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DAPAGLIFLOZIN IMPACT ON DIABETIC COMPLICATIONS

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Abstract: Diabetes mellitus poses a significant global health challenge, with associated complications impacting various organ systems. Dapagliflozin, an inhibitor of the sodium-glucose cotransporter 2 (SGLT2), has emerged as a novel therapeutic agent in the management of diabetes, offering unique mechanisms beyond glycemic control. This comprehensive review aims to systematically assess the role of dapagliflozin in mitigating diabetic complications.The review begins by elucidating the pharmacokinetics and mechanisms of dapagliflozin, providing a foundation for understanding its multifaceted impact. Clinical trials are scrutinized to evaluate dapagliflozin's efficacy in glycemic control and metabolic outcomes. Renoprotective effects are explored in the case of diabetic nephropathy, while cardiovascular benefits are assessed based on recent evidence. Special attention is given to ocular outcomes, including the potential impact on diabetic retinopathy, and the review delves into the emerging area of neuroprotective effects in diabetic neuropathy.By critically synthesizing the existing literature, this review identifies gaps in knowledge and suggests future research directions. The findings of this review contribute to a nuanced understanding of dapagliflozin's role in managing diabetic complications, fostering insights that may shape the landscape of diabetes care and stimulate further exploration in this evolving field.

Keywords: Diabetes mellitus, SGLT2 inhibitor, Dapagliflozin, diabetic nephropathy, cardiovascular complications, diabetic retinopathy, neuroprotection, cancer

INRODUCTION

Diabetes mellitus widely recognized as an emerging epidemic posing a significant public health challenge in the twenty-first century[1]. In 2021, the global prevalence of diabetes among individuals aged 20-79 years was estimated at 10.5%, equating to around 536 million people. By 2045, this percentage is projected to increase to 12.2 %, encompassing approximately 783.2 million people[2]. The typical complications linked to diabetes mellitus encompass macrovascular issues like coronary heart disease, peripheral arterial disease and stroke and as well as macrovascular problems such as diabetic ketoacidosis, retinopathy, and peripheral neuropathy[3].Heart failure often presents as an initial indication of cardiovascular disease in patients with type 2 diabetes mellitus(T2DM),carrying a substantial risk of mortality for individuals with either type 1 diabetes mellitus (T1DM) or T2DM[4].

SGLT2 inhibitors represent the newest oral antidiabetic drugs (OAD)distinguished by a novel mechanism. Their insulin independent ability to lower blood sugar levels works by inhibiting glucose reabsorption in renal tubules, thus promoting its elimination through urine[5].SGLT-2 inhibitors demonstrate impressive effectiveness, safety, and tolerability, with minimal risk of hypoglycemia[5]. In addition to enhancing glycemic regulation, SGLT-2 inhibitors

provide various benefits for body weight, blood pressure, hyperuricemia, dyslipidemia, and fatty liver disease[6].Dapagliflozin, a notably targeted inhibitor of sodium-glucose co-transporter 2 (SGLT2), enhances glycemic management and decreases body weight independently of insulin in individuals with type 2 diabetes mellitus (T2DM) by diminishing renal glucose reabsorption, leading to increased urinary glucose excretion[7].

PHARMACOLOGICAL PROPERTIES OF DAPAGLIFLOZIN

Dapagliflozin, a robust and reversible inhibitor of SGLT2, demonstrates greater selectivity over SGLT1 and enhances glucose uptake in the intestines. It elevates urinary glucose excretion and enhances both fasting and postprandial plasma glucose levels in individuals with T2DM[7].Dapagliflozin, upon oral intake, is swiftly absorbed, typically reaching peak plasma levels within 2 hours. With a dose of 10 mg, its absolute oral bioavailability stands at 78%. It exhibits an average volume of distribution of 118 L at steady state and is approximately 91% bound to proteins. Metabolism primarily occurs via UGT1A9, yielding its principal inert metabolite, 3-O-glucuronide. The drug is predominantly eliminated through urine, with 75% excreted and 21% via feces[7].

DAPGLIFLOZIN IN DIABETIC NEPHROPATHY

Diabetic nephropathy represents a significant microvascular complication affecting approximately 30% of individuals with type 1 diabetes and 40% of those with type 2 diabetes[8].Diabetic nephropathy is influenced by the duration of diabetes and the effectiveness of glycemic management. Elevated blood sugar levels are pivotal in initiating kidney damage. Hyperglycemia triggers glomerular hypertension and prompts changes within cells, leading to the breakdown of the selective glomerular barrier and the proliferation of the mesangial and interstitial matrix. This process culminates in glomerulosclerosis and fibrosis of the interstitial tubules[9].

