A systematic review, meta-analysis, dose-response, and meta-regression of the effects of acarbose intake on glycemic markers in adults

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Abstract

Background: Prior research has yielded mixed results regarding the impact of acarbose intake on glycemic markers. To provide a more comprehensive analysis, a systematic review and meta-analysis was performed to compile data from various randomized controlled trials (RCTs) examining the effects of acarbose intake on fasting blood sugar (FBS), insulin, hemoglobin A1C (HbA1c), and homeostasis model assessment of insulin resistance (HOMA-IR) in adults. Methods: To identify relevant literature up to April 2023, a comprehensive search was conducted on various scholarly databases, including PubMed, Web of Science, and Scopus databases. The effect size of the studies was evaluated using a random-effects model to calculate the weighted mean differences (WMD) and 95% confidence intervals (CI). Heterogeneity between studies was assessed using Cochran's Q test and I2. Results: This systematic review and meta-analysis included a total of 101 RCTs with a total of 107 effect sizes. The effect sizes for FBS in milligrams per deciliter (mg/dl), insulin in picomoles per liter (pmol/l), hemoglobin A1C (HbA1c) in percentage (%), and homeostasis model assessment of insulin resistance (HOMA-IR) were 92, 46, 80, and 22, respectively. The pooled analysis indicated that acarbose intake resulted in significant decreases in FBS ($p=0.018$), insulin ($p<0.001$), HbA1c ($p<0.001$), and HOMA-IR ($p<0.001$). Conclusion: The findings of this systematic review and meta-analysis suggest that acarbose intake can potentially lead to significant improvements in glycemic indices by decreasing the levels of FBS, HbA1c, and insulin. However, larger and more rigorously designed studies are still needed to further evaluate and strengthen this association.

Introduction

Hyperglycemia is a serious condition associated with various adverse consequences and an increased risk of non-communicable diseases, including diabetes, cardiovascular diseases, and metabolic syndrome (Sari & Artsanthia, 2019). Maintaining glycemic control is crucial to prevent chronic complications, especially in patients with diabetes (Fasil, Biadgo & Abebe, 2019; Jafari et al.). Lifestyle interventions, such as adopting a healthy diet and engaging in physical activity, have been found to be effective in preventing and managing hyperglycemia and its complications (Noormohammadi, Eslamian, Malek, Shoaibinobarian & Mirmohammadali, 2022; Sampson et al., 2021; Shoaibinobarian, Eslamian, Noormohammadi, Malek,

Rouhani & Mirmohammadali, 2022). However, when lifestyle interventions are not sufficient to control hyperglycemia, effective medications are prescribed that can significantly reduce plasma insulin and fasting blood sugar (FBS) levels (Alberti, Zimmet & Shaw, 2007).

α-glucosidase inhibitors, such as acarbose, are oral medications prescribed for the management of hyperglycemia. These drugs work by delaying the absorption of carbohydrates from the small intestine, achieved by blocking α-glucosidase enzymes. This mechanism results in lower postprandial blood glucose and insulin levels, which help to control hyperglycemia (Clissold & Edwards, 1988). Numerous studies have investigated the impact of acarbose intake on various glycemic markers. One study found that treatment with a dose of 150 mg/d of acarbose resulted in a significant reduction in serum insulin concentrations in individuals with impaired glucose tolerance (Pan et al., 2003). Another study reported that an intake of 150 mg/d of acarbose resulted in a significant reduction in hemoglobin A1C (HbA1c) levels in patients with type 2 diabetes mellitus (T2DM) (Li et al., 2016). In a separate study, a dose of 300 mg/d of acarbose was administered for a duration of 48 weeks, resulting in significant reductions in FBS, HbA1c, and homeostasis model assessment of insulin resistance (HOMA-IR) (Pan et al., 2016). Despite the positive effects observed in some studies, others have failed to report significant effects of acarbose intake. For example, one study found that a dose of 100 mg/d of acarbose did not lead to any significant reductions in FBS levels in patients with non-alcoholic fatty liver disease (Hajiaghamohammadi, Miroliaee, Samimi, Alborzi & Ziaee, 2013).

Given the varying results reported in studies examining the association between acarbose intake and glycemic markers, there is a need for a comprehensive evaluation of the available evidence. To date, no meta-analysis has been conducted to assess the effects of acarbose intake on glycemic markers, including FBS, insulin, HbA1c, and HOMA-IR in adult populations. Therefore, we have developed a systematic review and meta-analysis of randomized clinical trials to address this research question.

Materials and methods

The current study was conducted in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff & Altman, 2009). The study protocol was registered with PROSPERO (CRD42022352814) to ensure the transparency and credibility of the study design and methodology.

Search strategy

A systematic search including PubMed, Web of Science, and Scopus databases was conducted up to April 2023 to identify studies evaluating the effects of acarbose intake on glycemic markers and there were no limitations on language or time. The PICO (population, intervention, comparator, and outcome) design was used in this study. Search terms had both MESH and non-MESH keywords following: “acarbose” AND Intervention OR ”Intervention Study” OR ”Intervention Studies” OR ”controlled trial” OR randomized OR randomized OR random OR randomly OR placebo OR ”clinical trial” OR Trial OR ”randomized controlled trial” OR ”randomized clinical trial” OR RCT OR blinded OR ”double blind” OR ”double blinded” OR trial OR ”clinical trial” OR trials OR ”Pragmatic Clinical Trial” OR ”Cross-Over Studies” OR ”Cross-Over” OR ”Cross-Over Study” OR parallel OR ”parallel study” OR ”parallel trial”. We also looked through the papers’ references to see if any further studies would be useful for our purposes.

Study selection

According to the following criteria, trials were included: (a) RCTs (cross-over or parallel); (b) studies conducted on adults (older than 18 years old); (c) acarbose intervention; (d) with a minimum duration of 1 week (e) revealed glycemic markers on the baseline and after the intervention. Following types of studies: (a) reviews; (b) observational (c) animal or (d) *in vitro* studies and grey literature (books, conference abstracts, seminars) were excluded. We also excluded studies that examined the effects of acarbose in combination with other interventions. To determine which studies qualified, two authors (SRD and OA) independently reviewed the titles and abstracts of the articles that were included, extracted the results, and evaluated the quality of the selected research. Reviewer disagreements were settled through consensus.

Data extraction

Two separate researchers (SRD, OA) independently reviewed eligible trials and extracted the following data: Name of the first author, year, location and duration of the study, type of clinical trial, sample size, gender, mean age, and body mass index (BMI) of patients, acarbose dosage, mean and standard deviation of the FBS, insulin, HbA1c, HOMA-IR on baseline and end of the intervention.

Quality assessment

The risk of bias for each article was independently assessed by two researchers (SRD and OA) using the Cochrane criteria (Higgins et al., 2019). The methodological quality of studies was evaluated based on sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other sources of bias. Finally, studies were categorized into three groups: low, high, or unclear risk of bias. The risk of bias was then divided into three categories: High (general high risk > 2 high risk), Moderate (general moderate risk = 2 high risk), and Low (generic low risk 2 high risk). SRD and OA, two reviewers, each separately evaluated the work's quality; any disagreements between their assessments were resolved through conversation.

Statistical analysis

All statistical analyses were conducted using Stata software, version 11 (Stata Corporation, College Station, Tex), and $P < 0.05$ was recognized as statistically significant. Mean change and SD for FBS, insulin, HbA1c, and HOMA-IR in both intervention and control groups were used to calculate the pooled effect size. The combined effect sizes were calculated as weight mean difference (WMD) and 95% confidence interval (CI) of changes in outcomes across the two groups of acarbose intake and control, using the random-effects model. The potential non-linear potential effects of acarbose dose and treatment duration were examined using fractional polynomial modeling (Zhang, 2016). Mean differences in glycemic markers between the intervention and placebo groups were calculated and when the SD of the mean change was not available in the studies, we computed it using the following formula: SD =square root [(SD at baseline)^2+(SD at the end of study)^2 -(2 r×SD at baseline ×SD at the end of study)]. We used the Hozo et al. method to transform standard errors, 95% CI, and interquartile ranges to SDs, in each study that reported standard error instead of SD. The formula SD = SE × [?]n (n = the number of individuals in each group) was used to calculate SD (Hozo, Djulbegovic & Hozo, 2005). Heterogeneity was determined by Cochrane's Q test and I^2 statistic at a p-value < 0.1 (Higgins & Thompson, 2002). We considered I^2< 25% as low heterogeneity, 25-40% as moderate, and > 40% as high heterogeneity (Brondani, Assmann, de Souza, Boucas, Canani & Crispim, 2014). We conducted subgroup analysis for age, sex, dose of acarbose, intervention duration, and type of intervention. The sensitivity analysis was carried out by the omission of any of the studies, to explore the impact of each study on the overall effect size. Assessment of publication bias was executed using Begg's, and Egger's tests (Begg & Mazumdar, 1994; Egger, Smith, Schneider & Minder, 1997). Trim and fill were applied to account for the publication bias in the meta-analysis (Duval, 2005). The possible impact of acarbose (mg/d) dose and duration on glycemic variables was evaluated using meta-regression. To evaluate the effect of acarbose intake on glycemic variables, we also employed a non-linear model to include the associated dose-response data from several trials (Xie, Gou, Peng, Zheng & Chen, 2021; Xu & Doi, 2018).

Assessment of Certainty

The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology was utilized to evaluate and compile the included studies' degree of evidentiary certainty (**Table 4**) (Guyatt et al., 2008).

