Management of Uncontrolled Type 2 Diabetes Mellitus with Combination Therapy with Metformin and/or Glucagon-like Peptide-1 Receptor Agonists/ Sodium-Glucose Cotransporter-2 Inhibitors

Bertha Lorena Contreras

School of Nursing: The University of Texas at El Paso

Doctor of Nursing Practice (DNP) Program

DNP Chair: Hector R. Morales, DNP, APRN, PMG/CS-BC

DNP Quality Improvement Project

April 22, 2022

Abstract

The management of chronic medical conditions in a primary care practice requires knowledge and commitment, particularly when providing services for the underserved. Type 2 diabetes mellitus (T2DM) is a complex and difficult condition that can result in complications that affect multiple organ systems. Numerous studies have described GLP-1RAs and SGLT-2is as complementary agents that can be used to prevent the multi-organ complications associated with T2DM. The purpose of this Quality Improvement (QI) Project is to introduce combination therapy with metformin and GLP-1RAs or SGLT-2is as part of an overall effort to address hyperglycemia in patients with uncontrolled T2DM. The foundations of this QI practice include a 10-day reflective practice in which T2DM was among the most frequent diagnoses. My findings revealed that current therapeutic strategies used to manage T2DM were not fully effective and might benefit from a change in practice. The implementation of this QI Project and the adoption of effective therapy improve the future care of patients with uncontrolled T2DM, their medication compliance, and their quality of life.

Management of Uncontrolled Type 2 Diabetes Mellitus with Combination Therapy with Metformin and/or Glucagon-like Peptide-1 Receptor Agonists/Sodium-Glucose Cotransporter-2 Inhibitors

Background knowledge

Diabetes is a frequently-diagnosed chronic metabolic disorder that is associated with high rates of morbidity and premature mortality. T2DM is currently a global healthcare priority. While 360 million individuals were diagnosed with T2DM in 2011, this number is projected to increase to 552 million by 2030 (Wei Sim et al., 2017). Uncontrolled T2DM leads to chronic kidney disease, retinopathy, and neuropathy. The treatment for T2DM has evolved over the last ten years and new drugs have become available that can be used to improve glycemic control and reduce the incidence and progression of these complications. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose co-transporter-2 inhibitors (SGLT-2is) are two types of drugs that, in combination with metformin, are now considered first-line treatment for uncontrolled T2DM. The mechanisms of action of these drugs complement each other and thus are more effective at preventing hyperglycemia and its microvascular complications (Castellana et al., 2019).

Numerous studies have described GLP-1RAs and SGLT-2is as complementary agents that can be used to prevent the multi-organ complications associated with T2DM. The results of these studies suggest that these drugs can be used as an early and more aggressive treatment of T2DM in patients at low risk for developing hypoglycemia (Lajara, 2019). In their publication, Simes and MacGregor (2019) review the recent guidelines for T2DM management, including the recommendations provided by the American Diabetes Association. At this time, the first-line

treatment for T2DM includes comprehensive lifestyle modifications together with metformin. If there is no reduction in hemoglobin A1c (HbA1c) in response to first-line therapy, guidelines suggest the addition of GLP-1RA or SGLT-2is to the metformin regimen to manage uncontrolled T2DM and its complications.

The purpose of this Quality Improvement (QI) Project is to introduce combination therapy with metformin and GLP-1RAs or SGLT-2is as part of an overall effort to address hyperglycemia in patients with uncontrolled T2DM. The foundations of this QI practice include a 10-day reflective practice in which T2DM was among the most frequent diagnoses. My findings revealed that current therapeutic strategies used to manage T2DM were not fully effective and might benefit from a change in practice. The implementation of this QI Project and the adoption of effective therapy improve the future care of patients with uncontrolled T2DM.

Local problem

Uncontrolled T2DM is a common chronic medical condition in my primary care practice. The local problem to be addressed by this QI Project is the implementation of effective treatment. I realized the need for more effective therapy for patients with T2DM upon review of my 10-day reflective practice log. Cardiovascular and renal complications are also common among patients with uncontrolled T2DM. My review of the patient records revealed that uncontrolled T2DM was not unique to my 10-day reflective practice These observations were the critical factors leading to my decision to pursue a QI Project. The current medical literature attests to the efficacy of GLP-1RAs and SGLT-2is at reducing HbA1c levels and the associated cardiovascular and renal complications (Berkovic et al., 2020).

Intended improvement

An advanced practice registered nurse (APRN) plays a critical role in providing care for patients with T2DM. As an APRN working in a rural community in New Mexico, I need to evaluate every patient before deciding on the most appropriate treatment. In addition to the medical condition, I need to consider each patient's medical insurance and socioeconomic status. I recognize that every patient is a unique individual. Immigrants dominate this region, many of whom are uninsured. Suboptimal insurance coverage increases the need for new, effective, affordable, and cost-effective medical treatment for T2DM.

Frequent complications of T2DM include retinopathy, nephropathy, autonomic nerve dysfunction, foot ulcers, and cardiovascular disease (Betonico et al., 2016). Hyperlipidemia is frequently-identified as a comorbidity associated with T2DM that increases the risk of developing peripheral vascular disease and stroke (Natali et al., 2021). In my practice, I need to interpret the test results of each patient with T2DM and use this information to manage their metabolic status. In addition, I need to evaluate the therapeutic options available for T2DM treatment and their potential side effect.

This QI Project focuses on changing the current therapy of uncontrolled T2DM in my practice. While current guidelines offer clinical decision support, policies also may need to be updated. A report published by Bertoluci et al. (2020) provided updates of several guidelines and clinical decision support systems currently used to manage T2DM. An evidence-based approach recommends lifestyle modifications at all phases of treatment. First-line antidiabetic agents such as metformin can be introduced to control HbA1c levels between 6.5–7.5%. Dual therapy is recommended for patients presenting with higher HbA1c levels (7.5–9%); in the latter case, metformin can be supplemented with an SGLT-2i or a GLP-1RA to provide glycemic control as well cardiovascular and renal protection. Thus, metformin, SGLT-2is, and GLP-1RAs have

become first-line agents for T2DM as they can provide effective glycemic control and cardiovascular protection. The use of these first-line antidiabetic agents helps to control blood glucose levels, reduce mortality associated with cardiovascular disease, and limit hospitalizations for heart failure (Hernandez et al., 2018). Finally, if the HbA1c levels do not respond to either monotherapy or dual therapy with first-line antidiabetic agents, the latest guidelines recommend the use of three or as many as four agents.

Study question

My review of the 10-day reflective practice log highlighted the variety of chronic medical conditions experienced by the patients in my rural primary care practice. I identified three possible opportunities to improve the care provided to the patients. After meeting with my chairperson, I selected diagnosis and management of uncontrolled T2DM as the subject of my QI Project. T2DM has become highly prevalent among patients in my practice as well as in the population at large.

Many factors influence the lack of compliance with medication regimens and recommended lifestyle modifications. Consequently, many of the patients initially diagnosed with T2DM will continue to exhibit elevated levels of HbA1c. In addition, many patients lack the motivation to continue with recommended treatments when they do not attain the desired outcomes, i.e., weight loss and decreased glucose levels. I have witnessed many complications of T2DM in this patient population. The micro and macrovascular complications of uncontrolled T2DM are frequently reflected in diagnoses that include hypertension, hyperlipidemia, chronic kidney disease, and neuropathy (Simes & MacGregor, 2019). The development of these complications largely reflects the quality and effectiveness of their treatment regimens. In my practice, I was following the now-obsolete guidelines for T2DM management and added drugs to

reduce HbA1c levels to standard levels without monitoring an individual patient's increased risk for complications. I realized that this practice was not sufficient and that my patients with T2DM might benefit from more aggressive treatment. Therefore, once my chairperson approved my PICOT (patient/population, intervention, comparison, outcome, time) question, I performed a literature review and identified publications featuring the highest level of evidence to validate my QI Project. My goal was to introduce high-level evidence-based therapy to improve the care I currently provide for my patients. In the literature review for my QI Project interventions, I identified publications that discussed the benefits, glycemic efficacy, safety, combination efficacy, and tolerability of the first-line antidiabetic agents. Systematic reviews of randomized controlled trials (RCTs) and meta-analyses revealed that GLP-1RAs and SGLT-2is either alone or in combination therapy with metformin provide excellent glycemic control as well as cardiovascular and renal protection.