Research findings indicate that dapagliflozin holds promise for managing diabetic nephropathy. The DAPA-CKD trial revealed that dapagliflozin effectively mitigated the risk of major kidney and cardiovascular events in individuals with chronic kidney disease(CKD), irrespective of their diabetic status[10]. Research consistently shows the beneficial impacts of dapagliflozin on kidney health in patients with diabetic kidney disease as well as those with heart failure and reduced ejection fraction. The consistent improvement of kidney and cardiovascular outcomes with dapagliflozin appears unaffected by the use of various cardiovascular medications in patients. These results indicate that dapagliflozin shows potential for the treatment of diabetic nephropathy.

CARDIOVASCULAR BENEFITS OF DAPAGLIFLOZIN

Dapagliflozin has been demonstrated to produce a modest decline in blood pressure when compared to a placebo in individuals with T2DM. This effect was observed in both hypertensive and non-hypertensive patients, with changes in systolic and diastolic blood pressures subtracted from baseline values. The reduction in blood pressure remained consistent regardless of initial blood pressure levels, and there was a minimal risk of orthostatic reactions associated with dapagliflozin treatment. Furthermore, dapagliflozin treatment did not exhibit any clinically significant differences in heart rate compared to the placebo. These results indicate that dapagliflozin could provide advantages in controlling blood pressure in diabetic patients, potentially enhancing existing antihypertensive treatments[12].

Dapagliflozin has shown promising effects on iron deficiency in individuals with heart failure. In the DAPA-HF trial, dapagliflozin was linked to improvements in markers of iron metabolism, including reductions in transferrin saturation, hepcidin, and ferritin levels, as well as an increase in soluble transferrin receptor and total iron-binding capacity levels. These changes suggest increased iron mobilization and utilization, potentially leading to improved erythropoiesis[13]. Moreover, dapagliflozin showed the capacity to alleviate anemia in patients with either iron deficiency or those with sufficient iron levels at the beginning of the study. The research also revealed uniform clinical advantages of dapagliflozin irrespective of the initial presence or absence of iron deficiency. This suggests that iron deficiency should not be viewed as an obstacle to utilizing dapagliflozin in individuals with reduced ejection fraction and heart failure[14].

In the DECLARE–TIMI 58 trial, dapagliflozin was found to be similar to placebo regarding the primary safety measure of MACE (major adverse cardiovascular events). Although dapagliflozin did not lead to a significantly reduced occurrence of MACE, it showed a significant decrease in the occurrence of cardiovascular death and hospitalization because of heart failure compared to placebo in a diverse population of patients with T2DM[15].

DAPAGLIFLOZIN IN DIABETIC RETINOPATHY

Diabetic retinopathy (DR) is a microvascular complication arising from diabetes. It stands as the leading cause of vision loss among individuals of working age, and its prevalence is on the rise. Elevated blood sugar levels are recognized as a key factor in the onset of diabetic retinopathy (DR). In the retina, an excess of glucose within cells can exceed the capacity of the glycolytic pathway and be diverted to alternative metabolic routes, such as the sorbitol pathway. This

diversion results in the generation of oxidative and proinflammatory byproducts, along with substances that promote angiogenesis. These compounds play a significant role in the microvascular impairment characteristic of diabetic retinopathy, resulting in reduced blood flow, the formation of new blood vessels, and ultimately, vision impairment[16]. Dapagliflozin therapy successfully addressed both neural and vascular impairments within the retinas of mice afflicted with T2DM, consequently mitigating the progression of diabetic retinopathy. The treatment led to enhancements in electroretinogram (ERG) responses and a decrease in the number of acellular capillaries. These protective effects primarily stemmed from improvements in blood sugar levels, reductions in inflammation and wound healing responses, decreased glucose uptake, and enhancements in hematocrit levels. Collectively, these factors contributed to a shielding effect against neural and vascular dysfunction[17].

NEUROPROTECTIVE ACTION OF DAPAGLIFLOZIN

Type 2 diabetes accelerates the progression of atherosclerosis, a condition linked to heightened cardiovascular risk, thereby impacting life expectancy adversely. moreover, individuals with diabetes face an increased risk of experiencing cognitive impairment[18]. According to Erdogan MA. et al.'s findings, Dapagliflozin demonstrated a notable reduction in seizure activity, both in terms of electrophysiological measures and clinical manifestations, in a rat epilepsy model. Further studies showed that dapagliflozin might be a preferred SGLT2 inhibitor for individuals with diabetes who also have epilepsy due to its potential antiepileptic properties[19].