Results

The flow of study selection

We presented the flow chart in **Figure 1** and described the selection process and the references retrieved from

the database. We identified in the first step of the electronic databases search a total number of 5480 studies. We excluded duplicated (n = 1238) and irrelevant studies (n = 4242) based on titles and abstracts, and 115 full-text relevant articles were reviewed. A total of 14 studies were excluded due to the following reasons: insufficient outcome data reported, acute oral ingestion, or short duration of intake (<1 week). We included a total of 101 studies (AKAZAWA, KOIDE, OISHI, AZUMA & TASHIRO, 1982; Bachmann, Petzinna, Raptis, Wascher & Westermeier, 2003; Bao et al., 2010; Bayraktar, Hamulu, Ozgen, Yilmaz, Tuzun & Kabalak, 1998; Bayraktar, Van Thiel & Adalar, 1996; Buchanan, Collier, Rodrigues, Millar, Gray & Clarke, 1988; Chan et al., 1998; Chen et al., 2014; Chen, Tarng & Chen, 2016; Chiasson et al., 1996; Coniff, Shapiro & Seaton, 1994; Coniff, Shapiro, Seaton, Hoogwerf & Hunt, 1995; Costa, Pinol & Group, 1997; Derosa et al., 2009a; Derosa, Maffioli, D'Angelo, Fogari, Bianchi & Cicero, 2011; Derosa et al., 2011; Derosa et al., 2009b; Du et al., 2017; Fischer, Hanefeld, Spengler, Boehme & Temelkova-Kurktschiev, 1998; Fischer et al., 2003; Gao et al., 2022; Gao et al., 2020; Gentile et al., 2005; Gentile et al., 2001; Goke, 2002; Goke, Lubben & Bates, 2004; Guagnano, Loggia, Pace-Palitti, Spoltore, Capitanio & Sensi, 1998; Hajiaghamohammadi, Miroliaee, Samimi, Alborzi & Ziaee, 2013; Halimi, Le Berre & Grange, 2000; Hanefeld et al., 2002; Hanefeld et al., 2009; Hanjalic-Beck et al., 2010; Hasegawa et al., 2008; Hauner, Petzinna, Sommerauer & Toplak, 2001; Hirano et al., 2012; Hoffmann, 1997; Hotta et al., 1993; Hwu et al., 2003; Jenney, Proietto, O'Dea, Nankervis, Traianedes & D'Embden, 1993; Josse et al., 2003; Kageyama, Nakamichi, Sekino, Fujita & Nakano, 2000; Khalili & Sheikh-Aboomasoudi, 2018; Ko, Tsang, Ng, Wai & Kan, 2001; Koyasu et al., 2010; Lam, Tiu, Tsang, Ip & Tam, 1998; Laube, Linn & Heyen, 1998; Lee et al., 2014; Li, Ji, Liu & Wang, 2019; Li et al., 2016; Lin et al., 2003; Lopez-Alvarenga et al., 1999; Malaguarnera, Giugno, Ruello, Rizzo, Motta & Mazzoleni, 1999; Meneilly et al., 2000; Mo et al., 2019; Nijpels, Boorsma, Dekker, Kostense, Bouter & Heine, 2008; Noda, Umeda & Nawata, 1997; Oyama et al., 2008; Pan et al., 2003; Pan et al., 2008; Pan et al., 2016; Patel, Kirkman, Considine, Hannon & Mather, 2013; Penna, Canella, Reis, Silva de Sa & Ferriani, 2005; Rachmani, Bar-Dayan, Ronen, Levi, Slavachevsky & Ravid, 2004; Ren, Ma & Jiao, 2022; Rezai, Jamshidi, Mohammadbeigi, Seyedoshohadaei, Mohammadipour & Moradi, 2016; Riccardi et al., 1999; Rosenbaum, Peres, Zanella & Ferreira, 2002; Rosenthal & Mauersberger, 2002; Rudovich, Weickert, Pivovarova, Bernigau & Pfeiffer, 2011; Salman et al., 2000; Sanjari, Gholamhoseinian Najar, Asadikaram, Mashayekhi & Ghaseminejad Tafreshi, 2019; Schnell, Mertes, Standl & Group, 2007; Scott, Knowles & Beaven, 1984; Sels, Verdonk & Wolffenbuttel, 1998; Shi et al., 2017; Sonmez et al., 2005; Soonthornpun, Rattarasarn, Thamprasit & Leetanaporn, 1998; Standl, Baumgartl, Fuchtenbusch & Stemplinger, 1999; Su et al., 2015; Sugihara et al., 2014; Sun, Zeng, Liao, Chen & Wang, 2016; Suzuki et al., 2006; Takei et al., 2001; Tuğrul, Kutlu, Pekin, Bağlam, Kıyak & Oral, 2008; van de Laar, Lucassen, Kemp, van de Lisdonk, van Weel & Rutten, 2004; Vichayanrat, Ploybutr, Tunlakit & Watanakejorn, 2002; Wagner et al., 2006; Wang, Ni, Yang, Li, Li & Feng, 2013; Wang et al., 2011; Wang et al., 2021; Watanabe, Uchino, Ohmura, Tanaka, Onuma & Kawamori, 2004; Wolever et al., 1995; Wu et al., 2017; Yajima, Shimada, Hirose, Kasuga & Saruta, 2004; Yang et al., 2019; Yang, Zhang, Zhang & Niu, 2022; Yang et al., 2014; Yilmaz, Gursoy, Sahin & Guvener Demirag, 2007; Yun, Du, Chen, Liu & Xiao, 2016; Zheng, Yin, Lu, Zhou, Yuan & Li, 2013; Ziaee, Esmailzadehha & Honardoost, 2017) in the present systematic review and meta-analysis, and their characteristics are presented in **Table 1.**

Study characteristics

The publication years of the studies ranged from 1982 to 2022 and originated in China (n=25) (AKAZAWA, KOIDE, OISHI, AZUMA & TASHIRO, 1982; Bao et al., 2010; Chan et al., 1998; Du et al., 2017; Gao et al., 2022; Gao et al., 2020; Ko, Tsang, Ng, Wai & Kan, 2001; Lam, Tiu, Tsang, Ip & Tam, 1998; Li, Ji, Liu & Wang, 2019; Li et al., 2016; Mo et al., 2019; Pan et al., 2003; Pan et al., 2008; Pan et al., 2016; Ren, Ma & Jiao, 2022; Shi et al., 2017; Su et al., 2015; Sun, Zeng, Liao, Chen & Wang, 2016; Wang, Ni, Yang, Li, Li & Feng, 2013; Wang et al., 2021; Wu et al., 2017; Yang, Zhang, Zhang & Niu, 2022; Yang et al., 2014; Yun, Du, Chen, Liu & Xiao, 2016; Zheng, Yin, Lu, Zhou, Yuan & Li, 2013), New Zealand (n=1) (Scott, Knowles & Beaven, 1984), Germany (n=15) (Bachmann, Petzinna, Raptis, Wascher & Westermeier, 2003; Fischer, Hanefeld, Spengler, Boehme & Temelkova-Kurktschiev, 1998; Fischer et al., 2003; Göke, 2002; Göke, Lübben & Bates, 2004; Hanefeld et al., 2002; Hanefeld et al., 2009; Hanjalic-Beck et al., 2010;

Hauner, Petzinna, Sommerauer & Toplak, 2001; Hoffmann, 1997; Laube, Linn & Heyen, 1998; Rosenthal & Mauersberger, 2002; Rudovich, Weickert, Pivovarova, Bernigau & Pfeiffer, 2011; Schnell, Mertes, Standl & Group, 2007; Standl, Baumgartl, Füchtenbusch & Stemplinger, 1999), Australia (n=1) (Jenney, Proietto, O'Dea, Nankervis, Traianedes & D'Embden, 1993), USA (n=2) (Coniff, Shapiro & Seaton, 1994; Coniff, Shapiro, Seaton, Hoogwerf & Hunt, 1995), Canada (n=2) (Chiasson et al., 1996; Wolever et al., 1995), Japan (n=12) (Hasegawa et al., 2008; Hirano et al., 2012; Hotta et al., 1993; Kageyama, Nakamichi, Sekino, Fujita & Nakano, 2000; Koyasu et al., 2010; Noda, Umeda & Nawata, 1997; Oyama et al., 2008; Sugihara et al., 2014; Suzuki et al., 2006; Takei et al., 2001; Watanabe, Uchino, Ohmura, Tanaka, Onuma & Kawamori, 2004; Yajima, Shimada, Hirose, Kasuga & Saruta, 2004), Turkey (n=6) (Bayraktar, Hamulu, Özgen, Yilmaz, Tüzün & Kabalak, 1998; Bayraktar, Van Thiel & Adalar, 1996; Salman et al., 2000; Sönmez et al., 2005; Tuğrul, Kutlu, Pekin, Bağlam, Kıyak & Oral, 2008; Yilmaz, Gursoy, Sahin & Guvener Demirag, 2007), Italy (n=9) (Derosa et al., 2009a; Derosa, Maffioli, D'Angelo, Fogari, Bianchi & Cicero, 2011; Derosa et al., 2011; Derosa et al., 2009b; Gentile et al., 2005; Gentile et al., 2001; Guagnano, Loggia, Pace-Palitti, Spoltore, Capitanio & Sensi, 1998; Malaguarnera, Giugno, Ruello, Rizzo, Motta & Mazzoleni, 1999; Riccardi et al., 1999), Mexico (n=1) (Lopez-Alvarenga et al., 1999), United Kingdom (n=1) (Buchanan, Collier, Rodrigues, Millar, Gray & Clarke, 1988), Israel (n=1) (Rachmani, Bar-Dayan, Ronen, Levi, Slavachevsky & Ravid, 2004), Brazil (n=2) (Penna, Canella, Reis, Silva de Sá & Ferriani, 2005; Rosenbaum, Peres, Zanella & Ferreira, 2002), Sweden (n=1) (Wagner et al., 2006), India (n=1) (Patel, Kirkman, Considine, Hannon & Mather, 2013), Taiwan (n=5) (Chen et al., 2014; Chen, Tarng & Chen, 2016; Hwu et al., 2003; Lin et al., 2003; Wang et al., 2011), Iran (n=5) (Hajiaghamohammadi, Miroliaee, Samimi, Alborzi & Ziaee, 2013; Khalili & Sheikh-Aboomasoudi, 2018; Rezai, Jamshidi, Mohammadbeigi, Seyedoshohadaei, Mohammadipour & Moradi, 2016; Sanjari, Gholamhoseinian Najar, Asadikaram, Mashayekhi & Ghaseminejad Tafreshi, 2019; Ziaee, Esmailzadehha & Honardoost, 2017), Korea (n=2) (Lee et al., 2014; Yang et al., 2019), Spain (n=1) (Costa, Pinol & Group, 1997), Netherlands (n=3) (Nijpels, Boorsma, Dekker, Kostense, Bouter & Heine, 2008; Sels, Verdonk & Wolffenbuttel, 1998; van de Laar, Lucassen, Kemp, van de Lisdonk, van Weel & Rutten, 2004), France (n=1) (Halimi, Le Berre & Grange, 2000), Thailand (n=1) (Vichayanrat, Ploybutr, Tunlakit & Watanakejorn, 2002), Brazil (n=2) (Penna, Canella, Reis, Silva de Sá & Ferriani, 2005; Rosenbaum, Peres, Zanella & Ferreira, 2002), Sweden (n=1) (Wagner et al., 2006). We showed the study design characteristics in **Table 1** . The WMD and 95% CI of FBS, Insulin, HbA1c (%), HOMA-IR, and their changes are presented in **Figures 2A, 2B, 2C,and 2D** respectively.

