Treatment adherence and the contemporary approach to treating type 2 diabetes mellitus

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The rising burden of type 2 diabetes mellitus (T2D) poses a significant healthcare challenge on a global scale. The economic impact is also substantial and continually increasing. In Serbia**,** even though the prevalence is officially around 12 percent, nearly 40 percent of the adult population is estimated to be living with undiagnosed diabetes and more than half the population is obese or overweight.

This review comprehensively addresses the present approach to treating T2D, emphasizing the critical role of treatment adherence. We review the various components of T2D treatment, underlining the significance of lifestyle modifications. The pros and cons of medications used in treatment are discussed and factors influencing adherence are analysed. A healthy lifestyle remains the foundation of the treatment, and if not sufficient, early pharmacotherapy is initiated. Medications have been developed to lower blood sugar levels with cardiorenal protection, however, due to their still high cost, metformin remains the drug of first choice for most patients. Adherence to the treatment regimen is often poor. Factors associated with this are diverse and often multiple in a particular patient. Poor adherence is associated with poor glycaemic control, increased risk of disease complications, higher cardiovascular risk, increased mortality, hospitalizations, and healthcare costs. In addition to reducing the complexity of drug therapy and better informing the patient, improved education and motivation could lead to greater adherence. Enhanced communication between the patient and the physician and reduced treatment costs could also have a positive impact. The review concludes that addressing factors affecting adherence can significantly improve T2D outcomes and reduce costs. Further research is needed to identify region-specific risk factors for poor adherence.

Key words: type 2 diabetes mellitus, antidiabetic drugs, adherence, compliance

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INTRODUCTION

Modern approach to the treatment of type 2 diabetes mellitus

Type 2 diabetes mellitus (T2D) is a complex chronic disease which requires multifactorial behavioural, and pharmacological treatments for the prevention or delay of complications and the maintenance of quality of life, which include controlling blood glucose levels, managing body weight, controlling risk factors for cardiovascular diseases, comorbidities, and disease complications[1]. It requires an individualized, person-centred approach to enhance patient's engagement in self-care activities[2]. Individual treatment goals and strategies are established by considering the social determinants of health and the preferences of people living with diabetes[3]. Achieving target glycaemic levels leads to a significant and lasting reduction in the occurrence and progression of complications, and early intervention is crucial[4]. Despite the wide range of therapeutic options for T2D, less than 50% of patients achieve glycaemic levels recommended by the American Diabetes Association, and about two-thirds prematurely succumb to cardiovascular diseases[5].

The modern approach to T2D management involves the active participation of patients in their treatment, i.e., self-care. Self-care means that the patient actively monitors and responds to changing life and biological conditions, adapting different aspects of diabetes treatment to maintain metabolic control and reduce the risk of complications[1]. Such behaviour includes regular blood glucose monitoring, adjusting dietary intake, taking medications regularly, engaging in regular physical activity, foot care, routine medical check-ups, dental check-ups, etc. (ref.[3]). Adherence to diabetes treatment implies the active, voluntary participation of the patient in the treatment of the disease by following the agreed treatment regimen and sharing responsibility for treatment with healthcare professionals[6].

Adherence, compliance, and persistence

The World Health Organization (WHO, 2003) has defined adherence to long-term therapy as the extent to which a patient's behaviour aligns with the agreed recommendations of a healthcare professional, such as taking medication, following a diet, and/or executing lifestyle changes. According to the WHO, adherence to long-term therapy for chronic diseases is approximately 50% in developed countries, and even lower in developing countries. Methods for measuring adherence can be direct or indirect. Direct measurement methods are more sensitive but are often invasive or impractical (e.g., measuring drug levels or its metabolites in the blood, measuring biological markers, supervised medication intake) (ref.[7]). Indirect methods (patient self-reports, questionnaires, electronic monitoring devices, pill counts) are commonly used but can be inaccurate since patients are often unreliable sources of information. Electronic medical records are increasingly used to assess adherence. It involves tracking the proportion of picked up and prescribed medications over a specific period or the proportion of days supplied with the medication during a defined timeframe[6]. These measures provide data on the acquisition of medications but not on actual consumption and timing. Adherence is considered good when a patient takes at least 80–90% of the prescribed medication[8]. Compliance differs from adherence in that it does not consider the active involvement of the patient in the treatment or the patient's consent to the healthcare professional's recommendations. With compliance, the patient is in a passive position and is seen merely as an object[6]. Persistence refers to the duration of time during which a patient continues to take the therapy in proportion to the prescribed duration of treatment or the length of time from the start to discontinuation of treatment[9].