Based on the review process, the PICOT question guiding the QI Project was as follows:

P: Patients 18–80 years of age who have been diagnosed with uncontrolled T2DM and managed with metformin

I: Addition of a GLP-1RA and/or an SGLT-2i to metformin (i. e., combination therapy)

C: Monitor blood glucose via HbA1c levels

O: Reduction in HbA1c levels

T: Four weeks

Methods

Ethical issues

The PICOT question was generated upon review of a 10-day reflective practice from my family practice clinic at La Clinica de Familia (LCDF) in rural Chapparal, New Mexico. I

formulated the QI Proposal, including prescribing a GLP-1RA and/or an SGLT-2i to patients currently managed with metformin who presented with uncontrolled T2DM. The QI Proposal was submitted and accepted by my chairperson. The LCDF medical director, Dr. Gaston Berrios, approved my project and signed the work letter that allowed me to complete my project at this site. For ethical training in a QI intervention, I completed the Collaborative Institutional Training Initiative (CITI) training before submitting the University of Texas at El Paso (UTEP) Institutional Review Board (IRB) application. The UTEP IRB approved the QI Project on November 17, 2021, and provided me with a letter designating it as not a research project. The significance of this project involves efforts to initiate and monitor more effective treatment of T2DM patients by implementing GLP-1RA/SGLT-2i combination therapy with metformin. The goal of this project is to provide a more effective intervention that will control chronic hyperglycemia in my T2DM patient population. I ensured patient confidentiality and anonymity for the conduction of the QI Project.

Setting

Implementation of the QI Project took place at LCDF (Chaparral, New Mexico) beginning on January 17, 2022, and concluding on February 18, 2022. Unfortunately, the patients in my practice do not always have access to the most appropriate treatments. All medications must be approved by the patient's medical insurance carrier, and each insurance company has its own drug formulary. Thus, the medication prescribed by the APRN may vary based on insurance coverage. Similarly, medication selection for the uninsured depends on the drug price. Fortunately, drug representatives frequently provide me with samples that I then provide directly to the many uninsured patients with T2DM.

Evidence-based research support that both GLP-1RAs and SGLT-2is are of benefit to patients with T2DM whose condition remains uncontrolled on metformin alone. However, while all three of these medications can be used to reduce glycemic levels, selection will depend directly on the individual patient's cardiovascular and renal function (D'Marco et al., 2021). Initiation of metformin is contraindicated for patients with a glomerular filtration rate (GFR) below 45 mL/min; this drug should be discontinued immediately in patients with a GFR below 30 mL/min because of the risk of developing metabolic acidosis (Bertoluci et al., 2020).

SGLT-2is works by promoting glucose excretion in the urine and inhibiting glucose reabsorption in the kidneys' proximal tubules, thereby enhancing glycosuria and reducing glucose levels in the blood. By these actions, SGLT-2is limit the toxic effects of high serum glucose levels on beta-cells (Zaccardi et al., 2016). A patient must present with a GFR >45 mL/min to meet the criteria for use of these drugs. Likewise, the starting dose of each drug varies based on GFR. For example, empagliflozin (brand name, Jardiance®) can be initiated or continued in patients with a GFR as low as 20 mL/min. By contrast, ertugliflozin (brand name, Steglatro®) is not recommended for patients presenting with a GFR between 30 to <60 mL/min and is contraindicated in patients with a GFR <30 mL/min. Some factors that restrict the efficacy of these drugs include endogenous regulatory processes that limit hypoglycemia and caloric intake while undergoing treatment with SGLT-2is (Zhou et al., 2020).

When used in combination with metformin, GLP-1RA provides complementary hypoglycemic action, particularly after meals. GLP-1RAs mimic the actions of GLP-1, which is an endogenous hormone produced in the small intestine in response to oral ingestion of glucose. GLP-1RAs act at the GLP-1R to promote the secretion of incretin, which is a hormone that promotes glucose-dependent insulin release by inhibiting glucagon secretion and promoting a

sense of fullness associated with reduced intestinal motility (D'Marco et al., 2021). This mechanism of action promotes reductions in HbA1c with additional benefits including weight loss and the reduced risk of hypoglycemia. Administration of a GLP-1RA with metformin has been proven to be safe and effective in patients with uncontrolled T2DM and typically results in a marked reduction in HbA1c (Htike et al., 2017).

The main objective of therapy is to lower glycemic levels and prevent complications associated with T2DM. Both GLP1-RA and SGLT-2is reduce HbA1c and provide cardiovascular and renal protection via control of hyperlipidemia and blood pressure. Therefore, the purpose of this QI Project is to apply evidence-based practice to reduce the glucose levels as reflected by HbA1c in patients treated with metformin together with a GLP-1RA and/or an SGLT-2i.

Planning the intervention

The issue of uncontrolled T2DM and the selection of appropriate therapy has a substantial impact on both health and quality of life. The implementation of this QI Project will ensure that I am addressing the patient needs and will thus improve their satisfaction with my care. My priority is to provide them with a meaningful contribution to their health. I am obligated to safeguard patient health under my training and code of ethics. My efforts to reduce glycemic levels in patients with uncontrolled T2DM may also prevent future complications.

In T2DM management, values measured include both fasting and postprandial glucose levels as well as glycated hemoglobin in the form of HbA1c. Controlling glycemia includes an assessment of acute serum glucose levels and HbA1c, the latter measured at least every three months. Given the comparatively short timeframe for this intervention, I focused on more short-term measurements provided by fructosamine tests. Fructosamine levels obtained every two

weeks are currently the most inexpensive tests available for glucose monitoring (Selvin & Mulder, 2022).

The implementation of this QI Project in the primary care setting includes patients who meet the criteria who are for clinic visits during the four-week study period. Patients included are female and male adults aged 18 to 80 years who are diagnosed with T2DM and undergoing treatment with metformin. Each patient has scheduled a routine follow-up visit to evaluate T2DM and blood laboratory results from a previous routine visit. I will include all patients meeting these criteria, regardless of their insurance status. Patients with HbA1c levels between 7.5 – 9% were diagnosed with uncontrolled T2DM. Depending on their individual cardiovascular and renal risk profiles, I provide the patient with information on GLP-1RAs and SGLT-2is and prescribe the appropriate combination therapy. The following steps in the care process are determined by a collaborative effort on the part of the patient and the provider.

Following the new guidelines (Li et al., 2020), one can consider adding either a GLP1-RA or an SGLT-2is to metformin if the patient has no evidence of cardiovascular disease (CVD) or chronic kidney disease (CKD). An SGLT-2i is prescribed for patients with heart failure or CKD; if the patient is unable to tolerate this drug, a GLP1-RA can be substituted. Contraindications for SGLT-2is include a GFR <45mL/min. Contraindications for GLP-1RA include personal or family history of thyroid cancer (medullary thyroid cancer) or pancreatitis. If uncontrolled T2DM persists in obese patients after three months of dual therapy, both SGLT-2is and GLP-1Ras can be added to the initial metformin regimen. All patients are asked to self-record fasting and postprandial blood glucose levels after breakfast, lunch, dinner, and to bring the logs to their follow-up appointment in two weeks. Baseline and two-week post-treatment fructosamine levels are sufficient for an HbA1c calculation. Depending on the medical insurance

formulary or available samples, the specific medications prescribed are as follows: GLP-1RAs including dulaglutide (name brand Trulicity®) or semaglutide (name brands Ozempic® and Rybelsus®) and SGLT-2is including ertugliflozin (name brand Steglatro®) and empagliflozin (name brand Jardiance®).