There were 89 parallel (AKAZAWA, KOIDE, OISHI, AZUMA & TASHIRO, 1982; Bachmann, Petzinna, Raptis, Wascher & Westermeier, 2003; Bao et al., 2010; Bayraktar, Hamulu, Özgen, Yilmaz, Tüzün & Kabalak, 1998; Buchanan, Collier, Rodrigues, Millar, Gray & Clarke, 1988; Chan et al., 1998; Chen et al., 2014; Chen, Tarng & Chen, 2016; Chiasson et al., 1996; Coniff, Shapiro & Seaton, 1994; Coniff, Shapiro, Seaton, Hoogwerf & Hunt, 1995; Costa, Pinol & Group, 1997; Derosa et al., 2009a; Derosa, Maffioli, D'Angelo, Fogari, Bianchi & Cicero, 2011; Derosa et al., 2011; Derosa et al., 2009b; Du et al., 2017; Fischer, Hanefeld, Spengler, Boehme & Temelkova-Kurktschiev, 1998; Fischer et al., 2003; Gao et al., 2022; Gao et al., 2020; Gentile et al., 2001; Göke, 2002; Göke, Lübben & Bates, 2004; Guagnano, Loggia, Pace-Palitti, Spoltore, Capitanio & Sensi, 1998; Hajiaghamohammadi, Miroliaee, Samimi, Alborzi & Ziaee, 2013; Halimi, Le Berre & Grange, 2000; Hanefeld et al., 2002; Hanefeld et al., 2009; Hanjalic-Beck et al., 2010; Hasegawa et al., 2008; Hauner, Petzinna, Sommerauer & Toplak, 2001; Hirano et al., 2012; Hoffmann, 1997; Hotta et al., 1993; Hwu et al., 2003; Josse et al., 2003; Khalili & Sheikh-Aboomasoudi, 2018; Ko, Tsang, Ng, Wai & Kan, 2001; Koyasu et al., 2010; Lam, Tiu, Tsang, Ip & Tam, 1998; Laube, Linn & Heyen, 1998; Lee et al., 2014; Li, Ji, Liu & Wang, 2019; Li et al., 2016; Lin et al., 2003; Meneilly et al., 2000; Mo et al., 2019; Nijpels, Boorsma, Dekker, Kostense, Bouter & Heine, 2008; Noda, Umeda & Nawata, 1997; Oyama et al., 2008; Pan et al., 2003; Pan et al., 2008; Pan et al., 2016; Patel, Kirkman, Considine, Hannon & Mather, 2013; Penna, Canella, Reis, Silva de Sa & Ferriani, 2005; Rachmani, Bar-Dayan, Ronen, Levi, Slavachevsky & Ravid, 2004; Ren, Ma & Jiao, 2022; Rezai, Jamshidi, Mohammadbeigi, Seyedoshohadaei, Mohammadipour & Moradi, 2016; Riccardi et al., 1999; Rosenbaum, Peres, Zanella & Ferreira, 2002; Rosenthal & Mauersberger, 2002; Salman et al., 2000; Sanjari, Gholamhoseinian Najar, Asadikaram, Mashayekhi & Ghaseminejad Tafreshi, 2019; Schnell, Mertes, Standl & Group, 2007; Shi et al., 2017; Sonmez et al., 2005; Standl, Baumgartl, Fuchtenbusch &

Stemplinger, 1999; Su et al., 2015; Sugihara et al., 2014; Sun, Zeng, Liao, Chen & Wang, 2016; Suzuki et al., 2006; Takei et al., 2001; Tuğrul, Kutlu, Pekin, Bağlam, Kıyak & Oral, 2008; van de Laar, Lucassen, Kemp, van de Lisdonk, van Weel & Rutten, 2004; Wagner et al., 2006; Wang, Ni, Yang, Li, Li & Feng, 2013; Wang et al., 2011; Wang et al., 2021; Watanabe, Uchino, Ohmura, Tanaka, Onuma & Kawamori, 2004; Wolever et al., 1995; Wu et al., 2017; Yajima, Shimada, Hirose, Kasuga & Saruta, 2004; Yang et al., 2019; Yang, Zhang, Zhang & Niu, 2022; Yang et al., 2014; Yilmaz, Gursoy, Sahin & Guvener Demirag, 2007; Yun, Du, Chen, Liu & Xiao, 2016; Zheng, Yin, Lu, Zhou, Yuan & Li, 2013) and 12 cross-over (Bayraktar, Van Thiel & Adalar, 1996; Gentile et al., 2005; Jenney, Proietto, O'Dea, Nankervis, Traianedes & D'Embden, 1993; Kageyama, Nakamichi, Sekino, Fujita & Nakano, 2000; Lopez-Alvarenga et al., 1999; Malaguarnera, Giugno, Ruello, Rizzo, Motta & Mazzoleni, 1999; Rudovich, Weickert, Pivovarova, Bernigau & Pfeiffer, 2011; Scott, Knowles & Beaven, 1984; Sels, Verdonk & Wolffenbuttel, 1998; Soonthornpun, Rattarasarn, Thamprasit & Leetanaporn, 1998; Vichayanrat, Ploybutr, Tunlakit & Watanakejorn, 2002; Ziaee, Esmailzadehha & Honardoost, 2017). The mean age and baseline BMI of included studies ranged from 15 to 69.7 years and 21.1 to 35.87 kg/m^2 in the intervention group, respectively. The intake duration of included studies ranged from 1 to 156 weeks. The daily dosage of acarbose intake ranged from 75 to 600 mg. Ten studies included only males or females, and ninety-one included both sexes.

Studies included participants with T2DM (AKAZAWA, KOIDE, OISHI, AZUMA & TASHIRO, 1982; Bachmann, Petzinna, Raptis, Wascher & Westermeier, 2003; Bao et al., 2010; Bayraktar, Hamulu, Özgen, Yilmaz, Tüzün & Kabalak, 1998; Chan et al., 1998; Chen et al., 2014; Chen, Tarng & Chen, 2016; Coniff, Shapiro, Seaton, Hoogwerf & Hunt, 1995; Derosa et al., 2009a; Derosa et al., 2011; Derosa et al., 2009b; Du et al., 2017; Fischer et al., 2003; Gao et al., 2020; Göke, 2002; Göke, Lübben & Bates, 2004; Halimi, Le Berre & Grange, 2000; Hanefeld et al., 2002; Hwu et al., 2003; Josse et al., 2003; Ko, Tsang, Ng, Wai & Kan, 2001; Koyasu et al., 2010; Lee et al., 2014; Li, Ji, Liu & Wang, 2019; Li et al., 2016; Lin et al., 2003; Lopez-Alvarenga et al., 1999; Meneilly et al., 2000; Mo et al., 2019; Oyama et al., 2008; Pan et al., 2008; Rudovich, Weickert, Pivovarova, Bernigau & Pfeiffer, 2011; Salman et al., 2000; Sanjari, Gholamhoseinian Najar, Asadikaram, Mashayekhi & Ghaseminejad Tafreshi, 2019; Shi et al., 2017; Soonthornpun, Rattarasarn, Thamprasit & Leetanaporn, 1998; Standl, Baumgartl, Fuchtenbusch & Stemplinger, 1999; Su et al., 2015; Sugihara et al., 2014; van de Laar, Lucassen, Kemp, van de Lisdonk, van Weel & Rutten, 2004; Vichayanrat, Ploybutr, Tunlakit & Watanakejorn, 2002; Wagner et al., 2006; Wang et al., 2011; Watanabe, Uchino, Ohmura, Tanaka, Onuma & Kawamori, 2004; Wolever et al., 1995; Wu et al., 2017; Yajima, Shimada, Hirose, Kasuga & Saruta, 2004; Yang et al., 2019; Yang et al., 2014; Yilmaz, Gursoy, Sahin & Guvener Demirag, 2007; Zheng, Yin, Lu, Zhou, Yuan & Li, 2013), non-insulin-dependent diabetes mellitus (Bayraktar, Van Thiel & Adalar, 1996; Buchanan, Collier, Rodrigues, Millar, Gray & Clarke, 1988; Coniff, Shapiro & Seaton, 1994; Costa, Pinol & Group, 1997; Fischer, Hanefeld, Spengler, Boehme & Temelkova-Kurktschiev, 1998; Gentile et al., 2001; Guagnano, Loggia, Pace-Palitti, Spoltore, Capitanio & Sensi, 1998; Hoffmann, 1997; Hotta et al., 1993; Jenney, Proietto, O'Dea, Nankervis, Traianedes & D'Embden, 1993; Lam, Tiu, Tsang, Ip & Tam, 1998; Malaguarnera, Giugno, Ruello, Rizzo, Motta & Mazzoleni, 1999; Noda, Umeda & Nawata, 1997; Scott, Knowles & Beaven, 1984; Takei et al., 2001), impaired glucose tolerance (Chiasson et al., 1996; Nijpels, Boorsma, Dekker, Kostense, Bouter & Heine, 2008; Pan et al., 2003), overweight and obese (Hauner, Petzinna, Sommerauer & Toplak, 2001; Kageyama, Nakamichi, Sekino, Fujita & Nakano, 2000; Laube, Linn & Heyen, 1998), type 1 diabetes mellitus (Riccardi et al., 1999; Sels, Verdonk & Wolffenbuttel, 1998; Ziaee, Esmailzadehha & Honardoost, 2017), impaired glucose tolerance (Khalili & Sheikh-Aboomasoudi, 2018; Rudovich, Weickert, Pivovarova, Bernigau & Pfeiffer, 2011), obese hypertensive patients with normal glucose tolerance (Rachmani, Bar-Dayan, Ronen, Levi, Slavachevsky & Ravid, 2004), polycystic ovary syndrome (Hanjalic-Beck et al., 2010; Penna, Canella, Reis, Silva de Sa & Ferriani, 2005; Sonmez et al., 2005; Tuğrul, Kutlu, Pekin, Bağlam, Kıyak & Oral, 2008; Wang et al., 2021; Yang, Zhang, Zhang & Niu, 2022), T2DM and hypercholesterolemia (Suzuki et al., 2006), T2DM with newly initiated insulin therapy (Schnell, Mertes, Standl & Group, 2007), newly diagnosed T2DM (Hanefeld et al., 2009; Hasegawa et al., 2008; Pan et al., 2016; Patel, Kirkman, Considine, Hannon & Mather, 2013; Sun, Zeng, Liao, Chen & Wang, 2016; Wang, Ni, Yang, Li, Li & Feng, 2013), normal glucose tolerance participants (Rudovich, Weickert, Pivovarova, Bernigau & Pfeiffer, 2011), nonalcoholic fatty liver disease (Hajiaghamohammadi, Miroliaee, Samimi, Alborzi & Ziaee,

