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A comprehensive study for assessing the insulin resistance in women with gestational diabetes with respect to maternal dietary fat intake

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ABSTRACT

Gestational diabetes mellitus (GDM) is defined as the beginning or detection of glucose intolerance during pregnancy. It is associated with a variety of adverse outcomes for both moms and babies. Understanding the link between dietary fat consumption and insulin resistance in women with GDM is critical, since this illness affects 2-14% of pregnancies and presents severe health hazards to both mothers and their children. The paper synthesizes findings from various studies focusing on the impact of different types of dietary fats on metabolic health. It demonstrates the detrimental effects of saturated and trans fats, contrasting them with the protective roles of monounsaturated and polyunsaturated fats. The review employs a comprehensive analysis of dietary interventions, including the Mediterranean diet, and physical activity's role in mitigating GDM risk. The study aims to provide evidence-based dietary recommendations to optimize maternal health during pregnancy. Individualized dietary changes, especially the incorporation of healthy fats, can significantly lower the incidence of GDM and improve maternal and fetal outcomes. Finally, the study focused on the necessity of targeted dietary strategies to combat insulin resistance, thereby contributing to better long-term health for mothers and their children.

1. Introduction

Gestational Diabetes Mellitus (GDM) is a disorder that causes glucose intolerance during pregnancy and affects between 2% and 10% of pregnancies globally. Risks to the mother's and the child's health include hypertension, a greater need for cesarean sections during birth, and obesity and type 2 diabetes in the mother's and child's later years. Insulin resistance (IR) is a key factor in the pathogenesis of GDM because it affects the body's capacity to use glucose efficiently, resulting in hyperglycemia. Recent research has shifted its attention to dietary components that can alter insulin sensitivity, namely the significance of dietary fat consumption. The kind and amount of fat ingested when pregnant can have a significant impact on metabolic health and insulin resistance. For instance, high intakes of saturated and trans fats have been associated with increased IR, while monounsaturated and polyunsaturated fats can exert protective effects. Furthermore, the time and character of meals might impact glycemic responses, confounding the link between food and insulin resistance.

1.1 Overview of Gestational diabetes mellitus (GDM)

GDM is a prevalent medical problem during pregnancy, impacting around 14% of pregnancies, or one in every seven newborns worldwide [1]. Women with GDM and their children have heightened risks of both immediate and long-term problems. "Obesity, type 2 diabetes, and metabolic syndrome" are more common in children, and mothers can get type 2 diabetes later in life [2]. The detrimental intrauterine environment induces epigenetic modifications in the fetus that can lead to metabolic problems, creating a so-called vicious cycle of diabetes [3].

Medical nutrition therapy, weight management, and physical activity are the pillars of GDM treatment plans. Women can control their blood sugar levels by keeping track of their fasting and postprandial glucose levels and making targeted dietary and lifestyle changes. In almost two-thirds of women with GDM, this practical strategy achieves glycemic goals [4]. However, despite the significance of medical nutrition treatment and its extensive endorsement in clinical practice, there exists a paucity of evidence about the ideal diet for attaining maternal euglycemia [5]. The efficacy of dietary therapies aimed at regulating maternal glycemia in mitigating excessive fetal development and obesity remains uncertain [6].

1.2 Risk factor of GDM

The causes of GDM have shown several potential risk factors. A majority of these risk factors are strongly linked to insulin sensitivity or the activity of pancreatic β-cells in insulin production [7].

One of the most serious clinical outcomes of pregnancy is GDM, which can have several causes (both genetic and environmental). However, the most important ones are maternal obesity and nutritional inadequacies [8]. A body mass index (BMI) > 30 kg/m2 before pregnancy is a major risk factor. GDM and type 2 diabetes share a neighborhood. Hispanic, African, and certain Asian women are more likely than Caucasian women to acquire gestational diabetes. Excessive weight increase during pregnancy, advanced mother age, and past gestational diabetes mellitus are also risk factors. Other studies also link prenatal weight gain to gestational diabetes mellitus [9].

