General Medicine,ISSN:1311-1817, VOLUME 27 ISSUES 2, Page: 1796-1814
Journal link: https://general-medicine.org
Abstract Link: https://general-medicine.org/abstract-27-2-1796-1814/
April 2025

Comparative Analysis of SGLT-2 Inhibitors and GLP-1 Agonists in the Treatment of Type 2 Diabetes.

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Abstract

Introduction:

The two types of agonist receptors, like inhibitors Sodium Glucose Co-transporter-2 and Glycogen-like peptide-1 agonist receptors, are keenly associated with type-2 diabetes mellitus. This association is because of their ability to reduce the readings of HbA1C, which is glycated hemoglobin, with a low risk of developing hypoglycemic conditions, contrasting to their enhanced impact on blood pressure and body weight. This imposes their impact on nephroprotection and cardiovascular risk that emerges from the most frequent trials done for cardiovascular outcomes. This is the reason why there is a high chance that both of these mentioned chemicals have become more common; gathering and discussing more and more information is significant about their safety profile.

Area Covered:

Some of the safety concerns and adverse effects most often emerge in trials for these two chemicals, mainly the LAR, Lixisenatide, or maybe SGLT2i, Semaglutide, liraglutide, dulaglutide; these are mainly emphasizing dapagliflozin, canagliflozin, and SGLT2i, this was an attempt for comparing the molecule's safety profile for these mentioned classes.

Main Outcome Measures

Randomized control trials with multiple meta-analyses have been carried out with GRADE, this was used to certainly assess the evidence. The estimated absolute effects are included in this. The impact of 1000 patients was treated for a period of five years for those patients who are at a very low with no cardiovascular risk factors, three to four risk factors set as a low-risk factor, and moderate cardiovascular risk factors diagnosed with cardiovascular disease and the one who is at a high risk suffers from CKD and a category that is at a very high risk suffers from both chronic kidney disease and cardiovascular diseases. This systematic review was guided by a panel that provides oversight.

Results

The eligibility was proved for 421,346 patients those were obtained from 746 randomized control trials. All the referred results were based on the addition of GLP-1 agonist receptors and SLT-2 inhibitors to all the patients who are diagnosed with type-2 diabetes mellitus.All outcomes pertain to the incorporation of SGLT-2 inhibitors and GLP-1 receptor agonists into current diabetes management. Both drug classes reduced all-cause mortality, cardiovascular mortality, nonfatal myocardial infarction, and renal failure (high certainty evidence). Significant distinctions were identified between the two agents: SGLT-2 inhibitors decreased hospital admissions for heart failure more significantly than GLP-1 receptor agonists, while GLP-1 receptor agonists diminished the incidence of non-fatal stroke more effectively than SGLT-2 inhibitors, which had no impact. SGLT-2 inhibitors are associated with vaginal infections (high certainty), while GLP-1 receptor agonists may lead to severe gastrointestinal problems (low certainty). Evidence of poor certainty indicated that SGLT-2 inhibitors and GLP-1 receptor agonists may reduce body weight. Minimal to no evidence was discovered regarding the impact of SGLT-2 inhibitors or GLP-1 receptor agonists on limb amputation, blindness, ocular diseases, neuropathic pain, or health-related quality of life. The definitive advantages of these medications differ significantly among patients, ranging from low to very high risk of cardiovascular and renal outcomes (e.g., SGLT-2 inhibitors led to a reduction of 3 to 40 deaths per 1,000 patients over five years; refer to the interactive decision support tool (https://magicevidence.org/match-it/200820dist/#!/) for comprehensive outcomes).

Conclusion

Anyhow, some variances may occur comparing the advantages and the disadvantages of these. The inhibitors that are SGLT-2 with the agonist receptors that are GLP-1 are supposed to improve the renal and cardiovascular outcomes in patients those are suffering from T2DM. magnificent benefits are relying on the specific risk profile of the individuals that are supposed to have a significant consequence for commencing the clinical practices as this systematic study informs and recommend to BMJ rapid outcomes.

Expert Opinion

Irrespective of the individual SGLT-2 and GLP-IRA adverse effects, they have similarly identified safety profiles and both of the mentioned chemicals are easily assessable. The mode of action of both chemicals is potentially synergistic. As suggested by the nephroprotective and cardiology benefit team, the benefit of the prescribed medications they are supposed even to have a more profound effect when used in combination.