2013), infertile women with PCOS (Rezai, Jamshidi, Mohammadbeigi, Seyedoshohadaei, Mohammadipour & Moradi, 2016), metabolic syndrome (Khalili & Sheikh-Aboomasoudi, 2018), T2DM and hypertension (Rosenbaum, Peres, Zanella & Ferreira, 2002; Rosenthal & Mauersberger, 2002), hepatic encephalopathy and T2DM (Gentile et al., 2005), acute coronary syndromes patients with T2DM (Hirano et al., 2012), healthy participants (Sanjari, Gholamhoseinian Najar, Asadikaram, Mashayekhi & Ghaseminejad Tafreshi, 2019), T2DM and risk factors of gastrointestinal adverse reactions (Ren, Ma & Jiao, 2022) and T2DM patients with high cardiovascular risk (Gao et al., 2022).

In the investigation by Rudovich et al. 2011 (Rudovich, Weickert, Pivovarova, Bernigau & Pfeiffer, 2011), three types of participants (normal glucose tolerance, impaired glucose tolerance, and T2DM patients) participated in both females and males so three arms were considered for this study. Also, Sanjari et al. 2011 (Sanjari, Gholamhoseinian Najar, Asadikaram, Mashayekhi & Ghaseminejad Tafreshi, 2019) had two types of participants (healthy participants (n=14) and T2DM (n=14) who participated in both females and males so we considered two arms for this study. In the investigation by Fischer et al. 1998 (Fischer, Hanefeld, Spengler, Boehme & Temelkova-Kurktschiev, 1998), one type of participant (T2DM) participated in both females and males with different dose interventions (75, 150, 300, and 600 mg/d) so four arms were considered for this study.

Out of the 101 RCTs, 92 studies have shown a significant reduction effect of acarbose intake on FBS (mg/dl) (Bachmann, Petzinna, Raptis, Wascher & Westermeier, 2003; Bao et al., 2010; Bayraktar, Hamulu, Özgen, Yilmaz, Tüzün & Kabalak, 1998; Bayraktar, Van Thiel & Adalar, 1996; Buchanan, Collier, Rodrigues, Millar, Gray & Clarke, 1988; Chan et al., 1998; Chen et al., 2014; Chen, Tarng & Chen, 2016; Chiasson et al., 1996; Coniff, Shapiro & Seaton, 1994; Coniff, Shapiro, Seaton, Hoogwerf & Hunt, 1995; Costa, Pinol & Group, 1997; Derosa et al., 2009a; Derosa, Maffioli, D'Angelo, Fogari, Bianchi & Cicero, 2011; Derosa et al., 2011; Derosa et al., 2009b; Du et al., 2017; Fischer et al., 2003; Gao et al., 2022; Gentile et al., 2005; Gentile et al., 2001; Göke, 2002; Göke, Lübben & Bates, 2004; Guagnano, Loggia, Pace-Palitti, Spoltore, Capitanio & Sensi, 1998; Hajiaghamohammadi, Miroliaee, Samimi, Alborzi & Ziaee, 2013; Halimi, Le Berre & Grange, 2000; Hanefeld et al., 2002; Hanefeld et al., 2009; Hasegawa et al., 2008; Hauner, Petzinna, Sommerauer & Toplak, 2001; Hirano et al., 2012; Hoffmann, 1997; Hotta et al., 1993; Hwu et al., 2003; Jenney, Proietto, O'Dea, Nankervis, Traianedes & D'Embden, 1993; Josse et al., 2003; Kageyama, Nakamichi, Sekino, Fujita & Nakano, 2000; Khalili & Sheikh-Aboomasoudi, 2018; Ko, Tsang, Ng, Wai & Kan, 2001; Koyasu et al., 2010; Laube, Linn & Heyen, 1998; Lee et al., 2014; Li et al., 2016; Lin et al., 2003; Malaguarnera, Giugno, Ruello, Rizzo, Motta & Mazzoleni, 1999; Meneilly et al., 2000; Mo et al., 2019; Nijpels, Boorsma, Dekker, Kostense, Bouter & Heine, 2008; Noda, Umeda & Nawata, 1997; Oyama et al., 2008; Pan et al., 2003; Pan et al., 2016; Patel, Kirkman, Considine, Hannon & Mather, 2013; Rachmani, Bar-Dayan, Ronen, Levi, Slavachevsky & Ravid, 2004; Ren, Ma & Jiao, 2022; Rezai, Jamshidi, Mohammadbeigi, Seyedoshohadaei, Mohammadipour & Moradi, 2016; Rosenbaum, Peres, Zanella & Ferreira, 2002; Rosenthal & Mauersberger, 2002; Rudovich, Weickert, Pivovarova, Bernigau & Pfeiffer, 2011; Salman et al., 2000; Sanjari, Gholamhoseinian Najar, Asadikaram, Mashayekhi & Ghaseminejad Tafreshi, 2019; Schnell, Mertes, Standl & Group, 2007; Scott, Knowles & Beaven, 1984; Shi et al., 2017; Soonthornpun, Rattarasarn, Thamprasit & Leetanaporn, 1998; Standl, Baumgartl, Fuchtenbusch & Stemplinger, 1999; Su et al., 2015; Sugihara et al., 2014; Sun, Zeng, Liao, Chen & Wang, 2016; Suzuki et al., 2006; Tuğrul, Kutlu, Pekin, Bağlam, Kıyak & Oral, 2008; van de Laar, Lucassen, Kemp, van de Lisdonk, van Weel & Rutten, 2004; Vichayanrat, Ploybutr, Tunlakit & Watanakejorn, 2002; Wagner et al., 2006; Wang, Ni, Yang, Li, Li & Feng, 2013; Wang et al., 2011; Wang et al., 2021; Watanabe, Uchino, Ohmura, Tanaka, Onuma & Kawamori, 2004; Wu et al., 2017; Yang et al., 2019; Yang, Zhang, Zhang & Niu, 2022; Yang et al., 2014; Yilmaz, Gursoy, Sahin & Guvener Demirag, 2007; Yun, Du, Chen, Liu & Xiao, 2016; Zheng, Yin, Lu, Zhou, Yuan & Li, 2013; Ziaee, Esmailzadehha & Honardoost, 2017), 46 studies on serum insulin (pmol/l) (Bayraktar, Hamulu, Özgen, Yilmaz, Tüzün & Kabalak, 1998; Bayraktar, Van Thiel & Adalar, 1996; Chan et al., 1998; Chiasson et al., 1996; Coniff, Shapiro, Seaton, Hoogwerf & Hunt, 1995; Derosa et al., 2009a; Derosa, Maffioli, D'Angelo, Fogari, Bianchi & Cicero, 2011; Derosa et al., 2011; Derosa et al., 2009b; Fischer et al., 2003; Göke, 2002; Halimi, Le Berre & Grange, 2000; Hanefeld et al., 2002; Hanefeld et al., 2009; Hanjalic-Beck et al., 2010; Hasegawa et al.,

