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Original Research Article

Evaluation and Comparison of Microalbuminuria Reduction by Spironolactone and Telmisartan in Normotensive Patients of Early Diabetic Nephropathy

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Abstract:

Introduction: Diabetic Nephropathy is a serious complication of diabetes which is related to persistent albuminuria and decreasing glomerular filtration rate. Its majority varies globally, impacting well-being and boosting morbidity. Microalbuminuria, an earlier marker, indicates kidney disease advancement, underlining the necessity for vigilant monitoring. Spironolactone indicates commitment in mitigating albuminuria, oxidative stress, and inflammation, offering a probable therapeutic avenue for diabetic nephropathy.

Aim and Objectives: This study evaluates and compares the microalbuminuria reduction by Spironolactone and Telmisartan in normotensive patients of early Diabetic nephropathy.

Method: This was a six month prospective, open-label randomised controlled study. A total of 110 individuals with diabetes and age between 25-75 years with Urinary albumin creatinine ratio of 3-300 mg/g creatinine were selected at random, followed up with for 24 weeks, and then evaluated for safety and effectiveness by established ethical guidelines. Patients were divided into two groups using computer generated random table. Group 1 received Spironolactone 25 mg once a day and Group 2 received Telmisartan 40 mg once a day.

Result: There was significant decrease in urinary albumin creatinine ratio in both groups during six month treatment(p=0.0001).There was insignificant decrease in SBP and DBP in Group 1and significant decrease in Group 2.

Conclusion: Spironolactone and Telmisartan effectively reduce microalbuminuria. Spironolactone can be considered in early diabetic nephropathy for microalbuminuria reduction without causing hyperkalemia.

Keywords: Spironolactone, Diabetic nephropathy, Telmisartan, Microalbuminuria, Blood pressure.

Introduction

Diabetic Nephropathy, recognized as Diabetic Kidney Disease (DKD), stands as a grave complication stemming from both type 1 and type 2 diabetes. Its hallmark lies in persistent albuminuria, denoting increased urinary albumin excretion in the absence of other renal ailments, coupled with a gradual decline in the glomerular filtration rate (GFR) – the kidneys' blood filtration pace. This affliction looms as a primary driver of end-stage kidney disease (ESKD) within developed nations. The intricate interplay of factors encompassing elevated blood pressure, heightened blood sugar levels, and genetic predisposition intricately influences the trajectory of Diabetic Nephropathy, governing its progression and clinical course [1-3].

The occurrence of diabetic nephropathy, also referred to as diabetic kidney disease, showcases a diverse landscape in its prevalence across distinct populations. A collective investigation revealed a prevalence of 21.8% among individuals with type 2 diabetes, and another study showed that this prevalence of type 2 diabetes patients stood notably higher at 31.6% [3,4]. Contrarily, in Saudi Arabia, the overall prevalence among type 2 diabetes patients marked a lower figure of 10.8% [5]. In sub-Saharan African regions, the amalgamated prevalence of diabetic nephropathy amounted to 35.3%, reflecting a substantial variability in the prevalence rates across different ethnicities and geographical regions. [6,7].

Diabetic nephropathy, a consequential complication arising from diabetes, exerts a profound toll on patients' well-being and life quality. Its ramifications extend across multifaceted domains, encompassing altered insulin dynamics with heightened insulin levels but a muted metabolic response to standard insulin measures. The impact resonates further, entwined with elevated morbidity, amplified mortality rates, and substantial economic burdens. Moreover, its insidious progression culminates in the ominous specter of end-stage renal disease, propelled by a complex interplay of pathophysiological disruptions. The influence extends beyond, pervading the kidney cell metabolome, especially amidst diabetic stressors. Concomitantly, it fosters a milieu ripe with escalated cardiovascular risk factors and impaired kidney functionality, intertwining a web of complexities that significantly compromise health outcomes [8-11].

Microalbuminuria denotes an abnormal elevation in albumin excretion within urine, gauged typically through the albumin-to-creatinine ratio (ACR) within random or first morning urine samples. Presently, the accepted definition pegs microalbuminuria within an ACR span of 3-300mg/g, factoring in urine concentration and volume variations. This diagnostic threshold mirrors not just albumin levels but accommodates fluctuations in urine concentration and quantity. Regarded as an indicator of endothelial dysfunction, microalbuminuria emerges as a pivotal harbinger of escalated cardiovascular risks, bearing a heightened significance within high-risk cohorts such as individuals grappling with diabetes or hypertension. Its presence delineates an augmented propensity for cardiovascular morbidities and mortalities, spotlighting the imperative for vigilant monitoring and targeted interventions within these susceptible populations [12,13].