Keywords

Sodium-glucose co-transporter-2 inhibitor, Glycogen Peptide-1 agonist receptors, Cardiovascular diseases, Nephroprotection, Chronic Kidney Disease, Safety measures,

Introduction:

Understanding glucose homeostasis and the biology of type 2 diabetes has advanced significantly in recent decades [1]. An in-depth comprehension of the organs and hormonal systems governing blood glucose regulation has enabled the development of pharmaceuticals addressing various aspects of diabetes pathogenesis. This eventually aims to minimize the morbidity and mortality related to diseases

Managing cardiovascular risks and hyperglycemic conditions effectively is significant for minimizing the negative impacts of T2DM on the life of a patient. Treatment for T2DM with the two newly invented medicinal classes is being demonstrated by different meta-analyses and Randomized control trials. These two recently invented diseases are SGLT-2 inhibitors and

GLP-1RA. These two drugs produce significant effects on factors like cardiovascular risks, body mass index, and metabolic regulations. Multiple Facets are targeted by the treatment for type-2 DM, with its pathophysiology, including their distinguished complementary action methods. This renders their essentials for diminishing mortality and morbidity that may be associated with T2DM.

The main aim of this article is the analysis and evaluation of the present pieces of evidence that concern the potential and safety of serious adverse effects that are connected with the patients who are receiving GLP-1RA. This mainly includes exenatide LAR, loxonematid, semaglutide dulaglutide, liraglutide, and the other categories of SGLT-2 composed of canagliflozin, dapagliflozin, and empagliflozin. Already researched evidence related to overall safety may include conditions like diabetic ketoacidosis, hyperglycemia, and hypoglycemia, along with their adverse effects on amputations of body parts, disorders with Islets of Langerhans (alpha and beta cells), urinogenital disorders, and cardiovascular diseases.

We calculate the global number of patients suffering from type-2 diabetes mellitus. Around 500 million people globally are suffering from diabetes, and this caused around 1.5 million mortalities in the year 2016. Reduction of glucose intake is considered the fundamental aspect of treatment therapy for T2DM [2]. Individuals who are suffering from T2DM have an increased risk of cardiovascular diseases. Multiple extended Randomized Control Trials have been conducted to analyze the impact of SGLT-2 inhibitors and GLP-1RA actions that demonstrate a diminished death rate associated with cardiovascular diseases and also CVD that does not end in mortality [3,4]. The uneven reduction in mortality rate observed in different trials causes uncertain observations for clinicians and alters the extent of benefit [5,6].

The 2019 guidelines from the American Diabetes Association propose using SGLT-2 inhibitors and GLP-1 receptor agonists to treat diabetes in people with renal or cardiovascular disease whose glycemic goals have not been met [7,8]. The European Cardiology Society, in 2019, demonstrated the use of both of these two groups of medications on patients who are suffering from T2DM combined with some cardiovascular diseases or may be at a high risk of developing some CVDs [9]. The guidance provided by NICE (National Institute of Health and Care Excellence) in 2019 recommends a decent stepped approach that is meant for the intensification of diabetic treatment mainly designed for the representation of metformin as the initial treatment

with a subsidized addition of triple and dual therapies from multiple classes of drugs that includes SGLT-2 inhibitors [10].

Cardiovascular outcomes

The two identified pharmacological classes that are SGLT2 inhibitor and GLP-1 agonist receptors, are considered to efficiently reduce some major identified diseases like T2DM and some major adverse cardiovascular disorder. This is proved by conducting large level CVOTs, CANVAS, EMPA-REG, SUSTAIN-6, and LEADER. The outcomes obtained from different pharmacological classes varies are apparently different from each other. The ability of these classes to obtain these magnificent results with diagnosed cardiovascular disease and without cardiovascular diseases remains ambiguous. The major adverse results are somehow interconnected but still the results for both of these pharmacological classes remain variable. There is a particular inquiry that remains instant to if the particular patients features must be considered as a variable to inform the categorization of SGLT-2 inhibitor and GLP-1RA in a synchronized pattern. For the moderate to chronic kidney diseases the GLP-1RA is prescribed and for the patient coming with heart failure a prescription of SGLT-2 is given. Even though the results of the patients from recent CVOTS, the majority of patients are suspected to be eligible for these two classes do not receive them in some clinical setups. We also have observed some shift in paradigm in the patients suffering from T2DM, specifically the ones who are in the transition phase from just focusing on blood glucose control to an entire shift to treat renal and cardiovascular conditions.

