Trakia Journal of Sciences, Vol. 23, Suppl. 1, pp 22-27, 2025
Available online at:
http://www.uni-sz.bg
ISSN 1313-3551 (online) **doi:10.15547/tjs.2025.s.01.004**

TREATMENT OF TYPE 2 DIABETES MELLITUS WITH GLP-1 RECEPTOR AGONISTS, CHRONIC KIDNEY DISEASE AND INFLUENCE ON CARDIOVASCULAR RISK

N. Kostadinov[1]*, T. Totomirova[2]

[1]Medical Faculty, University Prof. Dr. Asen Zlatarov-Burgas, Bulgaria, General hospital for Active Treatment "Heart and Brain"- Burgas, Bulgaria
[2]Clinic of Endocrinology and Metabolic Diseases, MMA-Sofia, Bulgaria

ABSTRACT
Type 2 diabetes is a global problem with an increasing incidence. Globally, more than one in 10 adults are now living with diabetes. Late complications of diabetes mellitus represent a serious problem for patients. Diabetes mellitus is the most common cause of the development of chronic kidney disease (CKD).
Early identification and management of CKD is of utmost importance to minimize the risk of severe cardiovascular events and premature loss of life.
There are advances in available glucose-lowering agents for the treatment of type 2 diabetes that not only modify the disease itself, but also have important benefits in terms of associated cardiovascular risk factors.
The aim of the present study was to investigate the degree of influence of renal function-glomerular filtration and microalbuminuria, as factors increasing the incidence of cardiovascular risk, by using GLP-1 receptor agonists, in the treatment of type 2 diabetes mellitus.
In a total of 66 patients (100%) treated with GLP-1 receptor agonist - 26 men (39.4%) and 40 women (60.6%) serum creatinine was examined, GFR was calculated using the CKD-EPI (Equations for Glomerular Filtration RATE) method and microalbuminuria in the first morning urine. The difference between the mean values of glomerular filtration at the beginning of the study and after 6 months, which amounted to 5,780 ml/min. ($0.043<\alpha=0.05$) ($*p<0.05$) is statistically significant. The difference between the mean values of microalbumin MALB at the beginning of the study and after 6 months amounted to -1.015 mg/l, with no statistical dependence ($p\geq0.05$).
Given the additional protection they provide, GLP-1 receptor agonists should be considered as the mainstay in the treatment of DM type 2. The therapy of patients with DM2 should be complex and with a view beyond the glycemic effect, giving the opportunity to stop the development of chronic kidney disease and thus reduce the cardiovascular risk.

Keywords: diabetes mellitus, glomerular filtration, microalbuminuria, GLP-1 receptor agonists, cardiovascular risk

INTRODUCTION

The aim of the present study was to investigate the degree of influence of renal function-glomerular filtration and microalbuminuria, as factors increasing the incidence of cardiovascular risk, by using GLP-1 receptor agonists, in the treatment of type 2 diabetes mellitus.

Type 2 diabetes is a global pandemic and a known independent risk factor for atherosclerosis and subsequent decline in renal function. (1) Worldwide, ~700 million people have CKD. (2)

People with diabetes are also at increased risk of kidney failure, with approximately 40% developing chronic kidney disease (CKD). (3) Of note, CKD can be defined by either or both a reduced estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m 2 for 3 months or more, regardless of the underlying cause, and/or by the presence of defined albuminuria as a urine albumin-to-creatinine ratio (UACR) ≥30 mg/g in at least 2 spot urine samples. (4) Both a decrease in eGFR and the presence of albuminuria are independently associated with an increased risk of CVD and mortality. (5, 6)

***Correspondence to:** *Nikolay Kostadinov, Medical faculty, University Prof. Dr. Asen Zlatarov-Burgas, Yakim Yakimov Blvd. No. 1, e-mail- n.kostadinov_m.d@abv.bg, tel- 0888 53 59 10*

The mortality rate from cardiovascular disease in patients with DBZ is more than twice as high as in patients with type 2 diabetes with preserved renal function. (7) An estimated glomerular filtration rate (eGFR) < 60 mL/min per 1.73 m 2 is associated with a higher risk of cardiovascular death. (8)

The proinflammatory state of CKD can lead to deterioration of cardiovascular function through multiple mechanisms, such as the spread of atherosclerosis, vascular and valvular calcification, and myocardial fibrosis. (9)