Microalbuminuria stands as a crucial harbinger, especially within diabetic cohorts, heralding the trajectory of kidney disease progression. It signifies minute traces of albumin in urine, serving as an early alarm for potential kidney impairment. Robust studies have underscored its reliability in foretelling the onset of overt diabetic nephropathy, a formidable complication accompanying diabetes. Its presence sets the stage for an elevated vulnerability to cardiovascular events, heightened mortality rates, and a decline in renal functionality. The pivotal role of early microalbuminuria detection lies in enabling timely interventions aimed at stalling or mitigating the relentless progression of kidney disease, emphasizing the imperative for vigilant surveillance and targeted preventative strategies in high-risk diabetic populations [14-19].

Spironolactone emerges as a promising therapeutic avenue within diabetic nephropathy, showcasing considerable potential in mitigating kidney damage. Research findings highlight its efficacy in diminishing albuminuria, a critical indicator of renal impairment, spanning both type 1 and type 2 diabetes cohorts. Its notable antiproteinuric effect not only aligns with reducing albumin excretion but also showcases promise in decelerating the relentless progression of chronic kidney disease. Moreover, spironolactone's impact extends beyond mere albuminuria reduction, extending to the attenuation of oxidative stress markers and the reduction of urinary monocyte chemoattractant protein-1 (MCP-1) levels. This multifaceted action against oxidative stress and MCP-1 suggests a potential role in curbing the underlying mechanisms fueling the advancement of diabetic nephropathy, offering a promising avenue for targeted intervention and disease management [20-22].

Spironolactone, an antagonist targeting aldosterone receptors, unfolds as a promising intervention avenue in managing microalbuminuria within normotensive individuals grappling with diabetic nephropathy. The rationale behind its application in this domain converges upon multifaceted considerations. Aldosterone, the adrenal gland-produced hormone, assumes a pivotal role in exacerbating diabetic nephropathy, fueling renal inflammation, fibrosis, and oxidative stress that culminate in kidney impairment. Spironolactone, by impeding aldosterone's detrimental impact, emerges as a shield against these deleterious pathways, curbing their progression. Notably, amalgamated studies spotlight spironolactone's adjunctive role alongside standard antihypertensive therapies, showcasing marked reductions in urinary albumin excretion and improvements in renal function indicators. Beyond its blood pressure-lowering effects, spironolactone carves its renoprotective niche, fostering a distinct shield against renal deterioration. Crucially, spironolactone's repertoire extends to its anti-inflammatory prowess, a facet integral to its renoprotective mechanism. Its adeptness in quelling proinflammatory cytokine synthesis, notably monocyte chemotactic peptide-1 (MCP-1), and curtailing the activation of nuclear factor-kappa B (NF-kappaB), a linchpin in inflammation, underscores its potential in assuaging renal inflammation and fortifying the kidneys against diabetic nephropathy's ravages [23-27].

This study holds critical significance as it unravels the potential of spironolactone as a therapeutic intervention for normotensive individuals with diabetic nephropathy. By elucidating the mechanisms behind its efficacy in reducing microalbuminuria and safeguarding renal function,

this research paves the way for enhanced treatment strategies targeting kidney damage in diabetic patients, potentially altering the trajectory of disease progression and improving patient outcomes**.**

Method

Research Design

The research design was a randomised control study with open labels and a prospective design. It was anticipated that each participant would remain in the study for six months. A computer-generated random table separated 110 eligible consenting patients into two groups following informed consent. Group 1 got 25 mg of Spironolactone daily, while Group 2 received 40 mg of Telmisartan. Patients were phoned for follow-up every 4 weeks for 24 weeks. At 0 weeks, systolic and diastolic blood pressure, random urine albumin/creatinine ratio, HbA1c, serum sodium, and potassium were assessed. Follow-up assessments comprised the same measures and HbA1c at 12 and 24 weeks. At each follow-up appointment, patients were carefully checked and medication adverse events were assessed. Group 1 had no follow-up losses up to 12 weeks. However, 1 patient at 16 weeks and 2 at 20 and 24 weeks in Group 1 were lost. In Group 2, no patients were lost up to 8 weeks, but 1 was lost at 12 weeks, 2 at 16 and 20 weeks, and 3 at 24 weeks. Thus, 50 Group 1 and 47 Group 2 patients' data were analysed at the study's completion.