Planning the study of the intervention

The translational framework used in planning the study intervention and to provide structure to this QI Project was Lewin's Change Model. This is a three-phase model (Unfreeze, Change, and Refreeze) in which change results from a balance of both driving and restraining forces (White et al., 2021). As a first step, I realized the need for a change in my practice and to initiate more aggressive therapy for uncontrolled T2DM largely because of the growing number of patients in my practice with this diagnosis and the limited improvement observed in responses to the treatment provided (i. e., “Unfreeze”). The introduction of new medications to my practice resulted in a disturbance to the status quo. However, the driving force toward change provided me with the rationale needed to overcome resistance from existing barriers that would question the clinical value of this new intervention. This initiative provided me with the impetus to plan strategies to overcome problems, including the suboptimal medical insurance programs that predominate in my patient population, and thus strengthen the reinforcement of change (i. e., “Change”). This step permitted me to prepare to introduce the QI intervention. The change phase also includes real-world implementation of new therapeutic management strategies in my practice that depend on laboratory results and medication tolerance of each patient, as well as side effects, dose titration, and medication approval from insurance providers (i.e., “Refreeze”). The refreeze phase will be facilitated by reduced glucose and HbA1c levels among the patients enrolled in my QI Project. Furthermore, my evaluation of evidence-based practice outcomes for

T2DM patients revealed the need to improve their therapeutic management in my practice. My patients deserve to have access to optimal therapy that will prevent or reverse the complications associated with T2DM. Sustainability of these new behaviors will allow the implementation of these novel therapies as first-line treatment for uncontrolled T2DM in my practice.

I selected the Plan-Do-Study-Act (PDSA) as my QI Model. PDSA includes four cycles for analysis of the intended change for each patient included in the QI project (Institute for Healthcare Improvement [IHI], 2022). For my QI Project, the "Plan" phase involved the generation of the evidence-based intervention. As part of the "Do" phase, I reviewed the plan of treatment with the patients, including drug education and information on potential therapeutic benefits and side effects, as well as their responsibility for maintaining daily records of blood glucose levels, laboratory testing, and follow-up appointments. Real-world data are analyzed during the "Study" phase, including a review of the glucose logs and fructosamine levels. During this phase, the side effects of the new medication regimens are discussed and the next steps with respect to treatment are determined. While the blood glucose and fructosamine data provide me with information on the effectiveness of the new medication regimens, I also consider access to therapy and its cost to the patient. This is followed by the "Act" phase which involves an ongoing adjustment based on real-world evidence as the complete cycles bring opportunities to identify other modifiable factors such as drug titration and/or issues with therapy adherence.

A review of the medical insurance formulary is critical to determine whether the patients in my practice will have coverage for these medications. Although most of the patients in my practice are covered by Medicaid of New Mexico in this rural community, some are covered by Medicare and/or private insurance. As a provider, I researched the approved drug lists and prepared a drug sample inventory before implementing the QI Project.

Literature review

A Cochrane database search provided me with evidence-based literature to support the proposed QI Project. A primary search resulted in nine articles that supported my selected intervention. The secondary selection was somewhat more difficult due to the comparatively large amount of evidence-based material available.

Several systematic reviews and meta-analyses of RCTs consider the efficacy and tolerability of GLP-1RA and SGLT-2is. The overall conclusion is that use of these modalities in combination with metformin has been proven to be effective.

Among these reports, Hussein et al. (2020) conducted a systematic review and network meta-analysis on the efficacy and tolerability of SGLT-2Is and GLP-1RAs. The results of this study revealed that long-acting GLP-1RAs provided superior outcomes with respect to decreasing HbA1c, waist circumference, and body weight. By contrast, SGLT-2is were effective at reducing blood pressure. The review also provided an evidence-based guide to the management of T2DM. Among the adverse effects, GLP-1RAs have been associated with gastrointestinal problems and SGLT-2is with genital infections.

Castellana et al. (2019) conducted a meta-analysis on the efficacy and safety of GLP-1RAs as add-on therapy in cases in which SGLT-2is provided inadequate T2DM treatment. The evaluation included four RCTs with a follow-up of at least 24 weeks and tracked reductions in HbA1c to <7%. Weight loss and blood pressure control were also included in the outcome measures. The results of this review support intensification with GLP-1RAs in patients whose T2DM remains uncontrolled on SGLT-2is.

Ding et al. (2020) compared the efficacy and safety of GLP-1RAs with SGLT-2is for obese patients with uncontrolled T2DM that was managed with metformin. The study clearly indicated that GLP-1RAs were superior to SGLT-2is in this patient population, albeit with adverse effects including gastrointestinal events. Larger and longer-term follow-up clinical trials will provide more evidence on the sustainable effects and safety of GLP-1RAs compared to SGLT-2is.

RCTs focused on the safety and efficacy of a once-weekly dose of GLP-1RA together with daily SGLT-2i compared to each regimen alone were compared in patients with T2DM that was not adequately controlled with metformin. Jabbour et al. (2018) concluded that combination therapy resulted in sustainable decreases in glycemia, systolic blood pressure, and weight over 52 weeks. No unanticipated safety findings were reported.

Zhou et al. (2019) published the results of a meta-analysis that focused on the efficacy and safety of SGLT-2is and GLP-1RAs in combination *versus* SGLT-2is alone or with metformin and concluded that combination therapy that included GLP-1RAs provided greater benefits with respect to glycemic levels, weight, and systolic blood pressure control. However, the authors did emphasize the need for individualized treatment while selecting monotherapy *versus* a combination approach.

A systematic review and meta-analysis performed by Patoulias et al. (2019) also revealed the improved antiglycemic efficacy of GLP-1RAs and SGLT-2is together compared to SGLT-2is alone. In this study, reductions of HbA1c of 0.91% were observed (95% confidence interval [CI], -141 to -0.42, I2 = 94%) with combination therapy compared to SGLT2is alone. The authors suggest that combination therapy might provide important improvements in glycemic control and promote weight reduction. However, the regimen is associated with a moderate risk of

hypoglycemia and gastrointestinal side effects. Cardiovascular and renal outcomes are also improved by this synergy.

Zaccardi et al. (2016) published the results of a systematic review and network meta-analysis that focused on the efficacy and safety of SGLT-2is in T2DM. The results revealed that, although these agents increase the risk of contracting genital infections, the treatment is effective for glycemic control and prevention of cardiovascular complications. The long-term outcomes of these studies will need to be evaluated further.

Jia et al. (2020) performed a systematic review and meta-analysis focused on the use of GLP-1RAs and SGLT-2is as monotherapy or add-ons to pre-existing metformin regimens. The study outcomes revealed that GLP-1RAs have superior capacity to reduce HbA1c levels when added to metformin compared to results from other incretin mimetics or SGLT-2is, and that administration of SGLT-2is resulted in reductions in fasting plasma glucose both with or without concomitant metformin therapy. The authors concluded that combination therapy with GLP-1RAs or SGLT-2is resulted in reductions in HbA1c and fasting plasma glucose levels more effectively when used as add-ons to metformin. Among their conclusions, the authors recommended the use of GLP-IRAs or SGLT-2is as monotherapy to reduce the risk of hypoglycemia and noted that all drugs should be selected on a patient-centered basis.

Mantsiou et al. (2020) published the results of another systematic review and meta-analysis in which GLP-1RAs and SGLT-2is were used as combination therapy for the treatment of T2DM. Based on a review of four independent studies, the authors concluded that, compared to monotherapy, combination therapy resulted in significant reductions in HbA1c levels with a weighted mean difference of -0.61% (95% CI, -1.09% to -0.14%). While combination therapy

resulted in no increased risk of hypoglycemia risk, there were only a few findings that addressed cardiovascular outcomes and mortality.

