ISSN 1948-9358 (online)

World Journal of *Diabetes*

World J Diabetes 2022 January 15; 13(1): 1-69

Published by Baishideng Publishing Group Inc

World Journal of Diabetes

Contents

Monthly Volume 13 Number 1 January 15, 2022

World Journal of Diabetes

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Contents

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RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Diabetes

ISSN
ISSN 1948-9358 (online)

LAUNCH DATE
June 15, 2010

FREQUENCY
Monthly

EDITORS-IN-CHIEF
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https://www.wjgnet.com/1948-9358/editorialboard.htm

PUBLICATION DATE
January 15, 2022

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World Journal of Diabetes

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World J Diabetes 2022 January 15; 13(1): 1-4

DOI: 10.4239/wjd.v13.i1.1

ISSN 1948-9358 (online)

EDITORIAL

Acarbose is again on the stage

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Author contributions: Only Altay M contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: No potential conflicts of interest. No financial support.

Country/Territory of origin: Turkey

Specialty type: Endocrinology and metabolism

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

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Abstract

Acarbose is an agent that has been used to treat type 2 diabetes for about 30 years; it prevents postprandial hyperglycemia by inhibiting carbohydrate digestion in the small intestine. Since incretin-based treatments have been preferred over the last 10 to 15 years, the use of acarbose is not as common in treating type 2 diabetes as before. Some studies have shown that acarbose also produces a weight-loss effect by increasing glucagon-like peptide 1 (GLP-1). The positive effect of acarbose on GLP-1, and increasing evidence that it provides cardiovascular protection, suggests that acarbose may again be considered among the first-choice antidiabetic agents, as it was in the 1990s.

Key Words: Acarbose; Cardiovascular protection; Glucagon-like peptide 1; Obesity; Waist-to-height ratio

Core Tip: The prevention of obesity and reducing cardiovascular risks, together with blood glucose control in patients with type 2 diabetes, are the main components of the treatment's goals. New studies show that acarbose can provide the expected benefits of an ideal antidiabetic drug by increasing both insulin sensitivity and glucagon-like peptide 1 levels.

Citation: Altay M. Acarbose is again on the stage. *World J Diabetes* 2022; 13(1): 1-4
URL: https://www.wjgnet.com/1948-9358/full/v13/i1/1.htm
DOI: https://dx.doi.org/10.4239/wjd.v13.i1.1

Received: March 31, 2021
Peer-review started: March 31, 2021
First decision: June 5, 2021
Revised: June 19, 2021
Accepted: December 22, 1021
Article in press: December 22, 1021
Published online: January 15, 2022

P-Reviewer: Cigrovski Berkovic M, Forlano R, Sun XD, Xu R
S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

INTRODUCTION

Obesity is a key factor in the prevalence of type 2 diabetes mellitus (T2DM) worldwide. Therefore, in treating diabetes, researchers focus on the consequences of eliminating the negative effects of obesity, especially abdominal obesity, on reducing cardiovascular events and death. In a recently published study, Song *et al*[1] aimed to examine the effect of acarbose on abdominal obesity, and its determining factors in comparison with metformin[1]. They evaluated Metformin and AcaRbose in Chinese as the initial Hypoglycemic treatment (MARCH) study data[2] using a new anthropometric measure: Waist-to-height ratio (WHtR). The MARCH study is a randomized, open-labeled, noninferiority trial on Type 2 diabetes patients that was published in 2014[2]. It has been showen in this study that acarbose treatment is as effective and safe as metformin at the 24th and 48th weeks. A group of 343 patients who were newly diagnosed with T2DM were treated with acarbose, and 333 other patients were treated with metformin. The new report by Song *et al*[1] clarified that WHtR had significantly decreased in both groups in the 24th week after treatment, with women showing a more pronounced decrease. Between the beginning of the study and the 24th week of the treatment, the change in the waist-to-height ratio (ΔWHtR) was divided into two sets with large differences in one group and small differences in the other, thus, these data were subject to post-hoc analysis. In the acarbose group, women and those with a lower area under the glucagon-like peptide 1 (GLP-1) curve (AUCGLP-1) had a greater ΔWHtR. Among those using metformin, weight loss was greater in women as well as those with a high baseline AUCGLP-1. In conclusion, Song *et al*[1] found a relationship between high WHtR in the treatment of acarbose with gender, GLP-1 level, fasting glucose, and lipid profile. In addition, Song *et al*[1] emphasized the importance of WHtR for the measurement of abdominal obesity. They argued that, in both groups, a greater reduction in waist circumference in women was independent of the drug and was due to women's excessive desire and attempts to lose weight. The study observed that the circulating GLP-1 level increased over time in acarbose users. Previous studies reported that alpha glucosidase enzyme inhibition increased circulating GLP-1 levels by stimulating GLP-1 secretion and inhibiting dipeptidyl peptidase 4 (DPP-4) enzymes in healthy and T2DM patients[3-7]. Moreover, a recently published study showed this effect to be inhibited by exendin, a GLP-1 receptor antagonist[8]. This study found that acarbose is more effective for abdominal obesity, especially in those with low GLP-1 levels. The effect of lifestyle change on the results was not evaluated in the article, which is an important limiting factor.