Safety and tolerability were assessed by a complete history, clinical examination, therapy, family history, and lifestyle changes. Height, weight, blood pressure, RUA/CR, HbA1c, serum sodium, and potassium were measured. The ion exchange resin technique was used to analyse HbA1c in blood, while microalbuminuria and creatinine were measured in urine. The biochemical tests included Jaffe's colourimetric creatinine technique, ion-selective electrode serum potassium and sodium method, and particle-enhanced immunoturbidimetricmicroalbumin test. Standards were also used to measure height and weight. Biochemical assays were done on blood and urine samples using standard procedures. The study's rigorous methodology and extensive data collection allowed for a detailed analysis of Spironolactone and Telmisartan's effects on various parameters over 24 weeks, revealing their efficacy and safety in the specified medical conditions.

Inclusion and Exclusion Criteria

Inclusion

- Diabetic patients of either sex were included in the study
- Age range of 25 to 75 years.
- Hb1Ac<8%.
- Random urinary albumin to creatinine ratio of 30-300mg/gr Cr.

Exclusion

- Diastolic and systolic blood pressures more than 80 and 130 mmHg respectively.
- Serum potassium level > 5 meq/L.
- Prior acute MI or stroke during the preceding six-month period
- Collagen vascular disease.
- Obstructive uropathy
- Alcohol and substance abuse
- Pregnancy and lactation

Statistical Analysis

The results are presented in mean ± SD and percentages. The Chi-square test was used to compare the categorical variables. The Unpaired t-test was used to compare the continuous variables between the groups. The repeated measures of analysis of variance (ANOVA) were used to test the effect of time and time X group interaction in the change in continuous variables. The Paired t-test was used to compare the changes in the continuous variables within the group from 0 weeks to subsequent periods. The p-value<0.05 was considered significant. All the analysis was carried out on the SPSS 16.0 version.

Results

Table 1 shows age and gender distributions for Group 1 (n=50) and Group 2 (n=47) and assesses statistical significance using p-values. In Group 1, 7 persons (14%) are aged 40-50, 20 (40%) are 51-60, and 23 (46%) are beyond 60, with a mean age of 57.26±7.17 years. For Group 2, the age categories are 14.9%, 36.2%, and 48.9%, with a mean age of 56.90±7.14 years. Age distribution has no significant difference (p=0.9). Group 1 includes 56% men and 44% females, whereas Group 2 has 46.8% males and 53.2% females, with a non-significant p-value of 0.31. Age and gender distribution are not significantly different across groups.

Figure 1 urine albumin to creatinine ratios are compared throughout time. There was no significant (p>0.05) change in urine albumin to creatinine ratio between groups at any time. The repeated measures of analysis of variance indicated no significant influence of time (F=2.21, p=0.31) or time X group interaction (F=1.13, p=0.45) on urine albumin to creatinine ratio. Sodium levels throughout time. At 0 weeks, sodium levels were similar (p>0.05). At 4 weeks, the groups had substantially different sodium levels (p=0.001). The repeated measures of analysis of variance indicated no significant influence of time (F=1.11, p=0.55) or time X group interaction (F=2.10, p=0.33) on sodium change. At 0 weeks, potassium levels were similar (p>0.05). Potassium levels differed considerably

(p<0.05) between groups at 4 weeks and later periods. The repeated measures of analysis of variance indicated that time (F=112.12, p=0.0001) and time X group interaction (F=32.14, p=0.0001) affected potassium change.

Table 1: Distribution of age and gender between the groups

Age in years	Group 1(n=50)		Group 2(n=47)		p-value1
	No.	%	No.	%	
40-50	7	14	7	14.9	0.9
51-60	20	40	17	36.2	
>60	23	46	23	48.9	
Mean±SD	57.26±7.17		56.90±7.14		
Gender	**Group 1 (n=50)**		**Group 2 (n=47)**		**p-value1**
	No.	**%**	**No.**	**%**	
Male	28	56	22	46.8	0.31
Female	22	44	25	53.2	

A= Comparison of urinary albumin to creatinine ratio, B= Comparison of sodium, C= Comparison of potassium

