Research helps show which type 2 diabetes medication may work best

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After publishing research in 2022 that compared the effectiveness of four common medications for type 2 diabetes, University of Colorado Department of Medicine faculty member Neda Rasouli, MD, and a

national team of researchers decided to delve deeper into their data to help determine which medication(s) may be superior to others.

The results of these secondary analyses were recently published as 10 articles in *Diabetes Care*. Rasouli was the first author of one of these articles and a co-author on others. These papers offer further insight into differences between the four medications—insulin glargine, liraglutide, glimepiride, and sitagliptin—to help health care providers decide which medication may best help their patient.

This research was done as part of the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness (GRADE) Study, which is a nationwide clinical trial that took place from 2013 to 2021. The GRADE study had more than 5,000 participants and occurred at 36 clinical centers throughout the United States, including the CU Anschutz Medical Campus.

Rasouli, the associate division head for the Division of Endocrinology, Metabolism, and Diabetes and director of the CU Diabetes and Endocrinology Clinical Trial Program, was the lead investigator at the CU site, which included the Rocky Mountain Regional Veterans Affairs Medical Center.

"Because of the increased prevalence of obesity and diabetes, it's very important to answer the question of what is the best medication to treat people with type 2 diabetes," Rasouli says. "One of the differences among these four medications is their cost, so we need to investigate whether one is superior to the others and if there is sufficient data to support changes in treatment guidelines."

The need for the GRADE study

More than 38 million people in the U.S. have diabetes, and roughly

90-95% of them have type 2 diabetes—a condition where the pancreas does not produce enough insulin or the body's cells do not respond to insulin the way they should, leading to high blood sugar levels.

People with diabetes who keep their blood sugar levels in the near-normal range—also referred to as maintaining glycemic control—will generally have a much lower risk of developing complications such as heart disease or kidney disease, Rasouli explains. However, maintaining control can be difficult.

"Type 2 diabetes is a progressive disease, meaning that over time, blood sugar control will worsen because of beta cell dysfunction, which are the main cells that produce insulin," Rasouli says.

To help these patients maintain glycemic control, they are typically prescribed metformin, an anti-diabetic medication that helps lower blood sugar levels. Yet, many patients eventually reach a point where metformin can no longer control their blood sugar levels.

"Because of the progressive nature of diabetes, the majority of patients after five to 10 years of taking metformin, they need a second-level therapy treatment," Rasouli says. "Prior to the GRADE study, there was a lack of head-to-head studies comparing available medications to see which one had better efficacy and which improved glycemic control the best. That was the study's main purpose."

The GRADE study compared four commonly used medications to treat diabetes in combination with metformin: insulin glargine, liraglutide, glimepiride, and sitagliptin. Results of the study, published in 2022 in the *New England Journal of Medicine*, showed liraglutide and insulin glargine, when taken with metformin, allowed patients to achieve and maintain their target blood glucose levels for a longer period of time compared to glimepiride and sitagliptin.

Looking at beta cell function

Following the initial publication of these results, the GRADE study investigators continued to analyze their data and look at other angles of diabetes care. This further analysis led to the publication of 10 additional articles, one of which Rasouli was the first author of.

Rasouli's article compares the long-term effects of the four different medications, when added to metformin, on insulin sensitivity and beta cell function. Research suggests beta cell function progressively decreases by about 5-10% per year, resulting in a worsening of blood glucose control. Therefore, any medications that can preserve beta cell function would be of great value.

"What we found was that liraglutide showed significant improvement of beta cell function in the first year, but after that, beta cell function declined even more rapidly compared to other groups," she says. "Even though we saw some improvement with liraglutide in the short term, unfortunately, it didn't maintain as a long-term effect."

Liraglutide, at the end of the study, had better beta cell function compared to the rest of the medications, with the order being liraglutide, sitagliptin, insulin glargine, and glimepiride.

"But none of these medications could stop the loss of beta cell function" she says. "It shows us that there is a gap in knowledge, and we need better interventions to preserve beta cell function and maintain blood glucose control in the long run."

So, which medication is the best option?

There is no one-solution-fits-all option, Rasouli explains, but the

findings of the GRADE study offer valuable information to health care providers about the different impacts each medication may have.

"The best medication depends on the patient, and that's why we need to come up with better tools to personalize the treatment of complex diseases like diabetes," she says.

For instance, the GRADE study surprised Rasouli by demonstrating that insulin glargine can be safe and effective as a second-line therapy in type 2 diabetes, and it was well received by patients.

"Typically, insulin has been a last resort—something for when patients fail all other treatments," she says. "In GRADE, we show that, as a second-line treatment, insulin was somewhat a better option for maintaining glycemic control and did not have the highest risk of hypoglycemia, which is low blood sugar. However, insulin is associated with some weight gain."

The benefit of liraglutide, which is a glucagon-like peptide-1 (GLP-1) receptor agonist, is that it not only has a beneficial effect on glycemic control, but it also is associated with weight loss and does not show a risk of hypoglycemia unless given with another medication that can potentially cause hypoglycemia, she explains.

"If you look at the combination of the effect on glycemic control, weight, and hypoglycemia, then liraglutide performed better than insulin," Rasouli says. "But the problem is the cost of this medication, given that insurance coverage for these drugs is not widespread. These GLP-1 receptor agonists—which also include Ozempic, Trulicity, and Mounjaro—are the most expensive class of medications we have available."

"If cost was not an issue, and we were living in a utopia where anybody

could get any medication they want, then I think the class of GLP-1 is likely the preferred medication for many," she adds.

Continuing the research

GRADE study investigators' work is not over, as Rasouli says there is still a lot of data from the study that will be explored. One research area Rasouli hopes to see continue is the pursuit of an intervention that improves beta cell function in the long term.

"Intervention that can preserve beta cell function should be the focus of future treatments," she says.

Rasouli leads the CU Diabetes and Endocrinology Clinical Trial Program with the aim of bringing innovative trials for new medications targeting diabetes, obesity, and their metabolic complications to patients. Overall, she hopes the GRADE study spreads awareness that diabetes is a progressive disease and earlier, more intensive, and personalized therapy should be the goal.

"Ultimately, we need to make sure that these patients stay at their glycemic targets and prevent future complications of diabetes," she says.

"When it's late into the disease and people get complications, there is no way that we can reverse the course. Addressing type 2 diabetes aggressively from the beginning, I think that's the most important message we can take from GRADE."

More information: Matthew C. Riddle, Individualizing Treatment of Type 2 Diabetes After Metformin: More Insights From GRADE, *Diabetes Care* (2024). DOI: 10.2337/dci24-0008

Neda Rasouli et al, Longitudinal Effects of Glucose-Lowering

Medications on β-Cell Responses and Insulin Sensitivity in Type 2 Diabetes: The GRADE Randomized Clinical Trial, *Diabetes Care* (2024). DOI: 10.2337/dc23-1070