International Journal of Medical Toxicology & Legal Medicine Volume 27, No. 1s, 2024
e-ISSN: 0974-4614
p-ISSN: 0972-0448

Tailoring Nutrition to Combat Treatment Failure in Type 2 Diabetes with Genetic Variants

Sarvesh Sabarathinam[1], Akshay J Kumar[2], Vinitha Packirisamy[1], Lakshmi Thangavelu[1*]

[1]Center for Global Health Research, Saveetha Medical College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai 602105, Tamil Nadu, India.
[2]Department of Orthopaedics, Saveetha Medical College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai 602105, Tamil Nadu, India.
Email: lakshmi@saveetha.com
*Corresponding author

Received: 18.05.2024 Revised: 20.06.2024 Accepted: 26.07.2024

ABSTRACT
Pharmacogenomics emphasizes the correlation between the genetic code and variations in therapeutic drug outcome or drug toxicity, or side effects. Nutrigenomics helps the identification of suitable food-based and diet-based approaches along with Equipping individuals with T2DM with knowledge about the impact of genetic polymorphisms on treatment response and the potential for personalized dietary interventions to empower them to make informed decisions about their health. An in-depth literature review was permed relevant to the treatment failure and its correlation with genetic polymorphism and its impact on genetic changes. Followed by clinical evidence of nutrient gene interaction and treatment responses were enclosed in this study. Successful implementation of nutrigenomics into clinical practice necessitates collaboration among healthcare professionals, researchers, and policymakers, enabling the integration of genetic testing, dietary assessment, and personalized nutritional interventions into routine T2DM management.Nutrigenomics, a field focusing on the interaction between genes and nutrients, holds significant potential for advancing research in individuals with T2DM who experience treatment failure due to genetic polymorphisms affecting drug transporters and targets.

Keywords: Diabetes, Genetic polymorphism, Nutrigenomics, Nutrition, Pharmacogenomics.

INTRODUCTION

Type 2 diabetes mellitus is the most common endocrine disease globally. The International Diabetes Federation (IDF) estimates that 463 million adults (20-79 years old) globally have diabetes in 2019.The majority of these cases roughly 90–95% of all diabetes cases involve type 2 diabetes. Due to a number of variables, including ageing populations, sedentary lifestyles, and bad eating habits, the prevalence is anticipated to increase in the upcoming years.(1)In India, the prevalence of diabetes, especially type 2 diabetes, has significantly increased during the past few decades. India had an estimated 77 million adults (20-79 years old) suffering with diabetes, according to the IDF's Diabetes Atlas 2019. By 2030, this figure is anticipated to reach 101.2 million.(2)Earlier diagnosis and more strict management strategies to prevent cardiovascular disease risk has become crucial in TDM patients in order to decrease the rate of mortality and co-morbidities. The ultimate goal is to have a decent glycaemic control which implies increasing the lifespan of T2DM patients also prolong the time for the patient to develop macrovascular and microvascular complications.(3)Therefore the primary concern for the healthcare team was to decrease the cumulative glycaemic burden of the T2DM patients in the past decade which may not be considered as the best act since the patients since there were increased treatment failure due to idiopathic causes, and inadequate availability of predictors of failure, and methods to identify the exact cause of treatment failure in T2DM. (4) This narrative review aims to explore the role of pharmacogenomics and nutrigenomics in addressing treatment failure in T2DM by investigating genetic polymorphisms' impact on drug response and the potential for personalized dietary interventions. Through an in-depth literature review, we examine the correlation between genetic variations and therapeutic outcomes, nutrient-gene interactions, and their influence on treatment responses. We evaluate nutrigenomics' potential in developing personalized dietary strategies for T2DM patients with genetic predispositions affecting drug efficacy, aiming to empower individuals to make informed health decisions. The review underscores the need for collaboration among healthcare professionals, researchers, and policymakers to integrate genetic testing and personalized nutrition into routine T2DM management, ultimately enhancing treatment outcomes through tailored healthcare strategies.

1. Treatment failure and genetic polymorphism in T2DM

One of many elements influencing treatment failure Less is known about genetic variation in therapeutic targets and drug transporters since it has a complex and multifaceted association with T2DM treatment response, which is influenced by lifestyle, comorbid disorders, and medication adherence.(5)By influencing gene expression, which in turn significantly affects managing the metabolic pathways implicated in the aetiology of T2DM, nutrition has a key role in impacting the health of diabetes patients from a lifestyle perspective. For instance, processed foods such as refined grains, meats, sweets, and desserts sweetened artificially are associated to a higher risk of inflammatory reactions and the expression of genes that promote cancer. In those who take in more high-saturated fatty acids, the gene expression of glucose intolerance has been mostly observed. This is also typical for the gene expressions of inflammation, increased neuropeptide expression, and liver lipid accumulation. Obesity develops as a result of the aforementioned gene expression. On the other hand lack of protein in the diet leads to glucose intolerance and inflammatory responses. (6)

This shows that genes control how much food an individual consumes and how those nutrients are metabolised, while food also influences how many genes are expressed, either favourably or negatively. This suggests that a viable focus for long-term lifestyle management that may result in an improved treatment response and health-related quality of life (HR-QOL) is testing for genetic variation in obesity and T2DM-related genes. Nutrigenomics is the study of how diet affects how genes are expressed and how the genome functions. It is also possible to assess how nutrients affect different genes based on food intake.In order to improve disease prevention and management strategies, nutrigenomics is used to identify personalised dietary recommendations based on individual genetic profiles. To do this, we must also analyse and comprehend the complexities of gene-nutrient interactions in T2DM and their implications for individualised nutritional intervention.(7)

2. Gene- Nutrient interaction: therapeutic failure in T2DM

Gene-nutrient interactions may contribute to the failure of treatment in type 2 diabetes mellitus. Treatment failure occurs when the disease progresses despite treatment attempts or when sufficient glycaemic control cannot be achieved. An outline of how gene-nutrient interactions may be responsible for type 2 diabetes treatment failure is given below:

- **Genetic variants**

Genetic and molecular processes interact intricately to cause genetic variations to appear in T2DM. A susceptibility to get the condition may be inherited. A combination of genetic variations that affect genetic susceptibility will raise the likelihood of developing T2DM. There are 65 loci associated with T2DM, according to numerous cutting-edge analytical techniques and collaborative case-control genome-wide association studies of gene susceptibility. Among the individual risk factors the influence of age where the genotypes can help predict the gene susceptibly and the risk of developing T2DM in young population, referred to as T2DM genotypes. (8)Genetic risk scores are used to predict genetic risk variants where the scales are designed in such a way the effect alleles or risk alleles of an individual carriers are used. (9)