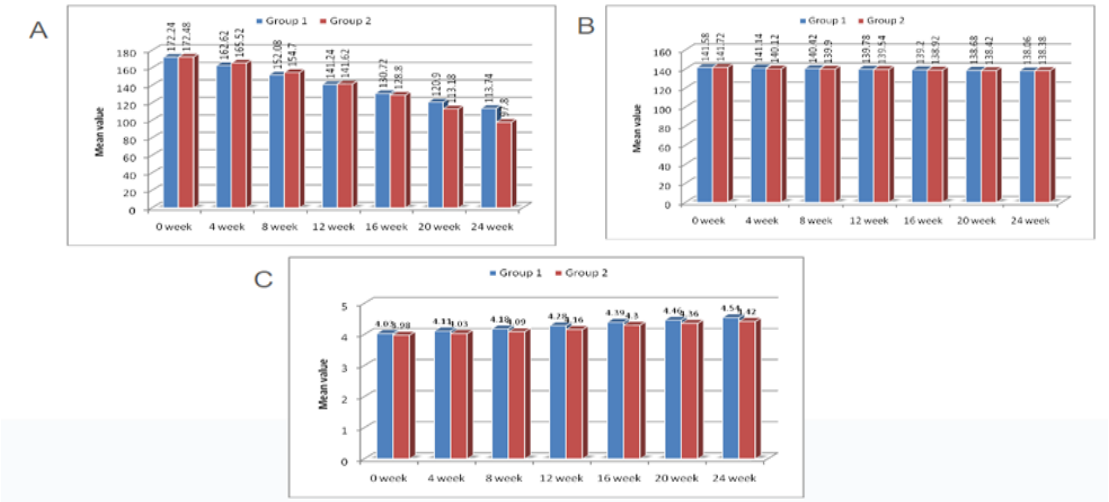

Figure 1: Comparison of urinary albumin to creatinine ratio, sodium and potassium between the groups across the periods

Table 3 shows the mean SBP change in weeks for Group 1 (n=50) and Group 2 (n=47). Asterisks (*) indicate extremely significant findings (p<0.0001) for each time period; p-values show statistical significance. Note that both groups show significant SBP decreases from 0 weeks to succeeding periods, indicating a persistent and considerable improvement. Specifically, Group 1's mean SBP change from 0 to 4 weeks is 8.16±4.67, whereas Group 2's is 3.52±2.19, with significant p-values. This trend persists throughout the trial, demonstrating a considerable drop in SBP in both groups.

Table 2: Comparison of mean change in SBP within the groups from 0 weeks to subsequent periods

Time periods	Group 1 (n=50)		Group 2 (n=47)	
	Mean Change	p-value[1]	Mean Change	p-value[1]
0 week-4 week	8.16±4.67	0.0001*	3.52±2.19	0.0001*
0 week-8 week	11.48±5.25	0.0001*	5.36±2.75	0.0001*
0week-12week	12.26±4.76	0.0001*	6.84±3.08	0.0001*
0week-16week	12.40±4.91	0.0001*	9.12±4.41	0.0001*
0week-20week	14.12±4.01	0.0001*	9.96±4.54	0.0001*
0week-24week	14.40±4.96	0.0001*	13.68±5.25	0.0001*

Table 3 shows the mean DBP change in weeks for Group 1 (n=50) and Group 2 (n=47). The statistical significance of changes is indicated by p-values, with asterisks for very significant findings (p<0.0001). In contrast to SBP, Group 1 and Group 2 have different DBP patterns. Both groups show considerable variations in DBP over time, with Group 1 exhibiting a mean change of 0.24±2.03 to 6.68±4.07 and Group 2 ranging from 3.24±3.10 to 6.32±2.47. DBP changes significantly in both groups during the research period, highlighting the

effect of the intervention or therapy on diastolic blood pressure.

Table 3: Comparison of mean change in DBP within the groups from 0 weeks to subsequent periods

Time periods	Group 1 (n=50)		Group 2 (n=47)	
	Mean Change	p-value[1]	Mean Change	p-value[1]
0 week-4 week	0.24±2.03	0.40	3.24±3.10	0.0001*
0 week-8 week	3.68±5.03	0.0001*	3.72±2.17	0.0001*
0week-12week	4.64±4.66	0.0001*	3.72±2.49	0.0001*
0week-16week	4.80±4.84	0.0001*	4.36±2.12	0.0001*
0week-20week	6.36±3.97	0.0001*	5.04±2.97	0.0001*
0week-24week	6.68±4.07	0.0001*	6.32±2.47	0.0001*

Figure 2 compares the mean change in urine albumin to creatinine ratio (UACR) across weeks in Group 1 (n=50) and Group 2 (n=47). There was significant change in UACR from 0 weeek to subsequent time periods(p=0.0001). Mean change was greater in group 2.