Polycystic ovary syndrome (PCOS) raises the risk of GDM due to metabolic and hormonal imbalance. It seems to be connected more to overweight or elderly mothers than to PCOS. Lifestyle variables, notably diet, appear to have a substantial role in first-trimester GDM [10]. Most lifestyle changes have a lasting influence on patients; thus, it should be made before pregnancy [11]. Gestational diabetes risk factors can be adjusted or not. Advanced mother age, ethnicity, polycystic ovarian syndrome, past GDM, and a family history of the illness are hereditary risk factors for gestational diabetes. Pregnant women and their parents smoking, BMI above 30 kg/m², poor physical activity, and food are modifiable risk factors.

1.3 Prevention of GDM

Modifying patients' dietary habits, physical activity, and glucose level management might mitigate difficulties associated with pregnancies in individuals with GDM. The crucial element is vigilant monitoring of glucose levels. There should be no more than 5 mmol/L (90 mg/dL) of fasting glucose and 7.8 mmol/L (140 mg/dL) of one-hour postprandial glucose. Dietary management is the primary intervention for GDM [12].

At now, there is no organized approach for the prevention of GDM. The pathophysiology and risk factors of T2DM and GDM, it is probable that interventions successful in avoiding T2DM can also be useful in preventing GDM. Diet, exercise, a lower obesity prevalence, and weight gain during pregnancy are all features that fall under this category. Identifying demographic characteristics is crucial for mitigating the increasing prevalence of GDM, similar to type 2 diabetes mellitus [13].

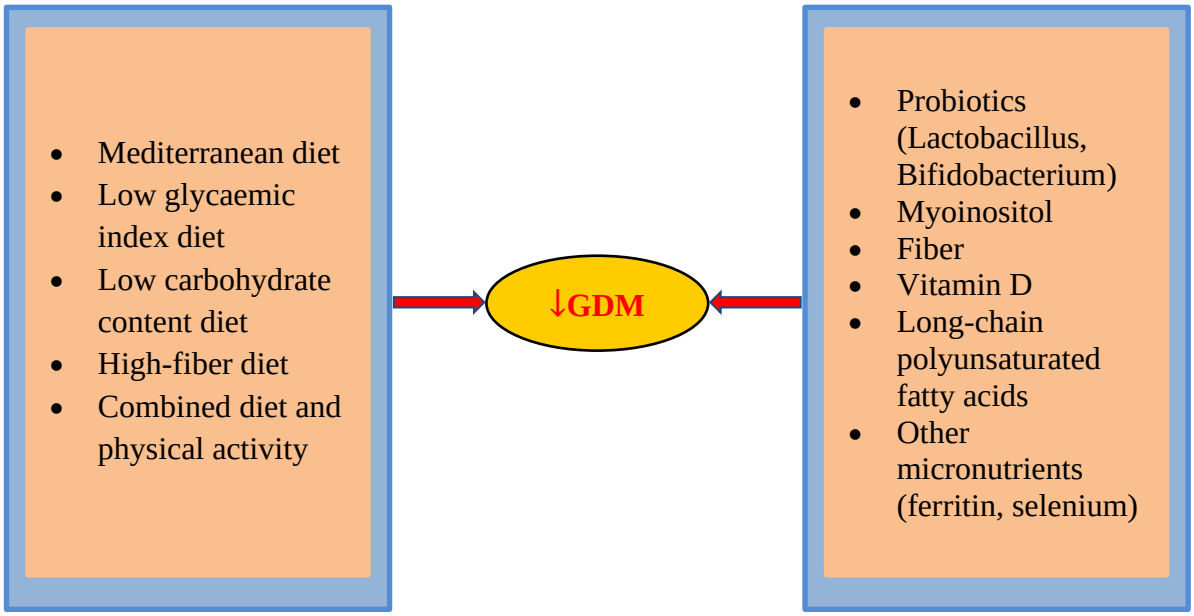

Figure 1: Diet and supplements as potential factors in GDM prevention.

