an indicator of kidney disease and substantial decline in kidney function. It is now generally accepted as an independent risk factor for CVD [1]. Normal protein excretion is less than 150 mg in 24 hours [2]. Presence of any abnormal concentrations of proteins in urine can either be due to systemic disease, overproduction of plasma proteins or defect in glomerular barrier [3]. Proteinuria is considered as alternative or nonspecific marker of CV risk [2]. The prevalence of proteinuria is 16% with hypertension and 29% with diabetes. In both patients with or without hypertension, proteinuria depicts CV mortality and morbidity [3]. Patient's prognosis is dependent on basis of cause, duration and the degree of proteinuria. Prevalence of hypertension is approximately 2.5 times high among patients with diabetes and these two diseases independently affect renal function which can result in proteinuria [4]. Apart from antihypertensive activity, Renin Angiotensin Aldosterone System (RAAS) inhibitors also have antiproteinuria and renoprotective effects. These effects may be due to haemodynamic and non haemodynamic effects of the drugs. Angiotensin Converting Enzyme Inhibitors (ACEI) and ARB have equal efficacy in terms of controlling BP and renoprotection however, there are differences between ACEIs and ARBs [5]. Although, ACEIs and ARBs belong to a family of therapies that block the renin angiotensin system and are suggested to improve proteinuria/albuminuria. There is evidence that blockade of angiotensin receptor might result in reduction in proteinuria and hence, morbidity and mortality [6].

Olmesartan, an ARB which has been approved for the treatment in hypertension is reported to have renoprotective as well as hepatoprotective advantages over other ARB's [7]. It increases the renal blood flow and also normalizes the circadian BP especially nocturnal BP which is one of the strong predictor of CV events [7]. Olmesartan believed to produce antiproteinuric effects through a different mechanism other than its antihypertensive action. It has been investigated in reduction of proteinuria and is being considered in clinical trials for its use in prevention of nephropathy irrespective of the cause [1].

The objective of this review is to assess cause, duration and degree of proteinuria which will be helpful in understanding patients prognosis, role of RAAS in proteinuria and understanding the current scenario of olmesartan therapy in management of proteinuria associated with CV disease and hypertension.

Methodology

We performed a comprehensive and systematic search of MEDLINE, PubMed and Google Scholar databases for all original research articles related to olmesartan, proteinuria associated with hypertension and CVD till June, 2017. In our search we included all research articles, review articles, meta-analysis, RCT, CT, guidelines and textbooks. We reviewed the reference lists of the articles and original studies identified by the electronic search for other potentially eligible articles. If multiple publications addressed the same dataset, the most recent complete report was included [Table/Fig-1].

Proteinuria

Proteinuria is a marker of renal injury that often detected earlier than any substantial decline in glomerular filtration rate [1].

Causes of proteinuria: Possible causes of Proteinuria are diseases of the glomeruli (glomerulonephritis), Urine Tract Infections (UTI), eclampsia. Vigorous exercise or high grade fever can also lead to temporary proteinuria. It can also be a due to some other diseases like congestive heart failure, hypertension, diabetes mellitus, myeloma, amyloidosis, connective tissue diseases and high cholesterol level [15].

Classification of proteinuria: Proteinuria can be classified as microalbuminuria, albuminuria, proteinuria [Table/Fig-2].

Proteinuria as a prognostic marker: Number of studies were undertaken to establish the correlation between proteinuria and CV risk. A study involving 2310 patients highlighted that albumin to creatinine ratio was higher in elderly groups which also corresponds to higher CV mortality and worsen the renal outcome [16]. A study done by Rein P et al., reported that albuminuria significantly predicts CV events in patients with T2DM [17]. According to European Prospective Investigation into Cancer (EPIC) Norfolk study,

