Personalizing Type 2 Diabetes Management: Use of a Patient-Centered Approach to Individualizing A1C Goals and Pharmacological Regimens

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IN BRIEF Caring for people with type 2 diabetes requires a patient-centered approach to treatment targets and medication regimens. Focusing on patients' individual characteristics, needs, and treatment responses can improve compliance and clinical outcomes. Medication selection can be guided by the mechanisms of action, advantages, disadvantages, and costs of available options; patients' behavioral and psychological variables, personal preferences, and socioeconomic status also should be taken into account. This article provides an overview of patient-centered and individualized diabetes management, offers pharmacological recommendations for specific clinical scenarios, and describes a complicated case illustrating the patient-centered approach in clinical practice.

The growing armamentarium of treatment options for type 2 diabetes has allowed clinicians to better target specific underlying pathophysiological defects associated with the disease. Traditionally, metformin, sulfonylureas, thiazolidinediones (TZDs), and insulin were the primary glucose-lowering agents prescribed. However, within the past decade and a half, newer agents targeting incretins and renal disposal of glucose have become available. Numerous factors must be taken into account when designing a treatment regimen. These include patient-specific factors such as the underlying pathogenesis of diabetes, BMI and risk of weight gain, risk of adverse effects such as hypoglycemia, and ability to administer and tolerate medications, as well as medication-specific factors such as efficacy, potency, and cost. Excellent comprehensive patient-centered algorithms for diabetes management are available and emphasize individualization of both glycemic targets and the selection of glucose-lowering agents (1–8).

Patient-Centered Care

The concept of patient-centered care has been described by many in the literature, but the exact definition is not completely clear. A review of the literature in 2000 found that most descriptions of this topic included five key concepts: *1*) a biopsychosocial perspective (social and psychological influences on illness and behavior), *2*) consideration of patients' personal experience of illness, *3*) shared power and responsibility (i.e., greater patient autonomy and participation in decision-making), *4*) a collaborative patient-provider relationship (i.e., mutual trust and understanding of treatment needs and goals), and *5*) the role of the personal qualities of the doctor (doctor subjectivity) (9). Patient-centered care in diabetes involves evaluating individual patients' unique characteristics, preferences, and abilities to devise a personalized treatment plan and therapeutic goals. Working to better understand patients' experience with taking diabetes medications, improve the patient-provider relationship to gain patients'

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trust, and obtain necessary health care system support for providers can promote adherence to the medication regimen in diabetes (10).

Evidence supporting the use of patient-centered care is provided by the Diabetes Care in General Practice (DCGP) study (11). The DCGP looked at the effects of 6 years of intervention with structured personal care versus routine care of type 2 diabetes over a 19-year follow-up period. Structured personal care involved quarterly patient visits at which individualized treatment goals (A1C and glucose, blood pressure, and cholesterol levels) were set and followed up on, with physician supports such as prompting, feedback, clinical guidelines, and continuing medical education. At 19 years, DGCP intervention resulted in lower risks of myocardial infarction (MI) and any diabetes-related endpoint for patients. Analysis of a subset of DCGP patients with diabetes and concurrent psychiatric illness demonstrated that structured personal care for these patients resulted in lower risks for all-cause mortality, diabetes-related death, any diabetes-related endpoint, and MI (12).

Glycemic Targets and Algorithms

Published algorithms for diabetes management recommend individualization of glycemic goals (1–8). The benefits of preventing or delaying progression of micro- and macrovascular complications must be weighed against the risks of tight glycemic control, including hypoglycemia, adverse effects from medications, and cost.

The landmark U.K. Prospective Diabetes Study (UKPDS) (13,14) and the Kumamoto study (15) demonstrated that intensive glycemic control aiming for an A1C of 7 and 6.5%, respectively, was beneficial in reducing the rate of microvascular complications. The impact of tight glycemic control on macrovascular complications is less certain. The UKPDS found a small, statistically nonsignificant ($P = 0.052$) reduction in the risk of MI with intensive treatment with insulin and sulfonylureas for 10 years (13). A significant reduction in risk of MI, diabetes-related death, and all-cause mortality was found only in a subset of overweight patients randomized to metformin in the UKPDS (14). However, as more events occurred during the additional 10-year follow-up of study (1997–2007), reductions in risk for MI and all-cause mortality did become apparent in the intensive treatment group (16).