1.3.1 Individualized Diet

Pregnancy is a chance for healthcare practitioners to influence lifestyle changes, promoting better behaviors for both the individual patient and society at large [14]. A healthy diet, like as "the Mediterranean diet, and limiting iron-rich foods, sugar-sweetened beverages, potatoes, fatty meals", and confections can reduce gestational diabetes mellitus, especially in high-risk groups and before conception. Combining these drugs can boost metabolism, minimize free radicals, and lower systemic oxidative stress. The greatest reduction in pregnancy weight gain was achieved with dietary changes. Reduced weight gain throughout pregnancy can have reduced gestational diabetes mellitus prevalence [15].

1.3.2 Mediterranean Diet (MedDiet)

The MedDiet is a very healthy diet. The diet consists of plant-based meals with olive oil as the primary source of added fat, moderate red meat (fewer than two servings per week), limited processed meat (one or fewer servings per week), eggs (two to four servings per week), moderate white meat (two servings per week), and fish or seafood (two or more servings). Low-fat dairy products are also a key component [16]. Pistachios and virgin olive oil, when added to the MedDiet, have been shown to prevent GDM [17]. The intervention reduced GDM risk by 17.1% compared to 23.4% in the control group ($p = 0.012$). At 24–28 and 36–38 weeks of gestation, the intervention group had significantly lower fasting blood glucose and HbA1c than the control group. After GDM diagnosis, 32% of the control group received insulin, compared to 19% of the intervention group ($p = 0.002$).

1.3.3 Physical Activity

Physical activity therapies did not provide comparable outcomes to dietary interventions in reducing the risk of GDM and the prevalence of macrosomic newborns in pregnant women who are overweight [18]. The "American Dietetic Association and the American Nutrition Society" found that pregnant women who exercised had lower adipose tissue accumulation and a lower risk of GDM. Two meta-analyses found that organized, low- to moderate-intensity aerobic exercise regimens reduced GDM by 28–31% and gestational weight gain by 1.1 kg between the intervention and control groups [19]. The risk of GDM was reduced by 36% when the exercise plan was continued throughout pregnancy [20].

1.3.4 Combined Diet and Physical Activity

Exercise and nutrition are said to prevent GDM. However, other studies found no effect in combining diet and exercise. This can also be linked to poor patient exercise compliance. The largest study on food and lifestyle changes during pregnancy, the LIMIT trial, found no benefits for gestational diabetes treatment or other maternal outcomes, including weight increase [21]. Thangaratinam found that pregnant women who follow

dietary advice and exercise had a 27% reduced risk of preeclampsia and a 26% lower chance of delivering a "large-for-gestational-age (LGA)" baby than non-obese patients who get conventional treatment [22].

1.4 Dietary Fat Intake: Types and Sources

There are four categories of dietary fat: "saturated, monounsaturated, polyunsaturated, and trans-fatty acids (present in processed foods)".

Type of Fat	Description	Sources
Saturated Fat	Solid at room temperature; can raise LDL cholesterol	butter, Red meat, palm oil, cheese, coconut oil
Monounsaturated Fat	Liquid at room temperature; can lower LDL cholesterol	Avocados, nuts (almonds, peanuts), Olive oil
Polyunsaturated Fat	Includes essential fatty acids; can lower LDL cholesterol	Flaxseeds, Fatty fish (salmon, mackerel), walnuts, sunflower oil
Trans Fat	Artificially created; raises LDL and lowers HDL cholesterol	Margarine, Processed foods, baked goods (cakes, cookies)
Omega-3 Fatty Acids	A category of polyunsaturated fat advantageous for heart health	Fatty fish, chia seeds, flaxseeds, walnuts
Omega-6 Fatty Acids	Another type of polyunsaturated fat; supports cell growth	Vegetable oils (corn, soybean, sunflower), nuts, seeds

