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ANALYSIS OF ADVANTAGES AND DISADVANTAGES OF MODERN HYPOGLYCEMIC DRUGS

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ABOUT ARTICLE

Key words: GLP-1RA, SGLT-2i, DPP-4i, type 2 diabetes, combination medicine, hypoglycemic medications, thiazolidinediones, sulfonylureas, incretin mimetic medications.

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Abstract: More alternatives for treating type 2 diabetes (T2DM) are provided by new hypoglycemic medications, such as sodium-glucose cotransporter 2 inhibitors (SGLT-2i), dipeptidyl peptidase-4 inhibitors (DPP-4i), and glucagon-like peptide 1 receptor agonists (GLP-1RA). They are usually well tolerated, though occasionally care must be used. In prediabetes and type 2 diabetes, combination therapy with novel hypoglycemic medications has demonstrated satisfactory glucose control in clinical studies (mainly traditional stepwise therapy); however, early combination therapy seems to offer faster, greater, and longer-lasting advantages. Now that oral semaglutide is widely used in clinical settings, it's time to create combination medications that include novel hypoglycemic medications, particularly SGLT-2i and/or GLP-1RA, to reduce the risk of prediabetes, newly diagnosed type 2 diabetes, and its cardiovascular complications while increasing patient compliance. SGLT-2i protects against heart failure through both direct and indirect effects, according to preclinical and clinical research. More research is required to determine how this all-encompassing protective effect controls the dynamic alterations of cardiac genes. From the standpoint of "clinical drug-mechanism-intensive disease treatment," we offer suggestions for the creation of medications for

heart failure. This will expedite the creation of medications for heart failure and, to some extent, direct their usage. Patients with type 2 diabetes who fast during Ramadan benefit clinically from the newer glucose-lowering drugs, according to this systematic review and meta-analysis.

ZAMONAVIY GIPOGLIKEMIK DORILARNING AFZALLIKLARI VA KAMCHILIKLARINI TAHLILI

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MAQOLA HAQIDA

Kalit so‘zlar: GLP-1RA, SGLT-2i, DPP-4i, 2-toifa qandli diabet, kombinatsiyalangan dori, gipoglikemik dorilar, tiazolidindionlar, sulfonilurealar, inkretin mimetik dorilar.

Annotatsiya: Yangi gipoglikemik dorilar, jumladan, natriy-glükoza kotransporter 2 ingibitorlari (SGLT-2i), dipeptidil peptidaza-4 ingibitorlari (DPP-4i) va glukagonga o‘xshash peptid 1 retseptor agonistlari (GLP-1RA) 2-toifa qandli diabet (T2DM)ni davolashda ko‘proq imkoniyatlar yaratadi. Ular odatda yaxshi qabul qilinadi, ammo ba’zan ehtiyotkorlik talab qilinadi. Klinik tadqiqotlarda (asosan an’anaviy bosqichma-bosqich terapiya) yangi gipoglikemik dorilar bilan kombinatsiyalangan terapiya prediabet va T2DMda glyukoza nazoratini qoniqarli darajada ta’minlagan; ammo erta kombinatsiyalangan terapiya tezroq, kuchliroq va uzoq muddatli foyda berishi ko‘rsatilgan. Hozirda og‘iz orqali semaglutid keng klinik qo‘llanilgani sababli, yangi gipoglikemik dorilar, ayniqsa SGLT-2i va/yoki GLP-1RAni o‘z ichiga olgan kombinatsiyalangan preparatlar yaratish vaqti kelgan, bu esa prediabet, yaqinda tashxislangan T2DM va uning yurak-qon tomir asoratlari xavfini kamaytirish, shuningdek bemorlarning dori qabul qilishga sodiqligini oshirish imkonini beradi. Preklinik va klinik tadqiqotlar SGLT-2i yurak yetishmovchiligidan himoya qilishi mumkinligini, bu esa bevosita va bilvosita ta’sirlar orqali sodir bo‘lishini ko‘rsatadi. Bu keng qamrovli himoya ta’sirining yurak genlaridagi dinamik o‘zgarishlarni qanday

boshqarishini aniqlash uchun qo‘shimcha tadqiqotlar talab etiladi. “Klinik dori-mexanizmga yo‘naltirilgan kasallik davolash” nuqtai nazaridan, yurak yetishmovchiligi uchun dorilar yaratishga oid tavsiyalar taqdim etiladi. Bu yurak yetishmovchiligi uchun dorilarni yaratishni tezlashtiradi va ularning qo‘llanilishini ma’lum darajada yo‘naltiradi. Ushbu tizimli sharh va meta-tahlilga ko‘ra, ro‘za tutayotgan 2-toifa qandli diabetga chalingan bemorlar yangi glyukoza tushiruvchi dorilardan klinik foyda ko‘rishadi.