The effects of intensive treatment on cardiovascular endpoints were specifically studied in three large trials: ACCORD (Action to Control Cardiovascular Risk in Diabetes) (17), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) (18), and VADT (Veterans Affairs Diabetes Trial) (19). ACCORD and VADT targeted a normal A1C (<6%), whereas ADVANCE targeted an A1C ≤6.5%. The duration of ADVANCE and VADT was 5 years; ACCORD was planned to run for ~5 years, but its intensive treatment arm was terminated after 3.5 years because of a higher mortality rate in that group. Those receiving intensive therapy were then transitioned to the standard therapy group until the completion of the study at 5 years. ADVANCE and VADT did not find any significant effect of intensive treatment on the rate of major cardiovascular events or death but did find a benefit of tight glycemic control on the development and progression of nephropathy (18,19). ACCORD also did not find a significant reduction in major cardiovascular events, but its unexpected finding of a 22% relative increase in total mortality, mainly due to an increase in death from cardiovascular causes, in the intensive group emerged 1–2 years after randomization (17).

Based on the results of these trials, the general consensus of guidelines and expert opinion is to recommend an A1C target of 7% for most patients, although a target of <6.5 or >8% may be appropriate for certain patients depending on their characteristics and comorbidities (2–4,20). Many algorithms have been published regarding how to individualize glycemic targets and what factors to consider (5–8), the most comprehensive and widely used of which can be found in an American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) joint position statement (2,3), the ADA's *Standards of Medical Care in Diabetes* (4), and a consensus statement and algorithm published by the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) (1). The ADA/EASD position statement and ADA standards recommend determining the stringency of glycemic control based on patients' attitude, treatment-associated risks (including hypoglycemia), disease duration, life expectancy, comorbidities, vascular complications, and resources. More stringent control is felt to be reasonable in healthy patients without cardiovascular disease (CVD) if it can be achieved without significant hypoglycemia, whereas higher A1C targets should be used in patients with severe hypoglycemia, extensive complications and comorbidities, and limited life expectancy. The AACE/ACE algorithm similarly recommends taking patients' characteristics into account but has a more stringent A1C goal of ≤6.5% for most patients and is more aggressive with initiating and adding glucose-lowering agents. The AACE/ACE algorithm recommends targeting a higher A1C of 7–8% for patients with hypoglycemia, comorbidities, macrovascular disease, advanced renal disease, or limited life expectancy (1).

Choice of Glucose-Lowering Agents

The choice of agent(s) to use must be based on patient-specific needs, keeping in mind the underlying pathogenesis of patients' diabetes, as well as their BMI and risk of weight gain, risk of adverse treatment effects (including hypoglycemia), and ability to administer and tolerate medications. The efficacy and potency of medications and their costs also must be considered.

Therapies targeting insulin resistance in the muscle and liver (metformin and TZDs) and β-cell insufficiency (sulfonylureas, meglitinides, and insulin) were considered the primary treatment options for type 2 diabetes until the past decade, when newer therapies with alternate targets became available. Newer therapies target the pathophysiological defects of incretin deficiency, excess glucagon production, and increased renal glucose reabsorption.

Incretin-based therapies include the glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors. GLP-1 receptor agonists stimulate glucose-dependent insulin secretion, suppress postmeal glucagon secretion, slow gastric emptying, increase satiety, and potentially stimulate insulin gene transcription and β-cell growth (21). These injectables are available as short-acting agents given daily or long-acting, once-weekly formulations. The short-acting agents include twice-daily exenatide, once-daily liraglutide, and once-daily lixisenatide. Long-acting once-weekly formulations include exenatide extended release, albiglutide, and dulaglutide.