Dietary fats are vital macronutrients that are integral to body activities, including energy storage, hormone synthesis, and nutrient absorption. Fats are classified into four primary categories: saturated fats, which are generally solid at ambient temperature and present in animal products such as red meat and dairy; monounsaturated fats, which are liquid at ambient temperature and commonly sourced from olive oil and avocados, known to reduce harmful cholesterol levels; polyunsaturated fats, encompassing omega-3 and omega-6 fatty acids, vital for cardiovascular health and sourced from fatty fish, seeds, and specific oils; and trans fats, synthetically produced via hydrogenation, which can elevate harmful cholesterol levels and are prevalent in numerous processed foods. A balanced intake of healthy fats is vital for overall health, while minimizing harmful fats is important for reducing the risk of cardiovascular disease [23].

1.5 Molecular pathway in GDM associated with insulin resistance

In GDM, key metabolic processes altered, which correspond with the dysregulated pathways in T2DM, including "glycolysis, beta-oxidation, and the metabolism of ketone bodies, asparagine, and one-carbon molecules". Furthermore, inflammation facilitated by the Toll-like receptor 4/Nuclear factor kappa B (TLR4/NF-κB) signaling pathway is critical in the progression of GDM.

1.5.1 Glycolysis, ketone bodies, asparagine metabolic pathways, and beta-oxidation

Phosphorylation of "insulin receptor substrates (IRS-1 and IRS-2)" occurs in response to insulin binding to its receptor (IRe) in living organisms. When IRSs are phosphorylated, two intracellular processes are initiated: The Mitogen-Activated Protein Kinase (MAPK) cascade enhances the expression of several proteins, particularly glucose transporter 1 and 4 (GLUT1 and GLUT4). It is the phosphatidylinositol 3-kinase (PI3K) that makes it possible for GLUT vesicles to go to the plasma membrane. The GLUT family of proteins plays a crucial role in the uptake of glucose by cells [24].

Plasma fatty acid concentrations increase during a lowering "intracellular glucose levels, healthy pregnancy", indicating fatty acids interfere with insulin-mediated glucose transport. PI3K activity and IRS-1 tyrosine phosphorylation decreased with these changes. Increasing plasma fatty acid levels requires regulating their metabolism. Numerous studies have indicated that increasing maternal bloodstream fatty acid release increases carnitine usage, reducing its circulation [25]. Ketone bodies, also known as "adenosine triphosphate

(ATP) via the tricarboxylic acid (TCA)" cycle, are produced by beta-oxidation of fatty acids in mitochondria, which is made possible by carnitine [26][27].

