Tropical Journal of Pharmaceutical Research February 2024; 23 (2): 349-354
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v23i2.14

Original Research Article

Effect of complex micronutrient supplement and vitamin D as adjunct to insulin therapy in patients with gestational diabetes mellitus

Fan Fu, Juan Yu*, Lulu Wang
Department of Obstetrics, Hangzhou Linping District Maternal and Child Health Care Hospital, Hangzhou City, Zhejiang Province 311100, China

For correspondence:* ***Email:* *yujuan3052201@163.com;* ***Tel:*** *+86-13606636800*

Sent for review: 18 September 2023 *Revised accepted: 2 February 2024*

Abstract

Purpose: *To determine the effect of complex micronutrient supplements and vitamin D as adjunct therapy on pancreatic function, oxidative stress, glucose metabolism and pregnancy outcomes in patients diagnosed with gestational diabetes mellitus (GDM).*

Methods: *100 GDM patients admitted to Hangzhou Linping District Maternal and Child Health Care Hospital, China between March 2022 and February 2023, were randomly allocated to control and study groups (50 patients each). Control group received insulin injections, whereas study group received complex micronutrients with vitamin D as supplements to insulin. Differences in terms of pancreatic function (homeostatic model assessment-insulin resistance index (HOMA-IR), homeostatic model assessment-beta-cell function index (HOMA-β)), oxidative stress (total antioxidant capacity (TAC), malondialdehyde (MDA)), glucose metabolism indicators (fasting blood glucose (FBG), 2-hour postprandial glucose (2hPG), glycated hemoglobin (HbA1c)) and pregnancy outcomes was assessed.*

Results: *After treatment, both groups showed reductions in serum levels of FBG, 2hPG and HbA1c, but study group exhibited a considerably greater decrease ($p < 0.05$). In addition, study group had lower HOMA-IR and MDA levels as well as higher HOMA-β and TAC levels ($p < 0.05$). Negative delivery outcomes occurred less frequently in study group than in control group ($p < 0.05$).*

Conclusion: *Complex micronutrient supplements (rich in magnesium, calcium, and zinc) in combination with vitamin D as adjunct to insulin treatment effectively reduce pancreatic function and oxidative stress, significantly control blood glucose levels and lower the occurrence of adverse pregnancy outcomes in GDM patients. Further studies will be required in a larger more diverse population to determine the mechanism of enhancing pancreatic function.*

Keywords: *Vitamin D, Complex micronutrient supplement, Gestational diabetes mellitus, Pancreatic function, Oxidative stress, Pregnancy outcome*

INTRODUCTION

Gestational diabetes mellitus (GDM) is a metabolic syndrome that results in disrupted glucose metabolism [1]. Abnormal blood sugar fluctuations result in the aberrant secretion of various hormones, as evidenced by a significant increase in HOMA-IR [2,3]. Hormonal influences during pregnancy may lead to insulin resistance, hinder insulin secretion and cause abnormal glucose metabolism [4,5]. These not only affect maternal health but also have adverse effects on fetal development. During the later stages of pregnancy, significant deficiency of micronutrients such as vitamin D, calcium and zinc occur, resulting in diminished antioxidant activity. This can lead to abnormal glucose metabolism, oxidative stress and inflammation, all of which have negative implications for pregnancy [6]. Currently, insulin is the primary treatment for diabetes in clinical practice. However, insulin resistance and other symptoms may occur in later stages. In recent years, studies have indicated that timely and appropriate supplementation of vitamin D, complex micronutrient supplements (rich in magnesium, calcium, and zinc) and other adjunct formulations during pregnancy regulates cell cycle, promotes antioxidant enzyme production and protects the β cells. This helps to alleviate insulin resistance, improve blood glucose metabolism, oxidative stress and related indicators, thereby preventing complications caused by gestational diabetes, and improving adverse pregnancy outcomes for patients [7]. Therefore, this study investigates the impact of complex micronutrient supplements in combination with vitamin D as an adjunct to insulin treatment in pancreatic function, oxidative stress, glucose metabolism and pregnancy results in GDM individuals.

METHODS

General information

A total of one hundred (100) patients with GDM were admitted to the Hangzhou Linping District Maternal and Child Health Care Hospital, China between March 2022 and February 2023. They were divided into two groups, a study group and a control group, using a random number table, with 50 patients in each group. All procedures performed in studies involving human participants were approved by the Ethics Committee of Hangzhou Linping District Maternal and Child Health Care Hospital (approval no. LLSC-KYKT-2022-0092-A) and also with those of the 1964 Helsinki Declaration and its later amendments for ethical research involving human subjects [8]. Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

Inclusion criteria

Patients who satisfied the following criteria were included in the study: meeting the diagnostic criteria for GDM as outlined in the 9th edition of "Obstetrics and Gynecology" [9]; meeting the indication for the study medication; had no recent history of taking other antidiabetic medications; and those who willingly signed the informed consent form.