- **Nutrient intake**

Consumption of nutrients is a critical and dual-edged factor in the development and treatment of diabetes. Investigations revealed that diabetics' epigenetic patterns are altered by a hypercaloric diet rich in fatty acids and glucose. (10)

- **Treatment response**

An individual’s type of carbohydrate diet intake is associated with the gene variant Transcription factor 7 like 2(TCF7L2)which increases the risk of patient to develop T2DM and glucose intolerance with abnormal lipid metabolism henceforth increases the risk of cardiovascular diseases. (11)Likewise vitamin D deficiency due to vitamin D receptor gene (VDR) variation can influence an individuals response to Vitamin D supplementation and also decreases the sensitivity to insulin. (12)In some cases genetic variations in FADS1 and FADS2 interferes with the conversion of Omega-3 fatty Acid into their active forms which are responsible for modulation of inflammation which is a major factor for development and progression of T2DM. (13)Genetic variations in Methylenetetrahydrofolate Reductase (MTHFR) alters the metabolism of vitamin B and homocysteine. Deficiency of vitamin B decreases the metabolism of homocysteine which is an amino acid associated with increased risk of CVD.(14)Based on the examples given above, genetic variants can impact how nutrients are absorbed, metabolized, and used by the body. These changes may affect the therapeutic value and accessibility of particular nutrients. Drug and therapeutic agent metabolism can be affected by genetic differences where there is deficiency or imbalance of nutrients. This may affect drug efficacy, clearance rates, and potential side effects.

- **Nutrient metabolism**

In people with type 2 diabetes, gene variations can affect how nutrients are metabolised and used. For instance, differences in genes related to dietary fat or carbohydrate metabolism may have an impact on how the body digests and uses these nutrients, which may have an impact on glycaemic control.(15)

- **Insulin gene signaling**

Regulation of metabolism by involving the concentration of proteins or by induction of post- translational modification of pre-existing molecules is handled by insulin. Insulin production, secretion, and action are regulated by intricate molecular processes known as insulin gene signalling. The pancreas produces insulin, which is essential for controlling the metabolism of glucose.(16)Insulin regulates glucose metabolism and is produced in pancreatic beta cells. It undergoes transcription of the insulin gene to form preproinsulin, which is then processed into proinsulin.(17)Increased blood glucose levels trigger insulin secretion through ATP production, KATP channel closure, depolarization, and calcium influx. Insulin binds to receptors on target cells, initiating a signaling cascade that promotes glucose uptake, glycogen and fatty acid synthesis, protein synthesis, cell growth, and metabolic processes. Disruption of insulin gene signaling can contribute to T2DM.(18)The intake of nutrition might influence the epigenetic modifications, in other words it can cause changes in gene expression without altering the underlying DNA sequence. (19)

- **Inflammation and oxidative stress**

In T2DM patients chronic low grade inflammation is observed which contributes to insulin resistance, a key characteristic of the disease where elevated levels of pro-inflammatory mediators like chemokines, cytokines, and adipocytokines: CRP, IL-6, TNF-α, MCP-1, TIMP-1, RBP-4, leptin and lower level of adiponectin caused due to various factors like obesity, a sedentary lifestyle, poor or unhealthy diet. (20)Reactive oxygen species (ROS) production and the availability of antioxidants to neutralise them are out of balance, which causes oxidative stress as a result of the chronic low-grade inflammation. Additionally, hyperglycemia in T2DM intensifies oxidative stress, which causes cellular damage. Damage to essential biomolecules like as DNA, proteins, and lipids results in the anti-oxidant defence mechanism failing.(21)For example, the balance between oxidants and anti-oxidants is based on the cells ability to synthesize glutathione. When a patient is diabetic the endogenous deficiency of glutathione contributes to oxidative stress due to polymorphism of Glutathione- Metabolizing Gene.(22)These situations can lead to impaired insulin signalling pathways, and worsening of insulin resistance. Also the inflammation and oxidative stress affects the beta cells of the pancreas and promotes the development of various complications and co-morbidities associated with T2DM. Because of this, managing blood sugar levels with common treatments like oral medicines or insulin therapy becomes tougher.(23)

3. Treatment failure

Epigenetic modifications and nutrition are interconnected factors that influence the development and treatment of T2DM, including the possibility of treatment failure. Epigenetic modifications, such as DNA methylation and histone modifications, can affect gene expression patterns relevant to T2DM.(24)Altered epigenetic patterns can contribute to insulin resistance and impaired glucose metabolism, key features of T2DM. (25)Additionally, epigenetic changes influenced by nutrition can impact the response to T2DM treatment, including the effectiveness of medications and lifestyle interventions.(26)

4. Gene related to T2DM and its treatment

- **Sulfonylureas**

Sulfonylureas (SU) belong to a class of drugs known as Oral Hypoglycaemic Agents (OHAs), which stimulate the release of insulin from beta cells in the pancreas by binding to and blocking potassium (KATP) channels that are ATP-sensitive on the surface of the cell.(27)ABCC8 gene encodes the sulfonylurea receptor 1 (SUR1) protein which is a regulatory subunit of the KATP channels in the pancreatic beta cells, when SU binds to the SUR1 along with the Kir 6.2, it inhibits the KATP channels resulting in depolarization of the beta cell membrane, calcium efflux, and subsequent insulin secretion. Mutation in KCNJ11 or ABCC8 genes might decrease or abolish the metabolic sensitivity of peta cell KATP channel function leading to hyperinsulinemia. (28)The intended mechanism of action of SU is disrupted due to change in protein structure which can affect the binding of SU to SUR1, this is also referred to as “Loss of Function” resulting in diminished insulin secretory responses and poor glycaemic control. (29)The TCF7L2 gene codes for the transcription factor 7-like 2 protein, which controls gene expression and the insulin signalling pathway. Any specific SNP or mutation in this gene may reduce the response to SU, which is linked to beta-cell malfunction and reduced insulin production.(30)

