ABSTRACT

Gestational diabetes (GD) is a common and deadly disorder with deleterious effects on both the mother and fetus. The current review assessed the role of the Mediterranean diet and metformin in the prevention of GD. The PubMed, Medline, and Google Scholar databases were searched for relevant articles, and the keywords metformin, Mediterranean diet, and gestational diabetes prevention were used with the proteans AND and OR. Out of the 252 articles retrieved, 48 full texts were assessed, and only nine articles fulfilled the inclusion and exclusion criteria. A data extraction sheet was used to collect the author's name, year of publication, country, methods of the study, risk reduction, odds ratio, relative risk, 95% CI, and P values. Three (33.3%) articles assessed the effectiveness of metformin on GD, and another six (66.7%) investigated the effects of the MedDiet on GD. The studies on metformin showed no reduction in GD (odds ratio, 1.07, 0.79–1.44, P value for overall effect=0.65, I² for heterogeneity=3%, P value=0.36. Chi-square=2.07, and the mean difference=2), while studies on the MedDiet showed a reduction in gestational diabetes risk ((odds ratio, 0.49, -0.32–0.73, P value for heterogeneity =0.0004, heterogeneity, I²=78%, P value for overall effect=0.0005, Chi-square=22.40 and mean difference=5. The Mediterranean diet was effective in the prevention of GD; however, metformin showed no significant risk reduction as an interventional measure.

Keywords: Metformin; mediterranean diet; gestational diabetes; prevention.
1. INTRODUCTION

The debate regarding the detection and treatment of gestational diabetes mellitus (GDM) continues in the twenty-first century. Although women with GDM are at risk of subsequent diabetes mellitus in the years following diagnosis, there is strong controversy regarding the long-term benefits of treatment [1].

GDM is increasing with high economic burden and severe pregnancy-related complications. Effective prevention strategies are lacking; in addition, the recommendations for lifestyles, oral hypoglycemic drugs, and healthy weight are contradictory and not uniform [2].

Metformin is the first-line oral hypoglycemic drug, and was shown to have anticancer and anti-inflammatory effects. In the prevention of the progression of prediabetes to diabetes mellitus, lifestyle modification is essential [3]. Metformin is an effective alternative to insulin for the treatment of gestational diabetes mellitus [4,5].

The Mediterranean diet (MD) is characterized by high consumption of fruits and vegetables, legumes, olive oil, fish, and unrefined cereals and avoidance of red meat; together with a moderate amount of alcohol and dairy products, the Mediterranean diet is one of the healthiest diets in the world. The American Diabetes Association recommended the MD for use among patients with diabetes mellitus [6,7]. Gestational diabetes mellitus is associated with various adverse effects to both the mother and fetus, and the level is increasing worldwide [8]. The prevention of GDM to prevent both short- and long-term effects of the mother and child is of paramount importance [9]. The literature on this important health issue is scarce. The current review aimed to assess the benefits of metformin and the Mediterranean diet in the prevention of GDM.

2. SUBJECTS AND METHODS

Eligibility Criteria according to PICOS:

Randomized controlled studies (RCTs) published in English and that contained information on metformin and the Mediterranean diet either in singleton pregnancy, prior to or during pregnancy were included. Studies assessing other pregnancy outcomes, cohort studies, case-control studies, case reports, animal studies, or studies published in a language other than English were not included.

2.1 Outcome Measures

Studies on metformin: There were three studies [10-12], the first study was conducted over 10 years, and the second evaluated the participants at 20 and 24-28 weeks. While the third recruited the participant between 1210 and 1516 gestational week.

Studies on Mediterranean diet: The primary outcome was the prevention of GD. There were six studies assessing the role of MedDiet in GDM, the first study [11] randomized the participants at 8-12 gestational weeks (GWs) and assessed at 24-28 weeks of pregnancy. In the second study [12], the patients were recruited at 12–14 versus, 8 weeks in control group and assessed at 24–28 gestational weeks; 36–38 and at delivery. The third study [13], enrolled the participants at 8–12 GWs and were followed-up at GWs 24–28, 34–36 and at 12–14 weeks post-partum. The fourth [14] gave dietary advice at 18, 20, and 28 GWs. The fifth study [15] randomization was at 12-14 Gestation week, and the patients were assessed for the outcomes at 24–28 GW, 36–38 GW and at delivery. While, the six study [16] was based on adherence to MedDiet at 24-28 gestational age.

