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Metabolomic profiling of women with gestational diabetes mellitus and their offspring: Review of metabolomics studies

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) reflects an increased risk of developing type 2 diabetes (T2D) after pregnancy in women. Offspring born to mothers with GDM are at an elevated risk of obesity and T2D at a young age. Currently, there are lack of ways for identifying women in early pregnancy who are at risk of developing GDM. As a result, both mothers and fetus are not treated until late in the second trimester when GDM is diagnosed. The recent advance in metabolomics, a new approach of systematic investigation of the metabolites, provides an opportunity for early detection of GDM, and classifying the risk of subsequent chronic diseases among women and their offspring.
Methods: We reviewed the literatures published in the past 20 years on studies using high-throughput metabolomics technologies to investigate women with GDM and their offspring.
Conclusions: Despite the inconsistent results, previous studies have identified biomarkers that involved in specific metabolite groups and several pathways, including amino acid metabolism, steroid hormone biosynthesis, glycerophospholipid metabolism, and fatty acid metabolism. However, most studies have small sample sizes. Further research is warranted to determine if metabolomics will result in new indicators for the diagnosis, management, and prognosis of GDM and related complications.

1. Introduction

Gestational diabetes mellitus (GDM), one of most common pregnancy complications, is defined as any degree of glucose intolerance with onset or first recognition during pregnancy.[1] The prevalence of GDM varies worldwide, ranging from 1 to 14% of all pregnancies depending on diagnostic criteria and study population.[2] Recent data have shown a significant increase in the prevalence of GDM among women of various ethnic/racial backgrounds and in different geographic regions.[3–7] The increase in prevalence of GDM is likely to continue as a rise in obesity rates for girls and women of reproductive age has been observed globally.

1.1. Diagnosis of GDM

The diagnosis of GDM relies on detecting elevated plasma glucose, often in the late of the second trimester; however, there currently is no global consensus on the diagnostic criteria. In 2010, The International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommended a "one-step" approach, in which all pregnant women without known diabetes (type 1 or 2) receive a 75 g 2-hour oral glucose tolerance test (OGTT) between 24 and 28 weeks gestation.[8] In 2013, the National Institutes of Health (NIH) expert panel recommended the "two-step" approach, in which pregnant women who screen positive after a 50 g 1-hour OGTT, take a subsequent 100 g 3-hour OGTT between 24 and 28 weeks gestation.[9] These approaches also differ on whether two abnormal values are required, and what diagnostic cut-off values should be used. Given that there are data to support both approaches, in 2014 the American Diabetes Association (ADA) recommended both options for diagnosing GDM.[1]

1.2. Health consequences for women with GDM and their offspring

Although most women return to a normal glucose status after delivery, 20% of women with GDM develop impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) during 6–12 weeks postpartum.[10,11] More importantly, women with GDM are at increased risk of developing of type 2 diabetes (T2D) later in life. The increased risk of T2D among women with GDM has been documented in different populations and countries. On average, the risk of developing of T2D is

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7.4 times greater for women with GDM compared to women without GDM.[10] A large retrospective cohort study in Australia demonstrated the risk of developing diabetes increased with time from women's index pregnancy: the cumulative incidence of diabetes was 2.6% at 2 years, 8.1% at 5 years, 17.3% at 10 years, and 25.8% at 15 years after diagnosis of GDM.[12] Recent data have also indicated that independent of T2D or obesity, women with GDM might be at an increased risk of hypertension,[13] metabolic disorders[14] and even cardiovascular disease (CVD) events.[15] In addition, emerging evidence tends to suggest that women with GDM represent a population who are more likely to develop CVD at a relatively younger age.[16]

GDM also has profound impacts on the offspring's health, both short- and long-term. Biologically, maternal glucose can cross the placenta but maternal insulin cannot. In response to the increased glucose load, the fetal pancreas increases insulin production, which in turn, promotes fetal growth and adiposity development.[17] There is a growing body of data that supports a positive association between maternal hyperglycemia and children's risk of health problems, including obesity, diabetes, insulin resistance, IGT, T2D, CVD risk factors,[18–21] and autism.[22] The available evidence suggests the higher risk of obesity and T2D in offspring of GDM mothers is likely due to the intrauterine environment which is independent of shared socioeconomic, lifestyle and genetic factors within families.[23,24] However, the molecular pathways underlying such associations remain unclear.

1.3. Metabolic features of GDM

GDM is a significant risk factor for development of T2D and CVD in women and offspring. Therefore, identifying women at high risk of GDM and understanding the metabolic changes in the early life of their offspring has important public health and clinical significance. During the past several decades, a number of risk factors for GDM have been identified, including advanced maternal age, family history of diabetes, pre-pregnancy obesity, and multiple pregnancies.[25] However, the etiology and pathogenesis of GDM remains unclear.

