



Role of Calcium Channel Blockers in Diabetic Nephropathy

(1) **Dr. Omer Farooq Sheikh, MBBS, MRCGP, DFSRH**
Family Medicine, Manchester, United Kingdom
Email: oommer_f@hotmail.com

(2) **Dr. Mir Saad Hussain, MBBS, MD, MRCP, MRCGP, PGDDM**
Family Medicine, PHCC, Doha, Qatar
Email: mirsaadhussain@googlemail.com
ORCID iD: <https://orcid.org/0000-0003-2586-3390>

Corresponding Author:

Dr. Omer Farooq Sheikh, MBBS, MRCGP,
Family Medicine, Manchester, United Kingdom
Email: oommer_f@hotmail.com

Abstract

Diabetes mellitus is a chronic condition worldwide. The prevalence of diabetes has increased significantly worldwide over last few decades. Diabetic nephropathy is a common microvascular complication and has long term effects on cardiovascular disease and mortality wise. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are commonly used medicines in the management of diabetic nephropathy and proteinuria. UK NICE guidance, UK SIGN 116 guidance and ADA guidance, all have made similar recommendations. This article has looked more specifically at the evidence of using antihypertensive group calcium channel blockers in the management of diabetic nephropathy and proteinuria. The literature review has explored around the evidence behind using non-dihydropyridine group like Verapamil and Diltiazem as well as the dihydropyridine group like amlodipine, felodipine, nicardipine in management of proteinuria and diabetic nephropathy.

Key Words: Diabetes Mellitus, Diabetic Nephropathy, Proteinuria, Calcium Channel Blockers



www.mecsj.com/

Multi-Knowledge Electronic Comprehensive Journal For Education
And Science Publications (MECSJ)

Issue (37),2020

ISSN: 2617-9563

نبذة مختصرة

مرض السكري هو حالة مزمنة في جميع أنحاء العالم. زاد انتشار مرض السكري بشكل ملحوظ في جميع أنحاء العالم خلال العقود القليلة الماضية. يعد اعتلال الكلية السكري من المضاعفات الشائعة للأوعية الدموية الدقيقة وله آثار طويلة المدى على أمراض القلب والأوعية الدموية والوفيات. مثبطات الإنزيم المحول للأنجيوتنسين وحاصرات مستقبلات الأنجيوتنسين هي أدوية شائعة الاستخدام في علاج اعتلال الكلية السكري والبيبة البروتينية. تقدم إرشادات UK NICE وتوجيه UK SIGN 116 وتوجيه ADA جميعها توصيات مماثلة. نظرت هذه المقالة بشكل أكثر تحديداً في الدليل على استخدام حاصرات قنوات الكالسيوم لمجموعة خافضة للضغط في علاج اعتلال الكلية السكري والبيبة البروتينية. استكشفت مراجعة الأدبيات حول الأدلة الكامنة وراء استخدام مجموعة غير ديهيدروبيريدين مثل فيراباميل ودلتياريم بالإضافة إلى مجموعة ديهيدروبيريدين مثل أملوديبين وفيلوديبين ونيكارديبين في إدارة البيبة البروتينية واعتلال الكلية السكري.

الكلمات المفتاحية: داء السكري ، اعتلال الكلية السكري ، بيلة بروتينية ، حاصرات قنوات الكالسيوم

Introduction

Diabetes mellitus (DM) is a chronic metabolic condition characterized by elevated blood glucose levels. Around 422 million people are affected with diabetes worldwide with a larger proportion living in low and middle income countries. The prevalence of DM has increased significantly worldwide over the last two decades (*Diabetes*, n.d.). As per National Diabetes Statistics report published in 2020 by Centre for Disease Control and Prevention (CDC), the crude estimates for prevalence of DM among US population in 2018 was 34.2 million people for all age groups or 10.5% of the US population. Around 7.3 million adults aged ≥ 18 years met the laboratory criteria for diabetes but were not aware of having diabetes i.e undiagnosed cases (*National Diabetes Statistics Report 2020. Estimates of Diabetes and its Burden in the United States.*, 2020). In UK, there are 4.7 million people diagnosed with diabetes and someone is diagnosed with DM every two minutes in UK. In 1996, there were 1.4 million people diagnosed with diabetes and in 2019 there were 3.8 million cases in UK (*1362B_Facts and Stats Update Jan 2019_LOW RES_EXTERNAL.Pdf*, n.d.).