I also reviewed several T2DM management guidelines, including those from the American Diabetes Association, the American Society of Nephrology (Li et al., 2020), the Portuguese-Brazilian evidence-based T2DM approach (Bertoluci et al., 2020), the clinical decision support system from the department of biochemistry of the National University of Singapore (Wei Sim et al., 2017) and results published by Hernandez et al. (2018). These guidelines recommend the use of GLP1-RAs and/or SGLT-2is in combination with metformin for patients with T2DM and atherosclerotic cardiovascular and renal complications. Berkovic et al. (2020) studied the efficacy of combination therapy in a series of RCTs and identified the benefits that might be realized in routine clinical practice and follow-up.

The results of the RCTs reviewed in these studies are reliable and provide high efficacy and internal validity. The studies and meta-analyses focused on GLP-1RAs and SGLT-2is verify that these RCTs were the results of well-conducted trials with rigorous methodology in controlled clinical settings. The guidelines consider all data from the published RCTs and provide results that can be used by medical providers as part of a highly structured approach for clinical practice.

Methods of evaluation

HbA1c measurements are used widely as an indirect measure of mean blood glucose levels and meet the United States Food and Drug Administration (FDA) requirements for diabetes diagnosis and treatment efficacy. The results from the RCTs reviewed for this QI Project measure treatment efficacy as reductions in HbA1c levels. This value reflects the average

glucose exposure over a period of time as it measures the accumulated fraction of Hb that has become glycosylated during the lifespan of a red blood cell (about 120 days). Other biomarkers can be used to measure this parameter over a shorter timeframe. Fructosamine, which is a measure of glucose linked to protein, is an excellent laboratory test for evaluating average glucose exposure for this QI Project; it is inexpensive and provides an indirect measure of blood glucose levels over the span of two to three weeks. Fructosamine levels ranging from 266 to 312 mmol/L are functionally equivalent to HbA1c levels of 7% (Selvin & Mulder, 2022). The formula for HbA1c calculation ([0.017 x fructosamine level] + 1.61) converts fructosamine levels in units of μmol/L to %HbA1c (Henderson et al., 2021). Each patient enrolled in the QI Project has lab results with current HbA1c levels on file. In this project, I obtained a baseline fructosamine level before initiating therapy and then again after two weeks for a short-term evaluation of its impact on HbA1c levels. Each patient was also asked to provide a two-week report of self-monitored of blood glucose levels (i.e., fasting, and post-prandial levels after breakfast, lunch, and dinner). These data will provide supporting documentation for the fructosamine levels measured after two weeks of treatment. I make certain that the patients have fully understood the educational process via a demonstration of self-monitoring, blood glucose recording, and fingerstick techniques. Documentation of blood glucose levels can be challenging for many of my patients. The efforts and actions required to obtain medical insurance approval of prescribed medications also present a significant barrier. To address this problem, I provide initial drug samples and prepare proper authorization forms for approval using data from the literature review for support. To ensure medical insurance coverage for the fructosamine levels, the patient records are adjusted to include both the International Classification of Diseases (ICD)

10 Code Z51.81, Encounter for therapeutic drug level monitoring as well as the primary ICD 10 Code E11.65, Diagnosis of T2DM with hyperglycemia.

Analysis

Implementation of this QI Project began on January 17, 2022. Ten patients with T2Dm were seen during the ensuing four weeks. The Study phase of the PDSA QI Model was used to direct this analysis. Baseline HbA1c values were measured before each of these appointments as part of the laboratory tests that were ordered after the previous follow-up visit. A baseline fructosamine level was obtained on the day of the appointment; a second fructosamine level was obtained at the two-week follow-up visit scheduled after the intervention. I analyzed the fructosamine results using the traditional parametric conversion method which permitted me to assess changes in HbA1c over the first two weeks on the new drug regimen. The next scheduled HbA1c measurement will be performed three months after implementation of the QI Project.

My analysis of the laboratory results determines the next step of treatment. As shown, fructosamine levels and thus calculated HbA1c decreased consistently in all patients. The plan was adopted based on these positive results.

Results

Outcomes

Patient 1 was a 56-year-old male who was first seen in my clinic on January 17, 2022. He has been taking metformin 1000 mg twice a day. Based on his laboratory results that included an HbA1c level of 10.2%, the patient was prescribed dulaglutide (Trulicity®) at a dose of 0.75 mg/0.5 mL once a week and empagliflozin (Jardiance®), one 10 mg tablet once a day. The first dose of dulaglutide was provided on the day of the clinic visit. A fructosamine level of 378

μmol/L was measured at this visit. The patient presented at his two-week follow-up visit on January 31, 2022. A second fructosamine level measured at this time was 318 μmol/L (calculated HbA1c 7.06 %). The patient reported that he was following a healthier diet since the initiation of the treatment although he noted occasional feelings of low energy. At a four-week follow-up appointment on February 14, 2022, the dulaglutide dose was kept in 0.75 mg/0.5 mL and the empagliflozin remained in 10 mg because of two episodes of hypoglycemia. Will follow up in three months for HbA1c. His medical insurance was Blue Cross Blue Shield (BCBS) Centennial (Medicaid of New Mexico) that required a prior authorization. I wrote a letter including data from my literature review and obtained approval for both drugs. Final result: outcomes met (see Figures 1 and 3).

Patient 2 was a 61-year-old female who was first seen in my clinic on January 17, 2022. She was taking metformin 1000 mg twice a day. Based on her laboratory results, including an HbA1c level of 10.7%, the patient was prescribed dulaglutide (Trulicity®) at a dose of 0.75 mg/0.5 mL once a week. She received the first dose of this medication on the same day as the clinic visit. She was not a candidate for an SGLT-2i because her GFR was <30 mL/hr. Her first fructosamine level was 437 μmol/L; the second fructosamine level measured at her two-week follow-up visit was 360 μmol/L (calculated HbA1c 7.73 %) . The patient reported that she had experienced no side effects. At her four-week follow-up visit (February 14, 2022), her dulaglutide dose was increased to 1.5 mg/0.5 mL. Will follow up in three months for HbA1c. Her medical insurance was Presbytrerian Centennial (Medicaid of New Mexico) that required a prior authorization. I wrote a letter including data from my literature review and obtained approval. Final result: outcomes met (see Figures 1 and 3).

Patient 3 was a 55-year-old female who was first seen in my clinical on January 18, 2022; Her HbA1c level at that time was 10.4%. She was taking metformin 1000 mg twice a day. She has a history of CVD; she had undergone a coronary artery bypass graft procedure and remains at ongoing risk for developing renal disease. Her lipid levels were mildly elevated and were treated with statin drugs. Her baseline fructosamine level was 410 μmol/L. She was prescribed dulaglutide (Trulicity®) 0.75 mg/0.5 mL once a week and ertugliflozin (Steglatro®) 15 mg once a day. She received the first dose of dulaglutide at the clinic. Her two-week follow-up fructosamine level on February 2, 2022, was 325 μmol/L (calculated HbA1c 6.115 %). The patient reports no side effects from these medications. She reports that this is reducing her carbohydrate intake, including the elimination of sugar-sweetened sodas. At the four-week follow-up appointment (February 15, 2022) she again reported no side effects. Her dulaglutide dose was increased to 1.5 mg/0.5 Ml and kept ertugliflozin at 15 mg (highest dose). Will follow up in three months for HbA1c. Her medical insurance was BCBS Centennial (Medicaid of New Mexico) that required a prior authorization. I wrote a letter including data from my literature review and obtained approval for both drugs. Final result: outcomes met (see Figures 1 and 3).

Patient 4 was a 57-year-old male who was first seen in my clinic on January 18, 2022. His HbA1c level at that time was 7.9%. He was taking metformin 1000 mg twice a day. His first fructosamine level was 279 μmol/L. He was prescribed ertugliflozin (Steglatro®) 5 mg tablets once a day. At his two-week follow-up visit (February 2, 2022) his fructosamine level was 265 μmol/L (calculated HbA1c 6.115 %). No side effects were reported. He will continue on this dose of ertugliflozin (5 mg/day) and will follow up in three months for HbA1c. BCBS Centennial was his insurance (Medicaid of New Mexico) that required a prior authorization. I

wrote a letter including data from my literature review and obtained approval. Final result: outcomes met (see Figures 1 and 3).

