International Journal of Clinical Medicine, 2019, 10, 251-258
http://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

Progress in Research on Nonalcoholic Fatty Liver and Gestational Diabetes

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How to cite this paper: Luo, Z.H. and Wu, Q.M. (2019) Progress in Research on Nonalcoholic Fatty Liver and Gestational Diabetes. *International Journal of Clinical Medicine*, **10**, 251-258.
https://doi.org/10.4236/ijcm.2019.104019

Received: February 24, 2019
Accepted: April 1, 2019
Published: April 4, 2019

Abstract

Although there is ample evidence that non-alcoholic fatty liver disease (NAFLD) is associated with impaired glucose homeostasis in the body, the clinical significance of NAFLD in pregnant women has not been established. Current studies have shown that women with NAFLD during early pregnancy have a significantly increased incidence of gestational diabetes mellitus (GDM) during pregnancy; whereas women with a history of GDM have a significantly increased probability of developing NAFLD in the future. Both may be a manifestation of an etiology in both systems, reflecting the impaired glucose homeostasis and the continuity of insulin resistance. For women with NAFLD found in early pregnancy, it is recommended to closely monitor blood glucose during pregnancy, and if necessary, early intervention to strengthen prenatal and postnatal care. The presence of GDM at a young age in women may be an early marker that helps to screen out women at higher risk of developing a disease before significant metabolic disease, and is of great significance in reducing associated morbidity and mortality.

Keywords

Nonalcoholic Fatty Liver Disease, Gestational Diabetes Mellitus, Tumor Necrosis Factor, Leptin, Estrogen

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) refers to a clinical syndrome characterized by the exclusion of hepatocyte fat accumulation caused by alcohol and other factors that are clearly damaging to the liver. It is a liver damage caused by insulin resistance and genetically related metabolic stress, including nonalcoholic fatty liver disease (NAFLD), steatohepatitis nonalcoholic, cirrhosis and liver cancer [1] [2]. In Western countries, 20% - 30% of people suffer from NAFLD

[3]. A recent study [4] showed that a quarter of Asian populations have NAFLD. A study published in 2016 showed that the prevalence of NAFLD in seven provinces and cities in China was 43.3% [5]. Clinical Diagnostic Criteria: Any of the following items 1 - 5 and 6 or 7 can be diagnosed as NAFLD. 1) Risk factors: obesity, type 2 diabetes, hyperlipidemia, etc.; 2) No history of alcohol consumption or alcohol consumption. Males < 140 g per week, women < 70 g per week; 3) Excluding viral hepatitis, drug-based liver disease, total parenteral nutrition, hepatolenticular degeneration and autoimmune liver disease can lead to specific diseases of fatty liver; 4) In addition to the clinical manifestations of the primary disease, there may be fatigue, liver pain, liver spleen, etc., symptoms and signs; 5) Serum transaminases or γ-GT, transferrin increased; 6) In line with the diagnostic criteria of fatty liver disease; 7) Liver histological changes in line with the pathological diagnostic criteria for fatty liver disease. NAFLD is closely related to obesity, type 2 diabetes, cardiovascular disease, etc., and its prevalence is also increasing [6] [7]. It is an increasingly common cause of cirrhosis and hepatocellular carcinoma and is becoming the most common indication for liver transplantation in the United States. Given the increasing prevalence and burden of disease in NAFLD, it is important to identify patients with NAFLD before advanced liver disease.

Gestational diabetes mellitus (GDM) is a common pregnancy complication that often manifests as spontaneous hyperglycemia that occurs during pregnancy [8]. Blood glucose levels in most patients with GDM return to normal after delivery, but GDM has an adverse effect on pregnancy outcomes and may have an impact on the long-term health of mothers and infants, including the mother's increased risk of developing type 2 diabetes and cardiovascular disease in the future, as well as the risk of future obesity, cardiovascular disease, type 2 diabetes and/or GDM in children [9]. The latest relevant literature reports mentioned that the prevalence of GDM in the United States was 7.6%, and 19.7% of women were diagnosed with diabetes at subsequent follow-up [10]. The incidence of GDM in China is 1% - 5%, and there has been a significant increase in recent years.

Although there is ample evidence that non-alcoholic fatty liver disease (NAFLD) is associated with impaired glucose homeostasis in the body, the clinical significance of NAFLD in pregnant women has not been established. More and more studies have confirmed the close relationship between NAFLD and GDM, and the two interact with each other. This paper describes the research progress of the correlation between NAFLD and GDM.

