Proceedings of ICBioMed 2024 Workshop: Computational Proteomics in Drug Discovery and Development from Medicinal Plants
DOI: 10.54254/2753-8818/74/2024.LA18822

# Association between dietary intake of macro-nutrient and type 2 diabetes mellitus

**Haojia Wang**

Department of Medical Sciences, University College London, London, UK

haojia.wang.22@ucl.ac.uk

**Abstract.** Diabetes mellitus, a chronic metabolic disorder characterized by hyperglycemia, has emerged as a major public health concern worldwide. From among, type 2 diabetes (T2DM) is the most common type, accounting for 90% of all diabetes cases, and the prevalence is the highest of middle-aged group, but has increased in young adults. Its pathophysiology is multifaceted, but mainly characterized by altered function of pancreatic β-cells for insulin production and diminished response of insulin by peripheral tissues. The reasons are heterogeneous, such as family history and age, however, unhealthy diet, inactivity and obesity act as the major modifiable risk factor in onset of the disease. The relationship between dietary factors and type 2 diabetes has been extensively studied, summarizing the components of macronutrients help to modulate insulin balance and glucose homeostasis. So, an effective regulation of dietary intervention is robust related to dieticians and related staff help patients to mitigate insulin balance, T2DM, and several complications. This essay reviews the relationship between intake of major macronutrients (carbohydrates, fat, and protein) and related diet regimen on insulin and glucose regulation. Insight into nutrigenetic interactions will aid in uncovering molecular mechanisms of T2DM and enable practical application of precision nutrition plan for T2DM patients.

**Keywords:** Diet regimen, macro-nutrients, diabetes, Type 2 diabetes (T2DM), insulin balance, glucose homeostasis nutrigenetic.

## 1. Introduction

Diabetes mellitus includes a collection of metabolic conditions that result from an inadequate control of carbohydrate metabolism [1]. In general, all diabetic patients have the issue of pancreatic B-cell dysfunction which causes an impairment of insulin production [2]. This would result a lack secretion of insulin, diminished glucose utilization for tissues that is highly depend on insulin (liver, skeletal muscle, and fat), and no significant decline of glucagon [3]. Altogether, the body system is dysregulated in producing glucose and using glucose as energy source, appearing its major clinical manifestation as hyperglycemia [4]. The typical symptoms would be polyuria, polyphresia, fatigue and unexplained weight loss, visual impairment, susceptibility to infection, susceptibility to ketoacidosis or nonketoacidosis, hyperosmolar syndrome, and risk of coma. Moreover, long term hyperglycemia leads to disturbances in insulin secretion which results in dysfunction in our body tissue which includes eyes, kidneys, nerves, heart, and blood vessels, which eventually lead cancer [5].

DOI: 10.54254/2753-8818/74/2024.LA18822

### *1.1. Burden to Healthcare System*

Diabetes imposes a considerable economic pressure due to the need for continuous management and its complications. Worldwide, about 1.3 trillion were spent by diabetic patients [6] and as the data updated in 2022 by American Diabetes Association (ADA), about $412.9 billion was cost for both health-care expenses ($306.6 billion), including continuous expenses for insulin, glucose monitoring supplies, and other essential medications. This gives rise to a 2.6 times higher budget for medical expenses to those of individuals without diabetes [7]. About $106.3 billion are compounded by indirect expenses, such as reduced productivity and premature mortality, which further strains economic resources and reduced labor [8]. Relevant researchers reported that half of the Americans with diabetes are suffer from financial burden and unable to satisfy their daily needs [9]. As a US study conducted by Dieleman, Joseph L. et al., diabetes accounted for the largest share of healthcare spending in 2013 [10]. Considering the current situation, it is essential to address diabetes through effective and cost-efficient methods. And by implementing the Diabetes Prevention Program (DPP) lifestyle changes, along with the use of metformin, offers a promising and affordable strategy for diabetes management. These approaches could serve as valuable components of a comprehensive diabetes care plan [11].

### *1.2. Diagnostic Criteria and Classification*

Diabetes is a chronic metabolic disorder mainly caused by the absolute or relative lack secretion of insulin and reduced insulin sensitivity of target tissue cells [12]. The major etiology is the dysfunction and destruction of pancreatic β-cells, and is the result of either genetic or environmental factors. There are four diagnostic criteria (Table 1) suggested based on WHO (2019) criteria which focus on venous plasma test, including fasting plasma glucose (FPG), 2-hour glucose test result for 75 g oral glucose tolerance test (OGTT), A1c test, random plasma glucose test for people with diabetes [13].