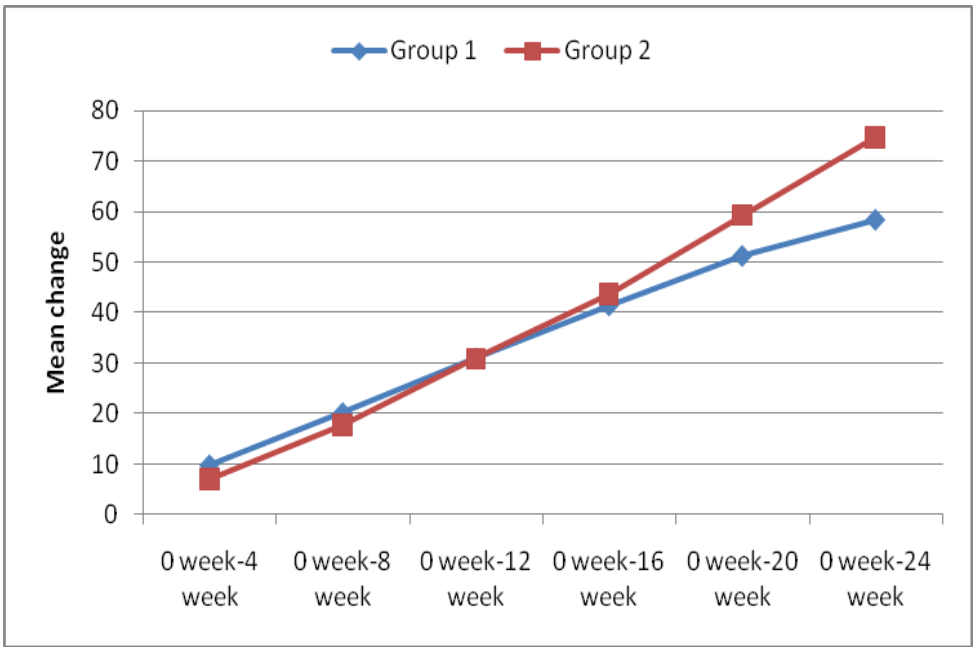

Figure 2: Comparison of mean change in urinary albumin to creatinine ratio within the groups from 0 week to subsequent periods

Figure 3 shows the mean potassium change in Group 1 (n=50) and Group 2 (n=47) across weeks. Significant changes are shown by p-values, with asterisks (*) indicating extremely significant findings (p<0.0001). Mean potassium levels grow consistently and statistically in both groups from week 0 to the following periods. For example, at weeks 0-4, Group 1 had a mean change of 0.08±0.07 while Group 2 had 0.04±0.06, both very significant. This pattern repeats at each interval, indicating a significant potassium increase in both groups throughout the trial. The data show that both groups' interventions or treatments may affect potassium homeostasis.

Discussion

Substantial evidence points toward the promising efficacy of spironolactone in mitigating microalbuminuria amid diabetic nephropathy cases. Robust investigations showcasing the integration of spironolactone alongside standard antidiabetic, renoprotective, or antihypertensive regimens underscore its profound impact in curbing albuminuria levels. These studies distinctly illuminate the ability of spironolactone to orchestrate a notable 30-40% reduction in albuminuria, delineating its pivotal role in ameliorating renal stress markers within diabetic nephropathy cohorts. Notably, the augmentative effects witnessed when spironolactone intertwines with other medications underscore its potential to confer supplementary renoprotective benefits, hinting at a multifaceted approach toward addressing the complexities of diabetic nephropathy [28-31].