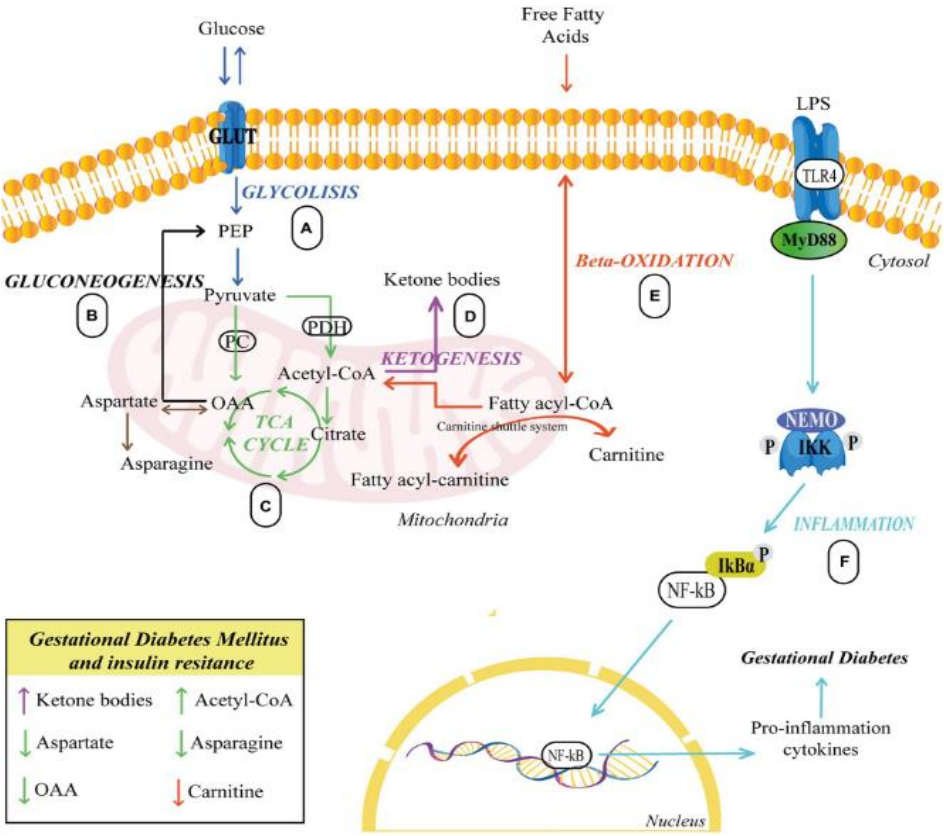

Figure 2 illustrates the alteration in glycolysis, beta-oxidation, and the metabolism of ketone body and asparagine in GDM [28].

1.5.2 One-carbon metabolic pathways

A functional group containing exactly one carbon atom is called a one carbon (1C) group. The transsulfuration pathway, the methionine and folate cycles, and one-carbon metabolism are shown in figure 3 [29]. "Amino acid balance, redox protection, and methylation processes" depend on 1C metabolism. During a healthy pregnancy, the baby's intrauterine development has 1C metabolism deficiencies [30]. In women with "GDM, serine, glycine, methionine, and histidine (1C units)" drop more, according to various studies. The cytosol and mitochondrion can create one-carbon units by converting serine to glycine via serine hydroxymethyltransferase. The placental SHMT meets the fetus' glycine demands. Glycine is also reduced in T2DM and GDM women, according to various studies. Moreover, GDM is associated with heightened oxidative stress, which stimulates glutathione manufacture owing to the placenta's enhanced antioxidant functions aimed at mitigating oxidative damage [31].

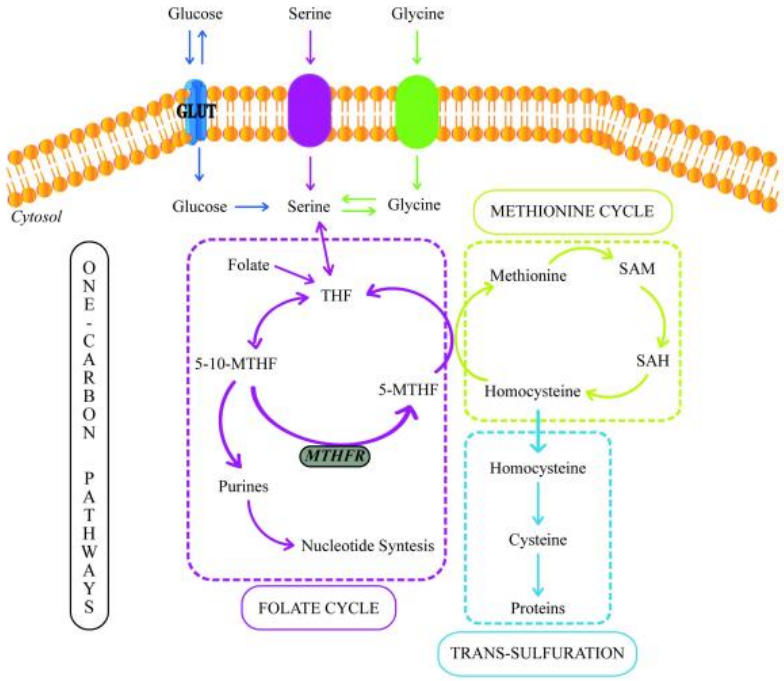

Figure 3 1C metabolism involves the methionine and folate cycles and the transsulfuration pathway and requires many 1C units [28].

