International Journal of Sciences

Research Article Volume 13 – May 2024 (05)

High-Fat Diet Aggravate the Glycolipid Metabolic Disorder in Offspring Mice of Gestational Diabetes Mellitus

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Abstract: Gestational diabetes mellitus (GDM) changes maternal uterine microenvironment, increasing the risk of metabolic diseases in offspring in adult. In this study, we explored the effects of diet intervention on glucose and lipid metabolism in adult mice of GDM offspring. The GDM mice model was established by high-fat diet (HFD), and the 8-week aged offspring-mice were randomly divided into Chow group and HFD group. Four weeks later, the levels of OGTT, serum total cholesterol (TC) and triglyceride (TG) were monitored. The results showed that the levels of blood glucose, serum TC and TG in the offspring of HFD group were significantly increased, especially in GDM-HFD group, but there was no significant difference between Normal-Chow group and GDM-Chow group. These data showed that under chow diet, the glucose and lipid levels of GDM offspring increased slightly, but under high metabolic stress, glucose and lipid metabolism were markedly disordered, which emphasized that high-calorie diet could aggravate the disorder of glucose and lipid metabolism in GDM-offspring mice.

Keywords: Gestational Diabetes Mellitus, Dietary Intervention, Glucose And Lipid Metabolism, Offspring

Introduction

Gestational diabetes mellitus (GDM) is a metabolic disorder characterized by poor glucose tolerance, which develops or is first discovered during pregnancy[1-3]. GDM not only seriously harms the health of pregnant women, but also has a profound impact on the health of their offspring[4-6]. It has been reported that long-term exposure of the fetus to high blood glucose during pregnancy can change the metabolism profile and health trajectory of newborns at birth[7-9]. The effects of intrauterine hyperglycemia on GDM offspring may last until birth and even adulthood. Studies have shown that GDM offspring have an increased incidence of type 2 diabetes (T2D), cardiovascular disease and GDM[10-12].

At present, the clinical treatment of metabolic diseases in GDM offspring is mainly through exercise, regular blood glucose detection and drug intervention[13, 14], but there are few studies in this area. In this study, the model of GDM was induced by high-fat diet (HFD), and the effects of different dietary interventions on blood glucose and blood lipids in GDM offspring were investigated by performing oral glucose tolerance test(OGTT) on the offspring mice and detecting the expression of serum total cholesterol (TC) and triglyceride (TG) levels, so as to provide new ideas for early prevention of metabolic diseases such as obesity and diabetes in GDM offspring.

Methods

Schematic of experimental design

Eight-week-old C57BL/6 mice were purchased from Beijing Vital River Laboratory Animal Technology Co., ltd. (license number: SCXK (J) 2016-0006). All mice were fed in the SPF Animal Experimental Center of Qingdao University, which had an ambient temperature of 22 ±1℃, a relative humidity of 50 ±1% and a light/dark cycle of 12/12 hours. All animal experimental operations were in accordance with the ethical review guidelines for experimental animal welfare of Qingdao University.

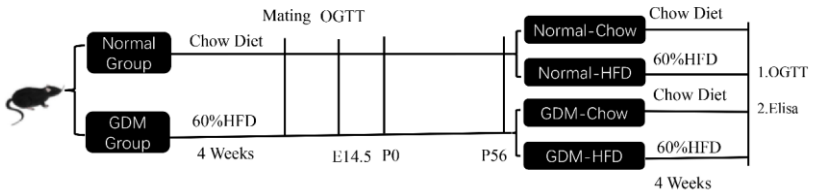

Figure 1 Schematic representation of animal experimental design.

All the animals were randomly divided into two groups. In order to obtain the GDM model, 8-week-old female C57BL/6 mice were fed with 60% HFD for 4 weeks, which was called HFD group; the other group was fed with chow diet, called Normal group. Corresponding feeds were continuously fed during pregnancy until delivery. OGTT was performed on the 14.5 day of pregnancy in order to screen the GDM maternal model. Eight weeks after birth, the offspring of each group were randomly divided into two groups and fed with

Published at: http://www.ijsciences.com/pub/issue/2024-05/
DOI: 10.18483/ijSci.2761; Online ISSN: 2305-3925; Print ISSN: 2410-4477

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chow diet and HFD respectively. Four weeks later, the offspring were tested by OGTT and the blood of each group were collected for Elisa.