Patient 5 was a 49-year-old female who was first seen in my clinic on January 19, 2022. Her HbA1c level at that time was 7.9%. She was taking metformin 1000 mg twice a day. Her first fructosamine level was 278 μmol/L. She was prescribed ertugliflozin (Steglatro®) 5 mg tablets once a day. His fructosamine levels decreased to 247 μmol/L (calculated HbA1c 5.8 %) at the two-week (February 4, 2022). She will continue on this dose of ertugliflozin (5 mg/day) and will follow up in three months for HbA1c. The patient is uninsured, will provide her ertugliflozin 5 mg monthly. Final result: outcomes met (see Figures 1 and 3).

Patient 6 was a 53-year-old male who was first seen on January 19, 2022, with an HbA1c level of 9.9%. He was taking metformin 1000 mg twice a day. His first fructosamine level was 417 μmol/L. He was prescribed semaglutide (Ozempic®) at a dose of 0.25 mg once a week. His fructosamine level at his two-week follow-up (March 2, 2022) was 335 μmol/L (calculated HbA1c 7.3 %). At his four-week follow-up visit on February 16, 2022, he reported no side effects, and the dose of semaglutide was increased to 0.5 mg once a week. Will follow up in three months for HbA1c. The patient is uninsured, will provide semaglutide one box once a month. Final result: outcomes met (see Figures 2 and 4).

Patient 7 was a 57-year-old male who was first seen on January 19, 2022, and presented with an HbA1c level of 9.5%. He was taking metformin 1000 mg twice a day. His fructosamine level at that time was 369 μmol/L. He was prescribed dulaglutide (Trulicity®) at a dose of 0.75 mg/0.5 mL once a week and provided with the first dose on that same day. At his two-week follow-up visit on February 2, 2022, his fructosamine level was 350 μmol/L (calculated HbA1c 7.56 %). He reported no lifestyle modifications. He reported one episode of nausea as a side

effect of the new medication. At the four-week follow-up on February 16, 2022, the dose of dulaglutide was increased to 1.5 mg/0.5 mL. He was instructed to report any side effects. He reported frequent nausea and the dose was adjusted back to 0.75 mg/0.5 mL. I recommended him lifestyle modifications reducing carbohydrate intake and increasing his physical activity. Will follow up in three months for HbA1c. BCBS Centennial was his insurance (Medicaid of New Mexico) that required a prior authorization. I wrote a letter including data from my literature review and obtained approval. Final result: outcomes met (see Figures 2 and 4).

Patient 8 was a 50-year-old female who was seen in my clinic on January 20, 2022, with an HbA1c level of 10%. She was taking metformin 1000 mg twice a day. Her fructosamine level at that time was 364 μmol/L. She was prescribed dulaglutide (Trulicity®) at a dose of 0.75 mg/0.5 mL once a week. At her two-week follow-up visit (February 3, 2022) her fructosamine level was 335 μmol/L (calculated HbA1c 7.31 %). She reported intermittent episodes of low fasting blood glucose levels. I increased the dose of dulaglutide to 1.5 mg/0.5 mL on February 17, 2022, at her four-week follow-up visit. Given her reports of episodes of hypoglycemia, an SGLT-2i was not added to her medication regimen. Will follow up in three months for HbA1c. Presbyterian Centennial was her insurance (Medicaid of New Mexico) that required a prior authorization. I wrote a letter including data from my literature review and obtained approval. Final result: outcomes met (see Figures 2 and 4).

Patient 9 was a 77-year-old male who was seen in my clinic on January 21, 2022, with an HbA1c level of 8.2%. He was taking metformin 1000 mg twice a day. His first fructosamine level was 281 μmol/L and dulaglutide (Trulicity®) was initiated at a dose of 0.75 mg/0.5 mL once a week. At the two-week follow-up visit (February 4, 2022), his fructosamine level was 264 μmol/L (calculated HbA1c 6.1 %). He reported no side effects and the dulaglutide dose was kept

on 0.75 mg/0.5 mL. Will follow up in three months for HbA1c. Medicare was his medical insurance and covered the drug once it was prescribed. Final result: outcomes met (see Figures 2 and 4).

Patient 10 was a 46-year-old female who was seen in my clinic on February 1, 2022, with an HbA1c level of 10.4%. She was taking metformin 1000 mg twice a day. She was prescribed semaglutide (Ozempic®) at a dose of 0.25 mg once a week. The first dose was provided to her at the clinic. Her first fructosamine level was 358 µmol/L. Her fructosamine level at her two-week follow-up visit (February 15, 2022) was 338 µmol/L (calculated HbA1c 7.4 %). She reported no side effects and her dose was increased to 0.5mg at the four-week follow-up on March 1, 2022. Will follow up in three months for HbA1c. The patient is uninsured, semaglutide will be provided one box every month. Final result: outcomes met (see Figures 2 and 4).

Changes in fructosamine levels detected in each patient are shown in Figures 1 and 2. The calculated HbA1c values are shown in Figures 3 and 4.