- **Thiazolidinedione**

Thiazolidinediones (TZDS) are one among the OHAs that are insulin sensitizing drugs and they are the potent peroxisome activated receptor (PPAR)- γ agonists and their major site of target is adipose tissue where it prevents the production of fat in the liver, skeletal muscle and pancreatic beta cells and directing the storage in adipose tissues; stimulation of adipogenesis. (31)Patients who had the Pro12Ala genotype in the PPAR2 gene responded to rosiglitazone more favourably than those who had the Pro12Pro genotype. Patients with T2DM mellitus may respond differently to rosiglitazone medication depending on genetic differences in the PPAR2 gene.(32)There are two polymorphisms observed in peroxisome proliferator- activated receptor -γ coactivator-1α (PGC-1α) and they are Thr394Thr and Gly482Ser on the response to the diabetes medication TZDS in patients with T2DM where the patients with A allele of the Thr394THr polymorphism had less

enhancement in HDL-c and no positive correlation with glycaemic profile TZDS treatment when weighed against patients who are carrying G alleles.(33)

- **Biguanides**

Drugs in the biguanide class, including metformin, function by lowering liver glucose production and raising peripheral tissues' sensitivity to insulin. (34)The amount of glucose released into the bloodstream is decreased by biguanides by suppressing gluconeogenesis, the process by which the liver produces glucose.Likewise they increase insulin sensitivity and encourage glucose uptake by cells by activating an enzyme known as AMP-activated protein kinase (AMPK) in numerous tissues. (35)Additionally, these drugs may lessen the intestinal absorption of glucose. In conclusion, biguanides lower blood sugar levels by reducing the amount of glucose produced by the liver, increasing insulin sensitivity, promoting the uptake of glucose by tissues, and affecting the release of gut hormones and the absorption of glucose from the intestine.(36)

Organic Cation Transporter-1 (OCT-1) also known as SLC22A1 is responsible for the transportation of organic cations across cell membranes which is majorly expressed in the liver. OCT-1 helps in uptake and elimination of endogenous and exogenous substances.(37)The OCT-1 involves in the transport of metformin into hepatocytes and it is encoded by SLC22A1 gene. This process takes place in order to promote the uptake of metformin from the bloodstream into the liver, where it exerts it glucose lowering effects. Genetic variation (rs622342, rs628031, rs683369, rs12208357, rs8192675) in the OCT-1 on metformin's mechanism of action was studied in the year 2007, which suggests deletion of OCT-1 led to decrease in the effect of metformin on AMPK phosphorylation and gluconeogenesis.(38, 39)

OCT2 is another transporter encoded by SLC22A2 gene expressed in the kidney which plays a prominent role in the renal secretion of metformin and involves in the uptake of metformin from the blood stream into the tubular cells and promote urinary excretion. rs316019 is the SNP is negatively associated with abnormal renal clearance of metformin especially in individuals who carry G allele tends to decrease the renal clearance and potentially leading to higher systemic exposure and risk of ADR or toxicity.(40)Similar results were found when the researches were conducted to study the effect of SNP in SLC22A2/ OCT2.(41, 42)Metformin is expelled from the cells through the multidrug and toxin extrusion (MATE) 1 or SLC47A1 enzyme, which is expressed in the luminal membranes of the renal proximal tubules and bile canalicular membranes of hepatocytes.(43)Results of metformin treatment have been investigated in relation to rs2289669. Metformin renal excretion may be affected by the minor allele (G) of rs2289669, which has been linked to lower MATE1 expression and function. This could lead to higher metformin plasma concentrations and a greater risk of metformin induced lactic acidosis.(44)

- **Meglitinides**

Meglitinides are secretagogues, like SU, but they have different structural characteristics. They bind to the pancreatic beta cell receptors, engage in the control of KATP channels, and boost insulin secretion. OATP1B1 encoded by SLCO1B1 transports meglitinides into the liver, where they are then processed by isoenzymes of the CYP family. (45)SLCO1B1 gene variants especially SLCO1B1*5 may affect the function of OAT1B1 protein which in turn decreases the uptake of repaglinide resulting in lower drug concentration in the liver and results in decreases therapeutic response. (46, 47)

5. DISCUSSION

- **Current status of pharmacogenetics**

The term "pharmacogenomics" has evolved to highlight this broader approach in drug discovery, development, and personalized therapy respective to one drug fits "to " right drug for the right patient at the right dose and time" based on the existing use of genomics and other -omics technologies. However, this does not imply that every patient will receive individualized care. Still, patients will be identified based on specific groups created based on genetic and other markers that forecast illness development and response to treatment.(48)Pharmacogenetics is the variation in drug reactions brought on by hereditary and environmental traits in people. (49)Pharmacogenomics emphasizes the correlation between the genetic code and variations in drug therapeutic outcome or drug toxicity or side effects. An early knowledge of this gene-drug pairing for a wide range of NCD treating essential medicines will helps in clinician to select drugs with the best efficacy, appropriate dose and lowest likelihood of serious side effects. Studies in humans, animals, and cell cultures have shown that various micronutrients, macronutrients and bioactive chemicals govern gene expression in distinct ways. (50)

Currently, clinical pharmacogenomics is still in its infancy. The inborn pharmacogenetic errors of metabolism are interlinked with the concept of nutrigenomics, Which includes interactions between food and inherited genes, called 'inborn errors of metabolism' The metabolism errors are treated by manipulating the diet. One such example is lactose intolerance; most adults in the world are lactose intolerant, meaning that they cannot digest milk products because the gene encoding lactase, the enzyme that breaks down lactose, usually 'turned off after weaning. This single nucleotide polymorphism—an SNP—resulted in the continued expression of the lactase gene into adulthood. (50)

- **Interplay between pharmacogenetics and nutrigenomics - Implications for targets and transporters of T2DM treatment**

A new era in both medicine and nutrition has been sparked by the accomplishments of the Human Genome Project and the amazing advancement of wide genomics techniques. As we all know, pharmacogenetics and nutrigenomics are expanding in the field of healthcare. They have the potential to act as an excellent tool in battling chronic diseases like T2DM, Cancer, and many other metabolic disorders as well as to prevent early onset of these conditions by reducing the occurrence of risk factors with advancements in large-scale genomics technologies.Pervious studies suggest that excessive and concurrent intake of refined carbohydrate is strongly associated with KCNJ11 gene polymorphism and also this results in increased risk of worsening of insulin resistance and obesity in the Indonesian population.(51, 52)While another study investigated the correlation between dietary intake, physical activity and genetic variation in TCF7L2 and KCNJ11 and their effect on Glucagon like peptide (GLP) 1 which is responsible for insulin secretion. The results suggest that improper diet with high carbohydrate and high fat consumption influences the body weight and also insulin signaling/GLP-1 in subjects with EK genotypes of KCNJ11 gene and also points out importance of functional foods.(53)