2. Clinical Relevance of NAFLD and GDM

2.1. Women with NAFLD during Early Pregnancy Have an Increased Probability of Developing GDM during Pregnancy

De Souza LR *et al.* [11] conducted a prospective cohort study in a clinic at a large obstetrics and gynecology hospital in Toronto: 476 pregnant women participated

in the study and assessed whether participants were assessed by ultrasound at 11 - 14 weeks of gestation With NAFLD, all study participants were tested for GDM by oral glucose tolerance test (OGTT) after 8 hours of overnight fasting at 24 - 28 weeks of gestation. De Souza LR believes that according to the examination, it is confirmed that women with NAFLD during early pregnancy can predict the blood glucose status of pregnant women in the middle and late pregnancy.

Seung Mi Lee *et al.* [11] recruited 678 women in the 14th week of pregnancy at the In Seoul Women's Hospital in Incheon and the Boramae Medical Center in Seoul National University. After screening, 608 women participated in the experiment. The results of the experiment showed that pregnant women with nonalcoholic fatty liver disease were more likely to develop GDM in the third trimester of pregnancy at 10 - 14 weeks, and the risk of developing GDM increased gradually according to the severity of NAFLD: grade 0 fat The incidence of GDM in degenerative women was 3.2%, 10.5% in patients with grade 1 steatosis, and 42.3% in patients with grade 2 steatosis.

The clinical practice guidelines recommend GDM screening at 24 - 28 weeks of gestation, but this may be too late and is not conducive to maternal and child outcomes. Fatty liver in early pregnancy suggests that the woman has insulin resistance (IR), a subclinical condition that may affect the health of pregnant and postpartum women [12]. Subtle anomalies in glucose homeostasis may also indicate pre-diabetes status during pregnancy [13]. Therefore, it is important to consider the changes in blood glucose found in women with NAFLD in early pregnancy in order to intervene in advance.

2.2. Increased Prevalence of NAFLD in Women with Previous GDM

Hypertriglyceridemia and high insulin levels caused by physiological stress during pregnancy may contribute to women who are at high risk of developing NAFLD [14]. Studies have shown that women with a history of GDM and a history of postpartum weight retention have increased systemic inflammatory responses and reduced insulin sensitivity [15]. In a cohort of Ajmera VH *et al.* [16] from a multidisciplinary coronary risk development in adolescents in the United States, 1115 women who had been pregnant were followed up for 25 years and found that in the next 25 years, there was GDM. Women with a history of disease were more than twice as likely to develop NAFLD as women without a history of GDM. This study demonstrates that the history of GDM is a risk marker for NAFLD in middle-aged women, suggesting opportunities to identify women at higher risk of developing a higher risk.

3. NAFLD and GDM Are Related to Insulin Resistance

Clinical studies have found that serum insulin levels and insulin resistance index are significantly elevated in patients with NAFLD, indicating insulin resistance in patients with NAFLD [17]. The more popular "second strike" theory holds that the fat caused by insulin resistance accumulates in the liver and is the first

blow; then oxidative stress and lipid peroxidation damage are based on this, which is the second blow, and finally leads to the liver inflammation [18]. Moreover, due to the persistence of steatohepatitis, a vicious circle of "inflammation-necrosis-inflammation" is finally formed [19].

When women's gestational age gradually increases, the nutritional needs of the fetus will increase, and the fasting blood glucose will be lower in the early pregnancy, which is about 10% lower than usual. In the middle and late pregnancy, with the increase of antagonistic insulin-like substances, in order to maintain the normal level of glucose metabolism, the insulin demand will increase accordingly. If the mother's insulin secretion is limited, GDM will appear [15].

3.1. Insulin Resistance Is an Important Factor in the Development of NAFLD

Insulin resistance leads to hyperinsulinemia and high levels of free fatty acids (FFA) in the blood, and hyperinsulinemia can increase insulin resistance as well as increased FFA. FFA can produce fat, and the activity of lipoprotein lipase and the synthesis of fat are decreased when insulin resistance is enhanced, resulting in an increase in FFA in the blood. The FFA enters the liver and leads to an increase in the synthesis of triglycerides. Increased triglycerides bind to apolipoproteins to form very low density lipoproteins [20]. Therefore, when the formation of triglyceride is greater than the output, lipid accumulation is formed in the liver, and finally fatty liver is gradually formed. When too much lipid is stored in the liver cells, it will damage the insulin receptor on the cell membrane, resulting in reduced reactivity and sensitivity to insulin [21]. It has been reported that patients with hypertriglyceridemia have increased serum FFA, interfere with insulin-receptor binding, decrease insulin sensitivity, produce insulin resistance, and high levels of serum FFA levels can inhibit insulin signaling [22]. At the same time, hyperinsulinemia leads to an increase in fatty acid synthesis, further enhancing the accumulation of lipids in the liver.