Numerous published meta-analyses and systematic reviews were used to synthesize some therapies that are meant to lower the blood glucose level in patients suffering from T2DM. They include the stepwise meta-analyses on the treatment intensification in association with sulfonylurea and metformin [11]. The studied metanalyses also indicate that the mortality rate and other major adverse cardiovascular diseases combined with renal dysfunctions might be treated by effectively using the two mentioned pharmacological classes, LP_1RA and SPLT-2 [12, 15]. A comprehensive metanalysis was conducted that encompasses the present therapies required for therapies used for lowering blood glucose levels. This is a complete spectrum accompanying the efficient outcomes, the spectrum with certainty GRADE rating with absolute benefit assessments and disadvantages to the patients with differential and reduced risk for renal

and cardiovascular disorders; this is likely the possibility. In addition to these mentioned meta-analyses, multiple trials were conducted on a low scale and were recently published to generate the need for revised syntheses evidence [5, 7, 8, 16]

We also performed a systematic review consequently along with review meta-analyses that help in better assessing the benefits and the drawbacks of both these pharmacological classes comprising SGLT-2 and GLP-1 receptor agonists to treat the people suffering from T2DM. The BMJ Rapid Recommendation Project has undertaken this study, which is considered a collaborative effort made by the organization known by the name MAGIC, which is a foundation for the evident ecosystem. The primary aim of this effort is the efficient delivery of reliable practice guidelines within 30 days of the recently published research data; this published information is supported by summaries provided by comprehensive evidence. The reference systematic review was considered part of a cluster of BMJ Rapid Recommendations along with a comprehensive version, which is available on all the MAGIC applications. The reference meta-analyses are supposed to encompass all the different types of medication used to treat diabetes, particularly emphasizing inhibitors SGLT-2 and GLP-1RA, in addition to multiple other glucose-lowering treatments while making a comparison with other oral medicines [17].

Methods Protocol registration

For this systematic review, our designed protocol was registered with PROSPERO.

Guideline panel involvement

For the success of our study and for running a successful systematic review, a guideline panel was designed according to the protocol set by BMJ Rapid Recommendations. The designed panel consists of experts with subject mastery, methodologists, neurologists, pathologists, gastroenterologists, endocrinologists, diabetologists, internal medicine, nephrologists, cardiologists and eligible patients that help in the provision of essential oversight to the evaluation process This designed protocol was evaluated by the panel, along with evaluation of protocol, population was defined, significant patient outcomes were prioritized, baseline risks were suggested, this helps in the calculation of absolute effects of the treatments.

Search strategy

In Cochrane Central Register, Embase and Medline information specialists conducted a literature search. This literature research was done for randomized control trials for a four-year span from March to August 2020, without any restriction on the language. Database records were created from March 2021 to August 2020 were explored with the help of a search from different earlier meta-analyses that were conducted [11].

Study selection

Utilization of multiple systematic reviews of Veritas Health Innovation's Covidence were reviewed in Melbourne and Sydney, Australia. Full-text records and citations were reviewed by the two independent reviewers; these reviews were recorded for the pertinent studies. The disappearances were reconciled through consensus by a third reviewer, such as SCP and BT. The patients suffering from T2DM were considered eligible for the randomized control trials if these mentioned pharmacological classes were antagonists to each other, or they may encounter therapies and other treatments for lowering their blood glucose levels. The studies also proved that the results obtained in the 24th week were published subsequently. Either the isolated administration of drugs was done, or they were administered with a combination of the other classes and the therapies used for lowering blood glucose levels.

This is the review that looks at the outcomes relevant to the patients; this affiliation is defined by the criteria set by the guideline panel, and this criterion was the result of the different meta-analyses and the randomized control trials, irrespective of the fact that the evidence of the quantifying studies. These outcomes included mortality from all causes, cardiovascular mortalities, non-fatal MI, cerebral hemorrhage, CKD, CHF hospitalisation, blindness, treated eye diseases, and quality of life depending on the health condition, body mass index, body parts extraction, diabetic ketoacidosis, and infections in multiple organ s of the body. Because certain decision-makers gave it a priority, glycated haemoglobin A1c was included in the assessment even though the guideline panel did not identify it as a patient-relevant outcome.