Exclusion criteria

Individuals who were contraindicated for the study medication; patients with pre-pregnancy diagnosis of diabetes; patients with presence of other pregnancy complications; and patients who took complex micronutrient supplements or vitamin D in the six months prior to the study were all excluded from the study.

Control group’s age ranged from 22 to 31 years, with an average age of 26.36 ± 2.47 years. Their gestational age varied from 23 to 27 weeks, averaging 25.16 ± 1.45 weeks, while their BMI spanned from 21 to 28 kg/m^2, averaging 24.48 ± 1.84 kg/m^2.

Study group’s age spanned from 23 to 31 years, with a mean age of 26.40 ± 2.29 years, 23 to 27 weeks pregnant, with a mean of 25.14 ± 1.43 weeks and BMI ranging from 21 to 28 kg/m^2, with a mean of 24.22 ± 1.82 kg/m^2. Comparing the overall features of the two groups, there are no significant differences ($p > 0.05$).

Treatment protocols

In control group, a subcutaneous injection of insulin (Tonghua Dongbao Pharmaceutical Co., Ltd; National Medical Products Administration Approval Number S20020092) was administered one hour before meals, at an initial dose of 0.5 – 1 U/kg, three times daily. The dose was adjusted as needed based on changes in blood glucose levels. In addition to the treatment given to control group, patients in study group were administered oral Star Shark Vitamin D drops (Sinopharm Holdings Star Shark Pharmaceutical, Co., Ltd, Xiamen; National Medicine Approval Number H35021450), at a dose of 3400 units per capsule, twice daily. They were also given oral complex micronutrient supplement Ailewei (Bayer Healthcare Co., Ltd. Qidong Branch; National Medicine Approval Number J20140155), one tablet daily. Both groups received continuous treatment until delivery.

Evaluation of parameters/indices

Pancreatic islet function indicators

The pancreatic β-cell function index (HOMA-β) and insulin resistance index (HOMA-IR) were computed both before and after treatment (Eq 1 and 2), with fasting insulin (FINS) measurements performed using a radioimmunoassay.

H - β = 20 × FINS/(FBH – 3.5) …….. (1)

H-IR = (FINS × FBG)/22.5 ……. (2)

where H - β = HOMA-β, FINS = fasting insulin, FBG = fasting blood glucose, H-IR = HOMA-IR.

Oxidative stress levels

Five milliliters (5 mL) of fasting venous blood were drawn from each patient before and after therapy and the malondialdehyde (MDA) levels and total antioxidant capacity (TAC) were assessed using a microplate assay.

Blood glucose indicators

Fasting plasma glucose (FPG), glycated hemoglobin A1c (HbA1c) and 2-hour postprandial glucose (2hPG) levels were determined using glucose oxidase assay.

Adverse pregnancy outcomes

Adverse pregnancy occurrence (macrosomia, premature birth, stillbirth and miscarriage) was monitored in both groups post-treatment.

Statistical analysis

The statistical software SPSS 26.0 was used to process the data. The χ^2 and *t*-test were used for comparison between groups and *p*-values less than 0.05 indicate statistically significant difference.

RESULTS

Blood glucose levels

The HbA1c, FPG and 2hPG levels in both groups decreased after treatment than before treatment. Study group exhibited significantly lower HbA1c, FPG and 2hPG levels than control group ($p < 0.05$; Table 1).

Islet function indices

Following therapy, the HOMA-IR levels were found to decrease significantly compared to control but HOMA- β levels were higher in both pre- and post-treatment conditions. In addition, study group was found to show significantly higher HOMA- levels than control group while control group had a significantly lower HOMA-IR level compared to study group ($p < 0.05$; Table 2).

Oxidative stress levels

Table 3 shows the result of the comparison of the TAC and MDA levels before and after therapy. The TAC levels increased in study group following treatment while the MDA levels were found to decrease compared to pre-treatment levels. Study group exhibited significantly higher TAC and lower MDA levels compared to control ($p < 0.05$).

Adverse pregnancy outcomes

From the results in Table 4, study group had significantly lower adverse pregnancy incidences (Macrosomia, Premature birth, Stillbirth and Miscarriage) than control group ($p < 0.05$).