Diabetic nephropathy (DN) is a common and a very serious complication related to both Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM). DN is also known as diabetic kidney disease (DKD) and around 25% to 40% people with DM develop DN (*Diabetic Nephropathy - Symptoms and Causes*, n.d.). DN is characterized by leakage of protein in urine (albuminuria), pathological changes within glomeruli and loss of glomerular filtration rate (GFR). Not all diabetics will develop DN and those with DN can have a variable rate of disease progression. Among main modifiable risk factors affecting the progression of DN are glycaemic control, hypertension, smoking and dyslipidaemia (Lim, 2014). DN is a leading cause of ESRD requiring renal replacement therapy (RRT) with an increased risk of cardiovascular disease and mortality and its management involves addressing the known risk factors including hypertension, hyperglycemia, dyslipidaemia and smoking. The role of renin-angiotensin aldosterone system (RAAS) blockers is widely known in prevention as well as in management of DN (Gross et al., 2005).

RAAS dysregulation plays an important role in pathogenesis and progression of DKD and RAAS blockers play a vital role in prevention as well as treatment of DKD. These include angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) (Lozano-Maneiro & Puente-García, 2015). Many studies have looked at the actions of ACE-i or ARBs in management of albuminuria and DN and have proven their efficacy and beneficial actions for the same (*Diabetic Nephropathy Treatment & Management*, 2020) (Lewis et al., 1993)(Lewis et al., 2001)(Haller et al., 2011). Similarly, UK NICE guidance (*1 Recommendations | Chronic Kidney Disease in Adults*, n.d.) , UK SIGN 116 guidance (Scottish Intercollegiate Guidelines Network, 2010) and American Diabetes Association (ADA) (Association, 2004) also recommend using ACEi or ARBs as treatment of choice in management of DN and albuminuria.

This literature review looks at other possible treatment options in management of DN and albuminuria, more specifically at calcium channel blocker medication group.

Literature Review

Calcium Channel Blockers

Calcium channel blockers (CCBs) are medications commonly used in the management of hypertension, angina, arrhythmia and Raynaud's phenomenon. Calcium is required to contract the muscular linings of blood vessels and contract heart muscle. CCBs block the entrance of calcium in heart and blood vessels causing relaxation of blood vessels and heart muscle, helping in hypertension, angina, Raynaud's phenomenon and arrhythmias. CCB are generally divided into two subtypes the dihydropyridines (like amlodipine, felodipine, nifedipine) and non-dihydropyridines which include Verapamil and Diltiazem. The first groups is more vascular selective and the second groups is more cardio selective in their actions (*Drug Cabinet*, n.d.).

Role of Non-Dihydropyridine CCBs in Diabetic Nephropathy

Non-Dihydropyridine CCB sub-group includes Verapamil and Diltiazem. Many studies have looked at the actions of non-dihydropyridine group CCBs in managing proteinuria in patients with diabetic nephropathy and have proven to be as effective as ACEi or ARBs in reducing proteinuria. According to a prospective study conducted by Bakris *et al* (1992) in T2DM with DN compared the actions of Verapamil with lisinopril both as single therapy and in combination with each other over one year period. The combination of Verapamil with Lisinopril was superior in reducing albuminuria with a 33% increase in serum albumin levels, lower fall in GFR rate and lower side effects (dizziness with lisinopril and constipation with verapamil) as compared to either agent alone (Bakris *et al.*, 1992).

A prospective study conducted by Pérez-Maraver *et al* looked at the effects of Diltiazem in T2DM patients with hypertension and persistent albuminuria, despite being treated with captopril. After one year of randomisation and treatment, the group treated alone with captopril (n=20) had higher albuminuria than the baseline



i.e 166mg/24 hrs vs 116mg/24hrs. The second group treated with combination of Captopril and Diltiazem (n=13) there was significant improvement in albuminuria i.e 74mg/24hrs vs 116mg/24hrs and this effect was independent of blood pressure or metabolic control. The results showed that addition of Diltiazem to an ACEI slowed the progression of microalbuminuria to macroalbuminuria and stabilised proteinuria. Five patients in captopril group and one patient in combination group progressed to macroalbuminuria and one patient in combination group had albuminuria resolved back to normal level i.e (<30mg/24hrs) (Pérez-Maraver et al., 2005).

