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Gestational Diabetes Mellitus: Treatment Progress

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Abstract: *Gestational diabetes mellitus (GDM) is one of the most common complications during pregnancy. The incidence of gestational diabetes mellitus increases year by year. Its pathogenesis may be related to insulin resistance, and its diagnostic criteria are more stringent than common type 2 diabetes. The management of gestational diabetes requires diet, exercise, drug therapy, blood glucose monitoring and diabetes knowledge education. Diet and exercise therapy are the main treatment measures, but for poor glycemic control on this basis, drugs are an essential treatment plan. Currently available drugs for pregnancy include insulin, metformin and glyburide. In addition to these traditional drugs, probiotics, inositol, insulin-like growth factor-1 and vitamin D have been found to be safer drugs, but the effectiveness of these drugs needs further study. The purpose of this paper is to review various gestational diabetes drugs, to help us fully understand the advantages and disadvantages of various drugs, better intervention in the occurrence and development of the disease.*

Keywords: *Gestational diabetes mellitus; Insulin; Metformin; Glyburide*

1. Introduction

Gestational diabetes mellitus (GDM) is one of the most common complications of pregnancy, which refers to blood glucose intolerance of varying degrees that first appears during pregnancy [1]. The incidence of the disease varies in different countries, but the global trend is increasing year by year. Major adverse outcomes in gestational diabetes include cesarean section, macrosomia, larger than gestational age, low 1-minute Apgar score, respiratory distress syndrome, neonatal jaundice, increased neonatal admission to the ICU, instrumental delivery, shoulder dystocia, postpartum hemorrhage, stillbirth, neonatal death, low 5-minute Apgar score, low birth weight, and small gestational age.

The goal of gestational diabetes treatment is to minimize maternal and maternal adverse events associated with hyperglycemia. Physiological changes in pregnancy include progressive increases in insulin resistance, weight gain, and changes in body composition, each of which may affect the pharmacological properties of diabetes treatment. Treatment options are different to the type of diabetes, mainly based on life interventions, such as exercise and diet control, but effectiveness and patient compliance are insufficient. Drug control is effective quickly and reliable for improving short-term adverse pregnancy outcomes. However, long-term adverse effects are still under study, long-term follow-up observation needed for children which born to gestational diabetes mellitus women [2]. Despite several recent large-scale studies addressing these issues, the debate surrounding the diagnosis and treatment of GDM continues. Therefore, we summarized various treatment programs of gestational diabetes mellitus, to sum up the advantages and deficiency, to provide better treatment programs for the clinic, and better help us to intervene the further development of disease early.

2. Screening and Diagnostic Criteria

IADPSG recommends a "one-step approach" that involves an oral glucose tolerance test (OGTT) at 24-28 weeks of gestation and suggests a diagnostic threshold for GDM. Subsequently, IADPSG's recommendations have been widely recognized as the preferred diagnostic criteria by most national and international institutions. The IADPSG standards are largely followed in Australia and Japan, and have been formally endorsed in Europe and globally by the International Federation of Obstetrics and Gynecology (FIGO) and the International Diabetes Federation. However, they are not widely used in the United States or Canada. Guidance issued by the UK's National Institute for Clinical Excellence

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(NICE) remains different from other countries in continuing to support selective testing based on risk factors. Much of the debate has focused on the increase in the number of women who may be diagnosed with gestational diabetes because of the change in thresholds and the shift from a "two-step" approach (screening test followed by a diagnostic test) to a one-step approach (diagnostic test only, i.e., a 75-gram glucose 2-hour test).

In summary, gestational diabetes is diagnosed by testing for hyperglycemia during pregnancy, and while not as severe as obvious diabetes, there is an increase in pregnancy complications, especially those related to fetal overgrowth. The current overall consensus supports IADPSG and WHO standards, which are based on a consensus overview of existing large-scale epidemiological data and randomized controlled trials, and which link diagnostic thresholds to the risk of pregnancy complications associated with hyperglycemia. However, they may not be suitable for uniform global application, and the FIGO guidelines recommend a more flexible approach that allows for different diagnostic procedures and blood glucose thresholds within specific geographic areas and ethnic groups.