3.2. IR Plays a Key Role in the Pathogenesis of GDM

With the development of pregnancy, the mother antagonizes the increase of insulin-like substances, such as: leptin, FFA, tumor necrosis factor-α (TNF-α), high levels of estrogen, prolactin, cortisol, Placenta prolactin and so on. TNF-[alpha] is a polypeptide produced by activated monocytes-macrophages. The placenta and uterine decidua contain a significant amount of macrophages, which, when stimulated by fetal antigens, activate to produce large amounts of TNF-α [23]. High levels of TNF-α in the blood reduce the degree of tyrosine phosphorylation of the insulin receptor and attenuate insulin signaling, leading to IR [24]. Increases the FFA in the blood, and then increases the expression of TNF-α through the lysosomal pathway, causing mitochondrial structure and function abnormalities in liver cells, oxidative stress, and fatty acid β oxidation overload, eventually leading to fat deposition in the liver [25] [26].

Leptin is a fat-soluble hormone synthesized and secreted by fat cells. During pregnancy, leptin levels increase, and oxidative stress is promoted by accumulation of reactive oxygen species, which induces islet β cell damage, which is closely related to the pathogenesis of GDM [27] [28]. In theory, leptin can strengthen fat breakdown and reduce synthesis. In fact, the study found that in patients with fatty liver, the level of leptin is increased, considering the presence of "leptin resistance" in patients with NAFLD [29]. Some scholars believe that there may be a "fat-insulin endocrine axis" between fat and islets, and a two-way feedback loop is formed between leptin and insulin through fat and islets [30]. Under normal circumstances, leptin promotes fat breakdown and inhibits islet secretion of insulin. In patients with NAFLD, due to leptin resistance, fat breakdown is limited, leptin inhibits the ability of insulin secretion from islets, leading to hyperinsulinemia, aggravating IR, and accumulation of fat in the liver [31] [32]. TNF-α and leptin play an important role in insulin resistance, eventually leading to the occurrence of NAFLD.

Estrogen at physiological concentrations has the effect of promoting insulin expression and increasing the body's sensitivity to insulin [33]. During pregnancy, the body's estrogen level is significantly increased, reaching a peak at the end of pregnancy. At this moment, the level of estriol is 1000 times that of non-pregnant women, and the levels of estradiol and progesterone are 100 times that of non-pregnant women. High concentrations of estrogen reduce insulin sensitivity by affecting insulin-like receptor expression, leading to IR [34] [35].

Glucocorticoids can inhibit the glycemic uptake function of insulin [36], which alters the receptors of insulin by transmembrane translocation of glucose, which may be the main target of diabetes [37]. Moreover, glucocorticoids have an "allowed effect" on progesterone and are indirectly related to IR.

NAFLD and GDM are related to insulin resistance. The diagnosis of NAFLD in pregnancy suggests that the pregnant woman may already have insulin resistance early or even before pregnancy. Combined with the physiological state of women during pregnancy, early insulin resistance promotes the development of GDM in the third trimester of pregnancy. GDM during pregnancy represents a state of pancreatic β-cell dysfunction, especially when glucose post-load increases. Previous studies have shown that women with a history of GDM and a history of postpartum weight retention may increase systemic inflammation and reduce insulin sensitivity, which may be associated with an increased probability of developing NAFLD in women with a history of GDM [36].

4. Summary

In summary, women with NAFLD during early pregnancy have a significantly increased incidence of GDM during pregnancy; whereas women with a previous history of GDM have a significantly increased probability of developing NAFLD in the future. The above discussion reflects the impaired glucose homeostasis and the continuity of IR, which may be the cause of an etiology in both systems.

The two may also have a relationship that promotes a vicious circle of chains. Currently, there are no guidelines on what populations should be screened for NAFLD, and some social guidelines specifically recommend not screening for NAFLD [37]. However, this may change as the number of people treating NAFLD increases and the screening method improves. For women with NAFLD found in early pregnancy, it is recommended to closely monitor blood glucose during pregnancy, and if necessary, early intervention to strengthen prenatal and postnatal care. A female GDM history may be an early marker that can screen young women who may have NAFLD in the future before a significant metabolic disease, and can be targeted to prevent NAFLD-related diseases.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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