Information sources and literature search: A systematic literature search was performed by two researchers, and the search was conducted in PubMed, Medline, and Google Scholar with an interest in articles (RCTs) reporting the relationship between metformin, the MedDiet, and GD risk. In addition, the reference lists were searched for additional studies [17,18]. The search engine was limited to the period from 2010 to September 2020.

A predetermined table was used to collect study information, including the author’s name, year of publication, patient number, study duration, criteria for patient selection, GDM diagnostic criteria and results and how the results were deduced. Data were cross-checked by the two authors for any errors and discrepancies. Any discrepancies were solved by consensus.

Data analysis: The RevMan system for meta-analysis was used, and the data were all dichotomized. The fixed effect model was used because no significant heterogeneity was found. Funnel plots were used to assess lateralization. A P value of <0.05 was considered significant.
Fig. 1. Metformin and the Mediterranean diet effects on gestational diabetes

Table 1. Metformin and gestational diabetes

| Author          | Year | Country | Duration | Methods | Intervention | Control | Results       |
|-----------------|------|---------|----------|---------|--------------|---------|---------------|
| Alroda et al.   | 2015 | USA     | 3.2 years| RCT     | 67/464       | 69/487  | Not significant|
| Sales et al.    | 2018 | Brazil  | 20w      | RCT     | 13/82        | 16/82   | Not significant|
| Valdes E et al. | 2018 | Chile   | 24w      | RCT     | 25/68        | 19/73   | Not significant|
Table 2. The Mediterranean diet and gestational diabetes prevention

| Author                      | Year | Country | Duration | Method | Intervention | Control | 95% CI | P value |
|-----------------------------|------|---------|----------|--------|--------------|---------|--------|---------|
| Assaf-Balut et al. [11]     | 2017 | Spain   | 20w      | RCT    | 74/434       | 103/440 | 0.57–0.98 | 0.039   |
| Assaf-Balut et al. [12]     | 2018 | Spain   | 1year    | RCT    | 15/115       | 41/136  | 0.18–0.67 | 0.003   |
| de la Torre et al. [13]     | 2019 | Spain   | 24w      | RCT    | 130/936      | 103/440 | 0.73–0.93 | 0.001   |
| H Al Alwattar et al. [14]   | 2019 | UK      | 17m      | RCT    | 84/477       | 124/497 | 0.47–0.91 | 0.01    |
| Melero et al. [15]          | 2020 | Spain   | 24w      | RCT    | 19/128       | 34/132  | 0.50–0.97 | 0.037   |
| Olmedo-Requena et al. [16]  | 2019 | Spain   | 16w      | Case-control | 62/102 | 377/377 | 0.39, 0.94) | 0.028 |

Table 3. Risk of bias of the included randomized controlled trials

| Study                      | Year | Selection | Performance | Attrition | Reporting | Other |
|----------------------------|------|-----------|-------------|-----------|-----------|-------|
| Assaf-Balut et al. [11]    | 2017 | High      | High        | Low       | Low       | Unclear |
| Assaf-Balut et al. [12]    | 2018 | High      | High        | Low       | Low       | Unclear |
| de la Torre et al. [13]    | 2019 | High      | High        | Low       | Low       | Low    |
| H Al Alwattar et al. [14]  | 2019 | High      | Low         | Low       | Low       | Low    |
| Melero et al. [15]         | 2020 | High      | Unclear     | Low       | Low       | Low    |
| Alroda et al. [19]         | 2015 | High      | Low         | Low       | Low       | Low    |
| Sales et al. [20]          | 2018 | High      | Unclear     | Unclear   | Low       | Low    |
| Valdes E et al. [10]       | 2018 | Low       | Unclear     | Low       | Low       | Low    |