Study, year	Number of Participant (n)	Mean age, year	Renal disease	Drugs used
Zandbergen AA et al., 2003 [8]	74	57	Type 2 DM	Losartan
	73	59		Placebo
Rossing K et al., 2003 [9]	24	59	Type 2 DM	Candesartan
	-	-		Placebo
Ishimitsu T et al., 2005 [10]	22	56	Other	Valsartan
	-			Placebo
Ono T et al., 2013 [11]	10	55	CKD	Olmesartan
	13	51		Losartan
	09	50		Candesartan
	09	56		Valsartan
Haller H et al., 2011 [12]	2232	57	Type 2 DM	Olmesartan
	2215	57		Placebo
Zeeuw D et al., 2004 [13]	751	60	Type 2 DM	Losartan
	762	60		Placebo
Raff U et al., 2014 [14]	736	58	Type 2 DM	Placebo
	777	56		Olmesartan

[Table/Fig-1]: Studies including Angiotensin-Receptor Blocker.
Type 2 DM- Type 2 Diabetes Mellitus, CKD- Chronic Kidney Disease

Diagnostic test	Normal	Microalbuminuria	Albuminuria	Proteinuria
24 hour urine albumin collection	<30 mg/24 hours	30-300 mg/ 24 hrs	>300 mg/24 hours	>300 mg/24 hours
Spot urine dipstick	<30 mg/dL	Not available	>30 mg/dL	> 30 mg/dL
Spot urine albumin creatinine ratio	<17 mg/ gm (men) <25 mg/gm (women)	17–250 mg/gm (men) 25–355 mg/ gm (women)	>250 mg/ gm (men) >355 mg/g (women)	N/A
Spot urine protein to creatinine ratio	<200 mg/ gm	<35 mg/mmoL	N/A	>200 mg/ gm

[Table/Fig-2]: Classification of proteinuria.
N/A-Not available

microalbuminuria is considered to be very important predictor of CV mortality and there was higher incidence of myocardial infarction in patients with higher proteinuria [18].

DoManski M et al., reported proteinuria was associated with three fold increase in CV risk Multiple Risk Factor Intervention Trial (MRFIT) [19]. Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study reported that decrease in proteinuria significantly reduced the risk of CV as well as renal outcomes [13].

Complications related to proteinuria include the following [3]:

- Pulmonary oedema due to fluid overload
- Acute renal failure due to intravascular depletion
- Increased risk of bacterial infection, including spontaneous bacterial peritonitis
- Increased risk of arterial and venous thrombosis, including renal vein thrombosis
- Increased risk of CV disease

Proteinuria and CV risk: Although, substantial data is available which highlighted that proteinuria has direct implication on CV morbidity and mortality. A meta-analysis on albuminuria and CV risk reported that eGFR<60 mL/minute/1.73 m^2 and a higher albuminuria were independently associated with higher CV risk [20]. In a study involving 40,000 patients, it was reported that there was 30% increase in CV mortality and two fold increase in albumin creatinine (A/G) ratio [21]. New prognosticator of CV disease is developed using the knowledge of proteinuria, dipstick test and albumin creatinine ratio [22]. A study by Jensen JS et al., reported four times higher risk of ischemic heart disease in patients with microalbuminuria [22]. Similarly, Lee M et al., also reported increased risk of stroke by 90% in patients with proteinuria [23]. Proteinuria being a marker for CV diseases and there are several studies which have reported increase CV risk in patients with sub clinical proteinuria [24].

There are no set well defined criteria or guidelines for correlating proteinuria and CV risks. This suggests that albuminuria may not just represent glomerular damage, but may be a marker for more diffuse endothelial dysfunction. In Pravastatin or Atorvastatin Evaluation and Infection Therapy Thrombolysis In Myocardial Infarction 22 trial (PROVE IT TIMI 22) suggests that after an acute coronary syndrome in statin treated patients, microalbuminuria may reflect traditional CV risk factor burden and offer little prognostic information [25]. It also suggested that macroalbuminuria was a better predictor of mortality than microalbuminuria for myocardial infarction [26]. In recent studies on heart failure which included patients of Grade III to IV symptoms New York Heart Association (NYHA) microalbuminuria was reported in 30%-32% patients and macroalbuminuria in 11% patients. Similar results were also reported by Wright JT et al., [27-29].