Another prospective study enrolled 60 normotensive patients with T2DM and albuminuria, compared Trandolapril 2mg alone with a combination of Trandolapril 2mg and Verapamil 180mg over a period of six months. 24-hour urinary protein excretion and creatinine clearance were measured at the beginning and end of study with a monthly patient evaluation. Both groups showed a statistically significant ($p<0.005$) decrease in mean proteinuria from baseline with a greater reduction in proteinuria in combination group as compared to Trandolapril alone group. Hence, the combination of Trandolapril with Verapamil was more effective in reducing proteinuria in normotensive T2DM patients than Trandolapril alone and was independent of blood pressure reduction (Rubio-Guerra et al., 2004).

A meta-analysis looked at seven randomised controlled trials (RCTs) involving 430 participants, compared ACEi with CCBs and showed that ACEi were not superior to CCBs in reducing systolic blood pressure, diastolic blood pressure, proteinuria and GFR in patients with diabetic nephropathy and CCBs and ACEi were equally effective in reducing the progression of diabetic nephropathy. Also, both medication groups had similar incidence of adverse events (Zhang et al., 2019).

Role of Dihydropyridine CCBs in Diabetic Nephropathy

Dihydropyridine CCB sub-group includes medications like Amlodipine, Felodipine, Nicardipine, Nimodipine and many more.



Many studies have shown variable results in management of proteinuria for this sub-group. A prospective randomised double-blind clinical trial compared the effects of Irbesartan 300mg, Amlodipine 10mg and placebo in 1715 hypertensive patients with T2DM and nephropathy. Irbesartan was more effective in reducing diabetic nephropathy progression and this effect was independent of blood pressure control. The renal outcomes between amlodipine group and placebo group didn't differ significantly but with more worse renal outcomes in amlodipine group (Lewis et al., 2001). Some CCBs like Nicardipine increase efferent arteriolar dilation thus decrease glomerular pressure and proteinuria. Other CCBs like Nifedipine dilate afferent and efferent arterioles both, thus causing increasing proteinuria. Studies in diabetic nephropathy patients have shown that individual CCBs vary in their individual actions on proteinuria and this variation is related to their different effects on intrarenal activity and their sites of action (Km, 1991). Similarly, other studies have shown mixed results, from fall in albuminuria to no effect to increased albuminuria with this sub-group of CCBs (Bakris et al., 1992) (Atkins et al., 2005) (Böhlen et al., 1994).

Discussion

Diabetic nephropathy is the most important microvascular complication of diabetes mellitus and affects around 25% to 40% patients with diabetes and is a leading cause of chronic kidney disease (CKD) and ESRD globally. It usually presents as proteinuria / albuminuria and is a strong predictor of mortality in patients with DM. The main aim is to prevent or delay the progression of DN. Close regulation of blood glucose, blood pressure, dyslipidaemia and treating proteinuria are the mainstay of management of DN (Wang et al., 2019).

RAAS blockers, preferably ACEi and ARBs are the first choice of medications used in management of proteinuria and diabetic nephropathy worldwide. As per SIGN 116 UK guidance, both ACEi or ARBS have reno-protective and cardioprotective actions and their use is recommended in diabetic patients with normal albuminuria or



microalbuminuria in both with T1DM or T2DM (*Scottish Intercollegiate Guidelines Network - 2010 - Management of Diabetes a National Clinical Guidel.Pdf*, n.d.). Similarly, NICE UK guidance and American Diabetes Association have similar recommendations (*1 Recommendations | Chronic Kidney Disease in Adults*, n.d.) (Association, 2004).

Calcium channel blockers are commonly used medicines in management of hypertension, angina, arrhythmias and Raynaud's phenomenon. Among CCBs the non-dihydropyridine subgroup which includes Verapamil and Diltiazem are more cardio selective and have shown to be beneficial and as effective as ACEi in terms of their actions and effects on diabetic nephropathy and proteinuria. This sub-group has shown to decrease proteinuria significantly when used in combination with an ACEi and improve renal outcomes in patients with diabetic nephropathy (Bakris et al., 1992) (Pérez-Maraver et al., 2005) (Rubio-Guerra et al., 2004) (Zhang et al., 2019).

On the contrary, the dihydropyridine sub-group of CCBs have shown variable results in terms of their effects on proteinuria and diabetic nephropathy. Some can improve albuminuria with some having no effect to some causing increased albuminuria. This variation is related to their different effects on intrarenal activity and their sites of action within glomeruli.