3. RESULTS

Out of the 252 articles identified (132 after the removal of duplicates), 48 full texts were assessed, and only nine articles met the inclusion and exclusion criteria. Three (33.3%) articles assessed the effectiveness of metformin on GD, and another six (66.7%) investigated the effects of the MedDiet on GD. Six articles were from Europe, one was published in the USA, and two were from South America. The studies assessing metformin included 1256 patients and 209 events, while studies on the MedDiet reported 1166 events and 4214 patients. The duration of the studies was (16 weeks to 3.2 years), and the studies on metformin showed no reduction in GD [19,20,10], while studies on the MedDiet showed a reduction in gestational diabetes risk [11–16] (Tables 1 & 2). In the current review, out of the three studies that were included, one showed no effects of metformin on GDM prevention, one study was neutral, and one study showed a positive effect (odds ratio, 1.07, 0.79–1.44, P value for overall effect=0.65, I² for
heterogeneity=3%, \( P \) value=0.36. Chi-square=2.07, and the mean difference=2, Fig. 2). Regarding the effects of the Mediterranean diet, out of the six studies included in the meta-analysis, five showed positive effects on GDM prevention (odds ratio, 0.49, -0.32–0.73, \( P \) value for heterogeneity =0.0004, heterogeneity, \( I^2 \)=78%, \( P \) value for overall effect=0.0005, Chi-square=22.40 and mean difference=5, Fig. 3).

4. DISCUSSION

The present meta-analysis showed that metformin is not effective in the prevention of gestational diabetes mellitus (1.07, 0.79–1.44, \( P \) value for overall effect=0.65, \( I^2 \) for heterogeneity=3%, \( P \) value=0.36), similar to a previous meta-analysis [21]. Another meta-analysis assessing a wide variety of diets and pharmaceutical interventions found a possible benefit of metformin on gestational diabetes prevention in obese women [22]. Metformin was found to be associated with an increased weight in offspring when they were exposed prenatally to the drug [23].

Nutritional intervention, as a cost-effective intervention, is a first-line treatment in the prevention of short- and long-term cardiometabolic risks in both the mother and child [24,25]. The Mediterranean diet (MD) is characterized by high consumption of fruits and vegetables, legumes, olive oil, fish, and unrefined cereals and avoidance of red meat; together with a moderate amount of alcohol and dairy products the MD is one of the healthiest diets in the world. The American Diabetes Association recommended the MD for use among patients with diabetes mellitus [4,5]. The current meta-analysis showed that the MedDiet is effective in the prevention of GDM (odds ratio, 0.78, -0.67–0.89, \( P \) value for heterogeneity <0.00001, heterogeneity, \( I^2 \)=85%, \( P \) value for overall effect=0.0004). Our findings were similar to those of Mijatovic-Vukas et al. [26], and the effects might be due to weight reduction [27], low red meat consumption, or the use of virgin olive oil [28–29]. A review conducted in the UK observed the beneficial effects of the MedDiet on GDM [30]. The protectiveness of the MedDiet on GDM ranged from 15%–38% depending on the patient’s compliance and the guidelines used for the diagnosis [30].

A limitation of the study: was the strict selection criteria that was adopted and the small number of randomized controlled trials that was included.

![Fig. 2. Metformin effects on GDM](image)

![Fig. 3. Mediterranean diet effects on GDM prevention](image)
5. CONCLUSION

The Mediterranean diet was effective in gestational diabetes prevention when recommended at the first visit during pregnancy. Prescribing the MedDiet for women in the reproductive age group is a simple and effective measure to prevent GDM. Metformin is not effective as a therapeutic intervention on GDM; physicians may need to limit their prescription of this drug to prevent women at risk of GDM, due to lack of a long-term safety profile.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Szmuilowicz ED, Josefson JL, Metzger BE. Gestational diabetes mellitus. Endocrinol Metab Clin North Am. 2019 Sep;48(3):479-493. DOI: 10.1016/j.ecl.2019.05.001. Epub 2019 Jun 18. PMID: 31345518; PMCID: PMC7008467.

2. Chieftari E, Arcidiacono B, Foti D, Brunetti A. Gestational diabetes mellitus: an updated overview. J Endocrinol Invest. 2017 Sep;40(9):899-909. DOI: 10.1007/s40618-016-0607-5. Epub 2017 Mar 10. PMID: 28283913.

3. Cameron AR, Morrison VL, Levin D, et al. Anti-Inflammatory Effects of Metformin Irrespective of Diabetes Status. Circ Res. 2016;119(5):652-665. DOI:10.1161/CIRCRESAHA.116.308445

4. Niromanesh S, Alavi A, Sharbat FR, Amjadi N, Moosavi S, Akbari S. Metformin compared with insulin in the management of gestational diabetes mellitus: a randomized clinical trial. Diabetes Res Clin Pract. 2012;98(3):422-429. DOI:10.1016/j.diabres.2012.09.031