3. Blood Glucose Monitoring

Blood glucose monitoring is the basic strategy of gestational diabetes management. Fasting and postprandial glucose monitoring is recommended for all types of diabetes. Although HbA1c does not reflect glucose concentration, HbA1c reflects recent blood sugar fluctuations and should also be used as an indicator of blood sugar monitoring [3]. Different international guidelines have different blood sugar indicators. Currently, the American Diabetes Association (ADA) recommends fasting glucose<95 mg/dl (5.3 mmol/L), 1 hour postprandial blood glucose<140 mg/dl (7.8 mmol/L), or 2 hours postprandial blood glucose<120 mg/dl (6.7 mmol/L), if measured at HbA1c, its level<6%.

A randomized controlled trial of 340 women with gestational diabetes divided into self-monitored blood sugar, self-monitored blood sugar plus intermittent continuous blood sugar monitoring (CGM) found that the use of CGM reduced the average birth weight of the fetus and reduced the incidence of macrosomia, pre-eclampsia, and primary cesarean section [4]. But another recent multicenter randomized controlled trial found no significant difference in the large infant risk between CGM and self-monitored glucose in 300 pregnant women with gestational and pre-pregnancy diabetes [5].

Rapid Glucose monitoring (FGM), in which users obtain glucose measurements in real time by scanning the glucose sensor with a reader, produces real-time data. Studies on the efficacy of FGM have been limited to non-pregnant adults. FGM was found to be associated with a reduced incidence of hypoglycemia and a reduced frequency of adverse events. Studies on the use of FGM during pregnancy have been limited to single case reports, but given the frequency of blood sugar monitoring during pregnancy, this technique is extremely promising for gestational diabetes.

In addition to hyperglycemia, excessive gestational weight gain has also been associated with excessive fetal growth in healthy pregnant women and women with gestational diabetes, leading to recommendations for weekly gestational weight gain targets based on a pregnant woman's pre-pregnancy body mass index. There is some evidence that even lower targets for obese women may be safe and associated with more appropriate fetal growth. For this reason, many clinicians will accept diets aimed at weight stabilization.

4. Treatment of GDM

Fetal obesity is closely related to elevated maternal blood sugar. The treatment of gestational diabetes mellitus is consistent with the type 2 diabetes, which requires diet control, exercise, drug therapy, blood glucose monitoring, and diabetes knowledge education. Because of the specificity of pregnant women, they are not strict in diet and exercise. Gestational diabetes mellitus patients not only should control blood sugar, but need to meet the energy needs of the fetus and their own. The pregnant women are not only need to exercise, but also should to prevent abortion, premature birth. According to the diabetes guidelines, insulin, metformin and glyburide can be given when necessary.

4.1. Lifestyle Intervention

Glucose is the main nutrient that promotes fetal growth. Elevated blood sugar in pregnant women is directly associated with fetal overgrowth and many pregnancy complications of gestational diabetes. Lifestyle changes including diet, exercise and weight management are the first line of treatment for

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women with gestational diabetes and are important adjunct to medication for pre-pregnancy diabetes and should be initiated immediately after diagnosis. 33%-50% of women with gestational diabetes mellitus are able to control their blood sugar through diet alone, but the optimal diet for pregnant women with diabetes remains controversial. ACOG and the Endocrine Society support a low-carbohydrate diet. Yamamoto et al. [6] found that, after controlling the diet of pregnant women with GDM, fasting and postprandial blood glucose decreased and the need for medication decreased; in neonatal pregnancy outcomes, birth weight and the incidence of macrosomia decreased. However, the ADA and the 5th International Symposium on Gestational Diabetes deem that low-carb diets may limit postprandial-glucose fluctuations and increase the related risk of fetal overgrowth. Besides, low-carb diets require increased dietary fat, which may promote insulin resistance in humans.

Exercise can improve glucose tolerance in women with gestational diabetes and reduce the risk of GDM. It is recognized by ACOG and ADA as a useful auxiliary therapy for diabetes. If maternal obesity is associated with excessive weight gain during pregnancy, it is important to evaluate physical activity programs that can be offered to obese pregnant women to help reduce the risk of adverse pregnancy outcomes, such as time-restricted diets and intermittent high-intensity training [7]. Lifestyle interventions also include recommendations for daily physical activity, such as walking, cycling and swimming. Diet and physical activity are sufficient to control the glycemic status of approximately 70-85% of women with GDM. In addition to more appropriate fetal growth, this lifestyle intervention has also been associated with a reduction in the occurrence of postpartum depression in mothers, and a systematic review showed that exercise interventions reduced postpartum weight retention in pregnant women.