Figure 1

Fructosamine Levels Before and After Implementation in Patients 1–5

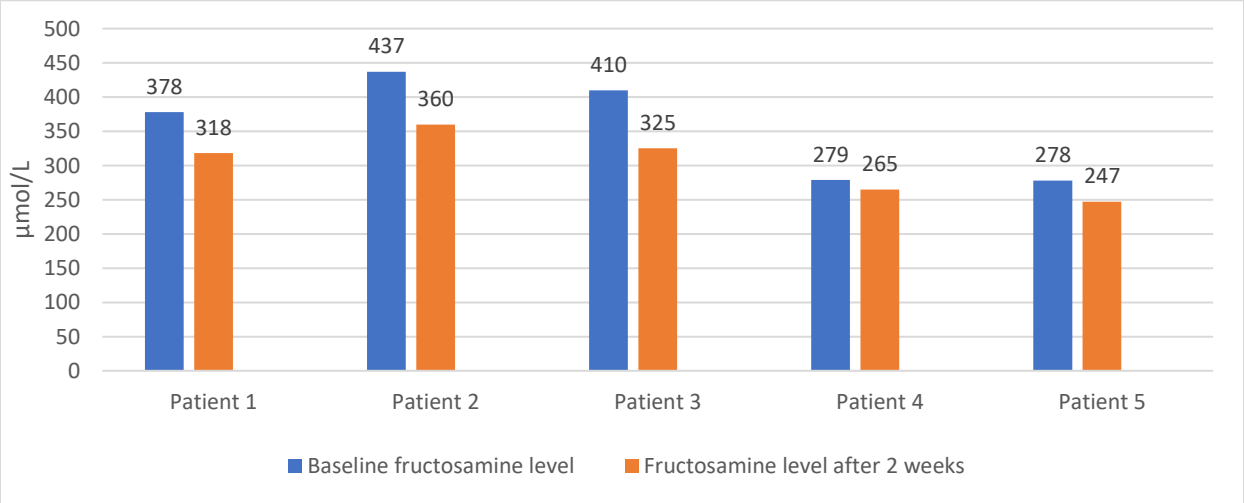


Figure 2

Fructosamine Levels Before and After Implementation in Patients 6–10

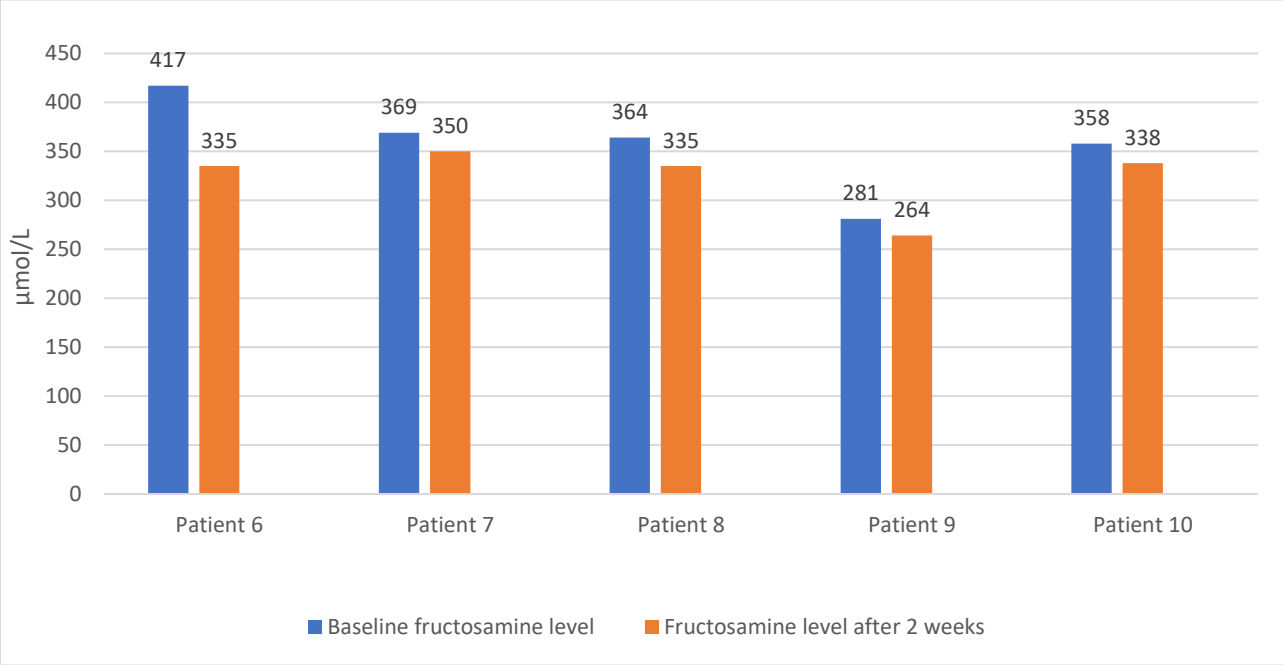


Figure 3

HbA1c Calculated from Fructosamine Levels Before and After Implementation in Patients 1–5

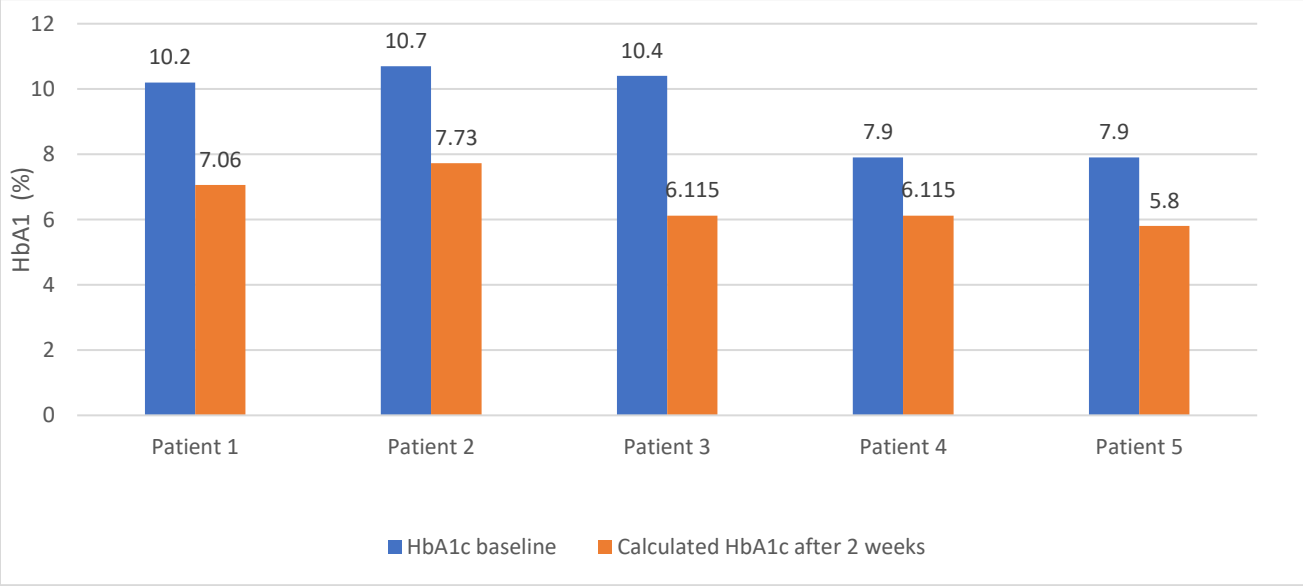
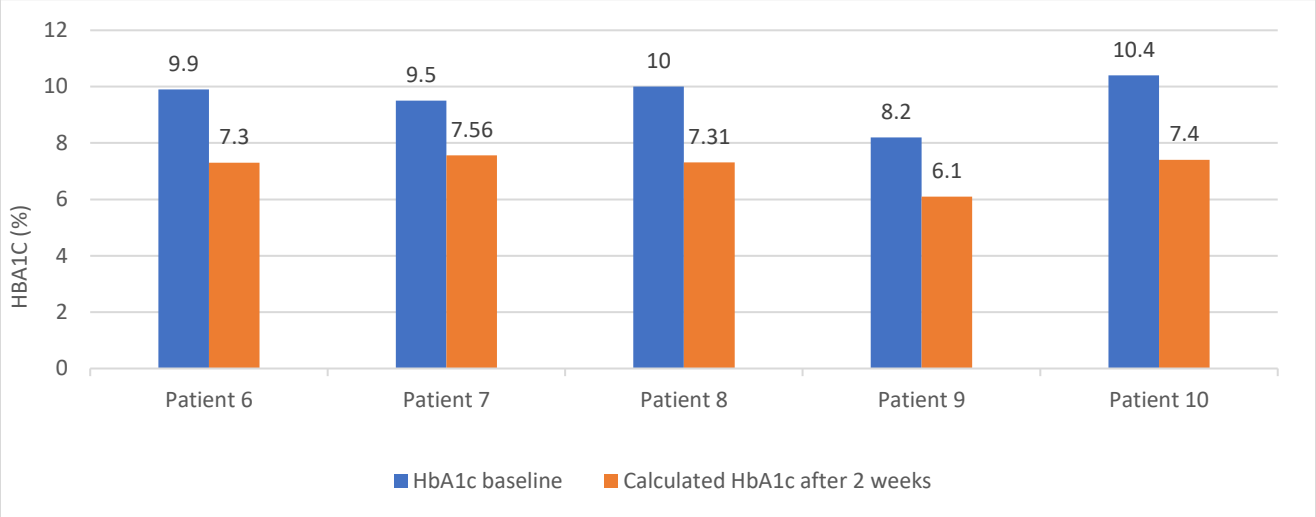


Figure 4

HbA1c Calculated from Fructosamine Levels Before and After Implementation in Patients 6–10



Discussion

Summary

With the development of new drugs, guidelines and recommendations for the management of uncontrolled T2DM have changed. The effectiveness, efficacy, and tolerability of the GLP-1RAs and SGLT-2is have been tested and proven repeatedly as indicated by the results of my literature review. The results of the implementation of this QI Project affirms that both GLP-1RA and SGLT-2i together with metformin are useful and effective and may be adopted as the first line of therapy for the management of uncontrolled T2DM. The outcome of the QI Project reveals the effectiveness of the therapy.

The patients accepted the new therapy and many were committed to pursuing lifestyle modifications. All patients exhibited reduced HbA1c levels as determined from serial fructosamine levels. The act of recording blood glucose levels also serves as motivation for continued adherence to this new therapy.