1.5.3 TLR4/NF-κB signaling pathway

Toll-like receptor 4 (TLR4) belongs to the Toll-like receptor (TLR) family and is a transmembrane glycoprotein. In order to recognize Pathogen-Associated Molecular Patterns (PAMP) and start the innate immune response, TLR4 is essential [32]. Additionally, there are two domains in TLR4: an interior Toll-interleukin-1 receptor (TIR) and an external leucine-rich repeat (LLR). Several proteins come together to form a complex when TLR4 detects a PAMP. Intracellular adaptor proteins are recruited by protein-protein interactions activated by conformational changes brought about by oligomerization. Five TIR domain-containing adaptor proteins are recognized: "MyD88 (myeloid differentiation primary response gene 88), TIRAP (TIR domain-containing adaptor protein), TRIF (TIR domain-containing adaptor inducing IFN-β), TRAM (TRIF-related adaptor molecule), and SARM (sterile alpha and HEAT-armadillo motifs-containing protein)" [33].

The innate immune response is stimulated by TLRs via the use of several adaptor proteins, which initiate an intracellular signaling cascade. Both metabolic pathways that rely on MyD88 and those that do not are activated when TLR4 is activated. NF-κB and MAPKs are activated by MyD88 via the pathway's signaling proteins being phosphorylated and ubiquitinated. The synthesis of proinflammatory cytokines, such as IL-6, is controlled by NF-κB, along with TNF-α and IL-1, upon their translocation to the nucleus. Without MyD88, TRIF activates IRF3, which in turn generates type I interferon (IFN-I) and genes that are inducible by IFN-I. Additionally, in subsequent stages, it triggers NF-κB and MAPK [34].

1.6 Insulin Resistance in Gestational Diabetes

GDM affects around fourteen percent of American pregnant women. GDM in mothers is characterized by dysregulation of adipokines and insulin resistance in the periphery [35], “altered lipid metabolism, low-grade inflammation” [36], and increased circulating free fatty acids [37]. These metabolic changes significantly elevate the likelihood of developing type 2 diabetes mellitus in the future [38].

The importance of Adipose Tissue (AT) malfunctions in GDM. Adipose tissue dysfunction is caused by excessive lipolysis (insulin resistance in adipocytes) and inflammation, which raises adipocyte-derived circulating lipids and cytokines, which impair insulin-mediated glucose consumption in skeletal muscle. Although not all fat people have adipocyte and systemic insulin resistance, obesity usually causes insulin resistance [39]. Overweight pregnant women often develop GDM, although not all. Investigating adipose tissue function changes during pregnancy can help explain GDM pathogenesis.

Obese guys with high levels of Ectonucleotide Pyrophosphate Phosphodiesterase-1 (ENPP1) have adipocyte malfunction and systemic insulin resistance (IR). ENPP1, or plasma cell membrane glycoprotein PC-1, is a class II transmembrane glycoprotein that inhibits downstream signaling by interacting with the β-subunit of the insulin receptor, downregulating insulin receptor activation. Adipocyte maturation arrest, cellular insulin resistance, and poor Triglyceride (TG) storage result from this condition. Thirteen to fifteen Transgenic mice studies support the mechanistic impact of ENPP1 overexpression on insulin resistance [40]. In AtENPP1 Tg animals, which have systemic insulin resistance, liver fat accumulation, and glucose intolerance, AT-specific ENPP1 overexpression directly affects adipocyte IR and tissue function [41][42].