Benefits of GLP-1 receptor agonists include A1C lowering of 1–2%, no hypoglycemia when used alone, and weight loss of 1.5–4 kg over 24–52 weeks (22). Two recent trials also demonstrated a reduction in cardiovascular risk and nephropathy with liraglutide (23) and semaglutide, a new drug in this class that has not yet been approved by the U.S. Food and Drug Administration (FDA) (24). The main drawbacks are concerns about the potential risk of pancreatitis and pancreatic cancer (25,26), C cell hyperplasia and tumors (27), and gastrointestinal side effects of nausea and vomiting.

An alternate method of increasing GLP-1 is inhibition of DPP-4, the enzyme that breaks down GLP-1. Four DPP-4 inhibitors are approved for use in the United States: sitagliptin, saxagliptin, linagliptin, and alogliptin. Compared to GLP-1 receptor agonists, agents in this medication class have modest glycemic efficacy (A1C reduction of 0.5–0.9%), are weight neutral, and do not cause nausea.

Pancreatitis has also been reported with the use of DPP-4 inhibitors. Other concerns include an FDA-issued warning in 2015 regarding severe joint pain with DDP-4 inhibition. In terms of cardiovascular risk, no increased risk of cardiovascular events or heart failure was found with any of drugs (28–31) except saxagliptin, which was associated with a higher rate of hospitalization for heart failure compared to placebo (28).

The newest class of glucose-lowering medications are the sodium–glucose cotransporter 2 (SGLT2) inhibitors. These medications have a unique, insulin-independent mechanism of action that involves blockade of renal reabsorption of glucose via SGLT2 in the proximal convoluted tubule of the kidney (32). Canagliflozin, dapagliflozin, and empagliflozin are the three available drugs in this class.

Benefits of SGLT2 inhibitors include a low risk of hypoglycemia, weight loss of 2–3 kg over 24–52 weeks, and blood pressure–lowering effects (33). The main adverse effects are increases in genital mycotic and urinary tract infections. In addition, because of the drugs' diuretic effect, symptoms of volume depletion have been described, particularly in elderly patients who may already be on a diuretic or other antihypertensive agent(s). Recently, additional adverse events, including euglycemic diabetic ketoacidosis with drugs from this class (34), an increase in bone fractures with canagliflozin (35), and toe/metatarsal amputations with canagliflozin (36), have been reported.

In terms of cardiovascular effects, empagliflozin was found to lower rates of death from CVD and hospitalization for heart failure (37), and canagliflozin showed a reduction in risks of cardiovascular events and heart failure hospitalization (36). Findings from the EMPA-REG OUTCOME (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial (37) led to the FDA's approval of a new indication for the agent to reduce the risk of cardiovascular death in patients with type 2 diabetes and CVD, making empagliflozin the first type 2 diabetes medication approved for this indication. Both empagliflozin and canagliflozin were found to slow the progression of albuminuria, the reduction in estimated glomerular filtration rate (eGFR), and the development of end-stage renal disease (ESRD) and to decrease death from renal causes (36,38).

Because these newer agents have a noninsulin-dependent mechanism of action, they tend not to increase weight and do not cause hypoglycemia on their own. The advantages of weight neutrality and even possible weight loss, decreased risk of hypoglycemia, and specific benefits such as reduction in cardiovascular risk and progression of kidney disease make these agents attractive options as second- or third-line therapies after metformin, or even as first-line therapy if metformin is contraindicated. However, the main disadvantage of these medications is their high cost. The potential benefits of incretin-based agents (GLP-1 receptor agonists and DPP-4 inhibitors) and SGLT2 inhibitors must be weighed against their expense, less extensive clinical

use to date, and infrequent but potentially serious adverse events.