Only one of the ten patients enrolled in this project received medication coverage at the time that it was prescribed. Continuation of therapy after the initial implementation is of course vital. In addition to the reduction in glycemic levels, I was also successful in obtaining prior authorization for the prescribed medications as part of the implementation of this project. The differences in fructosamine levels observed over a period of two weeks provided substantial motivation for my patients, many of whom were excited to see these results. While patient compliance with blood glucose recording remains a challenge, many became more motivated to do so after seeing the initial positive results and realizing the effectiveness of the therapy.

Among the strengths of this study, the therapeutic regimens prescribed resulted in a reduction in glycemic levels that could be appreciated at the two-week follow-up visit. The possibility of weight loss is another plus to this study, as noted by one patient at the four-week follow-up visit. Another strength of the strategy used here is the availability of sample drugs that can be provided to the patients at the first appointment. Likewise, information that I provided from my literature review virtually guaranteed pre-authorization approval by the various medical insurance providers.

Relation to other evidence

As part of this project, I identified studies on combination therapy and reviews of RCTs, and meta-analyses that all emphasized glycemic control. The impact of uncontrolled T2DM on the cardiovascular and renal systems and the role of effective intervention therapy was a common denominator of every study in the literature review. The studies discussed in the following paragraphs consider different approaches the therapy implementation.

Nelson et al. (2021) reviewed the cardiovascular outcomes associated with glycemic control. The data for this study were obtained from positive trials reported since 2015 in which

glucose-lowering therapy with SGLT-2is and GLP-1RAs resulted in the prevention of cardiovascular events. These authors note that primary care providers such as APRNs share responsibility with cardiologists and encourage them to include both drugs in the treatment of diabetic patients at risk for developing CVD.

Ding et al. (2020) published a systematic review and meta-analyses of RCTs to compare the efficacy and safety of GLP-1RAs and SGLT-2is for the treatment of uncontrolled T2DM in obese patients who were undergoing treatment with metformin. The results of this overview suggest that GLP-1RAs are superior to SGLT-2is in providing glycemic control specifically in obese patients. The side effects mentioned included gastrointestinal events only. Larger and longer-term follow-up clinical trials will be needed to provide more evidence in support of the safety and efficacy of GLP1-RAs compared to SGLT-2is.

A consensus statement by the European Renal and Cardiovascular Medicine (EURECA-m) and Diabetes and Obesity (DIABESITY) working groups of the European Renal Association and the European Dialysis and Transplant Association noted that the use of GLP-1RAs and SGLT-2is to reduce glycemia in patients with T2DM was associated with significant cardiovascular and renal benefits. The consensus was based on observations that both of these drugs promote effective control of glycemia, ameliorate progressive failure of pancreatic beta-cells, and limit weight gain; these benefits were introduced as “the unmet needs of nephroprotection and cardioprotection in diabetic kidney disease.” RCTs were used to prove their superiority to standard treatment in FDA filings (Sarafidis et al., 2019).

Limitations

The time frame (four weeks) was one of the main limitations of this QI Project. Similarly, the study included only a small group of patients, and the available therapies were limited to

drugs covered in the formularies provided by their medical insurance. While the initial follow-up for this QI Project was two weeks, some side effects first presented themselves at week three and four of therapy. Specific dose adjustments were made to three patients at that time. Thus, future patient outcomes may be somewhat more limited as side effects could have an impact on medication compliance. Other limitations include the fact that frequent laboratory tests are not usually covered by medical insurance. I found that I needed to include another ICD code in addition to the primary designation (uncontrolled T2DM) to obtain approval for fructosamine levels both at baseline and at two weeks; otherwise, the patient would be charged for this test. Finally, I was able to carry out this project because of the availability of samples from drug representatives; this variable is another limitation placed on those caring for the uninsured.

Interpretation

APRNs with DNP degrees are trained to analyze and interpret the needs for changes in their current practice. In this project, I identified critical evidence-based approaches aimed at improving drug therapy and attaining the desired patient outcomes. Combination therapy with metformin and/or a GLP-1RA or an SGLT-2i assures effective treatment. APRNs should consider adapting this QI Project intervention for the management of their patients who present with uncontrolled T2DM. This QI Project contributes to a high quality of care and the achievement of desired patient outcomes.

Conclusions

Uncontrolled T2DM and its complications are major public health problems. Observations linking persistent hyperglycemia to the progression of cardiovascular and renal disease have been among the reasons promoting significant changes in the current guidelines for diabetes management. The results of many reviews of RCTs and network meta-analyses have

documented the efficacy and safety of GLP-1RAs and/or SGL-2is in combination with metformin as a means to provide glycemic control and protection against cardiovascular and renal disease. The implementation of this DNP QI Project brought effective therapy to my practice. Project participants experienced reduced glycemic levels in only two weeks. As a leader and a doctorate-prepared nurse, my impact is perceived in my attention to patient care and the outcomes that result. My ongoing efforts will serve to improve my primary care therapy controlling T2DM.

Other information

Funding

Funds for this QI Project were provided by the Paso del Norte Health Foundation Graduate Fellows Program for Academic Excellence and Leadership.

References

Berkovic, M. C., Bilic-Curcic, I., Bozek, T., Mahecic, D. H., Majanovic, S. K., Canecki-Varzic, S., Andric, J., Marusic, S., & Mrzljak, A. (2020). Glucagon-like-1 receptor agonists and sodium/glucose cotransporter-2 inhibitors combination: Are we exploiting their full potential in a real life setting *World Journal of Diabetes*, *11*(11), 540–552 https://doi.org/10.4239/wjd.v11.i11.540

Berkovic, M. C., Bilic-Curcic, I., Bozek, T., Mahecic, D. H., Majanovic, S. K., Canecki-Varzic, S., Andric, J., Marusic, S., & Mrzljak, A. (2020). Glucagon-like-1 receptor agonists and sodium/glucose cotransporter-2 inhibitors combination: Are we exploiting their full potential in a real life setting? *World Journal of Diabetes*, *11*(11), 540–552. https://doi.org/10.4239/wjd.v11.i11.540

Bertoluci, M. C., Nunes Salles, J. E., Silva-Nunes, J., Cordeiro Pedrosa, H., Oliveira Moreira, R., Calado da Silva Duarte, R. M., da Costa Carvalho, D. M., Trujilho, F. R., Cancela dos Santos Raposo, J. F., Bezerra Parente, E., Valente, F., Ferreira de Moura, F., Hohl, A., Melo, M., Garcia Pestana Araujo, F., Monteiro Castro de Araujo Principe, R. M., Kupfer, R., Costa e Forti, A., Valerio, C. M.,...Bauermann Leitao, C. (2020). Portuguese-Brazilian evidence-based guideline on the management of hyperglycemia in type 2 diabetes mellitus. *Kiabetology & Metabolic Syndrome*, *12*(45), 1–30. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7245758/pdf/13098_2020_Article_551.pdf

Betonico, C. C. R., Titan, S. M., Correa-Giannella, M. L. C., Nery, M., & Queiroz, M. (2016). Management of diabetes mellitus in individuals with chronic kidney disease: therapeutic

perspectives and glycemic control. *Clinics*, *71*(1), 47–53. https://www.scielo.br/j/clin/a/BPqdPj8nRWRP8knrmp6KMGm/?lang=en

Castellana, M., Cignarelli, A., Brescia, F., Perrini, S., Natalicchio, A., Laviola, L., & Giorgino, F. (2019). Efficacy and safety of GLP-1 receptor agonists as add-on to SGLT2 inhibitors in type 2 diabetes mellitus: A meta-analysis. *Scientific Reports*, *9*(19351), 1–8. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6920368/

D'Marco, L., Morillo, V., Gorriz, J. L., Suarez, M. K., Nava, M., Ortega, A., Parra, H., Villasmil, N., Rojas-Quintero, J., & Bermudez, V. (2021). SGLT2i and GLP-1RA in cardiometabolic and renal diseases: From glycemic control to adipose tissue inflammation and senescence. *Journal of Diabetes Research*, *2021*(Article ID 9032378). https://doi.org/10.1155/2021/9032378