DAPAGLIFLOZIN IN CANCER

RENAL CELL CARCINOMA

Patients diagnosed with type 2 diabetes mellitus often exhibit an elevated levels of sodium glucose co-transporters 2 (SGLT2) and a notable prevalence of renal cell carcinoma (RCC). Dapagliflozin has displayed encouraging therapeutic potential against RCC in various in vitro and in vivo investigations. As an inhibitor of SGLT2, dapagliflozin reduced the viability of renal cell carcinoma cell lines, influenced cell cycle progression and apoptosis, and resulted in a reduction in tumor volume. The findings indicate that dapagliflozin could present novel diagnostic and treatment opportunities for renal cell carcinoma[20].

COLON AND BREAST CANCER

In mouse models of obesity-related cancers, namely E0771 breast cancer and MC38 colon adenocarcinoma, dapagliflozin was observed to impede tumor growth. This effect was attributed to the reversal of hyperinsulinemia, resulting in decreased tumor glucose uptake and oxidation. The involvement of insulin in this process implies that dapagliflozin holds promise as an anticancer agent by modulating systemic metabolism and insulin levels to impede tumor advancement in obesity-associated cancers[21]. In both laboratory and animal studies, dapagliflozin has demonstrated encouraging effects on breast cancer cells. The primary observations concerning the impacts of dapagliflozin on breast cancer according to study by Jun Zhou et al. comprises: 1) Treatment with dapagliflozin at a dose equivalent to clinical levels notably decelerated the growth of xenograft tumors derived from MCF-7 cells in mice, suggesting its potential as an anticancer treatment,2) Dapagliflozin demonstrated strong anti-proliferative activity in breast cancer cells, resulting in decreased cell proliferation and clonogenic survival in both laboratory experiments and animal models,3) Treatment with dapagliflozin prompted G1/G0 cell cycle arrest in breast cancer cells, suggesting a mechanism behind its anti-tumor effects,4) Dapagliflozin suppressed glucose uptake in breast cancer cells and stimulated the AMPK signaling pathway while simultaneously inhibiting the mTOR pathway, thereby enhancing its anticancer properties[22].

CONCLUSION

Dapagliflozin, as an SGLT2 inhibitor, offers unique mechanisms beyond glycemic control in diabetes care. Clinical trials have shown that dapagliflozin is effective in glycemic control, metabolic outcomes, and cardiovascular benefits. Dapagliflozin shows renoprotective effects in diabetic nephropathy and potential benefits in diabetic neuropathy and diabetic retinopathy. By identifying gaps in knowledge and suggesting future research directions, the review aims to contribute to a nuanced understanding of dapagliflozin's role in managing diabetic complications and shaping the landscape of diabetes care. Overall, the review underscores the significant potential of dapagliflozin as a therapeutic agent in addressing the diverse complications associated with diabetes, offering insights that may guide further exploration and advancements in this field.