The ADA/EASD algorithm recommends metformin as first-line therapy but is not prescriptive with regard to second- or third-line choices of agents. This algorithm recommends taking into account medications' cellular mechanism, primary physiological action, advantages, disadvantages, and cost when making a selection for a given patient (2,3,39). Specific advantages noted in this algorithm for older medications (metformin and sulfonylureas) include extensive experience, low cost, and evidence of macrovascular (metformin) and microvascular (sulfonylureas) risk reduction in the UKPDS (2,3,39). TZDs, although no longer commonly used because of concerns about increased MI and heart failure risk, still have a place in treatment in the ADA/EASD algorithm because of their low cost, low hypoglycemia risk, durability, and beneficial effects on lipids (2,3,39). Newer agents such as GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT2 inhibitors are noted by ADA/EASD to have the advantages of no hypoglycemia and weight loss or weight neutrality, but these benefits have to be weighed against their high costs and rare but potentially serious adverse associations.

The AACE/ACE glycemic control algorithm similarly uses a patient-centered approach, but is stratified based on the initial A1C and is more prescriptive. Pharmacological therapy with one agent is recommended for patients who present with an A1C <7.5%, whereas two agents are advised if initial A1C is ≥7.5%. Insulin is recommended if A1C is >9% with symptoms of hyperglycemia (1).

This more prescriptive algorithm ranks the medications based on strength of the expert consensus recommendation; those with fewer adverse events, especially weight gain and hypoglycemia, and greater possible benefits are listed higher. Metformin is considered the first-line therapy, with a suggested second-line hierarchy of GLP-1 receptor agonists, SGLT2 inhibitors, and then DPP-4 inhibitors. TZDs and sulfonylureas are much lower on the hierarchy of usage (1).

In addition to the pharmacological profile of the glucose-lowering agents, patients' behavioral and psychological variables, as well as their health status and comorbidities need to be taken into account when choosing glucose-lowering therapies.

Behavioral and psychological variables that may affect the choice of medications include patients' degree of motivation, acceptable level of treatment intensity, acceptance of and ability to administer injections, responses to and tolerance of past medications, support system, food and cultural preferences, level of physical activity, and socioeconomic status. Health status and comorbidities that may affect treatment decisions include patients' age, duration of diabetes, tendency to experience hypoglycemia, hypoglycemia unawareness, and severity of hyperglycemia, as well as the presence of overweight/obesity, macrovascular disease, renal impairment, liver dysfunction, or microvascular complications.

Medical Choices in Specific Clinical Scenarios

Overweight and Obesity

Choosing weight-neutral or weight loss–inducing medications for overweight or obese patients with diabetes is in accordance with the ADA/EASD guidelines (2–4) and Endocrine Society guidelines on the pharmacological management of obesity (40). Metformin, GLP-1 receptor agonists, and SGLT2 inhibitors are recommended for their dual benefit of improved glycemic control and potential weight loss. DPP-4 inhibitors are weight neutral and can also be considered. Other glucose-lowering agents that do not induce weight gain and are not described above (i.e., α-glucosidase inhibitors and pramlintide, an amylin mimetic) could be considered but typically are not used because of their side effects, modest efficacy, and frequency of administration.

Medications that can exacerbate weight issues include sulfonylureas and TZDs, which are associated with weight gain of 1.5–2.5 kg over 10 years (13) and 3 kg over 6 months (41), respectively. Insulin increased weight on average by 7 kg over 10 years in the UKPDS (13). If insulin is indicated, detemir may be a better option in overweight or obese patients because weight gain was found to be less with detemir than with NPH or glargine insulin, while no difference was found in weight gain between NPH and glargine (42).

High Risk for Hypoglycemia or Presence of Hypoglycemia Unawareness

Noninsulin-dependent medications such as metformin, SGLT2 inhibitors, GLP-1 receptor agonists, or DPP-4 inhibitors are preferred for patients who are prone to hypoglycemia or have hypoglycemia unawareness. Insulin secretagogues should be avoided. If insulin is needed, levemir and degludec have a lower incidence of hypoglycemia than glargine or NPH (41,43).