But few studies have evaluated the effects of vigorous exercise on maternal and fetal health. The effect of maternal exercise on blood flow to the uterus, placenta and fetus needs further study.

4.2. Drug Therapy

Due to the poor medical adherence of gestational diabetes patients and the lack of rigorous self-monitoring and management, it is often found that diet and exercise therapy alone cannot achieve the expected effect. Therefore, it is necessary to use drugs to control blood sugar to a certain extent. Commonly used medications, such as insulin, metformin, and glyburide, help reduce short-term adverse pregnancy outcomes (macrosomia and gestational hypertension), but increase the risk of long-term complications (obesity, impaired glucose tolerance, and cardiovascular disease) in both mother and child. It still needs to be used with caution.

4.2.1. Insulin

If lifestyle interventions do not achieve glycemic goals within 1-2 weeks, insulin is the primary treatment. Insulin, because it doesn't cross the placenta, is effective and safe for the fetus. There is growing evidence that insulin analogues are safe alternatives to human insulin during pregnancy, including ultra-short-acting, short-acting, medium-acting, and long-acting. Maintaining strict control during the first trimester and throughout pregnancy is critical to reducing adverse fetal outcomes, including structural abnormalities, macrosomia, neonatal hypoglycemia, adolescent and adult obesity, and diabetes.

Insulin is the preferred treatment for gestational diabetes, and several professional associations endorse it as a first-line treatment for gestational diabetes. The use and dosage vary widely between individuals and there is no uniform standard. The type of insulin, the time and frequency of administration depend on the blood glucose pattern of the individual. Insulin generally starts from a small dose, and adjusts as appropriate according to the condition and blood sugar condition. At present, the most common application is the combination of long-acting insulin and short-acting insulin. The specific implementation plan is to inject short-acting insulin (such as insulin aspartic) before three meals and long-acting insulin (such as insulin Detemir) before going to bed, starting from a small dose and gradually adjusting to the ideal blood glucose standard. For insulin injections, the American Diabetes Association (ADA) recommends the need for multiple daily injections, but continuous subcutaneous insulin infusion is currently considered a potential alternative[3]. Continuous subcutaneous injection of insulin pump is more effective than fractional subcutaneous injection of insulin, which is very beneficial for reducing the incidence of complications and controlling the blood glucose level of patients.

The main problem with insulin therapy is the burden on women, which can include discomfort, fear of injections, treatment costs and the risk of hypoglycemia. Mild hypoglycemic episodes occur

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frequently, and severe hypoglycemic episodes are rare. Insulin treatment is time-consuming for caregivers, requires training and education for pregnant women, and requires frequent contact with patients to adjust insulin dosages. Therefore, oral hypoglycemic agents, such as two recognized oral agents, metformin and glyburide sulfonylurea, have been studied in women with gestational diabetes. Other hypoglycemic agents are generally discouraged for pregnancy because of documented complications such as neonatal hypoglycemia, fear of unintended fetal complications, and metabolic or epigenetic changes that can occur in the developing fetus.

4.2.2. Metformin

Metformin is a biguanide that can prevent the development of type 2 diabetes for up to 15 years and is the first-line treatment for type 2 diabetes. It is especially recommended in women with high HBA1c and a history of GDM to reduce intestinal glucose uptake, decrease hepatic glucose output, and increase peripheral glucose uptake by muscle and fat cells. Furthermore, the discovery that metformin inhibits mitochondrial respiratory chain complex 1 places energy metabolism and activation of AMP-activated protein kinase (AMPK) at the center of its proposed mechanism of action. In women with gestational diabetes, metformin (alone or with insulin supplementation) was not associated with an increase in perinatal complications compared to insulin therapy. Metformin is becoming more acceptable and affordable in the treatment of gestational diabetes, and it performs well in the treatment of diabetes and can be considered as an insulin replacement for the treatment of gestational diabetes [8].