Proteinuria in hypertension: Hypertensive nephrosclerosis involves long-term hypertension, hypertensive retinopathy, progressive renal insufficiency, Left Ventricular Failure (LVF) and proteinuria [30]. The prevalence of proteinuria in patients with hypertension varies from 5% to 14% [31]. African Americans have more propensities to develop hypertensive nephropathy at younger age and hypertension is a leading cause of End Stage Renal Disease (ESRD) in blacks (46%). Combination of hypertension with mild reduction in glomerular filtration rate can be reported as important risk factor for the development of nephropathy. Other risk factors include diabetes, hypercholesterolemia, smoking and obesity [21]. According the reports from NHANES study (2005-2006). More than 26% of the patients with essential hypertension develop chronic renal insufficiency [32].

Hunt LP et al., noted that urinary protein excretion concentration was directly proportional to the renal function [24]. Apperloo AJ et al., reported that treatment induced decrease in urinary protein level led to improvement in renal function [26]. The African American Study of Kidney Disease (AASK) in hypertension investigated the patients with hypertension who were non diabetic and reported that there was higher decline rate in Glomerular Filtration Rate (GFR) among patients with higher baseline proteinuria [33].

The autoregulatory mechanisms which takes care of renal damage gets compromised when there is increase in threshold leading to disruptive injury which can result in amplification of renal injury due to failure of autoregulatory elements [34].

Pathogenesis of Nephrosclerosis

Nephrosclerosis may occur due to renal injury caused by enhanced interglomerular pressure or ageing associated glomerulosclerosis. This can lead to glomerular injury and podocyte dysfunction which further increases glomerular permeability to macromolecules resulting in proteinuria. Excessive tubular reabsorbtion induces tubular cells to release cytokines and other inflammatory mediators thereby initiating proinflammatory and fibrogenic effects leading to apoptosis which promote further exacerbation of proteinuria and glomerulosclerosis [16].

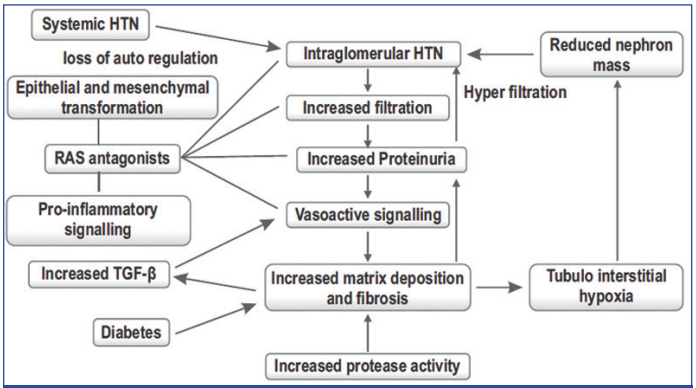
Approach to the Patients with Proteinuria

Evaluation of proteinuria was done between patients who are at increased risk for kidney disease and asymptomatic and the healthy patients who are not at risk. In at risk adults, the evaluation begins with testing of a random spot urine sample with an albumin specific dipstick. Alternatively, testing can begin with a spot urine test for the albumin-to-creatinine ratio. A positive test should be repeated using a quantitative measurement. Only patients with persistent proteinuria

are diagnosed with CKD. This is useful to family physicians because it eliminates the need for patients to provide a 24 hour urine sample for quantification of proteinuria. The suggestion to measure albumin excretion, rather than total protein excretion, is unique to the from current clinical practice. However, this albumin assays may not be available at all clinical laboratories [35].

Renin Angiotensin Aldosterone System (RAAS) and Proteinuria

It is reported that proteinuria directly activate RAAS in kidneys [36]. Angiotensin II is the mediator of proteinuria, which causes constriction of efferent arterioles and hence, raises in glomerular arteriolar resistance. Angiotensin II also induces upregulation of Transforming Growth Factor β1 (TGFβ1) which causes impairment of efferent arteriolar autoregulation. The entire process leads to elevation in transcapillary pressure, which is seen particularly in systemic hypertension. Thus, enhance the capillary filtration pressure leading to proteinuria [Table/Fig-3] [37].



