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Systematic review

Vitamin D and gestational diabetes mellitus: a systematic review based on data free of Hawthorne effect

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Background Gestational diabetes mellitus (GDM) is an increasingly prevalent disorder, associated with low blood vitamin D level.

Objectives To evaluate the relationship between vitamin D and GDM.

Search strategy EMBASE, MEDLINE, Cochrane Library and China Biology Medicine disc were searched up to May 2017. The references of previous studies were screened.

Selection criteria Observational studies on the relationship between vitamin D and GDM free from Hawthorne effect and randomised controlled trials of vitamin D supplementation during pregnancy for preventing or treating GDM were included.

Data collection and analysis Data and information of included articles were extracted by duplicate using piloted tables. Newcastle–Ottawa Scale and Cochrane Handbook were used for quality assessment. Random-effects models were used for meta-analyses. Heterogeneity tests, sensitivity analysis and analysis of publication bias were conducted.

Main results Eighty-seven observational studies and 25 randomised controlled trials involving 55 859 and 2445 women, respectively, were included. Low blood vitamin D level during pregnancy was associated with a higher risk of GDM (OR 1.850, 95% CI 1.471–2.328). Blood vitamin D level for women with GDM were lower than in the control women. Blood vitamin D level was associated with fasting plasma glucose (FPG) and homeostasis model of assessment for insulin resistance index (HOMA-IR) ($r = -0.100$ and $r = -0.351$), whereas the correlation between blood vitamin D level and fasting insulin (FINS) might be concealed by publication bias. Vitamin D intervention during pregnancy could change the blood levels of vitamin D, FINS, FPG, HOMA-IR, glutathione, C-reactive protein and lipid.

Conclusions Low blood vitamin D level could increase the risk of GDM, and vitamin D supplementation during pregnancy could ameliorate the condition of GDM.

Keywords blood glucose, gestational diabetes mellitus, insulin, meta-analysis, vitamin D.

Tweetable abstract Low blood vitamin D increases gestational diabetes mellitus (GDM) risk. Vitamin D supplementation ameliorates GDM condition.

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Introduction

Gestational diabetes mellitus (GDM) is hyperglycaemia that is first recognised at any stage of pregnancy, in which the blood glucose levels are slightly elevated. It was estimated that 13.8% of women having live births had GDM in 2015 globally. Women with GDM are at greater risk of adverse pregnancy outcomes, including high blood pressure and fetal macrosomia.[1] Hence, it is of significant importance to explore the prevention and treatment of GDM.

Numerous researchers have explored the possible risk factors of GDM. Vitamin D is one of the highlights in this

field, because low blood vitamin D level is a notable public health issue and intake of vitamin D can be practically modified. It is estimated that 7–98% of pregnant women suffer from vitamin D deficiency.[2,3]

Various study designs focused on the relationship between vitamin D and GDM. Some researchers investigated mechanisms for the effect of vitamin D on GDM, and implied that vitamin D could regulate hepatic metabolism, the function and development of pancreatic islets, blood calcium level, oxidative stress, the immune system and inflammation to mediate the onset of GDM.[4–7]

Meanwhile, population-based studies were implemented, but the results were inconsistent. Several prospective observational studies concluded that a low blood vitamin D level in the first and second trimesters could increase the risk of GDM,[8,9] whereas others failed to find such associations.[10–13] Besides, most randomised controlled trials (RCTs) supported the idea that supplementing with vitamin D during pregnancy could reduce the level of blood sugar and insulin,[14–16] whereas the results of other related biomarkers were far from consistent and valid.[14–20]

A valid conclusion is unlikely to be reached by simply enumerating the results above. Hence, several meta-analyses have been conducted and found that a low blood vitamin D level might increase the risk of GDM.[21–23] But these studies did not exhaust the databases to include as many studies and GDM-related indices as possible and include RCTs. Therefore, a systematic review and meta-analysis with more studies and related parameters was conducted to evaluate the relationship between vitamin D and GDM comprehensively.

Methods

Information sources and search strategy

MEDLINE, EMBASE and Cochrane Library were searched for studies describing the association between vitamin D and GDM up to 15 April 2017, and the China Biology Medicine (CBM) disc was searched up to 16 May 2017. In addition, the reference lists of the included studies were searched to identify additional relevant publications. Five themes of Medical Subject Heading terms and related exploded versions were focused on, including vitamin D, glucose, insulin, glycosylated haemoglobin and GDM. The detailed searching strategies are shown in the Supplementary material (Appendix S1).

Eligibility criteria

Only the data free of Hawthorne effect and related to GDM were included. Specifically, vitamin D should be supplemented within RCTs, and the blood used for analysing vitamin D concentration should be collected before or during oral glucose tolerance test or blood draw for other biomarker analyses in observational studies. Under this circumstance, participants would not adopt healthier behaviours because they would be unaware of their GDM condition. Besides, the core outcome sets including GDM occurrences, fasting plasma glucose (FPG), fasting insulin (FINS), homeostasis model of assessment for insulin resistance index (HOMA-IR), homeostasis model of assessment for β cell function (HOMA-B) and glycosylated haemoglobin (HbA1c) need to be reported in the original studies. Other biomarkers related to GDM including C-reactive protein (CRP), glutathione (GSH), total antioxidant capacity (TAC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triacylglycerol (TAG) and total cholesterol (TC) should also be included.

Studies were considered to be excluded if they were: (i) duplicate publications, (ii) non-original studies, (iii) non-human studies, (iv) studies irrelevant to pregnancies' blood vitamin D level, (v) studies with unreasonable and non-amendable data or statistical methods, or (vi) inaccessible data or full texts.

Eligible conference papers were included in this study, as it was not obvious that unpublished articles were of poor quality, and leaving out eligible articles could result in lower powerful tests and greater publication bias.[24]

Information extraction and quality evaluation

Two investigators (YZ and HX) extracted data and evaluated the quality of literature independently. Divergences were resolved by consensus, or by consulting with the third investigator (GC).

For observational studies, study characteristics, blood level of 25-hydroxyvitamin D (25OHD, which is formed from vitamin D in liver and is stable enough to be measured as a biomarker[25]) and disease outcomes were extracted with a piloted chart (see Table S1). For RCTs, study characteristics, intervention methods and outcomes of biomarkers related to GDM were extracted with a piloted chart (see Table S2). If the information was unavailable from a published report, the authors were contacted to obtain access to the data.

Low blood vitamin D level could be classified into vitamin D deficiency and vitamin D insufficiency. However, the cut offs used to differentiate vitamin D status are not reached in agreement. Some researchers used 50 nmol/l and 75 nmol/l to differentiate vitamin D deficiency, vitamin D insufficiency and vitamin D sufficiency,[10] whereas others used 25 nmol/l and 50 nmol/l.[26]

For the quality of observational studies, Newcastle–Ottawa Scale focusing on the selection of the study groups (four scores), the comparability of the groups (two scores), and the ascertainment of either the exposure or outcome for case–control or cohort studies (three scores) was used to score. Studies with a score of no less than seven were