MATERIALS AND METHODS

Our review covers the published literature on the contemporary approach to treating T2D, adherence to various therapies, the effects of suboptimal adherence, economic implications, and strategies for improving adherence. Key articles were retrieved from the scientific database PubMed. The search strategy used key terms such as "type 2 diabetes mellitus", "therapy", "adherence", "OAD". Only articles written in English language were included, without date restrictions. After the exclusion of conference papers, short communications, abstracts, duplicates and irrelevant articles, we analyzed 61 publications. Our inclusion criteria for publications related to the modern pharmacological treatment of T2D covered the period from 2018 to 2023, while publications related to adherence had no date restrictions.

RESULTS

Modern treatment of type 2 diabetes and adherence

Previous research has shown that when studying adherence to T2D treatment, it is important to consider each component of treatment (blood glucose self-monitoring, medication intake, following a diet, physical activity, foot care) independently because data suggests that the correlation between adherence to each component is low, indicating that adherence is not a one-dimensional concept[10].

A healthy lifestyle in the treatment of type 2 diabetes and adherence

The foundation of diabetes treatment is the promotion of a healthy lifestyle through medical nutritional therapy, physical activity, psychological support, weight control, and, if necessary, counselling regarding tobacco use[1]. Medical nutritional therapy conducted by a dietitian-nutritionist can significantly reduce blood glucose levels and prevent, delay, and treat diabetes-related comorbidities[11].

Physical activity has a significant impact on cardiometabolic health in T2D (ref.[12]). Regular aerobic exercise improves glycaemic management in adults with T2D, resulting in less daily time in hyperglycaemia and reductions of ~0.6% in glycated haemoglobin (HbA1c) levels[12]. The mentioned effects on glycemia can be enhanced if physical activity is performed for 45 min or more during the postprandial period[13]. Resistance exercise also improves glycaemic control, flexibility, and balance, which is important due to the increased risk of impaired physical function at an earlier age in T2D (ref.[12]). A wide range of physical activities, including leisure time activities, can significantly reduce HbA1c (ref.[14]). Even small but regular changes in physical activity can make a difference to long-term health benefits; an increase of just 500 steps a day is associated with a 2–9% reduction in the risk of cardiovascular morbidity[15].

Healthy sleep is considered an essential component of a healthy lifestyle in the treatment of T2D (ref.[16]). Disturbances in the quantity, quality, and timing of sleep are associated with an increased risk of obesity and glucose metabolism disorders[17].

Recently, it has been suggested that a weight loss of approximately 5–15% should be the primary goal in the treatment of many individuals with T2D (ref.[18]). Greater weight loss is associated with greater benefits; a 5–10% weight loss contributes to metabolic improvement, and a 10–15% weight loss can lead to disease-modifying effect and remission of diabetes[18].

Despite evidence of the benefits of physical activity and exercise, adherence to long-term exercise programs varies between 10–80% (ref.[19]). There is evidence that patients go through numerous cycles of weight loss and relapse before they can maintain the achieved weight loss, suggesting that healthcare professionals should consistently encourage patients to adopt a healthy lifestyle[20]. Factors affecting adherence to regular physical activity and exercise include injuries due to excessive use, lack of motivation, and whether the activity is supervised[21].

In one study on attitudes toward adherence to diet and exercise, patients with T2D and their educators had different views on the barriers affecting adherence[22]. Regarding exercise, educators believed that lack of motivation and physical limitations were the main barriers to adherence, while patients cited circumstances, including factors such as weather conditions. As for diet, patients were bothered by the type of food included in the weight loss program, while educators considered social factors (education, income, family and friend support) to be the most important[22].