Cardiovascular disease is the leading cause of death in both type 2 diabetes and chronic kidney disease patients. (10) In patients with diabetes and CKD, the adjusted risk difference for cardiovascular mortality was 16%, compared with the risks associated with diabetes alone (3%) or CKD alone (6%). (11) Although the first-line drug for type 2 diabetes is metformin, glucagon-like peptide-1 receptor agonists (GLP-1RAs) along with sodium-glucose cotransporter 2 (SGLT2i) inhibitors are recommended in patients with established atherosclerotic cardiovascular disease (CVD) or multiple risk factors for CVD. (12) GLP-1 receptor agonists represent a promising avenue to address complex cardiovascular-renal-metabolic health. (13,14) GLP-1 receptor agonists are known to stimulate insulin and inhibit glucagon, effectively regulating body weight and glucose levels, potentially exerting protective effects on renal function.(15,16) GLP-1 receptor agonists have several functions outside the pancreas, including reducing oxidative stress-induced autophagy and endothelial dysfunction. (17)

GLP1-receptor agonists also reduce inflammation by reducing cytokine production and immune cell infiltration. (18) The KDIGO guideline for the management of diabetes in patients with CKD recommends GLP1-receptor agonists as subsequent therapy after initiation of SGLT2 inhibitors, for further lowering of glycated hemoglobin or high risk of atherosclerotic cardiovascular disease. This class of drugs (GLP1-RA) has been given a stronger preference over other glucose-lowering agents given its cardiovascular benefits. (19, 20)

Albuminuria refers to the loss of albumin in the urine. Although both proteinuria and albuminuria serve as markers of kidney damage, quantification of albuminuria rather than proteinuria is recommended in clinical practice, since albumin is the major component of urinary protein (~50%) in most kidney diseases and is often the earliest marker of glomerular damage, where it often occurs before eGFR declines below the 60 mL/min/1.73 m 2 threshold. (21) Measurement of albumin in urine by assay is more sensitive at low concentrations. Therefore, urinary albumin serves as a more specific and sensitive early marker to indicate a change in glomerular permeability than total urinary protein. (22) Albuminuria is also associated with increased hepatic lipoprotein production, which accelerates atherosclerosis. (23) Prolonged hyperglycemic effects affect all types of organs and cells, but several hilar cells such as retinal capillary endothelial cells, renal glomerular mesangial cells, neurons, and Schwann cells in the peripheral nervous system are more susceptible to the effects of hyperglycemia. (24) In patients with HF, eGFR and albuminuria were independent predictors of HF exacerbation and increased risk of mortality. (25) Importantly, both markers are indicated as predictors of HF independent of other cardiovascular risk factors, such as type 2 diabetes mellitus. It should be noted that although renal dysfunction and the presence of concomitant type 2 diabetes mellitus in the setting of albuminuria is associated with the highest cardiorenal risk, many patients with HF who do not have predominant comorbidities such as type 2 diabetes mellitus may also have albuminuria. (26)

The causal pathophysiological relationship between albuminuria and cardiovascular damage is well documented. Several studies have shown that even moderately elevated levels of albuminuria are associated with an increased risk of cardiovascular events. (27)

The Framingham Heart Study, an FHS study found that abnormal albuminuria was associated with an increased risk of developing heart failure (HF). In particular, albuminuria was strongly associated with HF with reduced ejection fraction (HR 2.10, 95% CI 1.35–3.26), but no significant association with forms of HF with preserved ejection fraction (HR 1.26, 95% CI 0.78–2.03) In the Multi-Ethnic Study of Atherosclerosis (MESA) it was found that patients with diabetes and present albuminuria have a 90% higher risk of developing peripheral artery disease compared to those without albuminuria.(28)

The 2019 European Society of Cardiology (ESC) and European Association for the Study of Diabetes (EASD) guidelines. emphasize the key role of proteinuria in the assessment of cardiovascular disease risk in diabetic patients. (29) Proteinuria is an indicator of organ damage and alone is sufficient to classify a patient with diabetes into a category of very high cardiovascular risk, and this may influence the choice of antihyperglycemic drugs.