1.7 Recommendations for dietary fats intake

1.7.1 Reduction in fat intake

Adults in the United States were subject to new public health restrictions in 1977 that pushed for a 30% reduction in total fat consumption relative to calorie intake. The percentage of calories coming from fat was 28.6% and 25.3% in the Step I and Step II diets, respectively, with 9% and 6.1% of those calories coming from saturated sources. The early Step I diet recommendations matched those of the American Heart Association. After 40 years, people with “low HDL-cholesterol (1.03 mmol/L) and high triacylglycerol (1.7 mmol/L)” had a much higher rate of coronary artery disease (CAD) than those with lower levels [43].

1.7.2 Effects of low-fat diets on individuals

A crucial element often overlooked in research on dietary fat responses is individual variability. In a community of hypercholesterolemic individuals, persistent hyperresponders and minimum responders emerge due to variations in dietary saturated fat consumption, a phenomenon not attributable to the participants' dietary compliance. In consistent responders, high dietary saturated fat affects "baseline cholesterol ester transfer activity, total cholesterol levels, triacylglycerols, and apolipoprotein (apo) B" [44].

1.7.3 Impact of Low-Fat Diet Recommendations on Health Outcomes

Food industry reformulated commodities and processed foods to help consumers meet dietary fat needs. The "National Health and Nutrition Examination Survey data-collection" initiatives in the US show that replacing dietary fat with carbohydrate did not reduce obesity prevalence, despite improvements in food availability. Reduced dietary fat and increased carbohydrate consumption are linked, although carbohydrates' effect on weight growth is unclear. Carbohydrates raise blood glucose, which releases insulin and encourages adipose tissue growth, possibly causing weight gain. Obesity is linked to “metabolic syndrome and atherogenic hypertriacylglycerolemia” [45].

1.7.4 Controversy over saturated fat intake

Cholesterol accounts for 15.0% of calories and total fat for 34.3% in the typical American diet. Saturated fat makes up just 12% of calories, according to the "US Department of Agriculture and the third National Health and Nutrition Examination Survey" combined. Many high-fat diets increase saturated fat intake. Statistics show that saturated fats raise LDL cholesterol levels in certain people, which increases heart disease risk. Eating without saturated fat is impossible from a practical nutritional viewpoint [46].

1.7.5 Tissue accumulation of fatty acids

Certain fats are selectively oxidized and stored in adipose tissue for energy. People with various diets have similar fatty acid composition in their adipose tissue. Diet accounted for 25% of adipose fatty acid composition, according to research. However, nutrition impacts tissue composition, and current study suggests that particular fatty acids in adipose tissue signal dietary fatty acid intake [47].

1.8 Conclusion and future recommendations

The comprehensive investigation emphasizes the importance of maternal dietary fat consumption in regulating insulin resistance in women with gestational diabetes mellitus. The study suggests that particular kinds of dietary fats have a major influence on metabolic health during pregnancy. High saturated and trans-fat intake is connected with increased insulin resistance, aggravating the hazards of GDM, such as poor maternal and fetal health outcomes. However, consuming monounsaturated and polyunsaturated fats, especially from olive

oil and fatty fish, has been linked to enhanced insulin sensitivity and glycemic management. These findings emphasize the significance of dietary quality over fat quantity, suggesting that shifting to better fat sources might alleviate some of the negative impacts of GDM. Furthermore, adopting dietary patterns such as the Mediterranean diet can be a realistic approach for lowering the incidence of GDM and its long-term consequences, including the risk of type 2 diabetes in both mothers and their kids. Thus, tailored dietary treatments should be a key component of GDM care, with an emphasis on education and support to assist women in making educated dietary decisions. Future study should look at the best nutritional options for preventing and controlling GDM to improve maternal and child health outcomes. Future study should concentrate on longitudinal studies to determine the long-term impact of different dietary fat profiles on mother and fetal health. Additionally, studying the molecular processes underlying the association between dietary lipids and insulin resistance can help us understand and design tailored nutritional therapies for women who are at risk of gestational diabetes.

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