Renal Insufficiency or ESRD

DPP-4 inhibitors can be used in patients with renal insufficiency or ESRD. Dose reduction is recommended based on creatinine clearance for sitagliptin, saxagliptin, and alogliptin, whereas no dose adjustment is necessary for linagliptin. Metformin can now be used for patients with a lower eGFR but should be discontinued if the eGFR is <30 mL/min/1.73 m^2 and continued with a dose reduction and assessment of risk if the eGFR is 30–45 mL/min/1.73 m^2 (44). SGLT2 inhibitors can be used if the eGFR is >45–60 mL/min/1.73 m^2, depending on the specific agent. They should be used cautiously in renal insufficiency because cases of acute kidney injury

requiring hospitalization or dialysis have been reported to the FDA. Long-acting insulin secretagogues should be avoided because of accumulation of active metabolites and increased risk of hypoglycemia. Insulin doses may need to be reduced because of decreased elimination.

CVD

For patients with CVD, liraglutide, semaglutide (when it becomes available), canagliflozin, or empagliflozin have been shown to reduce risk of cardiovascular outcomes and death from cardiovascular causes (23,24,36,37). Sulfonylureas should be avoided given their uncertain impact and potential negative effect on cardiovascular outcomes. The TZD rosiglitazone, which has generally fallen out of favor, has uncertain effects on risk of MI and should be avoided (45,46).

Heart Failure

If heart failure is present, TZDs should be avoided given their association with fluid retention and increased risk of heart failure (44). Saxagliptin should also be avoided because patients taking it were found to have a higher rate of hospitalization for heart failure (28). In contrast, empagliflozin significantly reduced the risk of hospitalization for heart failure and should be considered in heart failure patients (37). Liraglutide was also found to result in fewer hospitalizations for heart failure compared to placebo, although the difference was not statistically significant (23).

Difficulty Complying With Injections

When injections are needed in patients who have problems with compliance or fear of injections, simplifying the regimen with a long-acting injectable such as a once-weekly GLP-1 receptor agonist and once-daily basal insulin or using premixed insulin or U-500 insulin twice daily are options.

Lack of Insurance or Financial Limitations

Physicians are often limited in their prescribing by patients' lack of adequate insurance coverage or high copayment requirements on prescription medications. In these cases, the least expensive oral agents available as generics are metformin, sulfonylureas, or TZDs. The least expensive insulins are NPH and regular insulin. Vials also tend to be more cost-effective than insulin pens.

If brand-name medications are prescribed, patient assistance programs and savings cards are available. AACE has launched a patient prescription savings directory that is available online at http://prescriptionhelp.aace.com. This directory includes a list of links to patient drug assistance and charitable copayment assistance organizations offering reduced or no-cost endocrine medications. Prescription assistance information on the ADA website is another excellent source for patients and physicians and can be accessed at http://www.diabetes.org/living-with-diabetes/health-insurance/prescription-assistance.html. This site includes information on drug discount programs and databases, in addition to financial assistance programs offered by pharmaceutical companies. An excellent website and mobile app that compares prices and discounts from more than 60,000 U.S. pharmacies is https://www.goodrx.com.

Some retailers offer free or discounted diabetes medications. For example, Meijer stores dispense metformin at no cost with a prescription (47). The stores of SpartanNash (Family Fare, D and W Fresh Market, Family Fresh Market, and VG's Grocery) have generic metformin, glipizide, glyburide, and glimepiride at no cost and also sell 1- and 3-month supplies of generic medications for $4 and $10, respectively (48–51). Walmart and Target also offer $4 (1-month) and $10 (3-month) generic medications (52,53). A recent Internet article available on www.verywell.com lists several additional stores that offer free and low-cost prescription drugs (54).

Case Study: Application of Personalized Diabetes Management

The following case study illustrates the patient-centered approach to setting treatment targets and determining a therapeutic regimen for type 2 diabetes.

Presentation

Judy, a 55-year-old woman with poorly controlled type 2 diabetes since the age of 35 years, hypertension, and hyperlipidemia, presented to the hospital with a complaint of episodic chest pain for 1 month. Cardiac catheterization revealed severe triple-vessel coronary artery disease (CAD) necessitating elective four-vessel coronary artery bypass grafting. Her A1C at admission was 10.2%. Additional complications included proliferative diabetic retinopathy treated with panretinal photocoagulation and diabetic nephropathy (urine albumin/creatinine ratio 241 mg/g and eGFR 80 mL/min/1.73 m^2).