MATERIAL AND METHODS

The survey was conducted in the period of November 2022. – July 2023 in the Burgas region of the Republic of Bulgaria. Participants are randomly selected based on clearly defined criteria including:

- age over 18 years;
-diagnosis of DM type 2 with a prescription of at least 6 months
- lack of treatment with GLP-1 receptor agonists before inclusion in the study
- voluntary consent to participate

The sources for collecting information are outpatient lists, epicrisis, laboratory tests. The study group included 66 patients with type 2 diabetes who started treatment with a GLP-1 receptor agonist. Metabolic control parameters that we monitored at the beginning and end of the six-month follow-up period were creatinine, calculated glomerular filtration using the CKD-EPI method (Equations for Glomerular Filtration RATE), microalbuminuria in the first morning urine test.

The statistical method used is the Independent Samples T-test. With this test, statistically significant differences between the mean values of the indicators with a high degree of statistical significance are established. The implementation was carried out with the statistical package SPSS 22.

RESULTS

From a total of 66 patients treated with a GLP-1 receptor agonist, 26 were men (39.4%) and 40 were women (60.6%) **(Figure 1)**

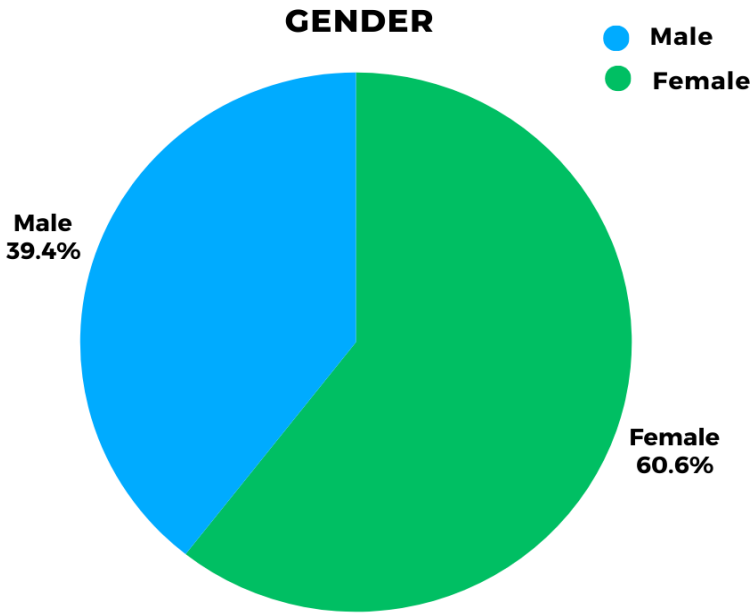

Figure 1. Distribution of patients treated with GLP-1 receptor agonists

The mean age of patients treated with GLP-1 receptor agonist was 54.74±10.22 years. The minimum age in this group is 33 years and the maximum age is 75 years.

The mean value of GF at the beginning was 88.35 ± 16.80, and after 6 months of follow-up it was 94.13 ± 16.15. **(Table 1)** The difference between the average values of glomerular filtration at the beginning of the study and after 6 months, which amounts to 5,780 ml/min. ($0.043<\alpha=0.05$) ($*p<0.05$) is statistically significant because the significance level of features t = -2.045 has significance levels Sig. = $0.043 < \alpha = 0.05$

Table 1.*Change in paraclinical parameters of patients taking a GLP-1 receptor agonist*

	period	mean	Standard deviation	Statistical significance
Glomerular filtration (ml/min)	In the beginning After 6 months	88.35 94.13	16.80 16.15	*p<0.05
creatinine (mkmol/l)	In the beginning	77.00	14.56	*p<0.05
	After 6 months	71.08	14.14	
microalbuminuria MALB (mg/l)	In the beginning After 6 months	43.54 44.55	73.62 87.54	p> =0.05

The mean value of creatinine at the beginning was 77.00±14.56 and after 6 months was 71.08 ±14.14 The difference between the mean values of creatinine at the beginning of the study and after 6 months which amounted to 5.916 mcmol/l (0.018<α=0.05)(*p<0.05) was statistically significant because the level of significance of characteristics t = -2.402 has significance levels Sig. = 0.018 < α = 0.05.

The difference between the mean values of microalbumin MALB at the beginning of the study and after 6 months amounts to -1.015 mg/l, not considering statistical dependence (p≥0.05) because the characteristic t =0.073 has a level of significance Sig. 0.942>α=0.05

DISCUSSION

The emergence of new medicinal products for the treatment of type 2 DM in recent years is increasingly displacing the traditional conventional treatment with metformin.