АНАЛИЗ ПРЕИМУЩЕСТВ И НЕДОСТАТКОВ СОВРЕМЕННЫХ ГИПОГЛИКЕМИЧЕСКИХ ПРЕПАРАТОВ

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О СТАТЬЕ

Ключевые слова: GLP-1RA, SGLT-2i, DPP-4i, сахарный диабет 2 типа, комбинированная терапия, гипогликемические препараты, тиазолидиндионы, сульфонилмочевины, препараты-миметики инкретина.

Аннотация: Новые гипогликемические препараты, такие как ингибиторы натрий-глюкозного котранспортера 2 (SGLT-2i), ингибиторы дипептидилпептидазы-4 (DPP-4i) и агонисты рецептора глюкагоноподобного пептида 1 (GLP-1RA), предоставляют больше возможностей для лечения сахарного диабета 2 типа (СД2). Они обычно хорошо переносятся, хотя иногда требуется осторожность. В клинических исследованиях (в основном при традиционной пошаговой терапии) комбинационная терапия с новыми гипогликемическими препаратами демонстрировала удовлетворительный контроль уровня глюкозы при предиабете и СД2; однако ранняя комбинационная терапия, по-видимому, обеспечивает более быстрое, выраженное и продолжительное улучшение. С появлением широкого клинического применения перорального семаглутида возникает необходимость создавать комбинированные препараты, включающие новые гипогликемические

препараты, особенно SGLT-2i и/или GLP-1RA, для снижения риска предиабета, недавно диагностированного СД2 и его сердечно-сосудистых осложнений, одновременно повышая приверженность пациентов лечению. Предклинические и клинические исследования показывают, что SGLT-2i защищает от сердечной недостаточности как прямыми, так и косвенными эффектами. Необходимо больше исследований, чтобы понять, как этот комплексный защитный эффект контролирует динамические изменения сердечных генов. С точки зрения «клинического лечения заболеваний с использованием препаратов, ориентированных на механизм действия», предлагаются рекомендации по разработке лекарств для сердечной недостаточности. Это ускорит создание новых препаратов для сердечной недостаточности и, в определённой степени, направит их применение. Согласно этому систематическому обзору и мета-анализу, пациенты с СД2, соблюдающие пост во время Рамадана, клинически выигрывают от использования новых препаратов для снижения уровня глюкозы.

Introduction. The purpose of treatment for diabetes, a chronic metabolic condition, is to effectively manage blood glucose and its consequences. Combination medication therapy has become a popular all-encompassing diabetes treatment strategy. A growing body of research has demonstrated that combination therapy, as opposed to monotherapy, can significantly improve clinical outcomes while managing blood pressure, weight, and blood glucose levels, as well as reducing the harm caused by specific complications and slowing the progression of diabetes, including type 1 diabetes (T1D), type 2 diabetes (T2D), and related complications. The advice of combination therapy for diabetes is strongly supported by this evidence, which also emphasizes the significance of combined treatment. One in ten persons worldwide between the ages of 20 and 79 have diabetes, according to the IDF Diabetes Atlas, 10th edition. Over 90% of the 537 million adult patients have type 2 diabetes (T2DM). This figure is projected to rise to 643 million by 2030 and 783 million by 2045. One person died from diabetes every five seconds in 2021, accounting for 6.7 million fatalities globally [1-5]. Chronically high blood sugar can harm the kidneys, nerves, eyes, and cardiovascular system, which can result in a number of diabetic problems. For people with diabetes, cardiovascular diseases (CVD), such as atherosclerosis and heart failure (HF),