Medications for lowering glucose

Sodium-glucose cotransporter 2 inhibitors

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are oral medications that lower plasma glucose by increasing urinary excretion of glucose. They have moderate to high glycaemic efficacy, with lower efficacy at lower estimated glomerular filtration rate (eGFR) values. Their use has significantly increased due to studies showing their positive impact on the cardiovascular system and kidneys[23]. Studies have demonstrated that these medications are effective in reducing the risk of cardiovascular death, myocardial infarction, hospitalization due to heart failure, all-cause mortality, and improving renal outcomes in patients with T2D and established cardiovascular disease or a high risk of cardiovascular disease[24]. Their use is associated with an increased risk of genital mycotic infections, which are typically mild and treatable. The use of SGLT2i can increase the risk of diabetic ketoacidosis (DKA). However, its incidence is low and can be reduced through education about the signs and symptoms of DKA, and the temporary discontinuation of the medication in situations that predispose to this condition (acute illness, fasting, perioperatively) (ref.[24]). Although early research suggested several safety areas of interest (acute kidney injury, dehydration, orthostatic hypotension, amputation, and fractures), longer-term prospective studies have not confirmed an increased risk of these conditions[25,26]. Patients with T2D and peripheral arterial disease benefit more from SGLT2i therapy than those without peripheral arterial disease, without an increased risk of severe limb ischemia[27]. In patients with T2D and chronic kidney disease, the use of SGLT2i is associated with a reduced incidence of kidney-related adverse events[28].

Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 receptor agonists (GLP-1 RA) augment glucose-dependent insulin secretion and glucagon suppression, decelerate gastric emptying, reduce postmeal glycaemic increments, reduce appetite, energy intake and body weight[29,30]. In addition to improving HbA1c in adults with T2D, some GLP-1 RAs are approved for reducing the risk of major adverse cardiovascular events in adults with T2D and established cardiovascular disease (dulaglutide, liraglutide, and subcutaneous semaglutide) or for individuals with multiple risk factors for cardiovascular disease (dulaglutide). They are also used for long-term weight management (subcutaneous liraglutide titrated to 3.0 mg once daily; subcutaneous semaglutide titrated to 2.4 mg once weekly). GLP-1 RA are primarily administered subcutaneously, but there is now an oral preparation available (oral semaglutide) (ref.[31]). Recent studies have shown greater benefits for blood glucose levels and body weight with higher doses of GLP-1 RA, with a higher proportion of patients achieving target glycaemic levels[32]. The most common adverse effects of GLP-1 RA are gastrointestinal in nature (nausea, vomiting, and diarrhoea), typically occurring during the initiation and dose escalation but diminishing over time. Gradual dose escalation is recommended to alleviate gastrointestinal effects[30]. Education is necessary when introducing GLP-1 RA that induce a sense of satiety, which helps reduce food intake. It is important to assist patients in distinguishing between the negative sensation of nausea and the positive sensation of satiety that aids in weight reduction[33]. GLP-1 RA are contraindicated in patients at increased risk of rare medullary thyroid carcinoma, as preclinical studies have shown C-cell tumors in rodents treated with GLP-1 RA. More frequent retinopathic complications can be explained by the rapid decrease in HbA1c levels in patients with pre-existing diabetic retinopathy and high glycaemic levels, as has already been seen in studies with insulin[34]. GLP-1 RA are associated with a higher risk of biliary tract diseases[35].

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 inhibitors (DPP4i) are oral medications that inhibit the enzymatic inactivation of endogenous incretin hormones, leading to the release of glucose-dependent insulin and a reduction in glucagon secretion[23]. They have a modest effect in lowering glycemia and a neutral effect on body weight. They are well-tolerated, with minimal risk of hypoglycaemia. They do not reduce cardiovascular risk, although a reduction in the risk of albuminuria progression has been observed with linagliptin[36]. While generally well tolerated, the use of saxagliptin has been associated with an increased risk of chronic heart failure and there have been rare reports of arthralgia and hypersensitivity reactions with the DPP-4i class[23]. Due to their high tolerability and modest efficacy, DPP4i may be suitable for specific populations. For instance, inpatient treatment of hyperglycaemia with basal insulin plus DPP4i has proven to be effective and safe in older adult patients with T2D, yielding similar glycaemic levels but with less glycaemic variability and fewer hypoglycaemic episodes compared with basal-bolus insulin regimens[37].

Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 receptor agonist

In May 2022, the U.S. Food and Drug Administration approved tirzepatide, a GIP and GLP-1 RA for glycaemic control in adults with T2D. Additional metabolic benefits include a favourable effect on liver fat content and reductions in visceral and subcutaneous abdominal adipose tissue volumen[38]. The most common side effects are gastrointestinal, especially nausea[39].