Table 1: Comparison of HbA1c, FPG, and 2hPG levels before and after treatment in the groups (n = 50)

Group	HbA1c (%)		FPG (mmol/L)		2hPG (mmol/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control	10.17±1.02	7.26±0.55	10.03±1.06	7.06±0.48	13.63±0.60	8.45±0.41
Study	10.32±0.79	5.65±0.50	10.06±1.01	5.70±0.51	13.47±0.62	7.38±0.35
t	0.792	15.252	0.116	13.781	1.286	13.911
P-value	0.430	0.000	0.908	0.000	0.201	0.000

Table 2: Comparison of HOMA-β and HOMA-IR levels before and after treatment in the groups (n = 50)

Group	HOMA-β (%)		HOMA-IR	
	Before treatment	After treatment	Before treatment	After treatment
Control	17.65±0.99	32.83±1.20	3.98±0.31	5.68±0.28
Study	15.62±0.96	54.01±1.54	3.66±0.32	2.74±0.37
t	0.092	10.379	0.386	16.275
P-value	0.947	0.000	0.852	0.000

Table 3: Comparison of TAC and MDA levels before and after treatment in the two groups (n = 50)

Group	TAC (mmol/L)		MDA (mmol/L)	
	Before treatment	After treatment	Before treatment	After treatment
Control	558.81±4.46	505.80±12.43	3.42±0.34	3.96±0.24
Study	546.18±3.38	610.51±18.13	3.31±0.29	2.61±0.32
t	0.392	3.972	0.256	9.631
P-value	0.753	0.000	0.820	0.000

Table 4: Comparison of adverse pregnancy outcomes between the two groups {(n (%)}

Group	Macrosomia	Premature birth	Stillbirth	Miscarriage	Adverse outcomes
Control	1 (2.00)	3 (6.00)	1 (2.00)	0 (0.00)	5 (10.00)
Study	0 (0.00)	1 (2.00)	0 (0.00)	0 (0.00)	1 (2.00)
χ^2	-	-	-	-	0.479
P-value	-	-	-	-	0.039

DISCUSSION

Gestational diabetes mellitus (GDM) is a metabolic condition marked by elevated blood glucose levels during pregnancy. Aside from resulting in insulin resistance and impaired glucose tolerance, it further disrupts indicators such as resulting in increased oxidative stress as well as depletion of trace elements in pregnant women. The conventional treatment approach involves controlling blood sugar, dietary intake and exercise. However, dietary restrictions may result in inadequate intake of trace elements, leading to various complications and adverse pregnancy outcomes [10]. Studies have shown that adjunctive treatment of GDM with vitamin D and mineral supplements significantly increases insulin sensitivity, insulin resistance levels and various aspects of metabolism, including glucose and oxidative stress [11].

In recent years, studies have shown that vitamin D2 and D3 (active vitamin D) cannot only regulate calcium and phosphate metabolism, but also upregulate insulin receptor genes and transcription to modulate intracellular calcium ions, thereby reducing insulin resistance, promoting glucose transportation to various tissues and organs, and exerting a positive role in promoting glucose metabolism [12]. Complex micronutrient supplements, including calcium, magnesium, potassium, zinc, and other elements, competitively inhibit voltage-gated calcium channels, thereby influencing the bioconversion of potassium and calcium ions and playing a role in insulin secretion. Additionally, zinc and magnesium have antioxidant properties, and their deficiency produces excessive oxidative stress that affects glucose metabolism and other related indicators. In this study, the results showed that after treatment, the HbA1c, FPG and 2hPG levels in study group were substantially decreased than control, along with higher HOMA-β and lower HOMA-IR. Patients in study group had greater pancreatic islet function than those in control group. These results indicate that with the adjunctive treatment of vitamin D combined with complex micronutrient supplement, study group exhibited a significant reduction in HOMA-IR and indicators related to glucose metabolism and oxidative stress were improved.

In diabetic patients, the non-enzymatic glycation reaction is enhanced under hyperglycemic conditions, leading to increased generation of free radicals and subsequent oxidative stress. Studies have indicated that GDM treated with complex micronutrient supplements has reduced MDA and increased TAC levels. Therefore, adjunctive therapy with complex micronutrient supplements can effectively improve the oxidative stress status of the body [13]. Trace elements such as copper (Cu) and zinc (Zn) are involved in the generation of superoxide dismutase (SOD). These elements catalyze the formation of hydrogen peroxide, which is subsequently decomposed by catalase. Additionally, ceruloplasmin plays a catalytic role in the ferrous oxidation reaction, aiding in the reduction of free radical damage caused by transition metals. Moreover, magnesium and zinc, as redox catalysts, effectively minimize the production of reactive oxygen species and hinder hydroxyl radicals formation by suppressing hydrogen peroxide [14].

Limitations of this study

Issues like the study's small sample size, limited subject selection and regional variations have hindered the research findings' universality and generalizability. Expanding the study's scope is necessary. Additionally, deficiencies in the literature review, including incompleteness, lack of depth and inaccuracies have impeded foresight and innovation in the research. Strengthening the literature review is essential.