Her diabetes was treated with metformin and glipizide. She had declined insulin in the past because of her job as a bus driver and the need to apply for a medical waiver if insulin were initiated.

Judy also had a recent diagnosis of rheumatoid arthritis (RA) treated with methotrexate. The RA caused pain and stiffness in her hands, resulting in difficulty checking her blood glucose.

Basal-bolus insulin therapy was initiated on admission to the hospital for cardiac surgery, and her oral glucose-lowering agents were stopped. Her discharge diabetes regimen included glargine 15 units every morning and aspart 2–4 units with each meal based on a correction scale. (After surgery, she was on medical leave from her job and not driving, so the use of insulin was not a problem.)

Judy presented to the clinic 3 months after discharge for help in managing her diabetes. With the insulin and significant dietary improvements, she lowered her A1C

to 6.2%. Her main concerns now include:

- Weight gain of 20 lb since hospital discharge, despite improvement in diet, resulting in a BMI of 31.2 kg/m^2
- Stiff, swollen hands from RA, resulting in difficulty with injecting multiple times daily and checking blood glucose
- The need for a noninsulin regimen if possible, in case she can return to her previous work as a bus driver
- Symptoms of sweating and hunger occurring about once a week before dinner and relieved by juice and crackers

Questions to Consider

1. What is the optimal level of glycemic control for Judy?
2. What are her treatment options?
3. What factors should be considered when determining which medications to prescribe for her?

Developing a Treatment Plan

For Judy, a reasonable A1C goal would be 7%. She is a motivated patient who complies with her diabetes regimen but has characteristics that increase her risk of hypoglycemia. These characteristics include difficulty with monitoring her glucose, a long duration of disease, and multiple comorbidities, including severe CAD. Her current A1C of 6.2% is too stringent given her comorbidities and symptoms of sweating and hunger that could indicate hypoglycemia.

With regard to treatment, she likely does not require multiple daily insulin injections because she is on a very low dose of insulin, her A1C is <6.5%, and she is likely experiencing hypoglycemia. To determine which medications would be best for Judy, several factors should be taken into consideration. First, she mentions that she has difficulty with injections because of her RA. Based on this, injectable agents, including insulin, should be avoided or limited to as few injections as possible. Second, she complains of weight gain with insulin and currently has a BMI in the obese range. Medications that are weight neutral or associated with weight loss such as metformin, GLP-1 receptor agonists, SGLT2 inhibitors, or DPP-4 inhibitors should be preferred. Because she has CAD, empagliflozin, canagliflozin, and/or liraglutide would be ideal choices based on recent cardiovascular outcomes trials demonstrating a decrease in cardiovascular risk with their use (23,36,37). These agents were also found to have a beneficial effect on nephropathy (23,36,38), a complication also present in this patient.

Judy and her provider discussed the treatment options, and she expressed interested in restarting metformin and adding liraglutide to her regimen. She chose liraglutide over the SGLT2 inhibitors because of its greater A1C-lowering efficacy and possibly greater associated weight loss. If a third agent is needed, reasonable choices would be empagliflozin or canagliflozin because her eGFR is >45 mL/min/1.73 m^2.

Conclusion

The case study presented above illustrates the importance of taking a patient-centered approach in the management of type 2 diabetes. Treatment of diabetes for this patient was complicated by hypoglycemia, difficulty with multiple injections, obesity, and a history of CAD and nephropathy. Based on these factors, glucose-lowering agents with potential beneficial effects on CVD and nephropathy and a low likelihood of hypoglycemia and weight gain were considered.

Current algorithms recognize that one size does not fit all in diabetes care. Tailoring glycemic goals and treatment regimens to patient-specific needs and preferences is associated with increased patient satisfaction, improved patient-provider relationship and communication, and enhanced patient well-being without compromising glycemic control (55).

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

Author Contributions

S.L. was the sole author and is the guarantor of this work and takes responsibility for the integrity and accuracy of the manuscript.

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