OGTT

The mice were fasted overnight for 10 hours and given glucose (2g/kg) by gavage. Blood glucose levels were measured by tail-snip blood sampling using Roche blood glucose meter before and 30, 60, and 120 minutes after gavage. The OGTT curve was plotted and the area under the curve was calculated.

Biochemical analysis

After taking blood from the infraorbital vein, the serum was obtained by centrifugation at 4°C and 3000rpm for 10 minutes. The contents of TC and TG in serum were determined by Elisa kit (Nanjing Jiancheng Technology Co., Ltd.).

Statistical analysis

GraphPad Prism 8.0 software was used for data analysis. An unpaired student's t-test was used for the comparison between the two groups, and one-way analysis of variance (ANOVA) was used for the comparison between three groups and above. $P < 0.05$ was considered to be statistically significant.

Results

HFD induced glucose metabolism disorder in pregnant mice.

The blood glucose values in the normal group were 11.9±0.78 and 8.46±0.76 mmol/L at 30min and 60min after glucose loading, respectively, while those in HFD group were 16.56 ± 1.45, 10.92 ± 0.68 mmol/L respectively, which were significantly higher than those in the normal group ($p < 0.001$), and AUC increased by 28% ($p < 0.01$; Figure 2). These results suggested that HFD induced a typical GDM phenotype in C57BL/6J pregnant mice.

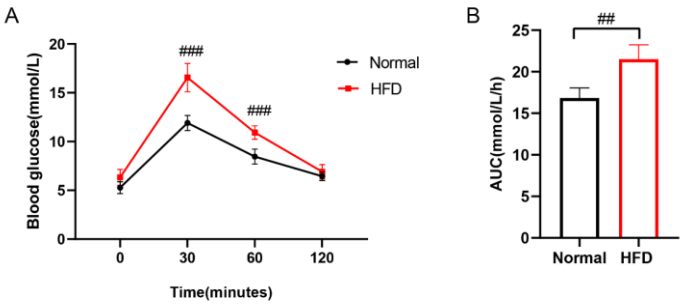

Figure 2 HFD induced glucose metabolism disorder in pregnant mice.
(A,B) Blood glucose levels and AUC of maternal mice during OGTT on E14.5. Data are presented as mean ± SD, n=5. $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ vs. Normal.

Adult mice of GDM offspring showed glucose metabolism disorder

OGTT was performed to evaluate the glucose metabolism of offspring adult mice. Compared with the chow diet groups, the blood glucose level and AUC of HFD group were significantly increased at 30min and 60min after glucose loading, and there was no significant difference in blood glucose level at 0 and 120 min. Adult mice in the GDM-Chow group had slightly higher blood glucose values at 30 min after glucose loading than those in the Normal-Chow group ($p<0.05$). The blood glucose and AUC at other time points showed an increasing trend, but there was no significant difference. The blood glucose level and AUC of GDM-HFD group were significantly higher than those of Normal-Chow group, Normal-HFD group and GDM-Chow group (Figure 3). The above results indicated that the glucose metabolism level of GDM offspring decreased slightly in adulthood under chow diet, but there was obvious oral glucose intolerance and serious disorder of glucose metabolism under high metabolic stress.

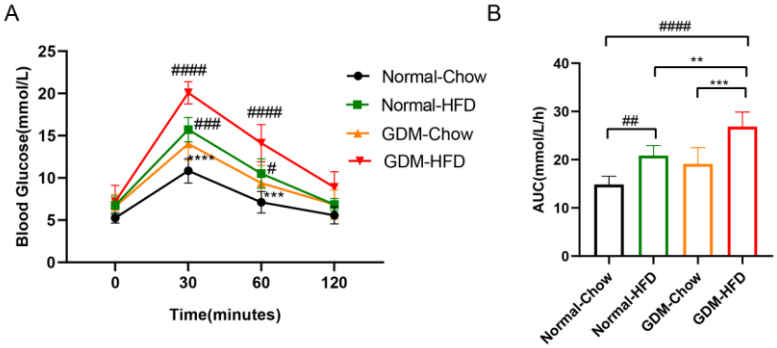

Figure 3 Adult mice of GDM offspring showed glucose metabolism disorder.
(A,B) Blood glucose levels and AUC of offspring adult mouse during OGTT. Data are presented as mean ± SD, n=6. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$, $^{\#\#\#\#}P < 0.0001$ vs. Normal-Chow; $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$ vs. GDM-HFD.