continue to be the leading causes of early death. Furthermore, blood glucose levels are linked to the risk of heart failure (HF) in diabetes patients: a 1% increase in glycated hemoglobin (HbA1c) raises the risk of HF in individuals with T1DM and T2DM by 30% and 8%, respectively. Maintaining blood glucose control and reducing the frequency of T2DM consequences (particularly CVD) are key objectives of T2DM treatment. An essential measure of blood glucose control and consequences from diabetes is HbA1c. A HbA1c control target of less than 7% (53 mmol/mol) is appropriate for many non-pregnant adults, and no serious hypoglycemia is advised. If it can be done safely, lowering HbA1c levels (<7%) may offer more advantages. Patients with shorter life expectancies or those receiving treatment that is more harmful than beneficial may be eligible for less strict HbA1c targets (e.g., <8%). For the past 60 years, metformin has been one of the most widely used oral hypoglycemic medications, and it continues to be the first-line treatment for the majority of people with type 2 diabetes [6-12]. DPP-4i, GLP-1RA, and SGLT-2i are just a few of the novel hypoglycemic medications that have been approved in recent years, giving T2DM patients greater treatment alternatives. Progressive organ dysfunction, including heart failure, can result from dynamic changes in gene expression. SGLT-2i's cardioprotective impact need to encompass both its direct and indirect effects. It is currently unknown how this all-encompassing action controls the expression of genes in the heart (both cardiomyocytes and non-cardiomyocytes) to enhance cardiac function. The full mechanism of SGLT-2i's cardioprotection will be better studied with the use of single-cell sequencing techniques like scRNA-seq and scATAC-seq. Future study on the major HF pathways that SGLT-2i is unable to control may be crucial for the development of HF medications. Finding new possible disease targets has been the focus of much study, however it is unclear if current therapeutic medications can affect these targets. As a result, we talked about SGLT-2i's cardioprotective mechanism and offered suggestions for the creation of HF medications from the standpoint of "clinical drug-mechanism-intensive disease treatment [13-18]." This will hasten the creation of medications for heart failure. To some extent, it may also direct the combination use of medications by analyzing the signaling pathways of various therapeutic agents. In this review, we first gave a quick summary of the pathophysiology and phenotype of diabetes before going over a number of traditional anti-diabetic drugs that are now utilized to treat the condition. The effectiveness and safety of several types of pharmacological combinations were then assessed by reviewing a number of clinical trials and pre-clinical animal studies on T1D, T2D, and their common consequences. Combination therapy is generally essential for managing diabetes. Combining the efficacy of many medications allows for more thorough and efficient blood glucose control without raising the risk of hypoglycemia or other dangerous side effects. Nonetheless, particular treatment plans ought to be customized for each patient and carried out under the supervision of medical experts [19-22].

The main purpose of the presented analytical article is to briefly describe the achievements and disadvantages of modern sugar-lowering drugs based on the results of a prestigious scientific study.

Drugs that mimic and enhance incretin. L and K cells scattered throughout the gastrointestinal tract release enteroendocrine hormones called incretins (Glucagon Like Peptide-1 and Glucose Dependent Insulinotropic Polypeptide) into the bloodstream. The main benefit of GLP-1 over sulfonylureas is that it prevents hypoglycemia by increasing glucose-dependent insulin release from the pancreatic islets. GLP-1 is produced in response to foods and its levels are reduced in type 2 diabetes. Additionally, it decreases food intake, inhibits improper postmeal glucagon release, and slows stomach emptying. Therapy with GLP-1 and its analogs is linked to weight reduction, partly due to the effects of GLP-1 on slower stomach emptying and its well-known adverse effects of nausea and vomiting. GLP-1-like analogs that are resistant to DPP-IV degradation and substances that raise GLP-1 by inhibiting DPP-IV have been the subject of research. According to experimental research, GLP-1 promotes the growth of mature β-cells and prevents B-cell death, indicating a possible role for incretin-mimetics in vivo in preventing β-cell malfunction, which is common in individuals with type 2 diabetes [3-9]. GLP-1 may improve cardiac contractility, enhance glucose absorption in both normal and postischemic rat hearts, and cause an endothelial-dependent decrease in rat lung vascular tone. Exendin-4 is a naturally occurring peptide found in Gila monster saliva. Its molecular structure makes it significantly more resistant to DPP-4 destruction than active GLP-1, and it shares 53% of the amino acid sequence of human GLP-1. The 39-amino acid peptide incretin mimetic exenatide, a synthetic form of exendin-4, has glucose-regulating properties comparable to those of human GLP-1, although it is more resistant to DPP-4 deactivation. Exenatide slows stomach emptying, inhibits glucagon secretion, binds to the GLP-1 receptor, increases glucose-dependent insulin secretion, and decreases food intake. More intriguingly, exenatide seems to improve β-cell function. In fact, exenatide reduces hepatic glucose production in the postprandial state by normalizing both the loss of first-phase insulin secretion and the hypersecretion of glucagon from α-cells, in addition to glucose-dependent insulin stimulation. According to clinical recommendations, individuals with type 2 diabetes who are currently taking metformin, a sulfonylurea, or both but still have subpar glycaemic control may benefit from it as an additional therapy. Exenatide should be started at a dose of 5 mcg twice a day, at any time during the 60-minute window before meals in the morning and evening. Exenatide reduces weight by 0.9 to 3.1 kg while lowering glycosylated hemoglobin (HbA1C) levels by 0.4% to 0.9%. There have also been reports of decreases in diastolic blood pressure (0.8–2.3 mm Hg) and systolic blood pressure (3.4–3.7 mm Hg) [11-19].