High fat diet consumption increases the risk of T2DM and also worsens the existing condition in individuals with TCF7L2 for rs12255372 TT risk genotype .(54)In Finnish people with IGT, the GGAA haplotype of the SUR1 gene predicts the development of type 2 diabetes. Furthermore, we showed that the SUR1 and Kir6.2 gene polymorphisms add to the risk of type 2 diabetes and unhealthy eating habits.(55)Genetic variations or specific SNPs can reduce the efficacy or may result in therapy failure in patients who consume a high-fat or refined carbohydrate diet, as the KCNJ11, TCF762, SUR1 gene plays a vital role in the effectiveness of SU treatment in T2DM patients.Researchers looked at the relationship between a particular gene variation called "Pro12AIa" in the PPAR- gene and its effects on insulin resistance, obesity, and weight loss. The Pro12Ala gene variant and insulin levels and insulin resistance were shown to be significantly correlated by the researchers. Insulin levels were lower in people with the Ala12 gene variant than in people with the Pro12Pro variant. In terms of body mass index (BMI) and body fat, they also found a connection between the Pro12Ala gene variant and consumption of monounsaturated fatty acids (MUFA). People with the Ala12 gene mutation lost less weight when they ingested a lot of fat than people with the more frequent variant and showed signs of insulin resistance.(56)Other previous studies showed similar results.(57, 58)PGC-1alpha, which plays a crucial role in how our bodies use energy in various tissues, including skeletal muscle. PGC-1alpha controls a metabolic program that influences how we burn fat for energy and how sensitive we are to insulin, a hormone that regulates blood sugar levels. Interestingly, this metabolic program is also activated by exercise and suppressed by a sedentary lifestyle and high-fat diets. (59)This demonstrates that nutrients-gene interaction reduces the effectiveness of TZDs in specific individuals.(60)

A high-calorie diet, especially one rich in fat and containing high-fructose corn syrup, can affect the expression of certain drug transport proteins in the liver and kidney of rats. Specifically, the levels of MATE1, OCT1, and OCT2 were examined. In the liver, the levels of certain enzymes involved in drug metabolism were decreased in the high-fat diet and high-fructose corn syrup/fat diet groups compared to the control group. The protein levels of OCT1 and MATE1, which are responsible for transporting metformin, were also significantly reduced. In the kidney, the protein levels of OCT1 and OCT2 were downregulated in the high-fat diet and high-fructose corn syrup/fat diet groups. These findings suggest that a high-calorie diet, particularly one high in fat and containing high-fructose corn syrup, can influence the expression of drug transport proteins such as MATE1, OCT1, and OCT2.This may have implications for metformin treatment failure, as reduced levels of these transport proteins can affect the uptake and elimination of metformin, potentially leading to decreased drug efficacy.

Based on the aforementioned discussion, it can be inferred that a diet rich in high-fat content or high-refined carbohydrates significantly contributes to the interaction between nutrients and genes, leading to treatment failure in individuals with type 2 diabetes mellitus (T2DM) who are undergoing oral hypoglycaemic agent (OHA) therapy. Consequently, it is imperative to explore and examine dietary approaches that can mitigate the adverse effects of this nutrient-gene interaction and improve treatment efficacy in T2DM. In the following sections, we will delve into the scientific investigation of optimal dietary strategies to minimize the impact of nutrient-gene interactions and enhance the therapeutic outcomes in individuals with T2DM receiving OHAs.

6. Dietary approaches in T2DM

- **American Diabetes Association diet**

American diabetes association laid the guidelines for diet to manage T2DM. the diet is strategically planned and focuses mainly on preventing T2DM progression, reducing the risk of cardiovascular complications and maintaining the weight and BMI of diabetic and pre diabetic patients. The diet lowers lipid levels, blood glucose and blood pressure. The diet is mainly focused on balancing nutrients and is based on the fact that every nutrient plays its own pivotal role in the management of T2DM and keeps the benefits sustained(61).

- **Low glycemic index diet**

Low glycemic index diet exerts versatile effects by lowering blood glucose levels, lipid levels, waist circumference, BMI and weight in diabetic and pre diabetic conditions. (62)Although the pattern helps in preventing cardiovascular complications, prevent progression of T2DM and maintain healthy weight and balanced blood pressure, it is highly dependent of the choice of food, pattern of cooking and type of starch and other nutrients present. This diet plan does not lay any limitation on the carbohydrates and can sometimes enhance the levels of blood glucose. Overall, it is a good option for the management of T2DM but caution should be taken to note the choice of food and pattern of cooking.(63)

- **Mediterranean diet**

Mediterranean diet has proven to be beneficial and better than low carbohydrate diet and low-fat diet. The diet is directly involved in diabetes homeostasis by which it exhibits vital actions like antioxidant effect, anti-inflammatory effect and also largely enhances gut health. Compared to other diet patterns, this approach has been significantly seen to reduce HbA1C levels. This diet aids in T2DM by maintaining oxidation balance thereby resolving insulin resistance to an extent.it also in involved in extrinsic and intrinsic pathways which help in lowering blood glucose levels. (64)

- **Low carbohydrate high fat diet (LCHF)**

LCHF diet has shown great potential in weight loss and overall glycemic control. It significantly reduces HbA1C levels and also ensures reducing medication load. The diet also lowers LDL, triglycerides and total cholesterol thereby ensuring cardioprotective effects. It also improves HDL, reducing cardiac complications and other associated metabolic disorders. The diet is considered feasible and is highly recommended as it offers multiple benefits.(65)

- **Low carbohydrate diet**

Low carbohydrate diet is characterized by limited carbohydrate intake paired with high intake of protein and unsaturated fats to balance the energy requirements of the body. The diet plan aids in weight loss and helps to maintain waist circumference and healthy BMI. With implementing this dietary approach, we observe a decline in the overall blood glucose levels specially HbA1C levels. Although, this diet is helpful in short term metabolic conditions, proper alterations are required when choosing for a long run. (66)This diet limits fibre intake which can severely create an impact on gut health and overall strength. Long term adherence to this diet can cause nutritional imbalance which can ultimately result in enhanced insulin resistance paving way for T2DM. (67)Certain diabetology centres do not approve of this diet in concern to its safety. (68)