Adult mice of GDM offspring showed lipid metabolism disorder

The disorders of glucose metabolism and lipid metabolism often coexist during pregnancy[15], so we detected the levels of TC and TG in serum (Figure 4). Compared with Normal-Chow group (TC:1.63 ±0.21 mmol/L; TG:0.4 ±0.068 mmol/L), the expression of TC and TG increased slightly in GDM-Chow group, and the expression level of GDM-HFD group was the highest, with TC reaching 4.37±0.95 mmol/L and TG reaching 1.0±0.076 mmol/L, both increased by about 2.5 times. The results were consistent with the indexes of glucose metabolism.

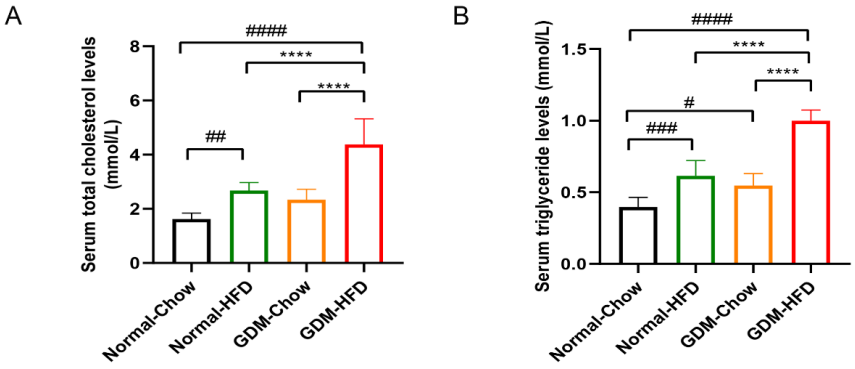

Figure 4 Adult mice of GDM offspring showed lipid metabolism disorder

(A) Serum total cholesterol levels of offspring adult mouse. (B) Serum triglyceride levels of offspring adult mouse. Data are presented as mean ± SD, n=6-8. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$, $^{\#\#\#\#}P < 0.0001$, vs. Normal-Chow; $^{****}P < 0.0001$ vs. GDM-HFD.

Discussion

At present, the incidence of GDM continues to rise worldwide[16], which is closely related to obesity and elderly pregnant women, and high-fat and high-sugar diet is an important aspect of inducing obesity[17, 18]. Lifestyle changes are crucial in the management of GDM, and different diets can alter energy intake, which plays a vital role in energy metabolism such as glucose and fat[19-21]. Dietary intervention can control blood glucose and improve insulin sensitivity, which is a more economical and effective treatment for people with glucose and lipid metabolism disorders[22-24]. In this study, the model of GDM was established by HFD, and the level of blood glucose in pregnant mice were monitored. The changes of blood glucose and blood lipids in the offspring of adult mice under different dietary interventions were observed to provide more references for the prevention of glucose and lipid metabolism disorders in human GDM offspring.

In this study, C57BL/6 mice were fed with 60% HFD for 4 weeks, and impaired glucose tolerance occurred in the second trimester of pregnancy, suggesting that the model was established successfully. The GDM animal model induced by diet is more in line with the physiological and pathological characteristics of GDM women[25, 26].

GDM has obvious short-term and long-term adverse effects on offspring[2, 27], the most profound of which is that GDM offspring are more sensitive to high-calorie diet during growth and adulthood, and are prone to glucose metabolic disorders, such as insulin resistance, oral glucose intolerance, and even diabetes[28]. In this study, compared with normal offspring, the levels of blood glucose, TC and TG showed an increasing trend in GDM offspring after adulthood, but the changes were not particularly significant. However, after 4 weeks of HFD, GDM offspring mice showed obvious abnormal glucose and lipid metabolism, which was characterized by the increase of blood glucose, serum TC and TG levels. For the normal offspring, although HFD also changed their blood glucose and blood lipid levels, the GDM-HFD group increased the most significantly. These results suggested that changes in the environment and lifestyle of the mother during pregnancy can affect the susceptibility of fetus to disease and can last into adulthood, and HFD aggravated the adverse outcome of metabolic diseases in adults of GDM offspring.

The intervention of diabetes and other chronic diseases often focuses on the formation of the disease or the occurrence of complications. How to identify high-risk groups of diabetes and intervene early is the root of the prevention and treatment of metabolic diseases. Our work shows that dietary intervention can affect glucose and lipid metabolism in adult offspring mice, which plays a positive role in preventing and blocking the occurrence of abnormal metabolism in adult offspring.

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