Novel hypoglycemic medications. Blood sugar and weight control. SGLT-2i have a unique hypoglycemic mechanism that does not depend on insulin. Instead, it decreases the proximal renal tubules' ability to reabsorb glucose, which increases the excretion of glucose from the urine and controls the blood glucose levels of T2DM patients. This inhibitory effect of glucose reabsorption is particularly noticeable in hyperglycemia. The brain, kidney, cardiomyocytes, and vascular endothelial cells are among the organs and cells that contain the GLP-1 receptor (Ban et al., 2008). When blood glucose levels are elevated, GLP-1RA activates the GLP-1 receptor, which increases insulin secretion from pancreatic β cells and decreases glucagon release from pancreatic α cells. GLP-1RA does not stimulate insulin release when blood glucose levels are low, which lowers the risk of hypoglycemia. SGLT2i is one of the primary medications used to treat individuals with heart failure, according to the 2021 ESC Guidelines on Heart Failure Management [5-11]. The 2022 American Diabetes Association Standards of Medical Care: The American Diabetes Association (ADA) suggests a regimen including SGLT-2i (for ASCVD/HF/CKD) or GLP-1RA (for ASCVD) for individuals with atherosclerotic cardiovascular disease (ASCVD) or indications of high risk, heart failure, and chronic kidney disease (CKD). When T2DM patients are switched from DPP-4i to GLP-1 RA, it is advised to stop using DPP-4i because to the overlapping hypoglycemic mechanisms. identifies variations in blood glucose and weight control in different situations, such as GLP-1RA vs. DPP-4i, GLP-1RA vs. SGLT-2i, GLP-1RA + SGLT-2i (sequential or simultaneous treatment), and SGLT-2i or GLP-1RA or SGLT-2i + DPP-4i vs. glimepiride or insulin. When compared to insulin and sulfonylureas, the primary benefits of novel hypoglycemic medications are their considerable hypoglycemic impact and low frequency of hypoglycemia adverse events. Furthermore, DPP-4i provides benefits for those who do not need to reduce weight, and SGLT2i and GLP-1RA have clear cardio-renal protective effects [13-21].

Hazards associated with new hypoglycemic medications beyond their hypoglycemic effects. Fractures and hypoglycemia. According to the meta-analysis by Kanie et al. (2021), there is uncertainty regarding the impact of GLP-1RA on hypoglycemia and bone fracture, and there may be somewhat certain evidence that SGLT-2i and DPP-4i have no significant effect. Actually, GLP-1RA is a form of incretin that acts as a hypoglycemic agent by stimulating pancreatic β cells to secrete more insulin in response to glucose. Only when glucose levels exceed roughly 3.5 mmol/L does insulin secretion rise. GLP-1RA has a low risk of hypoglycemia because its activity is glucose-dependent, unless it is used in conjunction with insulin or sulfonylureas. Similarly, when DPP-4i was added to sulfonylureas to treat type 2 diabetes, the risk of hypoglycemia increased by 50% over the first six months of treatment, and one out of every 17 patients experienced extreme hypoglycemia. This emphasizes the necessity of adhering to the guidelines for lowering the dosage of sulfonylurea medications when beginning DPP-4i [7-12].