The work of Song *et al*[1] throws up a question: "What role should acarbose play in the treatment of diabetes?" While acarbose continued to be part of diabetes guidelines and treatment algorithms, the appearance of new treatment agents in the last 10 to 15 years pushed acarbose to the background. In fact, there are large-scale studies that solidify the role of acarbose in treating impaired glucose tolerance (IGT) and T2DM. Over the past year, however, acarbose seems to have regained its importance. Prominent studies, such as the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) and the Acarbose Cardiovascular Evaluation (ACE) study, show that acarbose prevents the development of diabetes regardless of age, gender, and body mass index[9,10]. It has also been found that acarbose reduces cardiovascular events in patients with IGT and T2DM. In a recently published study, Zhang *et al*[11] found a 50% relative risk (RR) reduction in myocardial infarction and a 52% RR reduction in all-cause deaths after a 10-year follow-up with regard to acarbose therapy in patients with T2DM[11]. This effect is due to the reduction of oxidative stress caused by the lowering of postprandial two-hour blood sugar. Some studies have claimed that it is effective in quickly providing joint target controls. However, the fact that the study was conducted only in Chinese patients is an important limiting factor. An increasing number of studies focus on the mechanisms with which acarbose acts in diabetes treatment and how it provides additional benefits[8]. The possible effect mechanisms of acarbose on diabetic patients are shown in Table 1.

Acarbose inhibits carbohydrate digestion by competitively inhibiting the alpha glucosidase enzyme in the small intestine lumen. Consequently, it reduces glucose absorption, prevents postprandial hyperglycemia and hyperinsulinemia, and increases insulin sensitivity[12]. For this reason, it has been used in clinical practice since the 1990s, whether in monotherapy for mild cases of type 2 diabetes or as a combination agent with insulin and other antidiabetics in severe and advanced cases. Some studies have shown that acarbose has positive effects on intestinal flora[13]. In order to reduce gastrointestinal intolerance, a daily dose of 50 mg is offered just before meals, and a dose of 100 mg is offered three times a day after four to six weeks, when weekly titrations are reached. Acarbose can decrease hemoglobin A1c (HBA1c) by 0.5% to

Table 1 The possible mechanisms of effects of acarbose on diabetic patients

Type of effect	Net effect	Mechanism
Glucose absorption	Decrease	Competitively inhibits α-glucosidases absorption in small intestine
Insulin sensitivity	Increase	Lowers the postprandial blood glucose and insulin levels
DPP-4 activity	Decrease	Increases postprandial glucose in small intestine
Circulating GLP-1 level	Increase	Stimulates GLP-1 secretion in small intestine
Intestinal content	Increase	Positively effects microbiota *via* increasing content of oligosaccharides in the digestive tract

GLP-1: Glucagon-like peptide-1; DPP-4: Dipeptidyl peptidase 4.

1.5% and is especially effective on postprandial hyperglycemia[12].

The following are the advantages of acarbose: It is one of the rare agents that has been shown to prevent diabetes in the pre-diabetic period; the rate of hypoglycemia is low; its annual cost is lower than that of new antidiabetic drugs; it has weight-loss properties, or at least is weight neutral; it has a positive effect on the lipid profile by lowering the triglyceride level; and there is increasing evidence to show that it reduces the risk factors of cardiovascular disease. However, it shouldn't be forgotten that this hasn't yet been proven in Cardio Vascular Outcome Trials (CVOTs).

The disadvantages of acarbose are that it has to be used three times a day, and gastrointestinal side effects, such as gas, bloating, and diarrhea are relatively frequent.

CONCLUSION

In my opinion, we should remember that acarbose is an effective alternative to controlling postprandial hypoglycemia in countries that predominantly consume carbohydrates, like China or Turkey. The increasing evidence on its effects on GLP-1 and cardiovascular protection may lead to an extension of its use. It seems that acarbose, which has a high efficacy and is safe in terms of its side-effect profile, will be at the forefront of diabetes guidelines in the near future.

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