Conclusion

Diabetic nephropathy poses a great risk in terms of cardiovascular disease and mortality wise. RAAS blockers especially ACEi and ARBs are commonly used medicines and are recommended worldwide as treatment of choice. This literature review has looked at role of antihypertensive medicine calcium channel blockers in management of proteinuria and diabetic nephropathy. The non-dihydropyridine group containing Verapamil and Diltiazem have shown great benefits when used in combination with an ACEi in the management of diabetic nephropathy and proteinuria.



This group has shown a delay in nephropathy and proteinuria. On the other hand dihydropyridine sub-group has shown variable results are not an effective choice in management of diabetic nephropathy and proteinuria either alone or in combination with RAAS blockers. We need to explore further over the use of Verapamil and Diltiazem in combination with RAAS blockers with their long term benefits and side effects in the management of diabetic nephropathy.

References

- 1- *Recommendations | Chronic kidney disease in adults: Assessment and management | Guidance | NICE.* (n.d.). NICE. Retrieved 28 February 2020, from <https://www.nice.org.uk/guidance/cg182/chapter/1-Recommendations#frequency-of-monitoring-2>
- 2- *1362B_Facts and stats Update Jan 2019_LOW RES_EXTERNAL.pdf.* (n.d.). Retrieved 13 October 2020, from https://www.diabetes.org.uk/resources-s3/2019-02/1362B_Facts%20and%20stats%20Update%20Jan%202019_LOW%20RES_EXTERNAL.pdf
- 3- Association, A. D. (2004). Nephropathy in Diabetes. *Diabetes Care*, 27(suppl 1), s79–s83. <https://doi.org/10.2337/diacare.27.2007.S79>
- 4- Atkins, R. C., Briganti, E. M., Lewis, J. B., Hunsicker, L. G., Braden, G., Champion de Crespigny, P. J., DeFerrari, G., Drury, P., Locatelli, F., Wiegmann, T. B., & Lewis, E. J. (2005). Proteinuria reduction and progression to renal failure in patients with type 2 diabetes mellitus and overt nephropathy. *American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation*, 45(2), 281–287. <https://doi.org/10.1053/j.ajkd.2004.10.019>
- 5- Bakris, G. L., Barnhill, B. W., & Sadler, R. (1992). Treatment of arterial hypertension in diabetic humans: Importance of therapeutic selection. *Kidney International*, 41(4), 912–919. <https://doi.org/10.1038/ki.1992.139>
- 6- Böhlen, L., de Courten, M., & Weidmann, P. (1994). Comparative study of the effect of ACE-inhibitors and other antihypertensive agents on proteinuria in diabetic patients. *American Journal of Hypertension*, 7(9 Pt 2), 84S-92S. <https://doi.org/10.1093/ajh/7.9.84s>



www.mecsj.com/

Multi-Knowledge Electronic Comprehensive Journal For Education
And Science Publications (MECSJ)