[Table/Fig-3]: Pathophysiology of proteinuria.

Other than vasoconstriction and TGFβ1 inducing actions on angiotensin II in pathogenesis of proteinuria, it also suppresses nephrin transcription. Nephrin, a protein necessary for proper functioning of renal filtration barrier and its signalling is crucial for podocyte's survival. Abscence of nephrin leads to podocyte apoptosis [38]. Angiotensin II also increases the expression of Vascular Endothelial Growth Factor (VEGF) which is also thought to be responsible in the pathogenesis of proteinuria by increasing the permeability [39]. In conditions such as heavy proteinuria angiotensin is responsible for endocytosis of proteins from proximal convoluted tubule into tubular cells, which again stimulates RAAS thus, creating a vicious cycle. This accumulation of proteins causes increased severity of glomerulosclerosis, tubulointerstitial inflammation and progression to fibrosis. Thus, contributes to progressive renal failure [40].

Drugs having Role in Reducing Proteinuria

Medical management of proteinuria can be divided in two components, nonspecific and specific. In nonspecific management of proteinuria, patient has no contraindications to the treatment irrespective of the underlying cause. Whereas, specific management of proteinuria, depends on the underlying cause whether it is renal, nonrenal or immune mediated [3].

ACEIs and ARB are the preferred antihypertensives for treatment of proteinuria. They act by blocking the angiotensin II activity on efferent arteriole which causes vasoconstriction. Apart from their antihypertensive activity, these groups of drugs also have antiproteinuric action [41].

Diuretics: Moderate salt restriction and diuretic therapy should be considered in individuals with moderate to severe proteinuria as these patients usually have fluid overload. Addition of albumin infusion therapy may help in improvement in natriuresis in individuals with refractory salt and water retention but the potential benefits must be weighed against the costs and risks of albumin infusion [42].

Immunosuppressant: Such drugs should be reserved for the patients with progressive renal insufficiency or vasculitic renal lesions [43].

Vitamin D: It down regulates prorenin gene and hence, RAAS blockade occurs. Thus, It acts as a immunomodulator and decreases inflammation [44].

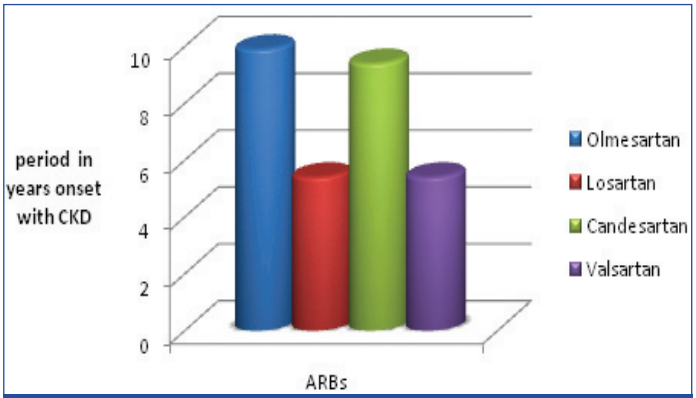
Anti-hyperlipidemics: Since there is increase in lipid levels in proteinuria which increase CV risk. Hence, it has been advised to avoid hyperlipaedemia. Nakamura T et al., reported renoprotective role of statins [45].

Role of Olmesartan in Proteinuria

Olmesartan medoxomil is the seventh approved ARB by US-FDA in 2002 and was developed by Sankyo in 1995 for the treatment of hypertension [46]. Olmesartan medoxomil is a prodrug that is converted into active drug olmesartan. It acts primarily at AT1 receptor as an antagonist in vascular smooth muscles to bring about its actions as majority of adverse actions of angiotensin II is through AT1 receptors [47]. Because of the adverse effects of angiotensin II, counter acting on its actions have been a major goal in the treatment of chronic conditions such as hypertension, heart failure and proteinuria. In several conditions such as metabolic, haemodynamic or local renal conditions olmesartan was found to be an effective nephroprotective drug, reducing the proteinuria and hence, further morbidity and mortality [46].