According to the 2021 ADA/EASD consensus report on the treatment of type 2 diabetes mellitus, glucose-lowering therapy focuses on GLP-1 receptor agonists and SGLT-2 inhibitors, taking into account some clinically relevant factors.

Treatment with GLP-1 receptor agonists is recommended in patients with diabetes mellitus with established cardiovascular disease or at high risk for such disease.

In patients with chronic kidney disease and heart failure, treatment with SGLT-2 inhibitors is recommended, given the beneficial effects in terms of reducing the progression of CKD, the nephroprotective effect and hospitalizations for HF.

A careful therapeutic approach is required for patients with TDM2. There should be increased control of risk factors beyond blood glucose and HbA1c control. The modern concept is that the therapy of patients with T2DM is shifted beyond the glycemic effect and an opportunity for complex treatment is given. Given the additional protection they provide, GLP-1 receptor agonists should be considered as a mainstay in the treatment of type 2 DM.These data highlight the importance of GLP-1 receptor agonists in the management of type 2 diabetes and lowering cardiovascular risk, emphasizing the need for individualized treatment and management of comorbidities.

Increased attention is required, as it is important to ensure increased control of risk factors, both related to blood sugar and beyond. Therapy in patients with type 2 diabetes (T2DM) no longer focuses solely on glycemic effects. Instead, the modern concept emphasizes a complex approach to treatment that can stop the development of chronic kidney disease and reduce cardiovascular risk. This multidisciplinary approach is key to improving long-term outcomes and quality of life for patients with diabetes.

Unfortunately, the present analysis did not find a statistically significant change in the level of microalbuminuria with treatment with GLP-1 receptor agonists.

CONCLUSION

The clinical significance of albuminuria in patients with type 2 diabetes (T2D) and factors contributing to its reduction have been the focus of research in recent years. Increased urinary albumin excretion in diabetics is associated with the highest cardiorenal risk.

Diabetes is a condition that carries a significant risk of developing micro- and macrovascular complications. Reduction of proteinuria in patients with diabetes, regardless of the treatment method, may delay the progression of renal and cardiovascular diseases.

Despite their well-described benefits in atherosclerotic cardiovascular disease and potential protective mechanisms for the kidney, GLP1-receptor agonists remain underutilized in clinical practice.

Advances have been made with therapeutic agents that can improve both cardiovascular and renal outcomes in patients with CKD.

The short follow-up period of the patients, the small number of included patients and the limited sample from only one region of Bulgaria can be mentioned as the main drawback of the study.

REFERENCES

1. Zheng, Y., Ley, S. H. & Hu, F. B. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat. Rev. Endocrinol.* 14, 88 (2018).
2. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al, for the DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med.* 2020;383:1436-1446
3. United States Renal Data System . National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; Bethesda, MD: 2018. 2018 USRDS annual data report: epidemiology of kidney disease in the United States. [Google Scholar]
4. Levey A.S., Eckardt K.U., Tsukamoto Y., et al. Definition and classification of chronic kidney disease: a position statement from kidney disease: improving global outcomes (KDIGO) Kidney Int. 2005;67(6):2089–2100. doi: 10.1111/j.1523-1755.2005.00365.x. [DOI] [PubMed] [Google Scholar]
5. Ninomiya T., Perkovic V., de Galan B.E., et al. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. *J Am Soc Nephrol.* 2009;20(8):1813–1821. doi: 10.1681/ASN.2008121270. [DOI] [PMC free article] [PubMed] [Google Scholar]
6. Fox C.S., Matsushita K., Woodward M., et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet.* 2012;380(9854):1662–1673. doi: 10.1016/S0140-6736(12)61350-6. [DOI] [PMC free article] [PubMed] [Google Scholar]
7. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the global burden of disease study 2017. *Lancet.* 2020;395:709–33.
8. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA consensus conference. *Diabetes Care*. 2014;37:2864–83.
   Article PubMed PubMed Central Google Scholar
9. Jankowski J., Floege J., Fliser D., Bohm M., Marx N. Cardiovascular disease in chronic kidney disease: pathophysiological insights and therapeutic options. *Circulation.* 2021;143(11):1157–1172. doi: 10.1161/CIRCULATIONAHA.120.050686 . [DOI] [PMC free article] [PubMed] [Google Scholar]
10. Almourani R, Chinnakotla B, Patel R, et al. Diabetes and cardiovascular disease: an update. *Curr Diab Rep*. 2019;19:161.Article CAS PubMed Google Scholar
11. Afkarian M., Sachs M.C., Kestenbaum B., et al. Kidney disease and increased mortality risk in type 2 diabetes. *J Am Soc Nephrol*. 2013;24(2):302–308. doi: 10.1681/ASN.2012070718. [DOI] [PMC free article] [PubMed] [Google Scholar
12. American Diabetes Association professional practice committee. 2. classification and diagnosis of diabetes: standards of medical care in diabetes-2022. *Diabetes Care*. 2022;45(Suppl 1):S17–38.
13. Ndumele, C. E. et al. Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association. *Circulation* 148, 1606–1635 (2023).
14. Ndumele, C. E. et al. A Synopsis of the Evidence for the Science and Clinical Management of Cardiovascular-Kidney-Metabolic (CKM) Syndrome: A Scientific Statement From the American Heart Association. *Circulation* 148, 1636–1664 (2023).
15. Müller, T. D. et al. Glucagon-like peptide 1 (GLP-1). Mol. Metab. 30, 72–130 (2019).
16. Totomirova Ts., Arnaudova M., Application of GLP1 agonists in patients with chronic kidney disease and diabetes mellitus. *Medinfo*, 2021, 9, 50-54