2008; Hirano et al., 2012; Jenney, Proietto, O'Dea, Nankervis, Traianedes & D'Embden, 1993; Josse et al., 2003; Kageyama, Nakamichi, Sekino, Fujita & Nakano, 2000; Khalili & Sheikh-Aboomasoudi, 2018; Koyasu et al., 2010; Laube, Linn & Heyen, 1998; Lin et al., 2003; Lopez-Alvarenga et al., 1999; Meneilly et al., 2000; Mo et al., 2019; Oyama et al., 2008; Pan et al., 2003; Patel, Kirkman, Considine, Hannon & Mather, 2013; Rosenthal & Mauersberger, 2002; Rudovich, Weickert, Pivovarova, Bernigau & Pfeiffer, 2011; Salman et al., 2000; Schnell, Mertes, Standl & Group, 2007; Sonmez et al., 2005; Standl, Baumgartl, Fuchtenbusch & Stemplinger, 1999; Sugihara et al., 2014; Sun, Zeng, Liao, Chen & Wang, 2016; Takei et al., 2001; Tuğrul, Kutlu, Pekin, Bağlam, Kıyak & Oral, 2008; van de Laar, Lucassen, Kemp, van de Lisdonk, van Weel & Rutten, 2004; Wagner et al., 2006; Yajima, Shimada, Hirose, Kasuga & Saruta, 2004; Zheng, Yin, Lu, Zhou, Yuan & Li, 2013), 80 studies on serum HbA1c (%) (AKAZAWA, KOIDE, OISHI, AZUMA & TASHIRO, 1982; Bachmann, Petzinna, Raptis, Wascher & Westermeier, 2003; Bao et al., 2010; Bayraktar, Van Thiel & Adalar, 1996; Buchanan, Collier, Rodrigues, Millar, Gray & Clarke, 1988; Chan et al., 1998; Chen et al., 2014; Chen, Tarng & Chen, 2016; Chiasson et al., 1996; Coniff, Shapiro, Seaton, Hoogwerf & Hunt, 1995; Derosa et al., 2009a; Derosa et al., 2011; Derosa et al., 2009b; Du et al., 2017; Fischer, Hanefeld, Spengler, Boehme & Temelkova-Kurktschiev, 1998; Fischer et al., 2003; Gao et al., 2022; Gao et al., 2020; Gentile et al., 2005; Gentile et al., 2001; Göke, Lübben & Bates, 2004; Guagnano, Loggia, Pace-Palitti, Spoltore, Capitanio & Sensi, 1998; Halimi, Le Berre & Grange, 2000; Hanefeld et al., 2002; Hanefeld et al., 2009; Hasegawa et al., 2008; Hauner, Petzinna, Sommerauer & Toplak, 2001; Hirano et al., 2012; Hoffmann, 1997; Hotta et al., 1993; Hwu et al., 2003; Jenney, Proietto, O'Dea, Nankervis, Traianedes & D'Embden, 1993; Josse et al., 2003; Ko, Tsang, Ng, Wai & Kan, 2001; Koyasu et al., 2010; Lee et al., 2014; Li, Ji, Liu & Wang, 2019; Li et al., 2016; Lin et al., 2003; Lopez-Alvarenga et al., 1999; Meneilly et al., 2000; Mo et al., 2019; Noda, Umeda & Nawata, 1997; Oyama et al., 2008; Pan et al., 2003; Pan et al., 2008; Pan et al., 2016; Patel, Kirkman, Considine, Hannon & Mather, 2013; Rachmani, Bar-Dayan, Ronen, Levi, Slavachevsky & Ravid, 2004; Ren, Ma & Jiao, 2022; Riccardi et al., 1999; Rosenbaum, Peres, Zanella & Ferreira, 2002; Rosenthal & Mauersberger, 2002; Salman et al., 2000; Schnell, Mertes, Standl & Group, 2007; Scott, Knowles & Beaven, 1984; Sels, Verdonk & Wolffenbuttel, 1998; Shi et al., 2017; Standl, Baumgartl, Fuchtenbusch & Stemplinger, 1999; Su et al., 2015; Sugihara et al., 2014; Sun, Zeng, Liao, Chen & Wang, 2016; van de Laar, Lucassen, Kemp, van de Lisdonk, van Weel & Rutten, 2004; Vichayanrat, Ploybutr, Tunlakit & Watanakejorn, 2002; Wagner et al., 2006; Wang, Ni, Yang, Li, Li & Feng, 2013; Wang et al., 2011; Watanabe, Uchino, Ohmura, Tanaka, Onuma & Kawamori, 2004; Wolever et al., 1995; Wu et al., 2017; Yang et al., 2019; Yang et al., 2014; Yilmaz, Gursoy, Sahin & Guvener Demirag, 2007; Yun, Du, Chen, Liu & Xiao, 2016; Ziaee, Esmailzadehha & Honardoost, 2017) and 22 studies on HOMA-IR (Bao et al., 2010; Chen et al., 2014; Derosa et al., 2009a; Derosa, Maffioli, D'Angelo, Fogari, Bianchi & Cicero, 2011; Derosa et al., 2011; Derosa et al., 2009b; Hajiaghamohammadi, Miroliaee, Samimi, Alborzi & Ziaee, 2013; Hasegawa et al., 2008; Hirano et al., 2012; Khalili & Sheikh-Aboomasoudi, 2018; Koyasu et al., 2010; Pan et al., 2016; Patel, Kirkman, Considine, Hannon & Mather, 2013; Penna, Canella, Reis, Silva de Sa & Ferriani, 2005; Rachmani, Bar-Dayan, Ronen, Levi, Slavachevsky & Ravid, 2004; Rosenbaum, Peres, Zanella & Ferreira, 2002; Shi et al., 2017; Sun, Zeng, Liao, Chen & Wang, 2016; Wang et al., 2011; Wang et al., 2021; Yang et al., 2019; Yang et al., 2014; Zheng, Yin, Lu, Zhou, Yuan & Li, 2013). The total sample size for FBS was 10675 (intervention: 5127, control: 5548), in terms of insulin was 3915 in total (intervention: 1961, control: 1954), and in terms of HbA1c was 10737 in total (intervention: 5041, control: 5696) and HOMA-IR 3099 individuals in total (intervention: 1562, control:1537).

Adverse events

Information on adverse effects was mentioned in the studies by Soonthornpun et al. (Soonthornpun, Rattarasarn, Thamprasit & Leetanaporn, 1998) (mild and tolerable gastrointestinal problems), Coniff et al. (Coniff, Shapiro & Seaton, 1994) (abdominal pain, nausea, diarrhea and flatulence), Costa et al. (Costa, Pinol & Group, 1997) (constipation, nausea, diarrhea and flatulence), Fischer et al. (Fischer, Hanefeld, Spengler, Boehme & Temelkova-Kurktschiev, 1998) (flatulence and meteorism), Josse et al. (Josse et al., 2003) (constipation, nausea, diarrhea and flatulence), Kageyama et al. (Kageyama, Nakamichi, Sekino, Fujita & Nakano, 2000) (gastrointestinal problems), Li et al. (Li et al., 2016) (gastrointestinal problems), Lin

et al. (Lin et al., 2003) (gastrointestinal problems), Nijpels et al. (Nijpels, Boorsma, Dekker, Kostense, Bouter & Heine, 2008) (gastrointestinal problems), Van de laar et al. (van de Laar, Lucassen, Kemp, van de Lisdonk, van Weel & Rutten, 2004) (flatulence, diarrhoea, abdominal pain or nausea, headache), Sels et al. (Sels, Verdonk & Wolffenbuttel, 1998) (flatulence, diarrhoea, and abdominal pain), Ren et al. (Ren, Ma & Jiao, 2022) (edema, nausea, gastrointestinal discomfort and hypoglycemia), Gao et al. (Gao et al., 2022) (constipation, nausea, diarrhea and flatulence), Yang et al. (Yang et al., 2014) (gastrointestinal problems, infections and infestations, metabolism and nutrition disorders, nervous system disorders, musculoskeletal and connective tissue disorders), Buchanan et al. (Buchanan, Collier, Rodrigues, Millar, Gray & Clarke, 1988) (diarrhea and flatulence), Coniff et al. (Coniff, Shapiro, Seaton, Hoogwerf & Hunt, 1995) (diarrhea and flatulence), Khalili et al. (Khalili & Sheikh-Aboomasoudi, 2018) (gastrointestinal disorders), Gao et al. (Gao et al., 2020) (gastrointestinal problems), Goke et al. (Goke, 2002) (increased liver enzymes, cardiac failure and gastrointestinal problems), Guagnano et al. (Guagnano, Loggia, Pace-Palitti, Spoltore, Capitanio & Sensi, 1998) (flatulence, abdominal cramps, and diarrhea), Hauner et al. (Hauner, Petzinna, Sommerauer & Toplak, 2001) (flatulence, abdominal pain and diarrhoea), Ko et al. (Ko, Tsang, Ng, Wai & Kan, 2001) (flatulence, diarrhoea and abdominal colic), Lee et al. (Lee et al., 2014) (gastrointestinal problems), Lopez-Alvarenga et al. (Lopez-Alvarenga et al., 1999) (gastrointestinal problems), Pan et al. (Pan et al., 2003) (gastrointestinal problems), Riccardi et al. (Riccardi et al., 1999) (gastrointestinal problems), Salman et al. (Salman et al., 2000) (flatulence, abdominal pain and diarrhoea), Schnell et al. (Schnell, Mertes, Standl & Group, 2007) (gastrointestinal problems), Sun et al. (Sun, Zeng, Liao, Chen & Wang, 2016) (abdominal distension and diarrhoea), Wang et al. (Wang et al., 2011) (abdominal distension and low back pain), Yun et al. (Yun, Du, Chen, Liu & Xiao, 2016) (gastrointestinal problems, Rachmani et al. (Rachmani, Bar-Dayan, Ronen, Levi, Slavachevsky & Ravid, 2004) (gastrointestinal problems). The adverse events are presented in**Table 1** .

Qualitative data assessment

We assessed the qualitative data based on the Cochrane risk of bias assessment tool. Eleven studies had a moderate risk of bias (Derosa et al., 2009a; Derosa, Maffioli, D'Angelo, Fogari, Bianchi & Cicero, 2011; Derosa et al., 2009b; Hanefeld et al., 2009; Hanjalic-Beck et al., 2010; Nijpels, Boorsma, Dekker, Kostense, Bouter & Heine, 2008; Pan et al., 2008; Rachmani, Bar-Dayan, Ronen, Levi, Slavachevsky & Ravid, 2004; Rosenbaum, Peres, Zanella & Ferreira, 2002; van de Laar, Lucassen, Kemp, van de Lisdonk, van Weel & Rutten, 2004; Wu et al., 2017). Ninety studies had a high risk of bias (AKAZAWA, KOIDE, OISHI, AZUMA & TASHIRO, 1982; Bachmann, Petzinna, Raptis, Wascher & Westermeier, 2003; Bao et al., 2010; Bayraktar, Hamulu, Ozgen, Yilmaz, Tuzun & Kabalak, 1998; Bayraktar, Van Thiel & Adalar, 1996; Buchanan, Collier, Rodrigues, Millar, Gray & Clarke, 1988; Chan et al., 1998; Chen et al., 2014; Chen, Tarng & Chen, 2016; Chiasson et al., 1996; Coniff, Shapiro & Seaton, 1994; Coniff, Shapiro, Seaton, Hoogwerf & Hunt, 1995; Costa, Pinol & Group, 1997; Derosa, Maffioli, D'Angelo, Fogari, Bianchi & Cicero, 2011; Derosa et al., 2011; Derosa et al., 2009b; Du et al., 2017; Fischer, Hanefeld, Spengler, Boehme & Temelkova-Kurktschiev, 1998; Fischer et al., 2003; Gao et al., 2022; Gao et al., 2020; Gentile et al., 2005; Gentile et al., 2001; Goke, 2002; Goke, Lubben & Bates, 2004; Guagnano, Loggia, Pace-Palitti, Spoltore, Capitanio & Sensi, 1998; Hajiaghamohammadi, Miroliaee, Samimi, Alborzi & Ziaee, 2013; Halimi, Le Berre & Grange, 2000; Hanefeld et al., 2002; Hasegawa et al., 2008; Hauner, Petzinna, Sommerauer & Toplak, 2001; Hirano et al., 2012; Hoffmann, 1997; Hotta et al., 1993; Hwu et al., 2003; Jenney, Proietto, O'Dea, Nankervis, Traianedes & D'Embden, 1993; Josse et al., 2003; Kageyama, Nakamichi, Sekino, Fujita & Nakano, 2000; Ko, Tsang, Ng, Wai & Kan, 2001; Koyasu et al., 2010; Lam, Tiu, Tsang, Ip & Tam, 1998; Laube, Linn & Heyen, 1998; Lee et al., 2014; Li, Ji, Liu & Wang, 2019; Li et al., 2016; Lin et al., 2003; Lopez-Alvarenga et al., 1999; Malaguarnera, Giugno, Ruello, Rizzo, Motta & Mazzoleni, 1999; Meneilly et al., 2000; Mo et al., 2019; Noda, Umeda & Nawata, 1997; Oyama et al., 2008; Pan et al., 2003; Pan et al., 2016; Patel, Kirkman, Considine, Hannon & Mather, 2013; Penna, Canella, Reis, Silva de Sa & Ferriani, 2005; Ren, Ma & Jiao, 2022; Rezai, Jamshidi, Mohammadbeigi, Seyedoshohadaei, Mohammadipour & Moradi, 2016; Riccardi et al., 1999; Rosenthal & Mauersberger, 2002; Rudovich, Weickert, Pivovarova, Bernigau & Pfeiffer, 2011; Salman et al., 2000; Sanjari, Gholamhoseinian Najar, Asadikaram, Mashayekhi & Ghaseminejad Tafreshi, 2019;