Metformin

Because of its high efficacy in lowering HbA1c, minimal risk of hypoglycaemia when used as monotherapy, weight neutrality with the potential for modest weight loss, a good safety profile, and low cost, metformin is traditionally recommended as the first-line therapy to lower glucose in T2D. However, there is an alternative approach that could be acceptable. The benefits of GLP-1 RA and SGLT2i for cardiovascular and renal outcomes have been shown to be independent of metformin use. Therefore, in patients with established or high risk of cardiovascular disease, heart failure, or chronic kidney disease, these agents should be considered independent of metformin use[40]. Early combination therapy may be considered at initiation when there is a need for additional glycaemic effect or cardiorenal protection[41]. The most common side effects of metformin include diarrhea, stomach ache, loss of appetite and nausea[42]. Vitamin B12 deficiency is also a common side effect of taking the drug in higher doses or for long periods of time[20]. Metformin should not be used in patients with eGFR < 30 mL/min per 1.73 m^2, and dose adjustment should be considered at eGFR < 45 mL/min per 1.73 m^2 (ref.[42]).

Sulfonylureas

Sulfonylureas (SU) are highly effective in lowering glycemia, but with a lack of durable effect. Their advantages include low cost and availability[29]. However, due to glucose-independent stimulation of insulin secretion, they are associated with an increased risk of hypoglycaemia and lead to modest weight gain[43]. In a prospective study, the use of sulfonylureas or insulin for early intensive blood glucose control significantly reduced the risk of microvascular complications, emphasizing the importance of early and continuous glycaemic management[44].

Thiazolidinediones

Thiazolidinediones are oral medications that increase insulin sensitivity and have a high glucose-lowering effect[29]. The glucose-lowering effect is long-lasting, most likely due to a potent impact on preserving beta-cell function[45]. Pioglitazone has positive effects on non-alcoholic fatty liver disease and non-alcoholic steatohepatitis[46]. Possible side effects include fluid retention and heart failure, weight gain and bone fractures[45,47,48].

Insulin

The primary advantage of insulin therapy is that it lowers glucose in a dose-dependent manner and can therefore lower almost any glucose level. However, its effectiveness and safety are largely dependent on patient education and support provided to facilitate self-management[29]. The pharmacokinetic and pharmacodynamic profile of available insulins should be carefully considered, and the one that best suits the physiological needs of the individual patient should be selected[3]. Numerous insulin formulations are available, with advances in therapy geared toward better mimicking physiological insulin secretion[49]. The challenges of insulin therapy include weight gain, the need for education and titration for optimal effectiveness, the risk of hypoglycaemia, the need for regular blood glucose monitoring, and cost.

Fixed combinations of basal insulin analogues with GLP-1 RA are more effective in lowering blood glucose levels than individual components. They lead to less weight gain and fewer hypoglycaemic episodes compared to intensified insulin regimens[49]. They have better gastrointestinal tolerability than with GLP-1 RA alone[49].

Combination therapy

Traditional recommendations have focused on the stepwise addition of therapy, allowing for a clear distinction between the positive and negative effects of new drugs. There is evidence indicating the advantages of combination approaches in treating T2D. Combination therapy has several potential benefits, including prolonged duration of glycemic effect, simultaneous targeting of multiple pathophysiological processes of T2D, impact on adherence and persistence, complementary clinical benefits (e.g., glycemic control, body weight, and cardiovascular risk) (ref.[50-52]).

Adherence to oral antidiabetic medications

Numerous studies indicate the lack of adherence to treatment with oral antidiabetic medications (OAD). It has been shown that there is an inverse relationship between taking a prescribed OAD and the level of HbA1c, with each 10% increase in OAD adherence associated with a decrease of 0.1% in HbA1c (ref.[53]). In an analysis of 11 retrospective studies conducted between 1966 and 2003, adherence to OAD therapy varied widely from 36% to 93% in patients who took the therapy for 6–24 months[54]. Prospective analyses of adherence using electronic monitors have shown that patients took 61–85% of OAD doses as prescribed[55]. In a comprehensive study of electronic medical records from 8,191 patients with diabetes prescribed OAD, only 39.6% of them remained persistent with the therapy after 24 months, and 4% never picked up the prescribed medication, even though 53% of them had HbA1c >7% (ref.[56]). Using self-reported compliance, a prospective assessment of 11,896 patients treated with one or two OHAs found that only 46% of cases demonstrated optimal compliance[57]. An analysis of medical records from 2,741 patients with T2D recently prescribed OADs showed that overall adherence was 81% (ref.[58]). A recent meta-analysis showed that treatment adherence differs between patients depending on the specific OADs they are using[59]. α-Glucosidase inhibitors – less commonly used glucose-lowering medications wich improve glycemic control by reducing postprandial glycemic excursions and glycemic variability had the lowest adherence rate (53%), followed by metformin (55%), insulin secretagogues (i.e., SU and meglitinides) and SGLT2i (both 61%), DPP4i (66%), and thiazolidinediones (68%) (ref.[59]). These differences in adherence may be attributed to the lower risk of side effects associated with SGLT2i, DPP4i and thiazolidinediones wich are generally well tolerated[23,25,45]. Also, it is worth noting that SGLT2i, DPP4i and thiazoli-