5. Ghomian N, Vahed SHM, Firouz S, Yaghoubi MA, Mohebbi M, Sahebkar A. The efficacy of metformin compared with insulin in regulating blood glucose levels during gestational diabetes mellitus: A randomized clinical trial. J Cell Physiol. 2019;234(4):4695-4701. DOI:10.1002/jcp.27238

6. Di Renzo L, Cioccoloni G, Falco S, et al. Influence of FTO rs939609 and Mediterranean diet on body composition and weight loss: a randomized clinical trial. J Transl Med. 2018;16(1):308. Published 2018 Nov 12. DOI:10.1186/s12967-018-1680-7

7. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020;43(Suppl 1):S98-S110. DOI:10.2337/dc20-S009

8. Sklepme Kocik I, Ivanisevic M, Biolo G, Simunic B, Kocik T, Pist0 R. Combination of a structured aerobic and resistance exercise improves glycaemic control in pregnant women diagnosed with gestational diabetes mellitus. A randomised controlled trial. Women Birth. 2018;31(4):e232-e238. DOI:10.1016/j.wombi.2017.10.004

9. Davenport MH, Ruchat SM, Poitras VJ, et al. Prenatal exercise for the prevention of gestational diabetes mellitus and hypertensive disorders of pregnancy: a systematic review and meta-analysis. Br J Sports Med. 2018;52(21):1367-1375. DOI:10.1136/bjsports-2018-099355

10. Assaf-Balut C, García de la Torre N, Fuentes M, et al. A high adherence to six food targets of the Mediterranean diet in the late first trimester is associated with a reduction in the risk of maternal-fetal outcomes: The St. Carlos Gestational Diabetes Mellitus Prevention Study. Nutrients. 2018;11(1):66. Published 2018 Dec 31. DOI:10.3390/nu11010066

11. de la Torre NG, Assaf-Balut C, Jiménez Varas I, Del Valle L, Durán A, Fuentes M et al., Effectiveness of following Mediterranean diet recommendations in the real world in the incidence of gestational diabetes mellitus (GDM) and Adverse Maternal-Foetal Outcomes: A Prospective, Universal, Interventional Study with a Single Group. The St Carlos Study. Nutrients. 2019 May 28;11(6):1210. DOI:10.3390/nu11061210.

12. Al Wattar B, Dodds J, Placzek A, Beresford L, Spyreli E, Moore A, Gonzalez A.
Carreras FJ, Austin F, Murugesu N, Roseboom TJ, Bes-Rastrollo M, Hitman GA, Hooper R, Khan KS, Thangaratinam S; ESTEEM study group. Mediterranean-style diet in pregnant women with metabolic risk factors (ESTEEM): A pragmatic multicentre randomised trial. PLoS Med. 2019 Jul 23;16(7):e1002857. DOI: 10.1371/journal.pmed.1002857.

13. Melero V, García de la Torre N, Assaf-Balut C, Jiménez I, Del Valle L, Durán A, Bordiu E, Valerio JJ, Herrera MA, Izquierdo N, Torrejón MJ, Runkle I, Barabash A, Rubio MA, Calle-Pascual EA. Effect of adherence to a Mediterranean diet-based nutritional intervention on the risk of developing gestational diabetes mellitus and other maternal-fetal adverse events in Hispanic women residents in Spain. Nutrients. 2020 Nov 14;12(11):3505. DOI: 10.3390/nu12113505.

14. Olmedo-Requena R, Gómez-Fernández J, Amezquita-Prieto C, Mozas-Moreno J, Khan KS, Jiménez-Moleón JJ. Pre-pregnancy adherence to the Mediterranean diet and gestational diabetes mellitus: A Case-Control Study. Nutrients. 2019 May 1;11(5):1003. DOI: 10.3390/nu11051003.

15. Madhuvrata P, Govinden G, Bustani R, Song S, Farrell TA. Prevention of gestational diabetes in pregnant women with risk factors for gestational diabetes: a systematic review and meta-analysis of randomised trials. Obstet Med. 2015 Jun;8(2):68-85. DOI: 10.1177/1753495X15576673. Epub 2015 Apr 2. PMID: 27512459; PMCID: PMC4935009.

16. Griffith RJ, Alsweiler J, Moore AE, Brown S, Middleton P, Shepherd E, Crowther CA. Interventions to prevent women from developing gestational diabetes mellitus: an overview of Cochrane Reviews. Cochrane Database Syst Rev. 2020 Jun 11(6):CD012394. DOI: 10.1002/14651858.CD012394.pub3. PMID: 32526091; PMCID: PMC7388385.