Issue (37),2020

ISSN: 2617-9563

- 7- *Diabetes*. (n.d.). Retrieved 13 October 2020, from <https://www.who.int/westernpacific/health-topics/diabetes>
- 8- *Diabetic Nephropathy Treatment & Management: Approach Considerations, Glycemic Control, Management of Hypertension*. (2020). <https://emedicine.medscape.com/article/238946-treatment#d10>
- 9- *Diabetic nephropathy—Symptoms and causes*. (n.d.). Mayo Clinic. Retrieved 13 October 2020, from <https://www.mayoclinic.org/diseases-conditions/diabetic-nephropathy/symptoms-causes/syc-20354556>
- 10- *Drug cabinet: Calcium channel blockers*. (n.d.). Retrieved 14 October 2020, from <https://www.bhf.org.uk/informationsupport/heart-matters-magazine/medical/drug-cabinet/calcium-channel-blockers>
- 11- Gross, J. L., Azevedo, M. J. de, Silveiro, S. P., Canani, L. H., Caramori, M. L., & Zelmanovitz, T. (2005). Diabetic Nephropathy: Diagnosis, Prevention, and Treatment. *Diabetes Care*, 28(1), 164–176. <https://doi.org/10.2337/diacare.28.1.164>
- 12- Haller, H., Ito, S., Izzo, J. L., Januszewicz, A., Katayama, S., Menne, J., Mimran, A., Rabelink, T. J., Ritz, E., Ruilope, L. M., Rump, L. C., & Viberti, G. (2011). Olmesartan for the Delay or Prevention of Microalbuminuria in Type 2 Diabetes. *New England Journal of Medicine*, 364(10), 907–917. <https://doi.org/10.1056/NEJMoa1007994>
- 13- Km, M. (1991, November). *Calcium-channel blockers for treatment of diabetic nephropathy*. *Clinical Pharmacy; Clin Pharm*. <https://pubmed.ncbi.nlm.nih.gov/1794222/>
- 14- Lewis, E. J., Hunsicker, L. G., Bain, R. P., & Rohde, R. D. (1993). The Effect of Angiotensin-Converting-Enzyme Inhibition on Diabetic Nephropathy. *New England Journal of Medicine*, 329(20), 1456–1462. <https://doi.org/10.1056/NEJM19931113292004>
- 15- Lewis, E. J., Hunsicker, L. G., Clarke, W. R., Berl, T., Pohl, M. A., Lewis, J. B., Ritz, E., Atkins, R. C., Rohde, R., & Raz, I. (2001). Renoprotective Effect of the Angiotensin-Receptor Antagonist Irbesartan



- in Patients with Nephropathy Due to Type 2 Diabetes. *New England Journal of Medicine*, 345(12), 851–860. <https://doi.org/10.1056/NEJMoa011303>
- 16- Lim, A. K. (2014). Diabetic nephropathy – complications and treatment. *International Journal of Nephrology and Renovascular Disease*, 7, 361–381. <https://doi.org/10.2147/IJNRD.S40172>
- 17- Lozano-Maneiro, L., & Puente-García, A. (2015). Renin-Angiotensin-Aldosterone System Blockade in Diabetic Nephropathy. Present Evidences. *Journal of Clinical Medicine*, 4(11), 1908. <https://doi.org/10.3390/jcm4111908>
- 18- *National Diabetes Statistics Report 2020. Estimates of diabetes and its burden in the United States.* (2020). 32.
- 19- Pérez-Maraver, M., Carrera, M. J., Micaló, T., Sahun, M., Vinzia, C., Soler, J., & Montanya, E. (2005). Renoprotective effect of diltiazem in hypertensive type 2 diabetic patients with persistent microalbuminuria despite ACE inhibitor treatment. *Diabetes Research and Clinical Practice*, 70(1), 13–19. <https://doi.org/10.1016/j.diabres.2005.02.019>
- 20- Rubio-Guerra, A. F., Arceo-Navarro, A., Vargas-Ayala, G., Rodriguez-Lopez, L., Lozano-Nuevo, J. J., & Gomez-Harper, C. T. (2004). The Effect of Trandolapril and Its Fixed-Dose Combination With Verapamil on Proteinuria in Normotensive Adults With Type 2 Diabetes. *Diabetes Care*, 27(7), 1688–1691. <https://doi.org/10.2337/diacare.27.7.1688>
- 21- Scottish Intercollegiate Guidelines Network. (2010). *Management of diabetes: A national clinical guideline*. Scottish Intercollegiate Guidelines Network.
- 22- *Scottish Intercollegiate Guidelines Network—2010—Management of diabetes a national clinical guidel.pdf.* (n.d.). Retrieved 28 February 2020, from <https://www.sign.ac.uk/assets/sign116.pdf>
- 23- Wang, G., Ouyang, J., Li, S., Wang, H., Lian, B., Liu, Z., & Xie, L. (2019). The analysis of risk factors for diabetic nephropathy progression and the construction of a prognostic database for chronic kidney diseases. *Journal of Translational Medicine*, 17(1), 264. <https://doi.org/10.1186/s12967-019-2016-y>



www.mecsj.com/

Multi-Knowledge Electronic Comprehensive Journal For Education
And Science Publications (MECSJ)

Issue (37),2020

ISSN: 2617-9563

- 24- Zhang, Z., Chen, C., Lv, S., Zhu, Y., & Fang, T. (2019). Comparing the Efficacy of Angiotensin Converting Enzyme Inhibitors with Calcium Channel Blockers on the Treatment of Diabetic Nephropathy: A Meta-Analysis. *Iranian Journal of Public Health*, 48(2), 189.