Because metformin can cross the placenta, the effects of maternal metformin treatment on fetal, infant and child growth trajectories are not known. In the comparison of metformin to insulin, some people thought that there is not different between children of mothers treated with metformin and of with insulin in growth and development assessments [9]. However, others have questioned the treatment of metformin. They conducted a systematic review and meta-analysis of patients treated with metformin and insulin. The results showed that newborns after intrauterine exposure to metformin for maternal GDM were significantly smaller than those whose mothers received insulin during pregnancy. Despite a lower average birth weight, children exposed to metformin appeared to experience accelerated postnatal growth, resulting in heavier babies and higher mid-childhood BMIs compared to children whose mothers were treated with insulin. This pattern of low birth weight and catch-up growth after birth has been reported to be associated with poor long-term cardiometabolic outcomes [10]. This suggests the need for further study of perinatal and childhood longitudinal outcomes after intrauterine metformin exposure.

Pregnant overweight and obesity are associated with recognized complications of pregnancy. Prenatal diet and lifestyle intervention had some effect on pregnancy weight gain, but did not affect pregnancy outcome. A multicenter, randomized, double-blind, placebo-controlled trial called GroW was done in Australia. The results showed that giving metformin at 10-20 weeks of pregnancy did not improve pregnancy and birth outcomes in overweight or obese pregnant women, in addition to diet and lifestyle recommendations [11]. However, GDM patients treated with metformin combined with insulin can significantly optimize pregnancy outcomes and reduce their blood glucose levels. In addition, a comparison of infants exposed to metformin with diet therapy found continued increases in butyrylcarnitine (C4), isovalerylcarnitine (C5), and glutarylcarnitine (C5D) in the metformin exposure group, representing the signature effects of fetal metformin exposure.

4.2.3. Glyburide

Glyburide belongs to the second generation of sulfonylureas, which bind to specific receptors in pancreatic cells to stimulate insulin secretion. At the same time, it can also increase the sensitivity of peripheral tissue to insulin, and achieve the effect of lowering blood sugar. Glyburide has negative placental transport and rarely crosses the placenta [12]. The drug is metabolized in the liver with low distribution rate and high clearance rate, and rarely occurs retention in the body. Glyburide offers a safer alternative to insulin for the treatment of gestational diabetes, the study suggests. Patients with mild GDM treated with glyburide have a low incidence of hypoglycemia and a low incidence of macrosomia. Specific causes and mechanisms need to be studied with a larger sample size.

In a meta-analysis comparing the efficacy and safety of insulin, metformin, and glyburide [13], glyburide was associated with higher birth weight and a higher incidence of macrosomia and neonatal hypoglycemia than insulin. Glyburide was associated with higher birth weight and a higher incidence of macrosomia compared with metformin. In the short term, glyburide was significantly lower than insulin and metformin in women with gestational diabetes who needed medication, while metformin (plus insulin when necessary) performed slightly better than insulin. Based on these results, glyburide should not be used for the treatment of gestational diabetes if insulin or metformin is available.

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However, a recent study showed different results, stating that glyburide use did not result in a higher rate of perinatal complications compared to subcutaneous insulin [14]. But that doesn't mean glyburide can be upgraded to a first-line drug.

In the comparison of the efficacy and safety of metformin and glyburide, the oral effects of metformin and glyburide are similar in terms of blood glucose control and adverse reactions, and the combination of metformin and glyburide can significantly reduce the need for insulin [10].

The efficacy of glyburide during pregnancy may also be related to changes in drug metabolism, and the doses used in some studies may not be ideal. During pregnancy, glyburide concentrations increase within 30 to 60 minutes, peak within two to three hours, and return to baseline within eight hours, and plasma concentrations are lower during pregnancy than in non-pregnancy. Therefore, the pre-breakfast dose may not provide adequate insulin response for dinner, and increasing the dose may cause hypoglycemia. This suggests that there may be a need to change the dose and administration regimen of glyburide in diabetic pregnant women to maximize therapeutic efficacy.

4.3. Other Treatments

Sugar digestion and absorption are mainly in the gut, and there is also a certain correlation between intestinal microbes and GDM. Pregnant women with GDM can alter the microbiome between mother and child. In the comparison of intestinal microflora between pregnancy and postpartum, a statistical difference was detected in the microflora before and after. Gut flora and diet help with human metabolism. However, it was found that additional probiotics did not prevent GDM in overweight and obese pregnant women, nor did specific intestinal flora cause GDM [15]. There appeared to be no benefit in reducing the risk of GDM or improving glucose metabolism.