- **High cereal fibre diet**

This diet focuses on high consumption of insoluble cereal fibres that do not increase the blood glucose levels and strictly avoids soluble dietary fibres which can greatly influence blood glucose levels.(68)The diet plan also limits carbohydrates, fats and proteins to a certain extent. A reduction in the fasting blood glucose levels and HbA1C levels is observed as the result. However, the impact of this diet is largely dependent on the type of fibres consumed rather than the whole diet. Also, selection of other fibres can result in increasing the risk of T2DM.(69)A high cereal diet also helps to maintain the blood pressure levels in an individual, maintain healthy weight and waist circumference and also largely helps to lower Lipid levels in the body.(69)

- **Paleolithic diet**

Paleolithic diet is also referred to as the old stone age diet as it dates back to million years. This dietary approach is considered to be effective in the management of T2DM and cardiovascular complications and has also shown positive effects on insulin resistance.(70),(71) The diet lowered the levels of cholesterol and blood glucose and also ensured weight loss, BMI balance etc. While the diet provided sufficient benefits few requirements like the calcium levels were not matched. The diet did not meet the calcium and other nutrient requirements which can affect bone health and other issues on a long run(70).

- **Ketogenic diet**

A ketogenic diet in general is established as a rapid weight loss technique which is primarily used in pediatric epilepsy and is now being studied for its effect in T2DM and cardiovascular diseases. This diet works on the principle of ketogenesis and gluconeogenesis. (72, 73)It has been reported that patients who are on OHA therapy are not appropriate to follow this diet as it will further reduced the glycemic status of the body that can potentially result in hypoglycemia. This diet plan limit the intake of carbohydrates and proteins and focuses on the consumption of fats combined with physical training. Although, this approach is being studied in various disease conditions like brain injury, cancers and other metabolic disorders, this can cause potential harm to the patients by inducing dyselectrolytemia, dehydration and hypoglycemia.(74-76)The outcomes of different diet plans advised for T2DM are listed in the table 1.

7. Role of clinical pharmacist

In people with T2DM who experience treatment failure due to genetic polymorphism, clinical pharmacist play a critical role in encouraging dietary adherence and enhancing treatment response. They can give individualised counselling, create custom meal plans, and inform patients about the importance of dietary changes. Clinical pharmacists can help patients overcome obstacles and form lifelong eating habits by using motivational

interviewing and behaviour modification approaches. On collaboration with healthcare experts, a clinical pharmacist can ensures that patient care is provided in a multidisciplinary manner. Regular monitoring and follow-up enable continuing support and progress evaluation can be performed by a clinical pharmacist. Clinical pharmacist can actively engage T2DM patients with these interventions, empowering them to make knowledgeable dietary decisions that eventually improve treatment responsiveness and overall health outcomes.

8. CONCLUSION

Nutrigenomics, a field focusing on the interaction between genes and nutrients, holds significant potential for advancing research in individuals with T2DM who experience treatment failure due to genetic polymorphisms affecting drug transporters and targets. This underscores the critical need to raise awareness about this emerging area. By elucidating the complex interplay between genes and dietary components, nutrigenomics enables the development of personalized dietary interventions, known as "precision nutrition," to optimize treatment outcomes. Furthermore, the exploration of biomarkers and the integration of genetic and dietary factors into predictive models can facilitate individualized therapy selection and proactive interventions. Nutrigenomics research opens doors to novel therapeutic strategies, such as tailored dietary interventions and repurposing existing drugs, to modulate gene expression and enhance treatment response in T2DM. Equipping individuals with T2DM with knowledge about the impact of genetic polymorphisms on treatment response and the potential for personalized dietary interventions empower them to make informed decisions about their health. Successful implementation of nutrigenomics into clinical practice necessitates collaboration among healthcare professionals, researchers, and policymakers, enabling the integration of genetic testing, dietary assessment, and personalized nutritional interventions into routine T2DM management.

Table 1. Outcomes of different dietary approaches on T2DM

Diet plan	Nutritional composition	Sources	Impact	Reference
American Diabetes Association diet	Carbohydrates, Fat, protein, fibre, calcium, vitamins	Non-starchy vegetables, eggs, nuts, grains, milk	Body weight balance. Lower high glycemic levels, blood pressure and lipid levels. Prevent complications associated with T2DM	77)
Low glycemic index diet	carbohydrates, fat, protein, calcium, magnesium, vitamins and minerals	Whole grains, cereals, milk, legumes, fish, nuts, olive oil	Lower post prandial blood glucose levels, HbA1C, FBS, cholesterol, LDL, BMI	62)
Mediterranean diet	Unsaturated fatty acids, limited carbohydrates, protein	Sea food, herbs, whole grains, legumes, fruits, spices, olive oil, seeds	Lower cholesterol, maintain blood glucose levels	78)
Modified Mediterranean diet	Protein, fibre, carbohydrates	Fresh fruits, vegetables, whole grains. Limit salt <2g/day. Avoid meat, dairy and dairy related products.	Lower overall blood glucose and maintains healthy weight	79)
Low carbohydrate high fat diet (LCHF)	Fats (60%-75% of the total calorie intake), protein, carbohydrates (very low), low fibre	Meat, eggs, fish, low carb nuts, olive oil, coconut oil	Reduce HbA1C levels, enhanced weight loss and led to reducing medication for hyperglycemia	80)
Low carbohydrate diet	Fat and very low carbohydrates	Limit cereals, fruits, vegetables	Low carbohydrate diet with high protein and fat consumption tends to lower the risk of T2DM in women	66)
High cereal fibre diet	Fibre, protein, unsaturated fat, minerals	Insoluble cereal fibres, Whole grains, cucumbers, nuts	Reduced risk of T2DM, increased insulin resistance.	81)
Paleolithic diet	Protein, fat, low carb, vitamins, fibre, sodium, iron, zinc	Lean meat, eggs, root vegetables, fish, nuts and fruits. Avoid, dairy, sugar, salt and refined fats	Lowers HbA1C, triacylglycerol, overall body weight, BMI and blood pressure. Increase HDL.	82)
Ketogenic diet	High fat, very low carb, moderate	Nuts and seeds, fish, fruits, unprocessed	Decline in HbA1C, reduced body weight.	(83)

	proteins.	grains. Avoid red meat, sodium and sugar.	But may cause electrolyte disturbances, hypoglycemia and dehydration	