Schnell, Mertes, Standl & Group, 2007; Scott, Knowles & Beaven, 1984; Sels, Verdonk & Wolffenbuttel, 1998; Shi et al., 2017; Sonmez et al., 2005; Soonthornpun, Rattarasarn, Thamprasit & Leetanaporn, 1998; Standl, Baumgartl, Fuchtenbusch & Stemplinger, 1999; Su et al., 2015; Sugihara et al., 2014; Sun, Zeng, Liao, Chen & Wang, 2016; Suzuki et al., 2006; Takei et al., 2001; Tuğrul, Kutlu, Pekin, Bağlam, Kıyak & Oral, 2008; Vichayanrat, Ploybutr, Tunlakit & Watanakejorn, 2002; Wagner et al., 2006; Wang, Ni, Yang, Li, Li & Feng, 2013; Wang et al., 2011; Wang et al., 2021; Watanabe, Uchino, Ohmura, Tanaka, Onuma & Kawamori, 2004; Wolever et al., 1995; Wu et al., 2017; Yajima, Shimada, Hirose, Kasuga & Saruta, 2004; Yang et al., 2019; Yang, Zhang, Zhang & Niu, 2022; Yang et al., 2014; Yilmaz, Gursoy, Sahin & Guvener Demirag, 2007; Yun, Du, Chen, Liu & Xiao, 2016; Zheng, Yin, Lu, Zhou, Yuan & Li, 2013; Ziaee, Esmailzadehha & Honardoost, 2017). The adverse events are presented in **Table 2** .

Effect of acarbose intake on FBS (mg/dl)

Combining 92 effect sizes from 43 studies, results have shown acarbose intake had a significant effect on FBS (mg/dl) compared to a placebo [(WMD= -2.90 mg/dl; 95% CI, -5.30 to -0.50; p=0.018; (I^2=92.2%, p<0.001)] (**Figure 2A**). Subgroup analyses have shown that acarbose intake had a reduction effect on FBS (mg/dl) in any baseline FBS (<100 mg/dl and [?]100 mg/dl), [(WMD= -3.58 mg/dl; 95% CI, -6.55 to -0.61; p=0.018; (I^2=75.5%, p<0.001)] and [(WMD= -2.93 mg/dl; 95% CI, -5.80 to -0.05; p=0.046; (I^2=93.2.1%, p<0.001)] respectively. Acarbose intake had a reduction effect on FBS (mg/dl) in trial duration [?]24 weeks, [(WMD= -3.80 mg/dl; 95% CI, -7.38 to -0.21; p=0.036; (I^2=94.6%, p=<0.001)]. Acarbose intake had a reduction effect on FBS (mg/dl) in intervention dose [?]300 mg/d, [(WMD= -4.08 mg/dl; 95% CI, -7.09 to -1.07; p=0.008; (I^2=93.6%, p<0.001)]. Also, acarbose intake had a reduction effect on FBS (mg/dl) in obese participants (obese (>30 kg/m^2)), [(WMD= -3.29 mg/dl; 95% CI, -5.67 to -0.91; p=0.007; (I^2=89.3%, p<0.001)]. Moreover, acarbose intake had a reduction effect on FBS (mg/dl) in two types of health status (T2DM and impaired glucose tolerance), [(WMD= -4.22 mg/dl; 95% CI, -6.90 to -1.55; p=0.002; (I^2=90.6%, p<0.001)] and [(WMD= -2.64 mg/dl; 95% CI, -4.85 to -0.42; p=0.019; (I^2=26.5%, p=0.253)] respectively.

Subgroup analyses indicated no significant between-study heterogeneity in studies conducted on the impaired glucose tolerance (I^2=26.5%, p=0.253) and T2DM patients (I^2=57.3%, p=0.071) were probable sources of heterogeneity (**Table 3**).

Effect of acarbose intake on serum insulin

Combining 47 effect sizes from 46 studies, results have shown acarbose intake had a significant effect on serum insulin (pmol/l) compared to a placebo [(WMD= -9.29 pmol/l; 95% CI, -13.14 to -5.54; p<0.001; (I^2=91.5%, p<0.001)] (**Figure 2B**). Subgroup analyses were conducted have shown that acarbose intake had a reduction effect on serum insulin (pmol/l) in any trial duration (<24 weeks and [?]24 weeks), [(WMD= -8.42 pmol/l; 95% CI, -14.82 to -1.94; p=0.011; (I^2=82.3%, p<0.001)] and [(WMD= -10.07 pmol/l; 95% CI, -15.47 to -4.67; p<0.001; (I^2=94.7%, p<0.001)] respectively. Acarbose intake had a reduction effect on serum insulin (pmol/l) in any trial dose (¡300 mg/d and [?]300 mg/d), [(WMD= -6.36 pmol/l; 95% CI, -10.53 to -2.18; p=0.001; (I^2=68.0%, p<0.001)] and [(WMD= -10.09 pmol/l; 95% CI, -14.45 to -5.72; p<0.001; (I^2=92.6%, p<0.001)] respectively. Also, acarbose intake had a reduction effect on serum insulin (pmol/l) in any baseline BMI (overweight (25-29.9) and obese (>30 kg/m^2)), [(WMD= -4.20 pmol/l; 95% CI, -6.62 to -1.77; p=0.001; (I^2=70.4%, p=0.009)] and [(WMD= -11.10 pmol/l; 95% CI, -19.41 to -2.79; p=0.009 (I^2=92.2%, p<0.001)] respectively. Moreover, acarbose intake had a reduction effect on serum insulin (pmol/l) only in T2DM patients, [(WMD= -4.20 pmol/l; 95% CI, -6.62 to -1.77; p=0.001; (I^2=70.4%, p=0.009)]. Subgroup analyses indicated a significant between-study heterogeneity in all subgroups except in studies conducted in the intervention dose ¡300 mg/d (I^2=0.0%, p=0.448), the impaired glucose tolerance patients (I^2=0.0%, p=0.469) and another health status (I^2=16.8%, p=0.305) (**Table 3**).

Effect of acarbose intake on serum HbA1c

Combining 9 effect sizes from 80 studies, results have shown acarbose intake had a significant effect on serum HbA1c (%) compared to a placebo [(WMD= -0.32 %; 95% CI, -0.44 to -0.20; p<0.001; (I^2=96.2%, p<0.001)] (**Figure 2C**).

Subgroup analyses were conducted have shown that acarbose intake had a reduction effect on HbA1c (%) in any trial duration (<24 weeks and [?]24 weeks), [(WMD= -0.27 %; 95% CI, -0.49 to -0.04; p=0.018; (I^2=94.2%, p<0.001)] and [(WMD= -0.36 %; 95% CI, -0.50 to -0.21; p<0.001; (I^2=96.9%, p<0.001)] respectively. Acarbose intake had a reduction effect on HbA1c (%) in intervention dose [?]300 mg/d, [(WMD= -0.38 %; 95% CI, -0.53 to -0.23; p<0.001; (I^2=96.8%, p<0.001)]. Also, acarbose intake had a reduction effect on HbA1c (%) in obese participants (obese (>30 kg/m^2)), [(WMD= -0.30 %; 95% CI, -0.44 to -0.16; p<0.001; (I^2=96.0%, p<0.001)]. Moreover, acarbose intake had a reduction effect HbA1c (%) only in T2DM patients, [(WMD= -0.36 %; 95% CI, -0.50 to -0.22; p<0.001; (I^2=96.4%, p<0.001)]. Subgroup analyses indicated a significant between-study heterogeneity in all subgroups (**Table 3**).

Effect of acarbose intake on HOMA-IR

Combining 9 effect sizes from 80 studies, results have shown acarbose intake had a significant effect on serum HOMA-IR compared to a placebo [(WMD= -0.32; 95% CI, -0.44 to -0.20; p<0.001; (I^2=96.2%, p<0.001)] (**Figure 2D**). Subgroup analyses were conducted have shown that acarbose intake had a reduction effect on HOMA-IR in overweight participants (overweight (25-29.9 kg/m^2), [(WMD= -0.45; 95% CI, -0.85 to -0.05; p=0.029; (I^2=0.0%, p=0.728)]. Subgroup analyses indicated a significant between-study heterogeneity in all subgroups except in overweight participants (overweight (25-29.9 kg/m^2) (I^2=0.0%, p=0.728) (**Table 3**).