REFERENCES

1. Zimmet P., Alberti K. & Shaw J. Global and societal implications of the diabetes epidemic. Nature 414, 782–787 (2001). https://doi.org/10.1038/414782a
2. International Diabetes Federation. IDF Diabetes Atlas,10th edition. Brussels,Belgium 2021,available at : https://www.diabetesatlas.org
3. Fowler M. J. macrovascular and Microvascular complications of diabetes. Clin. Diabetes 26, 77–82 (2008)
4. Shah, A. D. et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1·9 million people. Lancet Diabetes Endocrinol. 3, 105–113 (2015).
5. Hussain M, Elahi A, Iqbal J, Bilal Ghafoor M, Rehman H, Akhtar S. Comparison of Efficacy and Safety Profile of Sodium-Glucose Cotransporter-2 Inhibitors as Add-On Therapy in Patients With Type 2 Diabetes. Cureus. 2021 Apr 3;13(4): e14268. doi: 10.7759/cureus.14268. PMID: 33954073; PMCID: PMC8090899.
6. Kalra, S: A Review on Basic and Clinical Pharmacology of Sodium Glucose Co-Transporter-2 (SGLT2) Inhibitors. *Diabetes Ther* **5**, 355–366 (2014). https://doi.org/10.1007/s13300-014-0089-4
7. Dhillon S. (2019). Dapagliflozin: A Review in Type 2 Diabetes. *Drugs*, *79*(10), 1135–1146. https://doi.org/10.1007/s40265-019-01148-3
8. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. Clin J Am Soc Nephrol. (2017) 12:2032– 45. doi: 10.2215/CJN.11491116
9. Hostetter TH. Diabetic nephropathy. Metabolic versus hemodynamic considerations. Diabetes Care. (1992) 15:1205– 15. doi:10.2337/diacare.15.9.1205
10. Chertow, G. M., Correa-Rotter, R., Vart, P., Jongs, N., McMurray, J. J. V., Rossing, P., Langkilde, A. M., Sjöström, C. D., Toto, R. D., Wheeler, D. C., Heerspink, H. J. L., & DAPA-CKD Trial Committees and Investigators (2023). Effects of Dapagliflozin in Chronic Kidney Disease, With and Without Other Cardiovascular Medications: DAPA-CKD Trial. *Journal of the American Heart Association*, *12*(9), e028739. https://doi.org/10.1161/JAHA.122.028739
11. Wheeler DC, Stefansson BV, Batiushin M, Bilchenko O, Cherney DZI, Chertow GM, Douthat W, Dwyer JP, Escudero E, Pecoits-Filho R, et al. The dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial: baseline characteristics. Nephrol Dial Transplant. 2020; 35:1700–1711. doi: 10.1093/ndt/gfaa234
12. Sjostrom CD, Johansson P, Ptaszynska A, List J, Johnsson E. Dapagliflozin lowers blood pressure in hypertensive and non-hypertensive patients with type 2 diabetes. Diabetes and Vascular Disease Research. 2015;12(5):352-358. doi:10.1177/1479164115585298
13. Docherty, K. F., Welsh, P., Verma, S., De Boer, R. A., O'Meara, E., Bengtsson, O., Kober, L., Kosiborod, M. N, Hammarstedt, A, Langkilde A. M, Lindholm D, Little D. J, Sjostrand,M, Martinez F. A, Ponikowski P, Sabatine M. S, Morrow D. A, Schou M, Solomon S. D, Sattar N. DAPA-HF Investigators and Committees (2022). Iron Deficiency in Heart Failure and Effect of Dapagliflozin: Findings from DAPA-HF. *Circulation*, *146*(13), 980–994. https://doi.org/10.1161/CIRCULATIONAHA.122.060511
14. Docherty KF, Curtain JP, Anand IS, Bengtsson O, Inzucchi SE, Kober L, Kosiborod MN, Langkilde AM, Martinez FA, Ponikowski P, et al; DAPA-HF Investigators and Committees. Effect of dapagliflozin on anaemia in DAPA: HF. Eur J Heart Fail. 2021; 23:617–628. doi: 10.1002/ejhf.2132 15.
15. Wiviott, S. D., Raz, I., Bonaca, M. P., Mosenzon, O., Kato, E. T., Cahn, A., Silverman, M. G., Zelniker, T. A., Kuder, J. F., Murphy, S. A., Bhatt, D. L., Leiter, L. A., McGuire, D. K., Wilding, J. P. H., Ruff, C. T., Gause-Nilsson, I. A. M., Fredriksson, M., Johansson, P. A., Langkilde, A. M., Sabatine, M. S., … DECLARE–TIMI 58 Investigators (2019). Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *The New England journal of medicine*, *380*(4), 347–357. https://doi.org/10.1056/NEJMoa1812389
16. Hendrick, A. M., Gibson, M. V., & Kulshreshtha, A. (2015). Diabetic Retinopathy. *Primary care*, *42*(3), 451–464. https://doi.org/10.1016/j.pop.2015.05.005
17. Luo Q, Leley SP, Bello E, et al. Dapagliflozin protects neural and vascular dysfunction of the retina in diabetes. BMJ Open Diab Res Care 2022;10: e002801. doi:10.1136/ bmjdrc-2022-002801
18. Pawlos A, Broncel M, Woźniak E, Gorzelak-Pabiś P. Neuroprotective Effect of SGLT2 Inhibitors. *Molecules*. 2021; 26(23):7213. https://doi.org/10.3390/molecules26237213

19. Erdogan, M.A., Yusuf, D., Christy, J. *et al.* Highly selective SGLT2 inhibitor dapagliflozin reduces seizure activity in pentylenetetrazol-induced murine model of epilepsy. *BMC Neurol* **18**, 81 (2018). https://doi.org/10.1186/s12883-018-1086-4

20. Kuang, H., Liao, L., Chen, H., Kang, Q., Shu, X., & Wang, Y. (2017). Therapeutic Effect of Sodium Glucose Co-Transporter 2 Inhibitor Dapagliflozin on Renal Cell Carcinoma. *Medical science monitor : international medical journal of experimental and clinical research*, *23*, 3737–3745. https://doi.org/10.12659/msm.902530

21. Nasiri AR, Rodrigues MR, Li Z, et al. SGLT2 inhibition slows tumor growth in mice by reversing hyperinsulinemia. Cancer Metab. 2019; 7:10. doi:10.1186/s40170-019-0203-1

22. Jun Zhou , Jin Zhu , Sheng-Jian Yu , Huai-Lu Ma , Jie Chen , Xiao-Fei Ding , Guang Chen , Yong Liang , Qiang Zhang (2020):Sodium-glucose co-transporter-2 (SGLT-2) inhibition reduces glucose uptake to induce breast cancer cell growth arrest through AMPK/mTOR pathway https://doi.org/10.1016/j.biopha.2020.110821