Clinical Evidences of Olmesartan in Proteinuria

A recent retrospective study compared the efficacy of olmesartan and other ARBs in reduction of proteinuria and nephroprotection in patients with CKD other than diabetic nephropathy over a period of 24 months. Similarly, reduction in systolic BP in all the patients was reported however, there was significant reduction in diastolic BP in olmesartan group compared to other ARBs. There was significant reduction in proteinuria after one month in olmesartan group compared to, losartan, valsartan and candesartan group and this reduction was significant in olmesartan group over a period of 24 months. It also reported a significant difference between olmesartan and other ARBs in context to onset of CKD which is shown in [Table/Fig-4] [12].



[Table/Fig-4]: Difference between olmesartan and other ARB's onset and diagnosed with CKD.
ARB-Angiotensin Receptor Blocker, CKD-Chronic Kidney Disease

Randomised Olmesaran and Diabetes Microalbuminuria Prevention (ROADMAP) trial conducted in 262 collaborating centres over 19 countries of Europe, assigned 4447 patients to receive either olmesartan or placebo and were assessed over a period of 3.2 years with the primary end point of time to first onset of microalbuminuria [47]. It was reported that olmesartan delayed the risk of onset of microalbuminuria in diabetic patients by 23% irrespective of the BP control in a mean follow up of 3.2 years [47]. Patients of ROADMAP study were followed up to determine the longterm beneficial effects of olmesartan and it was reported that olmesartan had significant results with the benefits

of microvascular and macrovascular complications but the reduction in proteinuria was not significant [47].

Olmesartan also shown to have additional antioxidant and antifibrotic activities in appropriate doses and presents as a molecule which needs more attention to explore its benefits [48,49].

The results from comparative study between telmisartan and losartan in hypertensive T2DM patients with overt nephropathy reported that the Angiotensin Receptor 1 (AT1) [50] affinity was more for telmisartan compared to losartan and hence, the antiproteinuric effect and also the PPAR-γ agonism which is involved in antiinflammatory and antifibrotic activity at proximal tubular cells is more with telmisartan compared to losartan [1]. As per the reports by Norwood D et al., [51] and Whittaker A [52] olmesartan was reported to have a greater affinity towards AT1 receptors compared to telmisartan. Whittaker A in a review of olmesartan highlighted that olmesartan has 12,500 fold greater affinities for AT1 receptors compared to AT2 and also its affinity is even greater than candesartan, telmisartan and losartan which is based upon receptor binding assay studies. Results from above study shows olmesartan have AT1 affinity which is more compared to telmisartan and other ARBs and hence, the antiproteinuric effect.

CONCLUSION

Preliminary data demonstrated that, persistent proteinuria is an independent risk factor of CVD and mortality. Persistent proteinuria directly activates RAAS and AT II which increases oxidative stress. Oxidative stress is correlated with the progression of CKD and complications such as CVD. ARBs such as, olmesartan is believed to produce antiproteinuric effects through a different mechanism other than its antihypertensive actions. This decreasing oxidative stress of ARBs could be involved in its organ protection action in CKD patients. Hence, antioxidant effects are postulated mechanism of antiproteinuric action of olmesartan which might be an addition to its antihypertensive action. Olmesartan is indicated for treatment of hypertension to reduce the risk of fatal and non fatal CV events which may or may not be associated with proteinuria. Olmesartan has been demonstrated to have appreciable BP lowering effects and with its nephroprotective and proteinuria reducing effects makes this a molecule which is very well suitable for patients with hypertension along with diabetes who have nephropathy or prenephropathy status.

Conflict of Interest

Dr. Amit Omprakash Gupta and Dr. Onkar C Swami are full time employees of Torrent Pharmaceuticals Limited, which actively markets Olmesartan. The other authors report no conflict of Interest in this work.

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