Through complex pathways, inositol transfers glucose into cells for conversion into fatty acid synthesis. Inositol supplementation beginning early in pregnancy can reduce the likelihood of gestational diabetes in obese women and other at-risk groups [16]. However, the efficacy of inositol in the treatment of gestational diabetes was weak and did not affect pregnant women with a family history of diabetes [17].

Insulin-like growth factor-1 (IGF-1) is a multipotent hormone with functions far beyond its classic role of reduce intestinal blood glucose. It is a candidate for the treatment of obesity, diabetes, and neurodegenerative diseases. Pregnancy-associated protein A (PAPPA), a metalloproteinase secreted by the human placenta, regulates IGF-1 bioavailability through IGF-1-binding proteins, which are necessary for glucose homeostasis and have long-term metabolic risks and potential therapeutic uses [18].

Vitamin D, in addition to being involved in maintaining calcium and phosphorus balance in the body, also has a powerful immunomodulatory effect. Vitamin D deficiency in pregnant women is common throughout the world, and serum vitamin D levels are strongly associated with diabetes during pregnancy. Vitamin D binding protein (DBP) is present in pancreatic tissue, and vitamin D deficiency can lead to decreased insulin expression and secretion. Vitamin D is involved in the inflammatory response of islet cells and the occurrence of diabetes. The decrease of vitamin D level may affect blood glucose metabolism. Studies have shown that vitamin D has a significant association with cardiovascular disease and metabolic syndrome, so some scholars believe that vitamin D deficiency may be one of the causes of diabetes complications [19]. The detection rate of GDM is positively correlated with the degree of vitamin D deficiency. It has been confirmed that additional vitamin D supplementation can improve hyperglycemia and delay or even block the further development of diabetes. Vitamin D supplementation can increase the rate of vaginal delivery and reduce the rate of obstructed labor and neonatal complications. However, high doses of vitamin D supplements could not further improve maternal and infant pregnancy outcomes, but may lead to vitamin poisoning.

5. Summary and outlook

In conclusion, early diet and exercise guidance can be provided to high-risk groups of gestational diabetes to help them lose weight and prevent excessive weight gain during pregnancy, so as to prevent the occurrence of gestational diabetes mellitus or block the further development. For the treatment of gestational diabetes mellitus, in addition to the traditional treatment, some new therapeutic options have been introduced, such as probiotics, inositol and vitamin D, but the efficacy needs to be confirmed by further studies. Some factors and proteins are also involved in the occurrence and development of

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gestational diabetes, which provides a new idea for the study of new hypoglycemic drugs.