**Table 1.** The specific diagnostic testing standard for diabetes, including the difference between diabetes, prediabetes and normal.

| | HbA1c (%) | FPG (mg/dL) | OGTT (mg/dL) |
|---|---|---|---|
| Diabetes | ≥ 6.5 | ≥ 126 | ≥ 200 |
| Prediabetes | 5.7-6.4 | 100-125 | 140-199 |
| Normal | ~5.7 | ≤ 99 | ≤ 139 |

### *1.3. The subclassification of diabetes*

Diabetes is mainly divided into type 1 diabetes (T1DM); type 2 diabetes (T2DM); Gestational Diabetes mellitus (GDM); Other specific types of diabetes [13,14].

*1.3.1. Type 1 diabetes(T1DM).* This form considers as an autoimmune disease which damaged pancreatic β-cells and caused absolute lack of insulin [14]. The disease happens mostly in children which consider as juvenile or childhood onset but can occur at any life-stage. Globally, about 8.4 million of people undergo T1DM, however, it only makes up 5-10% of all diabetes cases [15].

The specific pathophysiology of T1DM is unknown but is heavily relevant to both genetic and environmental factors. Viruses, stressors, and dietary habits can affect its prevalence [15]. Also, Rich, Stephen S. et al. found that several genetic variations settled in the human major histocompatibility complex (MHC) increased its predisposition, such as human leukocyte antigen (HLA) class I (HLA-A, -B, and C) and class II (HLA-DR, -DQ, and -DP) loci [16]. When diagnosed, most patients would detect the autoimmune antibody in their serum, for example, glutamic acid decarboxylase antibody (GADA), islet cell antibody (ICA), islet antigen-2 antibody (IA-2A), and zinc transporter 8 autoantibody (ZnT8A). [15-17].

*1.3.2. Type 2 diabetes (T2DM).* Type 2 diabetes (T2DM) also known as adult-onset diabetes because it typically occurs in adulthood. Its main pathophysiology is insulin fails to regulate glucose metabolism, accompany with different level of pancreatic β-cells dysfunction, and a loss in insulin secretion

DOI: 10.54254/2753-8818/74/2024.LA18822

compensatory mechanism, which result relative reduction in insulin and sustained hyperglycemia [15-18].

There are several risk factors related to T2DM. In addition to genetics, family history, race, and aging, Ismail L. & et al. also found that serum uric acid, sleep quantity and quality, smoking, depression, hypertension, cardiovascular disease, dyslipidemia, physical inactivity and obesity is highly associated with T2DM. In this case, maintaining a healthy lifestyle and diet habits is the pillar for controlling and preventing T2DM [19].

Although the symptom of hyperglycemia is not evident to be diagnosed, but most patients with T2DM is typical obese and overweight, with a higher visceral fat percentage, which are likely to develop metabolic syndrome, such as dyslipidemia, vascular endothelial dysfunction [20]. The complication of diabetes is the determinants that put patients in danger, and can be divided into microvascular (diabetic retinopathy, diabetic neuropathy, diabetic foot ulcer) and macro-vascular (coronary heart disease, stroke, cerebrovascular disease) [21].

*1.3.3. Gestational Diabetes mellitus (GDM)*. GDM is a type of diabetes in which a woman first detected during gestation. About 15% of pregnancy women have suffered from the disease, which causes both mother and their offspring to be in danger [22,23]. The pathophysiology of GDM shares similarity with T2DM where a sustained defect in insulin response and action is observed and caused by placental hormones, such as corticotrophin releasing hormone, lactogen, estrogen, and cortisol [24]. In terms of treatments, a non-drug strategy is firstly suggested, including dietary modulation, postprandial exercise and ongoing glucose monitoring. In spite this, insulin injection and oral supplements are required if the glycemic level is under-control [25].

*1.3.4. Other specific types of diabetes*. The etiology of other specific type of diabetes is generally clear, which can be caused by genetic mutation (maturity-Onset Diabetes of the Young MODY, mitochondrial diabetes, and neonatal Diabetes Mellitus NDM), secondary to the other disease and infection (diabetes due to pancreatitis, cystic fibrosis related diabetes CFRD, rubella virus) and medication induced (Glucocorticoids, beta blockers) [26].

*1.4. Relationships between diabetes and nutrient*

Despite pharmacotherapy and regular physical activity, planning personalized dietary plan is pivotal to the management of diabetes, impacting glycemic control, controlling related complications and overall well-being [27]. According to American Diabetes Association (ADA) and Institute of medicine (IOM) [27][28], medical nutrition therapy (MNT) has been set as a priority when it comes to the treatment plan of diabetic patients. They have updated a guidance document named nutrition Therapy Recommendations for the Management of Adults With Diabetes in 2013 which specify the role of each nutrient (carbohydrate, fat, protein, micronutrient and herbal supplements, alcohol) that help patients to meet a relative healthy metabolic indexes (A1C < 7%; Blood Pressure < 140/80 mmH; LDL Cholesterol < 100 mg/dL; Triglyceride < 150 mg/dL; HDL > 40 mg/dL for men; >50 mg/dL for women) [29].