dinediones are usually prescribed in the advanced stages of T2D, when patients seem to have higher adherence to OADs (ref.[59]).

Adherence to insulin therapy

As diabetes progresses, insulin may be introduced as monotherapy or as additional therapy to OAD. Adherence to insulin therapy in T2D is poor. In retrospective insulin studies, adherence was 62% and 64% for long-term and new-start insulin users, respectively[54]. Of the latter, 4.5% did not start the therapy, and an additional 25.5% of patients soon abandoned it[56]. According to a study of 1,099 patients with T2D treated with insulin, the average adherence to insulin was 71% (measured as the percentage of the number of days per annum of insulin coverage) (ref.[60]). The level of adherence was a significant predictor of HbA1c, indicating that improved adherence resulted in better glycaemic control. A Spanish study of patients with T2D showed higher compliance among patients taking insulin alone (67%) than among those taking both, insulin and OAD (39%) (ref.[61]).

Factors influencing adherence to type 2 diabetes mellitus treatment

There are many potential factors that influence adherence, and often more than one is present in any given patient. Factors include duration of disease, the complexity of the dosing regimen, polypharmacy, patient perception of drug effectiveness, safety and tolerability of the drug, age, self-confidence, self-efficacy, stress, depression, alcohol abuse, the patient-healthcare provider relationship, social support, economic, geographic, cultural factors, etc. The duration of the disease is inversely related to adherence. The longer the disease duration, the lower the adherence to treatment, whether to pharmacotherapy, physical activity, or nutrition therapy[62]. Over the last two decades, the complexity of the pharmacotherapy for T2D has increased, and according to studies, the more medications a patient is prescribed, the lower their adherence to OAD tends to be[63]. The tolerability and safety profile of OAD can also impact adherence. Side effects of OAD, such as hypoglycaemia, weight gain, or gastrointestinal problems are associated with reduced adherence to therapy[64]. Younger patients and those recently diagnosed with diabetes have lower adherence to OAD medications[65]. Self-confidence and self-efficacy are associated with higher adherence to T2D therapy, suggesting that behavioural and cognitive interventions might improve adherence in certain patients[66]. Psychosocial stress is linked to poor adherence to T2D treatment regimens and poor metabolic control[67]. The incidence of depression is twice as high among patients with T2D as in the general population. Patients with depression are at greater risk of developing complications of T2D, have poorer glycaemic control, and are less adherent to self-care activities[68]. Alcohol consumption is related to poor adherence to diet, regular glucose monitoring, medication adherence and follow-up appointments[69]. The interaction between T2D patients and healthcare providers is also linked to adherence. A good patient-doctor relationship is associated with good adherence, while patients with poor adherence more often reported a bad relationship with their doctor. These patients also had higher HbA1c levels[70]. The same French study showed that poor adherence is associated with financial difficulties and a lack of family and social support.

Consequences of poor adherence

The main consequence of poor adherence to T2D treatment is decreased glycaemic control, leading to the known complications of diabetes, including microvascular and macrovascular diseases, an increased risk of morbidity, and mortality[5]. The economic impact of T2D is substantial and continually increasing. In 2007, it was estimated that the direct and indirect costs of diabetes in the United States were $218 billion annually[71]. An analysis of seven studies showed a reverse correlation between hospitalization costs and adherence and concluded that increased adherence leads to reduced costs of T2D treatment[72].