Publication bias

Although the visual inspection of funnel plots showed slight asymmetries, no significant publication bias was detected for FBS, insulin, and HOMA-IR. The p-value for Egger's test for FBS, insulin, and HOMA-IR were 0.333, 0.154, and 0.191 respectively (**Figure 3A, B, and D).** Although significant publication bias was detected for HbA1c**.** The p-value for Egger's test for HbA1c was 0.002 (**Figure 3C).**

Nonlinear dose-response analysis

For the dose-response analysis between acarbose intake and FBS, insulin, HOMA-IR, and HbA1c, we used a one-stage nonlinear dose-response analysis. The dose-response analyses revealed nonlinear associations between acarbose intake and FBS, insulin, HOMA-IR, and HbA1c. We did not find a significant nonlinear relationship between dose (mg/d) (coefficients=12.63, p=0.102) and duration (weeks) (coefficients=-20.88, p=0.388) of intervention and changes in FBS **(Figure 4A and 5A**). In addition, there was no significant nonlinear relationship between dose (mg/d) (coefficients=207.44, p=0.102) and duration of the intervention (weeks) (coefficients=-19.55, p=0.307) and changes in insulin **(Figure 4B and 5B**). Also, we did not find a significant nonlinear relationship between dose (mg/d) (coefficients=-1.07, p=0.549) and duration (weeks) (coefficients=-1.67, p=0.230) of intervention and changes in HbA1c**(Figure 4C and 5C**). We did not find a significant nonlinear relationship between dose (mg/d) (coefficients=4.26, p=0.257) and duration (weeks) (coefficients=-0.41, p=0.245) of intervention and changes in HOMA-IR **(Figure 4D and 5D**).

Meta-regression analysis

Meta-regression analyses were performed to assess whether FBS, insulin, HOMA-IR, and HbA1c was affected by acarbose doses and intervention durations. We did not find a significant linear relationship between dose (mg/d) (coefficients=-0.03, p=0.140) and duration (weeks) (coefficients=-0.02, p=0.776) of intervention and changes in FBS**(Figure 6A and 7A**). In addition, there was no significant linear relationship between dose (mg/d) (coefficients=-0.04, p=0.387) and duration of the intervention (weeks) (coefficients=0.08, p=0.734) and changes in insulin **(Figure 6B and 7B**). Also, we did not find a significant linear relationship between dose (mg/d) (coefficients=-9.98, p=0.494) and duration (weeks) (coefficients=-0.79, p=0.791) of intervention and changes in HbA1c **(Figure 6C and 7C**). We did not find a significant nonlinear relationship between dose (mg/d) (coefficients=-4.71, p=0.285) and duration (weeks) (coefficients=0.06, p=0.940) of intervention and changes in HOMA-IR**(Figure 6D and 7D**).

Sensitivity analysis

According to the sensitivity analysis, no study affected the overall results after removing individual study

effects for all outcomes.

GRADE assessment

We used the GRADE evidence profile and the certainty in outcomes of acarbose intake on FBS, insulin, HOMA-IR, and HbA1c were shown in**Table 4.** The quality of evidence was low due to the severe inconsistencies and indirectness for FBS, insulin, and HbA1c. although the quality of evidence was moderate due to the severe inconsistencies and imprecision of HOMA-IR.

Discussion

In this meta-analysis, we investigated the effects of acarbose intake on glycemic markers in adults through a dose-response analysis. Our results revealed that acarbose intake was associated with a significant decrease in three glycemic indices including FBS, insulin, and HbA1c, but had no significant effect on HOMA-IR in comparison to control groups. Additionally, we conducted a non-linear dose-response analysis and found no significant associations between acarbose intake and changes in glycemic markers mentioned for the lowest or highest doses and durations.

Our study has revealed a significant reduction in FBS and HbA1c levels with the intake of acarbose. The findings of our study are consistent with a meta-analysis conducted by Liu et al. (Liu, Zhao, Sun, Wang, Liu & Kang, 2017) showed that a combination of acarbose and metformin intake resulted in a significantly lower FBS in patients with T2DM when compared to metformin alone. This suggests that combining metformin and acarbose may be a more effective treatment approach than using either drug alone. The present results provide further evidence to support the effectiveness of this combination therapy. While there were some differences between the study by Liu et al. and our current study, such as the number of studies included and the focus on the combined effects of acarbose with metformin, our findings are consistent with previous research. One limitation of the study by Liu et al. was the inclusion of low-quality studies, which may have affected the overall results. Additionally, our findings align with a systematic review and meta-analysis study conducted by Hanefeld et al. which showed that acarbose intake can significantly reduce FBS in patients with abnormal glucose tolerance over a period of at least 52 weeks (Hanefeld, Cagatay, Petrowitsch, Neuser, Petzinna & Rupp, 2004). It is important to note that the study by Hanefeld et al. had a higher quality compared to other studies. However, our study expands on their findings by conducting subgroup analyses that involve a dose-response. Additionally, the results of a systematic review study support the effectiveness of acarbose intake, both alone and in combination with other antidiabetic drugs, in significantly improving FBS and HbA1c. Overall, our study adds to the growing body of evidence supporting the use of acarbose as an effective treatment option for managing T2DM (Derosa & Maffioli, 2012). In addition to medications, it appears that physical activity and a well-rounded diet are crucial for diabetic patients to control FBS and HbA1c (Siavoshy & Heidarianpour, 2017; Ziaee, Afaghi & Sarreshtehdari, 2012). In a study, the combination of combined aerobic and strength training and 300 mg/d of acarbose intake significantly reduced FBS and HbA1c in patients with mild diabetes after a 12-week intervention (Wagner et al., 2006).

In a study conducted by Lin et al., the intake of acarbose at a dose of 100 mg (TID) for 24 weeks in patients with T2DM did not result in a significant effect on FBS. However, it did significantly reduce 1-hour postprandial FBS compared to the placebo (Lin et al., 2003). These results do not confirm the findings of our study, and the controversy may be explained by the small sample size (65 participants in intervention and control groups) included in this study. Additionally, this study was conducted on Asian patients and therefore may not represent the entire global population. Acarbose, which is considered the first line of treatment for controlling hyperglycemia in diabetic patients, works competitively, dose-dependently, and reversibly inhibiting the α-glucosidase enzyme present on the surface of epithelial cells, causing a delay in carbohydrate absorption (Cheng & Josse, 2004). Another possible mechanism by which acarbose reduces FBS is by indirectly increasing glucagon-like peptide-1 (GLP-1) levels through its ability to reduce glucose absorption. GLP-1 can then act on the satiety center in the brain, reducing food and carbohydrate intake and ultimately leading to a decrease in FBS (Zhang et al., 2017). Acarbose therapy appears to prevent the absorption of carbohydrates, which are then metabolized into short-chain fatty acids (SCFAs) in the gastrointestinal (GI)

tract. A study conducted by Wolever et al. investigated the effects of rectal infusions of solutions containing sodium acetate and sodium propionate on blood glucose levels in six healthy participants. The results of the study provided compelling evidence that FBS decreased following each injection. Additionally, the decrease in free fatty acid (FFA) levels suggested that colonic SCFAs have an impact on carbohydrate metabolism. Furthermore, propionate has been shown to slow down the pace of starch digestion itself (Wolever, Brighenti, Royall, Jenkins & Jenkins, 1989). Short-chain fatty acid (SCFA) acetate affects body weight regulation, glucose homeostasis, and insulin resistance through various mechanisms. Acetate positively impacts host energy and substrate metabolism by releasing gut hormones such as glucagon-like peptide-1 and peptide YY, which affect appetite. It also reduces whole-body lipolysis, elevates systemic pro-inflammatory cytokine levels, and increases energy expenditure. As a result, acetate plays an important role in maintaining glucose homeostasis and preventing insulin resistance.

G-protein coupled receptors (GPCRs), specifically GPR43 (free fatty acid receptor [FFAR2]) and GPR41 (FFAR3), are expressed at both mRNA and protein levels in the human colon and small intestine, including the ileum. These receptors may be the mechanism through which acetate acts (Karaki et al., 2008; Nøhr et al., 2013; Tazoe et al., 2009). In addition, it has been demonstrated that these GPCRs are expressed at the mRNA level in a variety of insulin-sensitive organs, including adipose tissue, skeletal muscle, the liver, and pancreatic beta cells, highlighting their wide metabolic function. However, in several peripheral tissues, acetate may be converted internally into acetyl coenzyme A (acetyl-CoA) and integrated into the tricarboxylic acid (TCA) cycle (Knowles, Jarrett, Filsell & Ballard, 1974; Le Poul et al., 2003; Priyadarshini et al., 2015; Tang et al., 2015). Acetate may also influence metabolism by increasing the capacity for oxidation in various tissues, such as the liver and skeletal muscle, which could affect blood glucose levels (Maruta, Yoshimura, Araki, Kimoto, Takahashi & Yamashita, 2016; Yamashita et al., 2009).

Based on our findings, the intake of acarbose causes a significant decrease in hemoglobin levels. The results of a meta-analysis study conducted by Zhu et al. also demonstrated that acarbose intake can significantly reduce HbA1c levels in patients with T2DM, regardless of the patient's diet types, at a dose of 300 mg/d (Zhu, Tong, Wu, Li & Tong, 2013), which confirms the findings of our study. Additionally, in a clinical trial study that confirms our findings, it was shown that the intake of 300 mg/d of acarbose for 6 months causes a significant decrease in HbA1c levels in patients with T2DM (Lin et al., 2003).

The objective of medication treatment for patients with T2DM is to lower FBS levels and bring them closer to normal levels to decrease the risk of complications associated with diabetes. HbA1c is an important marker that indicates the level of hyperglycemia control over the past 2 to 3 months, and a decrease in the percentage of HbA1c indicates a reduction in the risk of microvascular complications of diabetes (Coniff, Shapiro, Seaton & Bray, 1995; Group, 1998). It seems that one of the mechanisms by which acarbose can decrease the level of HbA1c is the reduction of insulin resistance (Delgado, Lehmann, Bobbioni-Harsch, Ybarra & Golay, 2002).

Our subgroup analysis revealed that the efficacy of acarbose intake on FBS is significantly influenced by trial duration, intervention dose, BMI, and health status. Specifically, we found that acarbose intake at doses higher than 300 mg/d and for a duration of 24 weeks or more has a significant effect on FBS in obese individuals with diabetes or impaired glucose tolerance. Furthermore, our study demonstrated that acarbose at doses greater than 300 mg/d has a significant effect on HbA1c levels in obese diabetic individuals (BMI>30 kg/m^2).