Discussion. Relative insulin insufficiency, insulin resistance, and elevated hepatic glucose output are the hallmarks of type 2 diabetes. One or more of these metabolic abnormalities are intended to be corrected by the medications used to treat the illness. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) currently prescribe hypoglycemic medications in addition to diet and exercise as first-line therapy. Anti-hyperglicemic drugs actually belong to seven different classes, each of which has specific pharmacologic characteristics. The purpose of this review is to outline the pathophysiological underpinnings of their mechanism of action, which is an essential step in tailoring diabetes patients' care while appropriately accounting for the potential advantages and adverse effects of medications. In contrast to typical stepwise therapy, earlier research suggested beginning combination therapy to reach glycemic objectives more quickly while lowering the incidence of hypoglycemia. 2001 eligible T2DM patients (body-mass index (BMI), 22–40 kg/m2 and HbA1c, 6.5–7.5%) were randomly assigned to either the initial metformin monotherapy group (stable daily dose of 1, 1.5, or 2 g) or the early stage combination therapy group (50 mg vildagliptin (DPP-4i) twice a day + metformin). Three study periods make up the five-year treatment period. If the initial monotherapy failed to keep HbA1c < 7.0% during period 1, a combination treatment was used in its place [5-12]. All patients were treated with vildagliptin plus metformin at the start of period 2. According to research by Yusuf et al. (2021), participants who do not have CVD but are at moderate cardiovascular risk benefit long-term from polypill (with or without aspirin), which contains various antihypertensive medications and statins (average follow-up time is 4.6 years, polypill reduces the occurrence of cardiovascular events). According to Chow et al. (2017), participants with untreated hypertension respond well to quadpill treatment, which consists of four antihypertensive medications at quarterly doses: amlodipine 1.25 mg, atenolol 12.5 mg, hydrochlorothiazide 6.25 mg, and irbesartan 37.5 mg. The advantages of polypill and quadpill in individuals with moderate cardiovascular risk or initial antihypertensive therapy (drug dose reduction may help reduce adverse reactions and eliminate the need for dose adjustment) have significant reference value for the combination therapy of hypoglycemic medications (increase patient compliance, lower the failure rate of single-drug hypoglycemic, reduce single-drug dose to control costs). 541 million adults worldwide have IGT, according to the most recent data (IDF Diabetes Atlas, 10th edition) [14-18]. Reducing their risk of getting type 2 diabetes is very crucial. Over 75% of adults with diabetes reside in low- and moderate-income nations. As a result, managing the expense of diabetes care is crucial. The new hypoglycemia medications will undoubtedly see significant price reductions once their patents expire and they become broadly accessible. However, in both prediabetes and newly diagnosed T2DM patients, modifying the dosage of hypoglycemic medications and the initial combination therapy may assist increase

efficacy and lower expenses (both the cost of pricey medications and the medical burden due to treatment failure). Although DPP-4i and metformin, as well as the combination of SGLT-2i and metformin, have been approved in some countries and regions (like Japan and the European Union), they are primarily used in patients who have poor monotherapy or who are taking the drugs in the combination separately (e.g., empagliflozin and metformin hydrochloride). Thus, research on approved or unapproved combination medications for the initial management of type 2 diabetes and prediabetes should be expedited. This procedure will be aided by the approval of oral GLP-1RA (semaglutide) [19-22].

Conclusions. This thorough systematic review and meta-analysis shows that using DPP-4 inhibitors, GLP-1 agonists, and SGLT-2 inhibitors reduces HbA1c, weight, SBP, and DBP. The prevalence of hypoglycemia prior to and following Ramadan, however, is not well documented. According to the research, patients with type 2 diabetes who want to fast during Ramadan may benefit greatly from these more recent drugs, which are also safer. However, we stress the need for large randomized head-to-head investigations of various medicines during Ramadan and warn physicians against the interpretation of these findings due to the inconsistent quality of the included research.

Metformin and lifestyle changes are the first line of treatment. A second medication chosen from the sulfonylureas, thiazolinediones, incretin mimetics, and incretin enhancer medicines must be used if metformin alone is unable to provide adequate glycemic control, is not tolerated, or is contraindicated. In any case, avoiding therapeutic inertia is especially important, thus treatment should be adjusted as quickly as possible to maintain glycemic control HbA1c at roughly 7%. In order to customize treatment, a number of criteria, including the risk of hypoglycemia, comorbidities, patient age, the presence of diabetic complications, and treatment costs, must be appropriately taken into account in this second stage.

Although rare instances call for care, new hypoglycemic medications are typically well tolerated. Compound hypoglycemic medications, particularly those including SGLT-2i and/or oral GLP-1RA, should be researched and developed as soon as feasible for those with prediabetes and newly diagnosed type 2 diabetes. Based on this, we offer additional research suggestions for the management of HF problems in T2DM. These findings can help patients with prediabetes and type 2 diabetes manage their blood glucose levels and risk of complications, particularly heart failure.

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