Declarations

Ethics approval and consent to participate

Not applicable

Content for publication

Not applicable

Availability of data and material

All data and material are available upon request

Competing interests

The author declares no conflict of interest in the contents of the manuscript

Funding

No funding received

REFERENCE

1. Galaviz KI, Narayan KMV, Lobelo F, Weber MB. Lifestyle and the Prevention of Type 2 Diabetes: A Status Report. 2018;12(1):4-20.
2. Pradeepa R, Mohan V. Epidemiology of type 2 diabetes in India. Indian journal of ophthalmology. 2021;69(11):2932-8.
3. Brown JB, Nichols GA, Perry A. The Burden of Treatment Failure in Type 2 Diabetes. Diabetes Care. 2004;27(7):1535-40.
4. Rosengren A, Jing X, Eliasson L, Renström E. Why Treatment Fails in Type 2 Diabetes. PLOS Medicine. 2008;5(10):e215.
5. Avery P, Mousa SS, Mousa SA. Pharmacogenomics in type II diabetes mellitus management: Steps toward personalized medicine. Pharmacogenomics and personalized medicine. 2009;2:79-91.
6. Kiani AK, Bonetti G, Donato K, Kaftalli J, Herbst KL, Stuppia L, et al. Polymorphisms, diet and nutrigenomics. Journal of preventive medicine and hygiene. 2022;63(2 Suppl 3):E125-e41.
7. Fenech M, El-Sohemy A, Cahill L, Ferguson LR, French TA, Tai ES, et al. Nutrigenetics and nutrigenomics: viewpoints on the current status and applications in nutrition research and practice. Journal of nutrigenetics and nutrigenomics. 2011;4(2):69-89.
8. Hivert MF, Vassy JL, Meigs JB. Susceptibility to type 2 diabetes mellitus--from genes to prevention. Nature reviews Endocrinology. 2014;10(4):198-205.
9. Igo RP, Jr., Kinzy TG, Cooke Bailey JN. Genetic Risk Scores. Current protocols in human genetics. 2019;104(1):e95.
10. Davegårdh C, García-Calzón S, Bacos K, Ling C. DNA methylation in the pathogenesis of type 2 diabetes in humans. Molecular Metabolism. 2018;14:12-25.
11. Cornelis MC, Qi L, Kraft P, Hu FB. TCF7L2, dietary carbohydrate, and risk of type 2 diabetes in US women. The American journal of clinical nutrition. 2009;89(4):1256-62.
12. Usategui-Martín R, De Luis-Román DA, Fernández-Gómez JM, Ruiz-Mambrilla M, Pérez-Castrillón JL. Vitamin D Receptor (VDR) Gene Polymorphisms Modify the Response to Vitamin D Supplementation: A Systematic Review and Meta-Analysis. Nutrients. 2022;14(2).
13. Mansouri V, Javanmard SH, Mahdavi M, Tajedini MH. Association of Polymorphism in Fatty Acid Desaturase Gene with the Risk of Type 2 Diabetes in Iranian Population. Advanced biomedical research. 2018;7:98.
14. Moll S, Varga EA. Homocysteine and MTHFR Mutations. 2015;132(1):e6-e9.
15. Hoyas I, Leon-Sanz M. Nutritional Challenges in Metabolic Syndrome. 2019;8(9):1301.
16. Hancock ML, Meyer RC, Mistry M, Khetani RS, Wagschal A, Shin T, et al. Insulin Receptor Associates with Promoters Genome-wide and Regulates Gene Expression. Cell. 2019;177(3):722-36.e22.
17. Bhargava R, Mitsides N, Saif I, MacDowall P, Woywodt A. C-peptide and combined kidney-pancreas transplantation. NDT Plus. 2009;2(6):489-92.
18. Saini V. Molecular mechanisms of insulin resistance in type 2 diabetes mellitus. World journal of diabetes. 2010;1(3):68-75.
19. Tiffon C. The Impact of Nutrition and Environmental Epigenetics on Human Health and Disease. 2018;19(11):3425.