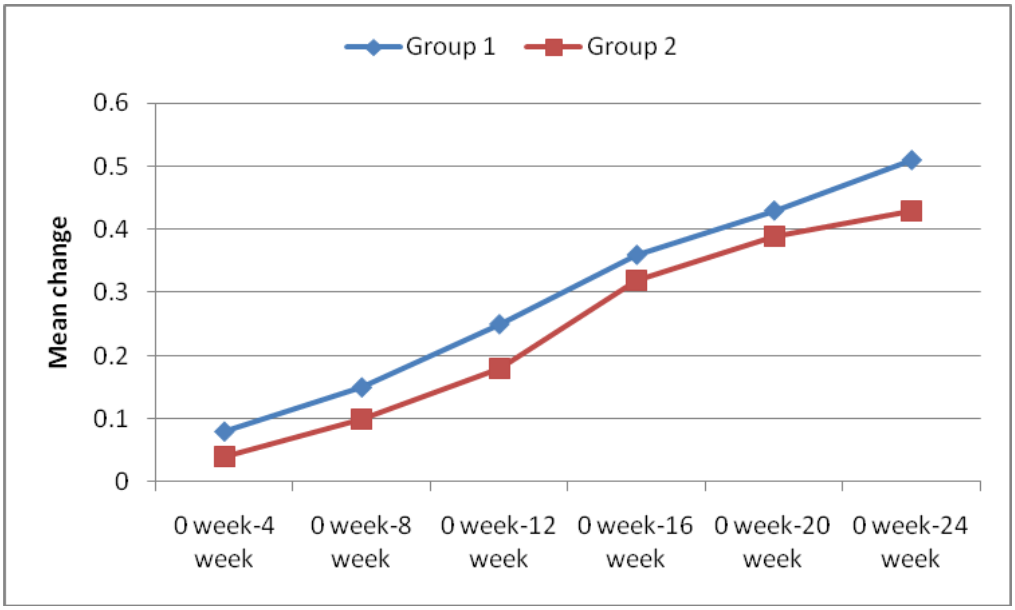

Figure 3: Comparison of mean change in potassium within the groups from 0 weeks to subsequent periods

In a prospective trial by Kato et al. (2015) involving 52 patients with diabetic nephropathy and elevated albuminuria despite ongoing treatment with renin-angiotensin system inhibitors, spironolactone addition at 25 mg daily showcased significant findings over an 8-week period. The study revealed a notable 33% reduction in albuminuria levels (95% CI: 22-54; P = 0.0002). The spironolactone group exhibited trends towards decreased blood pressure, and the estimated glomerular filtration rate experienced a significant decline compared to controls. Even after adjustments for blood pressure and glomerular filtration rate, spironolactone exhibited a substantial effect in reducing albuminuria (coefficient ± SE; 514.4 ± 137.6 mg/gCr, P < 0.0005) in a linear mixed model. This study highlights spironolactone's potential in mitigating albuminuria in diabetic nephropathy [28].

In a cross-over study involving 21 type 2 diabetic patients with nephropathy, Rossing et al. (2005) investigated spironolactone's safety and immediate impact when added to conventional antihypertensive therapy for 8 weeks. During the placebo phase, albuminuria averaged 1,566 mg/24 hours, 24-hour ambulatory blood pressure (ABP) was 138/71 mmHg, and glomerular filtration rate (GFR) was 74 ml/min per 1.73 m². Spironolactone demonstrated significant reductions in albuminuria by 33% (95% CI 25-41; P < 0.001) and fractional albumin clearance by 40% (P < 0.001), along with a decrease in 24-hour ABP by 6 mmHg for systolic and 4 mmHg for diastolic pressures (P < 0.001). Changes in albuminuria did not align with alterations in 24-hour ABP. Despite a minor reversible decline in GFR by 3 ml/min per 1.73 m² (P = 0.08), only one participant was excluded due to hyperkalemia, indicating well-tolerated treatment. This study highlights spironolactone's potential in improving renal and cardiovascular health in type 2 diabetic nephropathy patients [31].

Spironolactone's effectiveness in reducing microalbuminuria in diabetic nephropathy is underscored by its multifaceted actions. By antagonising aldosterone, it alleviates fluid retention and lessens the kidney's workload, subsequently reducing microalbuminuria. Simultaneously, its anti-inflammatory properties curtail chronic inflammation, diminishing renal damage and albuminuria[20,23]. Furthermore, spironolactone's antioxidative prowess shields the kidneys against oxidative stress, an active player in diabetic nephropathy progression. Additionally, its direct renoprotective impact maintains renal function, curbing fibrosis, and glomerulosclerosis, all contributing to reduced microalbuminuria. These collective mechanisms consolidate spironolactone's role in ameliorating albuminuria in diabetic nephropathy, heralding promising prospects for renal health in affected individuals [25,31].