Ding, L., Sun, G., & Xiao, X. (2020). Comparing the efficacy and safety of glucagon-like peptide 1 receptor agonists with sodium-glucose cotransporter 2 inhibitors for obese type 2 diabetes patients uncontrolled on metformin: A systematic review and meta-analysis of randomized clinical trials. *International Journal of Endocrinology*, *2020*(Article ID 1626484), 1–7. https://doi.org/10.1007/s00592-020-01542-4

Henderson, W. O., Parker, M. H., & Batch, B. C. (2021). How should you assess glycemic control if the hemoglobin A1c is inaccurate or uninterpretable? *Cleveland Clinic Journal of Medicine*, *88*(2), 81–85. https://doi.org/10.3949/ccjm.88a.19135

Hernandez, A. F., Green, J. B., Janmohamed, S., D'Agostino Sr., R. B., Granger, C. B., Jones, N. P., Leiter, S. A., Rosenberg, A. E., Sigmon, K. N., Somerville, M. C., Thorpe, K. M., McMurray, J. V., & Del Prato, S. (2018). Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): A double-

blind, randomized placebo-controlled trial. *Lancet*, *392*, 1519–1529. https://doi.org/10.1016/S0140-6736(18)32261-X

Htike, Z. Z., MBBS, Zaccardi, F., MD, Papamargaritis, D., PhD, Webb, D. R., PhD, Khunti, K., PhD, & Davies, M. J., MD. (2017). Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: A systematic review and mixed-treatment comparison analysis. *Diabetes Obesity and Metabolism*, *19*, 524–536. https://doi.org/10.1111/dom.12849

Hussein, H., Zaccardi, F., Khunti, K., Davies, M. J., Patsko, E., Dhalwani, N. N., Kloecker, D. E., Ioannidou, E., & Gray, L. J. (2020). Efficacy and tolerability of sodium-glucose co-transporter-2 inhibitors and glucagon-like peptide-1 receptor agonists: A systematic review and network meta-analysis. *Diabetes, Obesity and Metabolism*, *22*, 1857–1868. https://doi.org/DOI: 10.1111/dom.14008

Institute for Healthcare Improvement. (2022). *Plan-do-study-act (PDSA) worksheet*. Institute for healthcare improvement. http://www.ihi.org/resources/Pages/Tools/PlanDoStudyActWorksheet.aspx

Jabbour, S. A., Frias, J. P., Hardy, E., Ahmed, A., Wang, H., Ohman, P., & Guja, C. (2018). Safety and efficacy of exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patient with type 2 diabetes inadequately controlled with metformin monotherapy: 52-week randomized controlled trial. *Diabetes Care*, *41*, 2136–2146. https://doi.org/10.2337/dc18-0680

Jia, S., Wang, Z., Han, R., Zhang, Z., Li, Y., Qin, X., Zhao, M., Xiang, R., & Yang, J. (2021). Incretin mimetics and sodium-glucose co-transporter 2 inhibitors as monotherapy or add-

on to metformin for treatment of type 2 diabetes: a systematic review and network meta-analysis. *Acta Diabetologica*, *58*, 5–18. https://doi.org/10.1007/s00592-020-01542-4

Lajara, R. (2019). Combination therapy with SGLT-2 inhibitors and GLP-1 receptor agonists as complementary agents that address multi-organ defects in type 2 diabetes. *Postgraduate Medicine*, *131*(8), 555–565. http://doi.org/10.1080/00325481.2019.1670017

Li, J., Albajrami, O., Zhuo, M., Hawley, C. E., & Paik, J. M. (2020). Decision algorithm for prescribing SGLT2 inhibitors and GLP-1 receptor agonists for diabetic kidney disease. *CJASN*, *15*, 1678–1688. https://doi.org/10.2215/CJN.02690320

Mantsiou, C., Karagiannis, T., Kakotrichi, P., Malandris, K., Avgerinos, I., Liakos, A., & Tsapas, A. (2020). Glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter-2 inhibitors as combination therapy for type 2 diabetes: A systematic review and meta-analysis. *Diabetes, Obesity and Metabolism*, *22*, 1857–1868. https://doi.org/10.1111/dom.14108

Natali, A., Nesti, L., Trico, D., & Ferrannini, E. (2021). Effects of GLP-1 receptor agonists and SGLT-2 inhibitors on cardiac structure and function: A narrative review of clinical evidence. *Cardiovascular Dabetology*, *20*(196). https://doi.org/10.1186/s12933-021-01385-5

Nelson, A. J., Pagidipati, N. J., Aroda, V. R., Cavender, M. A., Green, J. B., Lopes, R. D., Al-Khalidi, H., Gaynor, T., Kaltenbach, L. A., Kirk, J. K., Lingvay, I., Magwire, M. L., O'Brien, E. C., Pak, J., Pop-Busui, R., Richardson, C. R., Reed, M., Senyucel, C., Webb, L.,...Granger, C. B. (2021). Incorporating SGLT2i and GLP-1RA for cardiovascular and kidney disease risk reduction. Call for action to the cardiology community. *Circulation*, *144*, 74–84. https://doi.org/10.1161/circulationaha.121.053766

Patoulias, D., Stavropoulos, K., Imprialos, K., Katsimardou, A., Kalogirou, M.-S., Koutsampasopoulos, K., Zografou, I., Papadopoulos, C., Karagiannis, A., & Doumas, M. (2019). Glycemic efficacy and safety of glucagon-like peptide-1 receptor agonist on top of sodium-glucose co-transporter-2 inhibitor treatment compared to sodium-glucose co-transporter-2 inhibitor alone: A systematic review and meta-analysis of randomized controlled trials. *Diabetes Research and Clinical Practice*, *158*, 107927. https://doi.org/10.1016/j.diabres.2019.107927

Sarafidis, P., Ferro, C. J., Morales, E., Ortiz, A., Malyszko, J., Hojs, R., Khazim, K., Ekart, R., Valdivielso, J., Fouque, D., London, G. M., Massy, Z., Ruggenenti, P., Porrini, E., Wiecek, A., Zoccali, C., Mallamaci, F., & Hornum, M. (2019). SGLT-2 inhibitors and GLP-1 receptor agonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. A consensus statement by the EURECA-m and the DIABESITY working groups of the ERA-EDTA. *Nephrology Dialysis Transplantation*, *34*(2), 208–230. https://doi.org/10.1093/ndt/gfy407

Selvin, E., & Mulder, J. E. (2022). Measurements of glycemic control in diabetes mellitus. In D. M. Nathan & J. I. Wolfsdorf (Eds.), *UpToDate*. Wolters Kluwer. https://www.uptodate.com/contents/measurements-of-glycemic-control-in-diabetes-mellitus

Simes, B. C., & MacGregor, G. G. (2019). Sodium-glucose cotransporter-2 (SGLT2) inhibitors: A clinician's guide. *Dove Press Journal: Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, *12*, 2125–2136. http://doi.org/10.2147/DMSO.S212003

Wei Sim, L. L., Kim Ban, K. H., Tan, T. W., Sethi, S. K., & Loh, T. P. (2017). Development of a clinical decision support system for diabetes care: A pilot study. *PLoS One*, *12*(2). https://doi.org/10.1371/journal.pone.0173021

White, K. M., Dudley-Brown, S., & Terhaar, M. F. (2021). *Translation of evidence into nursing and healthcare* (3rd ed.). Springer Publishing Company.

Zaccardi, F., Webb, D. R., Z Z., Htike, Youssef, D., Khunti, K., & Davies, M. J. (2016). Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. *Diabetes, Obesity and Metabolism*, *18*, 783–794. https://doi.org/10.1111/dom.12670

Zhou, Y., Geng, Z., Wang, X., Huang, Y., Shen, L., & Wang, Y. (2020). Meta-analysis on the efficacy and safety of SGLT2 inhibitors and incretin based agents combination therapy vs. SGLT2i alone or add-on to metformin in type 2 diabetes. *Diabetes Metabolism Research and Reviews*, *36*(2), e3223. https://doi.org/10.1002/dmrr.3223