Mediterranean Diet and Metformin Effects on Gestational Diabetes: A Review and Meta-Analysis of Randomized Controlled Trials

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Author’s contribution
The sole author designed, analysed, interpreted and prepared the manuscript.

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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 12\textsuperscript{16} and 15\textsuperscript{16} 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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Duration</th>
<th>Methods</th>
<th>Intervention</th>
<th>Control</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alroda et al. [12]</td>
<td>2015</td>
<td>USA</td>
<td>3.2 years</td>
<td>RCT</td>
<td>67/464</td>
<td>69/487</td>
<td>Not significant</td>
</tr>
<tr>
<td>Sales et al. [13]</td>
<td>2018</td>
<td>Brazil</td>
<td>20w</td>
<td>RCT</td>
<td>13/82</td>
<td>16/82</td>
<td>Not significant</td>
</tr>
<tr>
<td>Valdes E et al. [14]</td>
<td>2018</td>
<td>Chile</td>
<td>24w</td>
<td>RCT</td>
<td>25/68</td>
<td>19/73</td>
<td>Not significant</td>
</tr>
</tbody>
</table>
Table 2. The Mediterranean diet and gestational diabetes prevention

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Selection</th>
<th>Performance</th>
<th>Attrition</th>
<th>Reporting</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assaf-Balut et al. [12]</td>
<td>2018</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
</tr>
<tr>
<td>de la Torre et al. [13]</td>
<td>2019</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>H Al Alwattar et al. [14]</td>
<td>2019</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Melero et al. [15]</td>
<td>2020</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Alroda et al. [19]</td>
<td>2015</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Sales et al. [20]</td>
<td>2018</td>
<td>High</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Valdes E et al. [10]</td>
<td>2018</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

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, $I^2$ 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, I²=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, I² 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, I²=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.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alho et al. 2015</td>
<td>67</td>
<td>464</td>
<td>69</td>
<td>467</td>
<td>92.7%</td>
<td>1.02 [0.71, 1.47]</td>
<td></td>
</tr>
<tr>
<td>Steel et al. 2016</td>
<td>13</td>
<td>82</td>
<td>18</td>
<td>82</td>
<td>10.3%</td>
<td>0.78 [0.55, 1.04]</td>
<td></td>
</tr>
<tr>
<td>Valdés et al. 2018</td>
<td>26</td>
<td>68</td>
<td>19</td>
<td>77</td>
<td>14.5%</td>
<td>1.65 [0.81, 3.39]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>614</td>
<td>642</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>1.07 [0.79, 1.44]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>105</td>
<td>104</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 0.45 (P = 0.65)

![Fig. 2. Metformin effects on GDM](image1)

![Fig. 3. Mediterranean diet effects on GDM prevention](image2)
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.

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DOI: 10.3390/nu10060698. PMID: 29849003; PMCID: PMC6024719.

DOI: 10.1172/JCI10842.

DOI: 10.1161/CIRCULATIONAHA.109.924977.

DOI: 10.1007/s11892-013-0365-0

DOI: 10.3390/nu11051098. PMID: 31108910; PMCID: PMC6566342.


DOI:10.2337/dc18-1970

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