Several investigations delve into spironolactone's renoprotective impacts and its role in enhancing kidney function. A 2011 study by Ting et al. emphasised blood pressure reduction and inhibition of the renin-angiotensin-aldosterone system (RAAS) as pivotal in preserving renal function among chronic kidney disease (CKD) patients. It underscored that both angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), including spironolactone, mitigate proteinuria and sustain renal function. Highlighting the dose-dependent therapeutic responses, the study recommended administering these medications at maximal

tolerable dosages. In a separate animal model-based investigation published in 2012 by Lian et al., the effects of eplerenone, akin to spironolactone, on diabetic renal disease progression were explored. The findings revealed eplerenone's capacity to diminish glomerular volume, tissue transforming growth factor beta 1 (TGFβ1) levels, and glomerular collagen IV staining, signifying its potential renoprotective impact in diabetic renal disease [32,33].

A comprehensive analysis, a systematic review, and meta-analysis by Yasmin et al. (2023) scrutinized Spironolactone therapy versus standard treatments in diabetic nephropathy across seven randomised controlled trials encompassing 15,462 participants. The findings unveiled favourable outcomes tied to Spironolactone, indicating reduced risks of cardiovascular mortality, heart failure, and a decline in estimated glomerular filtration rate. However, an elevated incidence of moderate hyperkalemia was associated with its use. While suggesting promise as an alternative treatment for diabetic nephropathy, the study highlighted the imperative need for further trials to rigorously evaluate its safety and efficacy compared to existing treatments [34].

Substantial evidence underscores the clinical promise of spironolactone in curbing microalbuminuria among diabetic nephropathy cases. This mineralocorticoid receptor antagonist (MRA) has exhibited the capacity to reduce urinary albumin or protein excretion in patients with proteinuric chronic kidney disease (CKD), including those with diabetic nephropathy, when added to single renin-angiotensin system (RAS) blockade. Yet, it's crucial to acknowledge the scarcity of studies that scrutinise spironolactone's impact on critical renal outcomes, like the progression of CKD. Additionally, the use of spironolactone may pose limitations due to the heightened risk of hyperkalemia, particularly among CKD patients. The necessity for further exploration persists to unveil the enduring advantages and hazards linked to spironolactone therapy in the realm of diabetic nephropathy [35].

Research indicates promising prospects for Spironolactone, an antagonist of aldosterone receptors, in managing microalbuminuria among normotensive patients with diabetic nephropathy. Multiple investigations have demonstrated that the incorporation of Spironolactone into conventional renoprotective therapy leads to a reduction in urinary albumin excretion, presenting additional renoprotective effects that are not contingent on blood pressure regulation. However, a comprehensive understanding of the enduring impacts and advantages of Spironolactone in this specific patient cohort necessitates further investigation [20,24,28].

Conclusion

This study concluded that spironolactone and telmisartan both have anti-albuminuric effects without systemic hemodynamic effects or hyperkalemia. Especially when hyperkalemia risk is low, spironolactone is a potential choice for diabetic and early nephropathy patients. At different time points, the groups had significant variations in SBP, DBP, salt, potassium, urine albumin to creatinine ratio, and HbA1c. Over 24 weeks, spironolactone and telmisartan affect blood pressure, electrolytes, and metabolic parameters differently, therefore the research recommends careful evaluation.

While the study on Spironolactone therapy in normotensive patients with Diabetic Nephropathy provides valuable insights, notable research gaps and future prospects emerge. The study's limited follow-up of 24 weeks suggests a research gap in understanding the long-term effects of Spironolactone on microalbuminuria reduction. Additionally, the exclusive focus on normotensive patients calls for further exploration of its efficacy across diverse hypertensive profiles. Future research should include comparative analyses with a broader spectrum of standard treatments for Diabetic Nephropathy to guide clinicians. Mechanistic insights into Spironolactone's impact on oxidative stress and inflammation warrant exploration for a more comprehensive understanding. Embracing personalized medicine and assessing patient-reported outcomes can enhance the study's clinical relevance. In conclusion, extending follow-up durations, diversifying patient profiles, exploring mechanistic insights, and considering personalized approaches will contribute to advancing the understanding and applicability of Spironolactone therapy in Diabetic Nephropathy.

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