Our findings are consistent with the results of the meta-analysis study by Yu et al. which reported that acarbose intake did not have a significant effect on FBS in non-diabetic obese and overweight individuals (Yu et al., 2021), Similarly, our study found that acarbose intake only had a significant effect on FBS in diabetics and impaired glucose tolerance patients and not in non-diabetic individuals, such as those with polycystic ovary syndrome. Given the World Health Organization's report that one-third of individuals with impaired glucose tolerance eventually develop diabetes within 10 years (Nijpels, Boorsma, Dekker, Kostense, Bouter & Heine, 2008), our findings suggest that the intake of acarbose with a dose of more than 300 mg/d for 6 months or more may improve glucose tolerance disorder and its progression towards T2DM. Also, our study is in line with the study by Hauner et al. which demonstrated that acarbose intake at a dose

of 300 mg/d for 16 weeks in non-diabetic obese individuals did not have a significant effect on FBS and HbA1c (Hauner, Petzinna, Sommerauer & Toplak, 2001), confirming the present findings from our study that acarbose only in diabetic or impaired glucose tolerance patients has a significant effect on FBS.

Our dose-response results showed no significant associations were found between acarbose intake and FBS and HbA1c in the lowest or highest non-linear dose-response analysis. In the current meta-analysis, we found that acarbose intake resulted in a significant reduction in insulin levels, while it had no significant effect on HOMA-IR in the overall analysis.

In a clinical trial study conducted by Chan et al., it was shown that the intake of acarbose for 24 weeks at a dose of 300 mg/d in T2DM patients can significantly decrease the level of HbA1c and FBS, but its effects on plasma insulin levels were not significant (Chan et al., 1998). The results of this study confirm the findings of the present meta-analysis. In one study, the intake of acarbose for 4 months at a dose of 300 mg/d in patients with impaired glucose tolerance caused a decrease in insulin levels, which was in line with our study. On the other hand, it also caused a significant decrease in insulin sensitivity (Chiasson et al., 1996); the results in terms of statistical significance were not aligned with our findings, which is probably due to the small sample size in this study (18 patients in intervention and control groups). In addition, Reaven et al. demonstrated that acarbose intake improved insulin resistance, which results are not consistent with our study, likely due to the small sample size (12 patients) and the absence of a control group (Reaven, Lardinois, Greenfield, Schwartz & Vreman, 1990). Having regular physical activity in diabetic patients can significantly regulate the secretion of insulin and the HOMA-IR (Kadoglou et al., 2007). Therefore, it is possible that the intake of acarbose along with regular physical activity can cause a further decrease in insulin sensitivity and improve its secretion, these results have also been shown in Kumar et al. meta-analysis study (Kumar et al., 2019).

Acarbose has been shown to delay carbohydrate metabolism and reduce blood glucose absorption, leading to a decrease in insulin secretion after a meal (Derosa, Maffioli, D'Angelo, Fogari, Bianchi & Cicero, 2011). Furthermore, research suggests that acarbose can improve insulin sensitivity in certain doses (Rossetti, Giaccari & DeFronzo, 1990). Acarbose's role in regulating the secretion of insulin and proinsulin, as well as glucagon-stimulated insulin secretion, may lead to increased efficiency of pancreatic beta cells and ultimately improved insulin sensitivity (Delgado, Lehmann, Bobbioni-Harsch, Ybarra & Golay, 2002; Rosak & Mertes, 2009). In individuals with T2DM, there is often an increase in inflammatory markers. Acarbose may decrease insulin resistance by reducing these inflammatory markers (Derosa & Maffioli, 2012; Khalili & Safavipour, 2020).

Also, in the subgroup analysis, our results showed that only health status significantly affects the insulin level, however, it was shown that only the BMI has a significant effect on the HOMA-IR levels. Although the number of studies that have investigated the effects of acarbose intake on insulin and HOMA-IR levels in non-diabetic patients is small, this makes it difficult to compare the analysis of subgroups. In one study conducted by Rachmani et al., it was shown that acarbose at the dose of 150 mg/d for 24 weeks reduces HOMA-IR in obese-hypertensive patients with normal glucose tolerance (Rachmani, Bar-Dayan, Ronen, Levi, Slavachevsky & Ravid, 2004). The results of this study are in line with our findings because although acarbose intake did not have a significant effect in reducing HOMA-IR, its effect was significant in the subgroup of overweight individuals.

In our study, we found that although there was a decrease in HOMA-IR percent with acarbose intake, the decrease was not statistically significant. This finding is consistent with the results from a study by Derosa et al. where acarbose intake at increasing doses from 50 to 300 mg/d for 7 months in diabetic patients resulted in a significant decrease in HOMA-IR but not in insulin levels compared to the control group (Derosa et al., 2011). However, the small sample size and variable dose of acarbose in their study could explain the inconsistency with our results. It is possible that combining acarbose intake with regular physical activity and following a healthy diet could lead to a significant improvement in insulin sensitivity in diabetic patients (Rodriguez-Rodriguez, Perea, Lopez-Sobaler & Ortega, 2009).

Furthermore, our dose-response analysis revealed no significant associations between acarbose intake and

changes in insulin and HOMA-IR in the lowest or highest doses by non-linear dose-response analysis. This suggests that the effect of acarbose intake on insulin and HOMA-IR changes is not dependent on the dosage.

It is important to note that our study has several limitations. One of the limitations is the high risk of bias in the included studies. We also did not assess the effects of acarbose on 2-hour postprandial glucose levels due to the lack of data in the RCTs. Moreover, the role of diet and physical activity in improving glycemic markers was not considered as a subgroup in most of the studies, which could have influenced our findings. Another limitation is the heterogeneity in the doses and durations of acarbose used in the trials, as well as the variation in the brand of acarbose utilized, its bioavailability, and individual compliance. Additionally, different outcome assessment techniques were used in the included trials, which might have led to different outcomes.

Despite these limitations, our study has several strengths. It is one of the first comprehensive dose-response meta-analysis studies with a high sample size of 101 studies to evaluate the effects of acarbose intake on glycemic markers in adults. We performed a dose-response analysis considering different subgroups to evaluate the effects of acarbose intake on glycemic markers. Another strength of our study is the low publication bias among the included studies. We also used the GRADE methodology to assess the quality of evidence. Furthermore, we conducted a sensitivity analysis and thoroughly examined all adverse effects, and most of the studies have recorded and reported their occurrence.

Conclusions

Our systematic review and dose-response meta-analysis provide evidence that supports the association between acarbose intake and decreased levels of FBS, insulin, and HbA1c in adults. While the use of acarbose alone may not result in a significant improvement in HOMA-IR, we suggest that it could be a valuable addition to a treatment strategy for diabetes, when combined with a healthy diet and regular physical activity. We did not observe any significant changes in glycemic indices based on acarbose dose or duration. However, further well-designed studies that account for factors such as dietary intake and physical activity levels are needed to evaluate this association more accurately.

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Not applicable

Author Contributions

The authors' responsibilities were as follows SRD: designed the study; SRD and OA: developed the search strategy; SRD, MNS, and OA: extracted the data and conducted the analyses; NP, MD, NR, and SR: drafted the manuscript; SRD, and OA: assessed the risk of bias of the meta-analyses; FSH, OA, and MNS: interpreted the results; FSH, RB, and OA revised manuscript, and all authors: read and approved the final manuscript.

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Availability of data and materials

Data will be made available upon a reasonable request

Competing interests

None of the authors have any conflicts of interest or financial ties to disclose.

Abbreviations

RCTs, randomized clinical trials; HbA1c, hemoglobin A1C; HOMA-IR, homeostasis model assessment of insulin resistance; WMD, weighted mean differences; CI, confidence intervals; NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; GRADE, Grading of Recommendations Assessment, Development, and

Evaluation; T2DM, type 2 diabetes Meletus; GLP-1, glucagon-like peptide-1; SCFAs, short chain fatty acids; FFA, free fatty acid; GPR, G protein-coupled receptors; acetyl-CoA, acetyl-coenzyme A, TCA, tricarboxylic acid; FFAR, free fatty acid receptor; WHO, world health organization; IGT, impaired glucose tolerance.

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Figure legends

Figure 1. Flow chart of study selection for inclusion trials in the systematic review.

Figure 2. Forest plot detailing weighted mean difference (WMD) and 95% confidence intervals (CIs) for the effect of acarbose intake on A) FBS (mg/dl); B) insulin (pmol/l); C) HbA1c (%); D) HOMA-IR. FBS, fasting blood sugar; HOMA-IR, homeostasis model assessment for insulin resistance; hemoglobin A1c, HbA1c; CI, confidence interval, weighted mean difference; WMD. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from random-effects analysis.

Figure 3. Funnel plots for the effect of acarbose intake on A) FBS (mg/dl); B) insulin (pmol/l); C) HbA1c (%); D) HOMA-IR. FBS, fasting blood sugar; HOMA-IR, homeostasis model assessment for insulin resistance; hemoglobin A1C, HbA1c; CI, confidence interval, weighted mean difference; WMD.

Figure 4. Non-linear dose-response relations between acarbose intake and absolute mean differences. Dose-response relations between dose (mg/d) and absolute mean differences in A) FBS (mg/dl); B) insulin (pmol/l); C) HbA1c (%); D) HOMA-IR. FBS, fasting blood sugar; HOMA-IR, homeostasis model assessment for insulin resistance; hemoglobin A1C, HbA1c; CI, confidence interval, weighted mean difference; WMD.

Figure 5. Non-linear dose-response relations between acarbose intake and absolute mean differences. Dose-response relations between duration of the intervention (week) and absolute mean differences in A) FBS (mg/dl); B) insulin (pmol/l); C) HbA1c (%); D) HOMA-IR. FBS, fasting blood sugar; HOMA-IR, homeostasis model assessment for insulin resistance; hemoglobin A1C, HbA1c; CI, confidence interval, weighted mean difference; WMD.

Figure 6. Linear dose-response relations between acarbose intake and absolute mean differences. Dose-response relations between dose (mg/d) and absolute mean differences in A) FBS (mg/dl); B) insulin (pmol/l); C) HbA1c (%); D) HOMA-IR. FBS, fasting blood sugar; HOMA-IR, homeostasis model assessment for insulin resistance; hemoglobin A1C, HbA1c; CI, confidence interval, weighted mean difference; WMD.

Figure 7. Linear dose-response relations between acarbose intake and absolute mean differences. Dose-response relations between duration of the intervention (week) and absolute mean differences on A) FBS

(mg/dl); B) insulin (pmol/l); C) HbA1c (%); D) HOMA-IR. FBS, fasting blood sugar; HOMA-IR, homeostasis model assessment for insulin resistance; hemoglobin A1C, HbA1c; CI, confidence interval, weighted mean difference; WMD.

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