17. Cai X, She M, Xu M, et al. GLP-1 treatment protects endothelial cells from oxidative stress-induced autophagy and endothelial dysfunction. Int J Biol Sci. 2018;14:1696–708.
18. Lee Y.S., Jun H.S. Anti-inflammatory effects of GLP-1-based therapies beyond glucose control. *Mediators Inflamm*. 2016;2016 doi: 10.1155/2016/3094642. [DOI] [PMC free article] [PubMed] [Google Scholar
19. Kidney disease: improving global outcomes diabetes work G. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int.* 2022;102(5S):S1–S127. doi: 10.1016/j.kint.2022.06.008. [DOI] [PubMed] [Google Scholar]
20. Michos E.D., Tuttle K.R. GLP-1 receptor agonists in diabetic kidney disease. *Clin J Am Soc Nephrol*. 2021;16(10):1578–1580. doi: 10.2215/CJN.18771220. [DOI] [PMC free article] [PubMed] [Google Scholar
21. Kidney Disease: Improving Global Outcomes CKD evaluation and management https://kdigo.org/guidelines/ckd-evaluation-and-management/, Accessed 14th Mar 2021 Google Scholar
22. National Clinical Guideline Centre (UK) Chronic kidney disease (partial update): early identification and management of chronic kidney disease in adults in primary and secondary care National Institute for Health and Care Excellence (UK), London (2014)
23. J.F. Moorhead, M. El-Nahas, M.K. Chan, Z. Varghese Lipid nephrotoxicity in chronic progressive glomerular and tubulo-interstitial disease *Lancet*, 320 (1982), pp. 1309-1311
24. Pashkunova S., Ivanov V., Savov A., A modern view of the pathogenesis of diabetic nephropathy, *Topmedika*, 1,47-50
25. C.E. Jackson, S.D. Solomon, H.C. Gerstein, et al. Albuminuria in chronic heart failure: prevalence and prognostic importance *Lancet*, 374 (2009), pp. 543-550
26. K. Damman, D.J. van Veldhuisen, G. Navis, A.A. Voors, H.L. Hil lege Urinary neutrophil gelatinase associated lipocalin (NGAL), a marker of tubular damage, is increased in patients with chronic heart failure *Eur J Heart Fail*, 10 (2008), pp. 997-1000
27. Nayor M, Larson MG, Wang N, et al. The association of c hronic kidney disease and microalbuminuria with heart failure with preserved vs. reduced ejection fraction. *Eur J Heart Fail*. 2017;19:615-623.
28. Mann J.F., Yi Q.-L., Gerstein H.C.E., Mann Q.-L.Y.J.F. Albuminuria as a predictor of cardiovascular and renal outcomes in people with known atherosclerotic cardiovascular disease. *Kidney Int*. 2004
29. Wattanakit K., Folsom A.R., Criqui M.H., Kramer H.J., Cushman M., Shea S., Hirsch A.T. Albuminuria and peripheral arterial disease: Results from the Multi-Ethnic Study of Atherosclerosis (MESA) Atherosclerosis. 2008