17. Aroda VR, Christofi CA, Edelstein SL, et al. The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the Diabetes Prevention Program outcomes study 10-year follow-up. J Clin Endocrinol Metab. 2015;100(4):1646-1653. DOI:10.1210/jc.2014-3761

18. Sales WB, Nascimento IBD, Dienstmann G, Souza MLR, Silva GDD, Silva JC. Effectiveness of Metformin in the Prevention of Gestational Diabetes Mellitus in Obese Pregnant Women. Efetividade da metforminanaprevenção do diabetes mellitus gestacional em gestantes obesas. Rev Bras Ginecol Obstet. 2018;40(4):180-187. DOI:10.1055/s-0038-1642632

19. Valdés E, Sepúlveda-Martínez A, Candia P, et al. Metformin as a prophylactic treatment of gestational diabetes in pregnant patients with pregestational insulin resistance: A randomized study. J ObstetGynaecol Res. 2018;44(1):81-86.

20. Assaf-Balut C, García de la Torre N, Durán A, et al. A Mediterranean diet with additional extra virgin olive oil and pistachios reduces the incidence of gestational diabetes mellitus (GDM): A randomized controlled trial: The St. Carlos GDM prevention study. PLoS One. 2017;12(10):e0185873. Published 2017 Oct 19. DOI:10.1371/journal.pone.0185873

21. Xu Q, Xie Q. Long-term effects of prenatal exposure to metformin on the health of children based on follow-up studies of randomized controlled trials: a systematic review and meta-analysis. Arch Gynecol Obstet. 2019 May;299(5):1295-1303. DOI: 10.1007/s00404-019-05124-w. Epub 2019 Apr 5. PMID: 30953188.

22. Broekhuizen K, Simmons D, Devlieger R, van Assche A, Jans G, Galjaard S, et al. Cost-effectiveness of healthy eating and/or physical activity promotion in pregnant women at increased risk of gestational diabetes mellitus: economic evaluation alongside the DALI study, a European multicenter randomized controlled trial. Int J Behav Nutr Phys Act. 2018 Mar 14;15(1):23. doi: 10.1186/s12966-018-0643-y. PMID: 29540227; PMCID: PMC5853142.

23. Simmons D. GDM and Nutrition-answered and unanswered questions-there's more work to do! nutrients. 2019 Aug 17;11(8):1940. DOI: 10.3390/nu11081940. PMID: 31426514; PMCID: PMC6722957.

24. Mijatovic-Vukas J, Capling L, Cheng S, Stamatakis E, Louie J, Cheung NW, Markovic T, Ross G, Senior A, Brand-Miller JC, Flood VM. Associations of diet and physical activity with risk for gestational
diabetes mellitus: a systematic review and meta-analysis. Nutrients. 2018 May 30;10(6):698.
DOI: 10.3390/nu10060698. PMID: 29849003; PMCID: PMC6024719.

25. Kahn BB, Flier JS. Obesity and insulin resistance. J. Clin. Investig. 2000;106:473–481.
DOI: 10.1172/JCI10842.

26. Micha R., Wallace S.K., Mozaffarian D. Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes mellitus: A systematic review and meta-analysis. Circulation. 2010;121:2271–2283.
DOI: 10.1161/CIRCULATIONAHA.109.924977.

27. Feskens EJM, Sluik D, van Woudenbergh GJ. Meat consumption, diabetes and its complications. Curr. Diabetes Rep. 2013;13:298–306.
DOI: 10.1007/s11892-013-0365-0

28. Amati F, Hassounah S, Swaka A. The impact of mediterranean dietary patterns during pregnancy on maternal and offspring health. Nutrients. 2019 May 17;11(5):1098.
DOI: 10.3390/nu11051098. PMID: 31108910; PMCID: PMC6566342.

29. Karamanos, B. Thanopoulou A, Anastasiou E, Assaad-Khalil S, Albache N, Bachaoui M, Slama, C.B et al. Relation of the Mediterranean diet with the incidence of Gestational Diabetes. Eur. J. Clin. Nutr. 2014:68:8–13.

30. Diabetes prevention program research group. Long-term effects of metformin on diabetes prevention: identification of subgroups that benefited most in the diabetes prevention program and diabetes prevention program outcomes study. Diabetes Care. 2019;42(4):601-608.
DOI:10.2337/dc18-1970