Data extraction

Two independent reviewers for every study were appointed to every quantitative study and helped in the collection of the relevant data; the study data may include particular traits for the

studies, including the publication year, country or state of the journal, duration of the study and the significant outcomes of the study, the population of the study that includes demographics, comorbidities, setting of the study, population size, intervention description as the name, pharmacological class and dosage of the medicine is involved. The disagreements were settled by the reviewers by reconsidering it over if required, and then a third reviewer must be consulted.

Risk of bias assessment

The technique, which is Cochrane, is meant to address the concealment allocation and sequential randomized generation. Blinding, selected result reporting was utilized by the reviewers as SCP, this in better evaluation of the biases possibility in different meta-analyses and RCTS which has to be independently reviewed by the reviewers [18]. The risk of bias was rated as low, ambiguous, or high for each domain. When no techniques for concealment allocation were mentioned, and neither study participants nor the study conductor knew the treatment allocation, allocation concealment was considered by the reviewer to be low risk.

Analysis and Synthesis of Data

For the direct comparison of every treatment, we used a constrained maximum likelihood estimate in a frequentist pairwise meta-analysis. We presented standardized mean differences for quality of life-related to health, odds ratios for dichotomous outcomes, and associated 95% CIs for contingent outcomes of mean differences (body weight and glycated HbA1C) [19]. In analyses with 10 or more trials, statistical heterogeneity was assessed with the help of funnel plots and statistical tests to find possible modest study effects.

We conducted a network meta-analysis by assuming a consistent estimate of heterogeneity across different setups, this was done with significant help from the techniques and therapies that are used with a minimum probability of the estimation of the heterogeneity of the evaluated network. The node-spitting was also used in our study that was used to assess the direct and indirect estimated concordance in each of the evidence of a closed loop. A treatment interaction was designed in our study that was used to assess the entire network [20]. The standard deviation was also used in our study coming from similar RCTs that are meant to replace the non-significant SD for the independent variables [21,22].

The five baseline risk factors recommended by the guideline panel were meant for different categories that usually represent the marginal clinical situations aiming to practice the absolute effects measures on the cardiovascular and renal outcomes in the groups from different conditions and different backgrounds. Very minimal or no proteinuria has a very low risk, mainly defined as a probability of less than 30 mg/mmol or 300 mg/g. This has an estimated GFR of 16-34 mL per 1.89 m^2. The patients with a high risk may include the patients who are suffering from CKD and CVDs. The event rates are used from the most reliable sources of data, including systematic studies, RCTs, meta-analysis, equations predicting suspectable risk, cohort studies, and the pertinent trials for the placebo arm. The absolute treatment was calculated by the designed panel that were used for the estimation of the effects of network [23 – 28].

A consistent yearly risk was assumed for the desired outcomes for every year for the whole decade, and absolute baseline risk was also calculated for 1500 patients for the entire duration. These outcomes surpass the data from the short-term data if required. For the presentation of these outcomes as the absolute effects, an estimated average for the presentation of the absolute outcomes was calculated, and treatments were compared, the comparison was made in association with the estimated baseline risks. The analysis of the subgroups were categorized by the length of the trial, the body mass index, a high cardiovascular and renal risk presence was analyzed depending on the availability of the ample amount of data [29].

Evidence Certainty Assessment

Methods for assessing the confidence of the evidence for both the mentioned pharmacological classes are provided by the GRADE technique [30, 31]. The variables that are included in this aspect is the evidence rating direct estimation that includes the evaluation depending to be biased in publication, their imprecision, the biased risk, indirections, and inconsistency.

The confident rating obtained from the indirect estimates was initially dependent on the low rating of the two distinguished estimates, making up the dominating first-hand loop containing any necessary extended intransitivity reductions. The network estimation dependability of the study was based on the average provided by the information from significant direct or indirect resources. A more significant confident judgement was made on the conditions if the estimated yield had the equivalent data. The estimate is the most dependable one due to the impact of the

treatment that determines the use of the estimated outcomes with the most excellent assurance. This was supposed to determine if the estimation was direct or indirect. This downgrades the estimated network confidence on the condition if there is evidence of discrimination between the indirect and direct outcomes. for this purpose, the MAGIC application was used.
For effective use of the GRADE technique for constructing the tables that are summarizing the obtained results. Relying on the best-calculated average, the effect was obtained by the effective use of network meta-analyses. This helps us to provide absolute estimates of the related uncertainty effects for the category covering every related uncertainty and risk. Some of the evidences are summarized, and decision aids are presented by the use of the MAGIC application. This application contains multiple tools to record the findings.