References

[1] Sweeting, A., Wong, J., Murphy, H.R., and Ross, G.P. (2022) A Clinical Update on Gestational Diabetes Mellitus. Endocrine reviews, 43, 763-793.
[2] Gunderson, E.P., Sun, B., Catov, J.M., Carnethon, M., Lewis, C.E., Allen, N.B., et al. (2021) Gestational Diabetes History and Glucose Tolerance After Pregnancy Associated With Coronary Artery Calcium in Women During Midlife: The CARDIA Study. Circulation, 143, 974-987.
[3] American Diabetes Association. (2020). Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes-2020. Diabetes Care, 43(Suppl 1),S183-S192.
[4] Yu, F., Lv, L., Liang, Z., Wang, Y., Wen, J., Lin, X., et al. (2014) Continuous glucose monitoring effects on maternal glycemic control and pregnancy outcomes in patients with gestational diabetes mellitus: a prospective cohort study. J Clin Endocrinol Metab, 99, 4674-4682.
[5] Voormolen, D.N., DeVries, J.H., Sanson, R.M.E., Heringa, M.P., de Valk, H.W., Kok, M., et al. (2018) Continuous glucose monitoring during diabetic pregnancy (GlucoMOMS): A multicentre randomized controlled trial. Diabetes Obes Metab, 20, 1894-1902.
[6] Yamamoto, J.M., Kellett, J.E., Balsells, M., García-Patterson, A., Hadar, E., Solà, I., et al. (2018) Gestational Diabetes Mellitus and Diet: A Systematic Review and Meta-analysis of Randomized Controlled Trials Examining the Impact of Modified Dietary Interventions on Maternal Glucose Control and Neonatal Birth Weight. Diabetes care, 41, 1346-1361.
[7] Almenning, I., Rieber-Mohn, A., Lundgren, K.M., Shetelig Lovvik, T., Garnaes, K.K., and Moholdt, T. (2015) Effects of High Intensity Interval Training and Strength Training on Metabolic, Cardiovascular and Hormonal Outcomes in Women with Polycystic Ovary Syndrome: A Pilot Study. PLoS One, 10, e0138793.
[8] Rowan, J.A., Hague, W.M., Gao, W., Battin, M.R., Moore, M.P., and Mi, G.T.I. (2008) Metformin versus insulin for the treatment of gestational diabetes. The New England journal of medicine, 358, 2003-2015.
[9] Landi, S.N., Radke, S., Engel, S.M., Boggess, K., Stürmer, T., Howe, A.S., et al. (2019) Association of Long-term Child Growth and Developmental Outcomes With Metformin vs Insulin Treatment for Gestational Diabetes. JAMA pediatrics, 173, 160-168.
[10] Tarry-Adkins, J.L., Aiken, C.E., and Ozanne, S.E. (2019) Neonatal, infant, and childhood growth following metformin versus insulin treatment for gestational diabetes: A systematic review and meta-analysis. PLoS medicine, 16, e1002848.
[11] Dodd, J.M., Louise, J., Deussen, A.R., Grivell, R.M., Dekker, G., McPhee, A.J., et al. (2019) Effect of metformin in addition to dietary and lifestyle advice for pregnant women who are overweight or obese: the GRoW randomised, double-blind, placebo-controlled trial. The lancet. Diabetes & endocrinology, 7, 15-24.
[12] Hebert, M.F., Ma, X., Naraharisetti, S.B., Krudys, K.M., Umans, J.G., Hankins, G.D., et al. (2009) Are we optimizing gestational diabetes treatment with glyburide? The pharmacologic basis for better clinical practice. Clin Pharmacol Ther, 85, 607-614.
[13] Balsells, M., Garcia-Patterson, A., Sola, I., Roque, M., Gich, I., and Corcoy, R. (2015) Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. BMJ (Clinical research ed.), 350, h102.
[14] Sénat, M.V., Affres, H., Letourneau, A., Coustols-Valat, M., Cazaubiel, M., Legardeur, H., et al. (2018) Effect of Glyburide vs Subcutaneous Insulin on Perinatal Complications Among Women With Gestational Diabetes: A Randomized Clinical Trial. Jama, 319, 1773-1780.
[15] Pellonpera, O., Mokkala, K., Houttu, N., Vahlberg, T., Koivuniemi, E., Tertti, K., et al. (2019) Efficacy of Fish Oil and/or Probiotic Intervention on the Incidence of Gestational Diabetes Mellitus in an At-Risk Group of Overweight and Obese Women: A Randomized, Placebo-Controlled, Double-Blind Clinical Trial. Diabetes care, 42, 1009-1017.
[16] Santamaria, A., Di Benedetto, A., Petrella, E., Pintaudi, B., Corrado, F., D'Anna, R., et al. (2016) Myo-inositol may prevent gestational diabetes onset in overweight women: a randomized, controlled trial. J Matern Fetal Neonatal Med, 29, 3234-3237.
[17] Farren, M., Daly, N., McKeating, A., Kinsley, B., Turner, M.J., and Daly, S. (2017) The Prevention of Gestational Diabetes Mellitus With Antenatal Oral Inositol Supplementation: A Randomized Controlled Trial. Diabetes care, 40, 759-763.
[18] Rojas-Rodriguez, R., Ziegler, R., DeSouza, T., Majid, S., Madore, A.S., Amir, N., et al. (2020) PAPPA-mediated adipose tissue remodeling mitigates insulin resistance and protects against gestational diabetes in mice and humans. Sci Transl Med, 12.
[19] Holick, M.F. (2007) Vitamin D deficiency. The New England journal of medicine, 357, 266-281.