20. Rehman K, Akash MSH. Mechanisms of inflammatory responses and development of insulin resistance: how are they interlinked? Journal of Biomedical Science. 2016;23(1):87.
21. Albano E. Alcohol, oxidative stress and free radical damage. Proceedings of the Nutrition Society. 2006;65(3):278-90.
22. Azarova I, Klyosova E, Polonikov A. The Link between Type 2 Diabetes Mellitus and the Polymorphisms of Glutathione-Metabolizing Genes Suggests a New Hypothesis Explaining Disease Initiation and Progression. Life (Basel, Switzerland). 2021;11(9).
23. Wronka M, Krzemińska J, Młynarska E, Rysz J, Franczyk B. The Influence of Lifestyle and Treatment on Oxidative Stress and Inflammation in Diabetes. 2022;23(24):15743.
24. Ahmed SAH, Ansari SA, Mensah-Brown EPK, Emerald BS. The role of DNA methylation in the pathogenesis of type 2 diabetes mellitus. Clinical Epigenetics. 2020;12(1):104.
25. Bansal A, Pinney SE. DNA methylation and its role in the pathogenesis of diabetes. Pediatric diabetes. 2017;18(3):167-77.
26. Parrillo L, Spinelli R, Nicolò A, Longo M, Mirra P, Raciti GA, et al. Nutritional Factors, DNA Methylation, and Risk of Type 2 Diabetes and Obesity: Perspectives and Challenges. 2019;20(12):2983.
27. Sola D, Rossi L, Schianca GP, Maffioli P, Bigliocca M, Mella R, et al. Sulfonylureas and their use in clinical practice. Archives of medical science : AMS. 2015;11(4):840-8.
28. Song J, Yang Y, Mauvais-Jarvis F, Wang Y-P, Niu T. KCNJ11, ABCC8 and TCF7L2 polymorphisms and the response to sulfonylurea treatment in patients with type 2 diabetes: a bioinformatics assessment. BMC Medical Genetics. 2017;18(1):64.
29. Walczewska-Szewc K, Nowak W. Structural Determinants of Insulin Release: Disordered N-Terminal Tail of Kir6.2 Affects Potassium Channel Dynamics through Interactions with Sulfonylurea Binding Region in a SUR1 Partner. The Journal of Physical Chemistry B. 2020;124(29):6198-211.
30. Holstein A, Hahn M, Körner A, Stumvoll M, Kovacs P. TCF7L2 and therapeutic response to sulfonylureas in patients with type 2 diabetes. BMC Medical Genetics. 2011;12(1):30.
31. Hondares E, Mora O, Yubero P, de la Concepción MR, Iglesias R, Giralt M, et al. Thiazolidinediones and Rexinoids Induce Peroxisome Proliferator-Activated Receptor-Coactivator (PGC)-1α Gene Transcription: An Autoregulatory Loop Controls PGC-1α Expression in Adipocytes via Peroxisome Proliferator-Activated Receptor-γ Coactivation. Endocrinology. 2006;147(6):2829-38.
32. Kang ES, Park SY, Kim HJ, Kim CS, Ahn CW, Cha BS, et al. Effects of Pro12Ala polymorphism of peroxisome proliferator-activated receptor γ2 gene on rosiglitazone response in type 2 diabetes. 2005;78(2):202-8.
33. Zhang K-H, Huang Q, Dai X-P, Yin J-Y, Zhang W, Zhou G, et al. Effects of the Peroxisome Proliferator Activated Receptor-γ Coactivator-1α (PGC-1α) Thr394Thr and Gly482Ser Polymorphisms on Rosiglitazone Response in Chinese Patients With Type 2 Diabetes Mellitus. 2010;50(9):1022-30.
34. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia. 2017;60(9):1577-85.
35. Bertrand L, Ginion A, Beauloye C, Hebert AD, Guigas B, Hue L, et al. AMPK activation restores the stimulation of glucose uptake in an in vitro model of insulin-resistant cardiomyocytes via the activation of protein kinase B. American journal of physiology Heart and circulatory physiology. 2006;291(1):H239-50.
36. Pernicova I, Korbonits M. Metformin—mode of action and clinical implications for diabetes and cancer. Nature Reviews Endocrinology. 2014;10(3):143-56.
37. Lozano E, Herraez E, Briz O, Robledo VS, Hernandez-Iglesias J, Gonzalez-Hernandez A, et al. Role of the Plasma Membrane Transporter of Organic Cations OCT1 and Its Genetic Variants in Modern Liver Pharmacology. BioMed Research International. 2013;2013:692071.
38. Shu Y, Sheardown SA, Brown C, Owen RP, Zhang S, Castro RA, et al. Effect of genetic variation in the organic cation transporter 1 (OCT1) on metformin action. The Journal of Clinical Investigation. 2007;117(5):1422-31.
39. Shu Y, Brown C, Castro RA, Shi RJ, Lin ET, Owen RP, et al. Effect of Genetic Variation in the Organic Cation Transporter 1, OCT1, on Metformin Pharmacokinetics. Clinical Pharmacology & Therapeutics. 2008;83(2):273-80.
40. Chen Y, Li S, Brown C, Cheatham S, Castro RA, Leabman MK, et al. Effect of genetic variation in the organic cation transporter 2 on the renal elimination of metformin. Pharmacogenetics and Genomics. 2009;19(7).
41. Song I, Shin H, Shim E, Jung I, Kim W, Shon J, et al. Genetic Variants of the Organic Cation Transporter 2 Influence the Disposition of Metformin. 2008;84(5):559-62.
42. Wang Z-J, Yin OQP, Tomlinson B, Chow MSS. OCT2 polymorphisms and in-vivo renal functional consequence: studies with metformin and cimetidine. Pharmacogenetics and Genomics. 2008;18(7).

43. Becker ML, Visser LE, van Schaik RH, Hofman A, Uitterlinden AG, Stricker BH. Genetic variation in the multidrug and toxin extrusion 1 transporter protein influences the glucose-lowering effect of metformin in patients with diabetes: a preliminary study. Diabetes. 2009;58(3):745-9.
44. Toyama K, Yonezawa A, Masuda S, Osawa R, Hosokawa M, Fujimoto S, et al. Loss of multidrug and toxin extrusion 1 (MATE1) is associated with metformin-induced lactic acidosis. British journal of pharmacology. 2012;166(3):1183-91.
45. Yan F-F, Casey J, Shyng S-L. Sulfonylureas Correct Trafficking Defects of Disease-causing ATP-sensitive Potassium Channels by Binding to the Channel Complex*. Journal of Biological Chemistry. 2006;281(44):33403-13.
46. Kalliokoski A, Neuvonen M, Neuvonen PJ, Niemi M. Different Effects of SLCO1B1 Polymorphism on the Pharmacokinetics and Pharmacodynamics of Repaglinide and Nateglinide. 2008;48(3):311-21.
47. Kalliokoski A, Neuvonen M, Neuvonen PJ, Niemi M. The effect of SLCO1B1 polymorphism on repaglinide pharmacokinetics persists over a wide dose range. 2008;66(6):818-25.
48. Sadée W, Dai Z. Pharmacogenetics/genomics and personalized medicine. Human Molecular Genetics. 2005;14(suppl_2):R207-R14.
49. Daly AK. Pharmacogenetics: a general review on progress to date. British Medical Bulletin. 2017;124(1):65-79.
50. Mead MN. Nutrigenomics: The Genome–Food Interface. 2007;115(12):A582-A9.
51. Huriyati E, Luglio FH, Sadewa HA, Juffrie M. The Interaction between KCNJ11 Gene Polymorphism and Refined Carbohydrates Intake on Obesity in Indonesian Adolescents. Current Nutrition & Food Science. 2020;16(2):185-9.
52. Haghvirdizadeh P, Mohamed Z, Abdullah NA, Haghvirdizadeh P, Haerian MS, Haerian BS. KCNJ11: Genetic Polymorphisms and Risk of Diabetes Mellitus. Journal of diabetes research. 2015;2015:908152.
53. Luglio H, Huriyati E. The role of genetic variation in TCF7L2 and KCNJ11, dietary intake, and physical activity on fasting plasma glucagon-like peptide-1 in male adolescents. Paediatrica Indonesiana. 2018;57:239.
54. Mattei J, Qi Q, Hu FB, Sacks FM, Qi L. TCF7L2 genetic variants modulate the effect of dietary fat intake on changes in body composition during a weight-loss intervention. The American journal of clinical nutrition. 2012;96(5):1129-36.
55. Laukkanen O, Pihlajamäki J, Lindström J, Eriksson J, Valle TT, Hämäläinen H, et al. Polymorphisms of the SUR1 (ABCC8) and Kir6.2 (KCNJ11) Genes Predict the Conversion from Impaired Glucose Tolerance to Type 2 Diabetes. The Finnish Diabetes Prevention Study. The Journal of Clinical Endocrinology & Metabolism. 2004;89(12):6286-90.
56. Garaulet M, Smith CE, Hernández-González T, Lee Y-C, Ordovás JM. PPARγ Pro12Ala interacts with fat intake for obesity and weight loss in a behavioural treatment based on the Mediterranean diet. Molecular Nutrition & Food Research. 2011;55(12):1771-9.
57. Song Y, Li S, He C. PPARγ Gene Polymorphisms, Metabolic Disorders, and Coronary Artery Disease. 2022;9.
58. Memisoglu A, Hu FB, Hankinson SE, Manson JE, De Vivo I, Willett WC, et al. Interaction between a peroxisome proliferator-activated receptor gamma gene polymorphism and dietary fat intake in relation to body mass. Hum Mol Genet. 2003;12(22):2923-9.
59. Benton CR, Wright DC, Bonen A. PGC-1α-mediated regulation of gene expression and metabolism: implications for nutrition and exercise prescriptions. 2008;33(5):843-62.
60. P P, Justin A, Ananda Kumar TD, Chinaswamy M, Kumar BRP. Glitazones Activate PGC-1α Signaling via PPAR-γ: A Promising Strategy for Antiparkinsonism Therapeutics. ACS Chemical Neuroscience. 2021;12(13):2261-72.
61. Evert AB, Dennison M, Gardner CD, Garvey WT, Lau KHK, MacLeod J, et al. Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report. Diabetes Care. 2019;42(5):731-54.
62. Zafar MI, Mills KE, Zheng J, Regmi A, Hu SQ, Gou L, et al. Low-glycemic index diets as an intervention for diabetes: a systematic review and meta-analysis. The American journal of clinical nutrition. 2019;110(4):891-902.
63. Thomas D, Elliott EJ. Low glycaemic index, or low glycaemic load, diets for diabetes mellitus. The Cochrane database of systematic reviews. 2009;2009(1):Cd006296.
64. Martín-Peláez S, Fito M, Castaner O. Mediterranean Diet Effects on Type 2 Diabetes Prevention, Disease Progression, and Related Mechanisms. A Review. 2020;12(8):2236.
65. Ahmed SR, Bellamkonda S, Zilbermint M, Wang J, Kalyani RR. Effects of the low carbohydrate, high fat diet on glycemic control and body weight in patients with type 2 diabetes: experience from a community-based cohort. 2020;8(1):e000980.
66. Halton TL, Liu S, Manson JE, Hu FB. Low-carbohydrate-diet score and risk of type 2 diabetes in women. The American journal of clinical nutrition. 2008;87(2):339-46.