Patient and public involvement

The involvement of the normal public was also assured, and 6 T2DM patients were considered part of the publication and development of the supervision. The patient advisory group, in collaboration with the Cochrane Task Exchange, compels to provide the partner's patients. We also altered our study question, which helps in the determination and prioritization of the significant patients considering the participation outcomes. we did not include the civilians in this initiative.

Result

Statistical Data

The research outline was included in the computerized search, bringing about 23167 enrolments. A total of 764 studies were analyzed, covering a very large population sample. 421,343 patients were analyzed after running a screening test. We further confined our study to the type of drug used for maintaining blood glucose levels; in our analyses, the patients were treated with 11 different drugs, as presented in Figure 01. The comparison of the treatment network from the available trials is presented in Figure 02. The sample size of these trials was variable, and it ranged from 23 to 18,112 patients. The median age of the participants was 54.4 years, the percentage of female participants was 54%, the aggregate BMI was 32.3, and the median HbA1C reading was found to be a baseline of 7.7%. The considered eligibility criteria for the nine studies was the CHF, in 37 trials, the patients complaining of CKD complementing proteinuria were considered, and the rest of the trials focused on some coronary conditions like atrial fibrillation

[4, 5, 16, 32-38]. Typically the conditions treated with SGLT-2 or GLP-1RA were given in contrast with the medicines that a person is already consuming to treat hyperglycemic conditions.

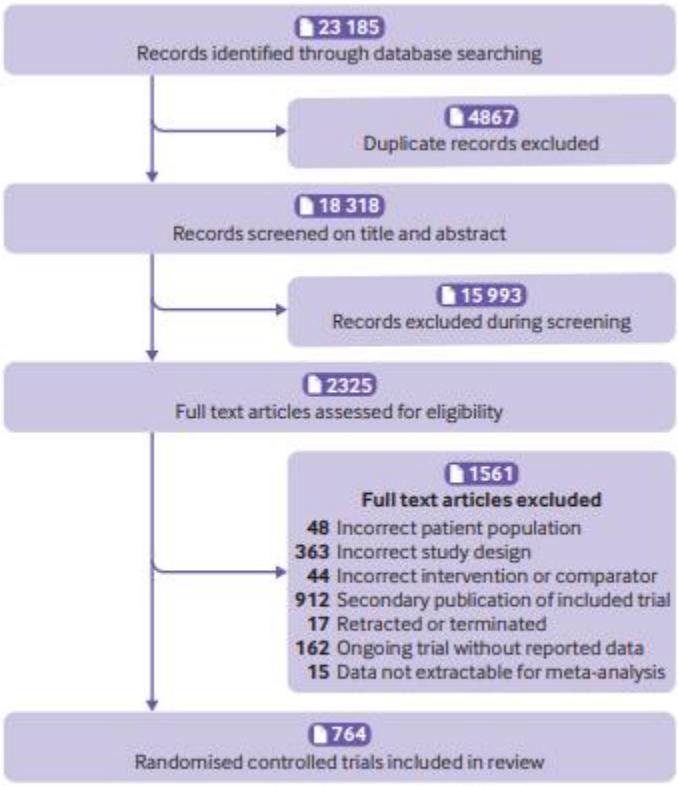

Fig 1 | PRISMA flow diagram of studies included in the review of glucose lowering treatments for type 2 diabetes