DISCUSSION

The aim of this paper was to present the contemporary approach to the treatment of T2D and emphasize the importance of adherence in it. Lifestyle changes remain crucial for the effective treatment of T2D. Healthy eating, increased physical activity, and weight reduction are the foundation of success[1]. Diabetes is a very heterogeneous disease with variable age at onset, related degree of obesity, insulin resistance and tendency to develop complications. As such, it requires personalized treatment tailored to individual needs, taking into account clinical characteristics, comorbidities, patient preferences, and barriers such as financial, cultural and geographic barriers, poorly organized healthcare systems, and transportation-related barriers[73]. The treatment of diabetes is a dynamic process, and the treatment plan can change over time depending on the patient's individual therapeutic response and disease progression. Therefore, constant communication and collaboration with healthcare providers are necessary from the beginning of treatment[2]. Pharmacological treatment of T2D is in constant development, significant progress has been made, and new drugs have been developed. Despite compelling indications for SGLT2i and GLP-1 RA for high-risk patients with cardiovascular diseases, heart failure, or chronic kidney disease, metformin remains the first-line therapy for most T2D patients due to its effectiveness in lowering blood glucose, minimal risk of hypoglycaemia, weight neutrality and cost-effectiveness[25]. In patients with non-alcoholic fatty liver disease and non-alcoholic steatohepatitis pioglitazone should be considered[46]. Shared decision making is essential, and an individualized approach is crucial to maximize the benefits of modern drugs[73]. Suboptimal medication-taking behaviour and low rates of continued medication use affects almost half of people with type 2 diabetes, leading to suboptimal glycaemic and CVD risk factor control as well as increased risks of diabetes complications, mortality and hospital admissions and increased healthcare costs[43,74,75].

There are many reasons for poor adherence, including age, social and psychological factors, poor education, a lack of understanding of the long-term benefits of treatment, treatment regimen complexity, high treatment costs, and negative opinions about therapy. Poor communication between healthcare providers and patients, side effects such as weight gain and hypoglycaemia can also have effects on poor adherence. The WHO has emphasized that increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments[76]. So far, interventions aimed at improving adherence have only been partially successful, and a potential explanation for this can be found in the multifactorial nature of adherence. In addition to reducing the complexity of pharmacotherapy by fixed combinations, factors such as better patient information, improved education, and motivation are associated with better adherence[77]. Improving communication between patients and healthcare providers and reducing treatment costs could also have a favourable impact on adherence.

CONCLUSION

Type 2 diabetes mellitus is a progressive disease, and its treatment involves lifestyle changes and pharmacological therapy, which are equally important in glycaemic control and reducing cardiovascular consequences. When healthy eating and physical activity are not sufficient, early initiation of pharmacotherapy is a critical aspect and should be tailored to each patient individually. Although there is convincing evidence supporting the use of SGLT2i and the GLP-1 RA class in the treatment of many people with T2D due to their organ-protecting effects, regrettably these agents are currently expensive. In the setting of limited resources, priority should be given to the most vulnerable patient groups with cardiorenal disease. Even though adherence to treatment leads to a better disease outcome, it is often poor. By addressing the known factors associated with poor adherence, there would be a significant improvement in T2D outcomes and cost reduction. Further research is needed to explore the risk factors specific to our region that are associated with poor adherence so that we can act more effectively on them.

Search strategy and selection criteria

Our research approach focused on incorporating studies discussing the modern approach to treating type 2 diabetes, as well as those addressing adherence in general and specifically in the treatment of type 2 diabetes. We conducted a search of existing literature using the scientific database PubMed, utilizing key terms such as “type 2 diabetes mellitus” and “therapy” or “adherence”. The four terms were combined using the Boolean operator “AND”. The search encompassed publications in English language, without any restrictions on the publication date. Through this search, we identified 469 scientific publications spanning the period from 1989 to 2023. Conference papers, short communications, and abstracts were excluded. Our inclusion criteria for publications related to the modern pharmacological treatment of T2D covered the period from 2018 to 2023. Publications related to adherence had no restrictions on the publication date. After eliminating duplicates and irrelevant articles, we analysed 55 publications, and an additional 6 were discovered and analysed through citations.

ABBREVIATIONS

T2D, Type 2 diabetes mellitus; WHO, World Health Organization; HbA1c, glycated haemoglobin; SGLT2i, Sodium-glucose cotransporter 2 inhibitors; eGFR, estimated glomerular filtration rate; DKA, diabetic ketoacidosis; GLP-1 RA, Glucagon-like peptide-1 receptor agonists; DPP4i, Dipeptidyl peptidase-4 inhibitors; GIP, Glucose-dependent insulinotropic polypeptide; SU, Sulfonylureas; OAD, oral antidiabetic medications.

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