67. Barber TM, Hanson P, Kabisch S, Pfeiffer AFH, Weickert MO. The Low-Carbohydrate Diet: Short-Term Metabolic Efficacy Versus Longer-Term Limitations. Nutrients. 2021;13(4).
68. Krejčí H, Vyjídák J, Kohutiar M. Low-carbohydrate diet in diabetes mellitus treatment. Vnitrni lekarstvi. 2018;64(7-8):742-52.
69. McRae MP. Dietary Fiber Intake and Type 2 Diabetes Mellitus: An Umbrella Review of Meta-analyses. Journal of chiropractic medicine. 2018;17(1):44-53.
70. Lindeberg S, Cordain L, Eaton SB. Biological and Clinical Potential of a Palaeolithic Diet. Journal of Nutritional & Environmental Medicine. 2003;13(3):149-60.
71. Eaton SB, Konner M. Paleolithic nutrition. A consideration of its nature and current implications. The New England journal of medicine. 1985;312(5):283-9.
72. Jagadish S, Payne ET, Wong-Kisiel L, Nickels KC, Eckert S, Wirrell EC. The Ketogenic and Modified Atkins Diet Therapy for Children With Refractory Epilepsy of Genetic Etiology. Pediatric neurology. 2019;94:32-7.
73. Mohorko N, Černelič-Bizjak M, Poklar-Vatovec T, Grom G, Kenig S, Petelin A, et al. Weight loss, improved physical performance, cognitive function, eating behavior, and metabolic profile in a 12-week ketogenic diet in obese adults. Nutrition research (New York, NY). 2019;62:64-77.
74. Włodarek D. Role of Ketogenic Diets in Neurodegenerative Diseases (Alzheimer's Disease and Parkinson's Disease). 2019;11(1):169.
75. Guzel O, Uysal U, Arslan N. Efficacy and tolerability of olive oil-based ketogenic diet in children with drug-resistant epilepsy: A single center experience from Turkey. European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society. 2019;23(1):143-51.
76. Armeno M, Araujo C, Sotomontesano B, Caraballo RH. [Update on the adverse effects during therapy with a ketogenic diet in paediatric refractory epilepsy]. Revista de neurologia. 2018;66(6):193-200.
77. American Diabetes Association position statement: evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. Journal of the American Dietetic Association. 2002;102(1):109-18.
78. Guasch-Ferré M, Willett WC. The Mediterranean diet and health: a comprehensive overview. 2021;290(3):549-66.
79. Katz Sand I, Benn EKT, Fabian M, Fitzgerald KC, Digga E, Deshpande R, et al. Randomized-controlled trial of a modified Mediterranean dietary program for multiple sclerosis: A pilot study. Multiple sclerosis and related disorders. 2019;36:101403.
80. Ahmed SR, Bellamkonda S, Zilbermint M, Wang J, Kalyani RR. Effects of the low carbohydrate, high fat diet on glycemic control and body weight in patients with type 2 diabetes: experience from a community-based cohort. BMJ open diabetes research & care. 2020;8(1).
81. Weickert MO, Pfeiffer AFH. Impact of Dietary Fiber Consumption on Insulin Resistance and the Prevention of Type 2 Diabetes. The Journal of nutrition. 2018;148(1):7-12.
82. Jönsson T, Granfeldt Y, Ahrén B, Branell U-C, Pålsson G, Hansson A, et al. Beneficial effects of a Paleolithic diet on cardiovascular risk factors in type 2 diabetes: a randomized cross-over pilot study. Cardiovascular Diabetology. 2009;8(1):35.
83. Tinguely D, Gross J, Kosinski C. Efficacy of Ketogenic Diets on Type 2 Diabetes: a Systematic Review. Current diabetes reports. 2021;21(9):32.