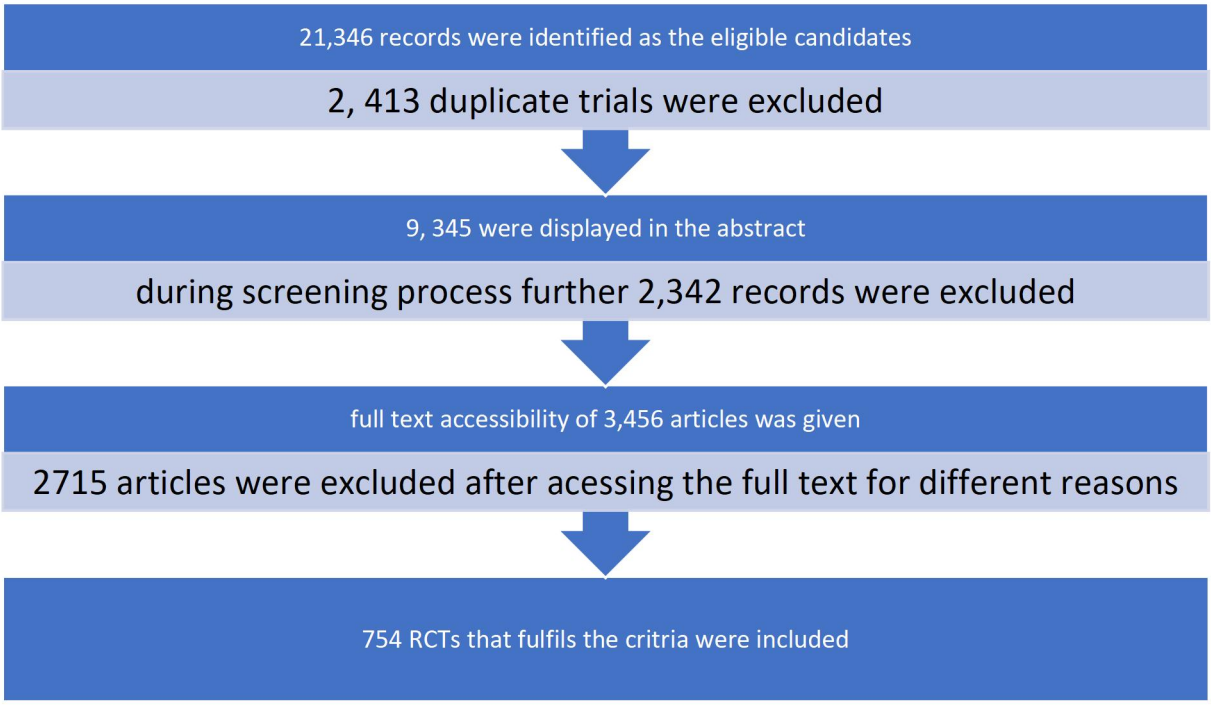

Figure 01: Prisma Flow Chart of the Studies that were reviewed for glucose-lowering therapies for T2DM.

Outcomes

No proof of the heterogeneity and inconsistency of the global network was identified, except for health quality. Yet, no additional significant concern was identified related to the indirect and direct coherence.

Discussion

Principal findings

Including the two identified drugs from two different pharmacological classes to treat the patients suffering from T2DM has exceptionally reduced the mortality rates. The robust evidence in the absence of head-to-head trials demonstrates a significant difference between GLP-1RA and SGLT-2, which has resulted in a lowering of the rate of hospitalization because of CHF as compared to the incorporation of GLP-1RA. The other drug conversely demonstrates a more obvious reduction in the cases with non-fatal hemorrhage without disturbing the other results. The distinguished results obtained from both of these drugs on the outcomes relevant to patients are inclusive of the reduction in the patient's body weight and enhances the life quality. The arm from them varies from patient to patient. Genital infections may result from the use of SLT-2, and gastrointestinal problems may arise due to GLP-1RA

Strengths and limitations of this study

The strength of this study covers detailed research searching for the eligible trials for the study that are independent processes and are not being impacted by the methodology, data selection process, identification of study, and screening by the two individuals. The study follows a new GRADE approach for assessing the reliability of the available data; this also provides an estimated absolute risk for reliable results. The study's limitation is its heterogeneity of the clinical settings of the considered trials, anyhow the congeniality of the study presented in different clinical setup initiate the concern.

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Conclusions

There are competent safety issues that are connected with the treatment of T2DM; the T2DM patients who are taking SGLT-2 or GLP-1RA are summarized in Figure 01. The most prominent negative effect of using GLP-1RA, along with other therapies for lowering blood sugar levels, is some issues in their gastrointestinal problems; these issues are not fatal. Contrary to this, the most common side effect of using SGLT-2 is some genital problems; in females, the most common side effect is an infection in the vagina. Although T2DM patients are suffering from glucosuria, the probability of developing UTI is very unlikely after the use of SGLT-2 inhibitors. Still, the chances of amputation of the lower limb certainly increase after the use of SGLT2 inhibitors, yet no significant evidence is present. According to recent studies, the probability of pancreatic cancer and pancreatitis increases after the use of GLP-1RA.

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