Pregnancy is accompanied by numerous metabolic changes in women, one of which is a substantial decrease in insulin sensitivity. Pregnancy-induced insulin resistance progressively develops in the second and third trimesters and is thought to be secondary to increases in maternal adiposity, as well as increases in placental and other hormones (e.g. human placental lactogen, placental growth hormone, progesterone, estradiol, leptin, cortisol, prolactin, human chorionic gonadotropin, tumor necrosis factor-alpha (TNF-α), and other inflammatory mediators).[26–28] Pregnant women have an increased insulin secretion compared to a non-gravid state.[29] In some women their β-cell function cannot compensate for the increased insulin requirements in late pregnancy, and as a result develop GDM or hyperglycemia.[30] Why these women have inadequate β-cell compensation is not well known. GDM may be caused by a complex set of interactions between genetic and environmental factors, triggered by a series of metabolic challenges during pregnancy (e.g. promoting adipose tissue accumulation in middle gestation and developing insulin resistance in late pregnancy).

Although the etiology and pathogenesis of GDM is not fully understood, the majority of women with GDM appear to have β-cell dysfunction that occurs in the background of chronic insulin resistance. To date, only a few potential biochemical mediators of chronic insulin resistance associated with GDM have been investigated. It is likely that there is not a single pathway or etiology that contributes to the development of GDM. In addition, GDM may influence fetal organ development and growth through maternal-placental-fetal glucose/insulin physiology and these may result in a downstream effect on the fetal brain and peripheral systems. This complexity presents a challenge for completely understanding the spectrum of molecular mechanisms associated with maternal diabetes and how they impact physiological and metabolic changes in offspring. The examination of one or several targeted molecules utilizing traditional methods has failed to detect the relevant underlying molecular changes.

1.4. Overview of metabolomic

Progress in this research may be facilitated by recent developments in technologies for comprehensive metabolic analysis, known as "metabolomics".[31] This approach allows for large-scale simultaneous analysis of numerous metabolites, and detects subtle changes in the metabolic network in human bio-fluids or tissues. In addition, metabolomics can provide certain advantages relative to other "omics" technologies (genomics, transcriptomics, or proteomics) because it measures molecular phenotypes that are the net results of other 'omics', therefore providing the most integrated profile of biological status.

The use of metabolomics for better understanding the etiology and pathogenesis of disease consists of two sequential steps. The first step is an experimental technology, based on liquid or gas chromatography–mass spectrometry (MS), or proton (^{1}H) nuclear magnetic resonance (NMR) spectroscopy. MS provides higher sensitivity and the opportunity of optimized targeted analysis, and NMR offers an overview of mode metabolites, structural information, and higher reproducibility. Using these new technologies, metabolomics can investigate the complete set of metabolites or low-molecular-weight intermediates (molecular weight < 1000) in a given biological sample. The second step is to perform multivariate data analysis to determine differences in the metabolic profiles of individuals with certain health conditions/diseases versus healthy controls. In brief, metabolomics is a comprehensive method for qualitative and semi-quantitative analyses of metabolites in human bio-fluids or tissues. It has been rapidly used in the early detection of diseases, measuring biological responses to treatments/interventions, identifying the underlying pathways between risk factors and diseases, and discovering novel biomarkers associated with certain health stages/conditions.

1.5. Metabolomics in GDM

Metabolomics has been used to analyze metabolic profiles and identify novel biomarkers associated with insulin resistance and T2D. The metabolic groups have been reported included carbohydrate metabolites (e.g. glucose and fructose), lipid metabolites (e.g. phospholipids, sphingomyelins, and triglycerides), and amino acid metabolites (branched-chain amino acids, aromatic amino acids, glycine, and glutamine).[32–35] The pathophysiological changes that occur in T2D and GDM are similar and use of this new technology may aid our understanding of the etiology and pathogenesis of GDM. Furthermore, metabolomics may increase our ability to identify early predictors of GDM or classify the risk of subsequent CVD among women and their offspring. These innovations call for a thorough review of what has been reported in this area of literature to inform future directions for research, summarize what has been found, and elucidate any challenges in the field.

2. Literature research

We searched PubMed from January 2007 to April 2017 for studies using high-throughput metabolomic technologies (i.e. MS or NMR) to investigate women with GDM and their offspring. Key-words used included "diabetes," "gestational," "gestational diabetes," "metabolome", "metabolomics," "metabolic disease", "metabolic syndrome", "impaired glucose", "HOMA-IR", "HOMA-beta", "insulin resistance", "overweight", "obesity", "body mass index", "BMI", "body weight", and "adiposity" (see Appendix A). Additionally, hand searching of the references cited in identified articles was performed. Two authors (QC & EF) independently searched the literature, reviewed the studies, and extracted the data. Then two senior author (LC and GH) double checked the literature search and the information extracted from each included article.

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