CONCLUSION

The use of complex micronutrient supplements (rich in magnesium, calcium, and zinc) in combination with vitamin D as adjunct to insulin therapy for gestational diabetes mellitus (GDM) improves pancreatic islet function, mitigates oxidative stress, controls blood glucose levels and decreased the occurrence of undesirable pregnancy outcomes. Future studies to determine the mechanism of this complex micronutrient supplement enhancing pancreatic function will be required in a larger more diverse population.

DECLARATIONS

Acknowledgements

None provided.

Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Fan Fu, Juan Yu and Lulu Wang designed the study and carried them out, supervised the data collection, analyzed and interpreted the data, prepared the manuscript for publication and reviewed the draft of the manuscript. All authors read and approved the manuscript for publication.

Open Access

REFERENCES

1. *Shuyun Z, Yunjie W, Ling Z, Ziyang Y, Aihua G. IRF2BP2 attenuates gestational diabetes mellitus by activating AMPK signaling. Trop J Pharm Res 2022; 21(7): 1459-1465.*
2. *Guo-Zhen T, Zhang ZX, Ai-Xiang T, Jun-ru M, Jiang-yan X, Xiao-li Y. Effects of Deltamine in combination with insulin aspart on levels of cystatin C and homocysteine in patients with gestational diabetes mellitus and maternal and neonatal outcomes. Chin J Modern Med 2016; 26(2): 76-79.*
3. *Sun HFC, Gao JL. Study on the correlation between serum miR-21, PPAR y and IGF-1R expression levels in patients with gestational diabetes and blood coagulation function and pregnancy outcome. J Modern Laboratory Med 2021; 36(5): 143-147.*
4. *Zhao L, Dong X, Gao Y, Jia Z, Han S, Zhang J, Gao Y. Effects of exercise combined with diet intervention on insulin resistance, serum adiponectin and visfatin levels in patients with gestational diabetes. Maternal and Child Health Care of China 2017; 32(9): 1869-1871.*
5. *Qiu HY, Chu YL, Li M, Sun YY, Li HF. The tyrosine phosphorylation and protein expression of insulin receptor and insulin receptor substrate-i are associated with skeletal muscle insulin resistance in gestational diabetes mellitus. Chinese J Obst Gynecol 2007; 42(4): 249-252.*
6. *Shepherd E, Gomersall JC, Tieu J, Han S, Crowther CA, Middleton P. Combined diet and exercise interventions for preventing gestational diabetes mellitus. Cochrane Database Syst Rev 2017; 11(11): CD010443.*
7. *Mirzaei-Azandaryani Z, Mohammad-Alizadeh-Charandabi S, Shaseb E, Abbasalizadeh S, Mirghafourvand M. Effects of vitamin D on insulin resistance and fasting blood glucose in pregnant women with insufficient or deficient vitamin D: a randomized, placebo-controlled trial. BMC Endocr Disord 2022; 22(1): 254. doi: 10.1186/s12902-022-01159-4*
8. *Shrestha B, Dunn L. The Declaration of Helsinki on medical research involving human subjects: a review of seventh revision. J Nepal Health Res Council 2019; 17(4): 548-552.*
9. *Xie X, Kong B, Duan T. Obstetrics and Gynecology. 9th Edition. Beijing: People's Medical Publishing House 2018; 107.*
10. *Ding J. Effect of diet management combined with exercise training on delivery outcome of pregnant*

women with diabetes during pregnancy. Chinese General Practice Nursing 2021; 19(6): 792-794.

11. *Ostadmohammadi V, Samimi M, Mobini M, Zarezade Mehrizi M, Aghadavod E, Chamani M, Dastorani M, Asemi Z. The effect of zinc and vitamin E supplementation on metabolic status and its related gene expression in patients with gestational diabetes. J Matern Fetal Neonatal Med 2019; 32(24): 4120-4127.*
12. *Zhang Y, Gong Y, Xue H, Xiong J, Cheng G. Vitamin D and gestational diabetes mellitus: a systematic review based on data free of Hawthorne effect. BJOG 2018; 125(7): 784-793.*
13. *Zhang C, Wei Y, Feng Y. Changes in biomarkers of oxidative stress and their clinical significance in gestational diabetes mellitus. Progress in Modern Biomed 2019; 19(1): 62-67.*
14. *Liu J, Zhao G, Lu L. Effects of magnesium zinc calcium vitamin D complex supplement on inflammation, oxidative stress and pregnancy outcome in patients with gestational diabetes. Maternal Child Health Care China 2020; 35(14): 2584-2586.*