The aim of nutrition therapy can be different between T1DM and T2DM. For patients with T1DM who need to have continuous injection of insulin on a daily basis, the key is to cooperate insulin administration with carbohydrate consumption to avoid both hyperglycemia and hypoglycemia [30]. In addition, providing comprehensive and individualized diet to ensure children and adolescents with T1DM to develop properly and maintain optimal glycemic level is crucial [30].

Since most people with T2DM are consider as overweight or obese [31,32], reducing excess weight is the dominant goal when it comes to nutrition therapy [33]. Achieving modest weight loss can improved insulin resistance, lipid profile, and blood glucose, thus lowering motility and morbidity of T2DM. Several studies have showed a calorie-restricted diets and Mediterranean diet with proper physical activity provide weight-loss, at the same time, enhance A1C and reduce incidence of CVD [34,35].

DOI: 10.54254/2753-8818/74/2024.LA18822

## 2. Main Body

### *2.1. Carbohydrates*

Carbohydrates are organic compounds composed of three elements: carbon, hydrogen and oxygen. They are the major energy source to the body system, especially for the brain with 4 kcal per grams. Their intake accounts for more than 50% of the daily energy, it is essential for tissue development and heat production. After consumption, carbohydrates simply break down into glucose and stimulates insulin secretion which further affect energy storage and lipid metabolism. In this case, it is essential to understand the type, source, digestion, and absorption process of carbohydrates related to glucose level, allowing diabetic patients to be instructed effectively on the diet of carbohydrate-based foods.

*2.1.1. Type and source*. Our daily diet normally includes certain subset of carbohydrates which can be divided into simple and complex carbohydrates. Simple carbohydrates, a type of sugar contains one or two sugar units, including monosaccharides (glucose, fructose, galactose) which are naturally found in fruits, honey, and vegetables. Disaccharides includes sucrose, lactose, maltose, which can be describe as table sugar, milk sugar and malt sugar. They can be found in either processed food or natural products. This type of carbohydrates acts as quick energy provider as they can be easily digested. Hence, rapidly increasing blood glucose. Complex carbohydrates are made up of long chain of sugar units, composing oligosaccharides and polysaccharides, providing glucose slowly. Digestible polysaccharides include starches, glycogen, and dextrin. Starch acts as the most common type in our diet, existing in grains, tubers and legumes. Amylose and amylopectin are the two components of starch, accounting 20% and 80% respectively. Amylose is tightly packed and non- soluble in water which makes them difficult for digestion. For non-digestible complex carbohydrates that is fibers, including pectin, cellulose, semicellulose, lignin, etc. Soluble fibers form water-gel structure in the intestine to help with satiety, slowing down cholesterol, glucose and fructose absorption, controlling LDL and postprandial glycemic index. Fleshy fruits, barley and oats are examples that are high in soluble fibers. Insoluble fibers provide nutrients to the gut microbiota for digestion, increasing intestinal motility and helping with defecation, normally found in brans, brown rice and skins of produce [36].

*2.1.2. Metabolism*. Monosaccharides is the only form that can be directly absorbed by the gut. After consumption of carbohydrates, the α-amylase produced by the salivary gland breaks the complex carbohydrates (e.g., starches) into smaller sugar molecules. After the molecules undergoes the acidic environment in the stomach, the pancreatic α-amylases hydrolyze them into maltose, malt oligosaccharides, α-limit dextrin undergoing the maltase-glucoamylase (MGAM) and sucraseisomaltase (SI) lining in the small intestinal mucosal cells to be hydrolyzed into glucose and enter the bloodstream, and that is when the insulin produced by the pancreas comes into place [37]. Insulin helps the excess glucose enter liver via portal vein to be stored as glycogen. Others will convert to triglycerides. Different sources of starch have varied degree of digestion rate, slowly digested starch (SDS) takes longer time to yield glucose, which derived from whole grains, legumes and starchy nuts. Thus, initiating moderate insulin response. However, rapidly digested starch (RDS) from rice, white bread, and processed food would stimulate an accelerated insulin response [38]. Dietary Fibers is resistant to the enzyme of our digestive system due to their rigid chemical structure. They can either partially breakdown by the bacteria in the colon for providing short chain fatty acid to maintain intestinal health or add bulk to the stool to prevent constipation.

*2.1.3. Effect on blood sugar and insulin response*. Carbohydrates consumption is double-edged when it comes towards T2DM. For people with T2DM, they can produce insulin at certain level, but the major problem is insulin resistance. Therefore, it is important to limit the insulin level that your body need by managing blood sugar. Different types of saccharides have varied effect on glucose homeostasis, which can be divided into starch, sugars, dietary fibers. Among them, dietary fibers bring the benefits in controlling T2DM. A systematic review concludes 36 studies shows high DF diets help patients with

DOI: 10.54254/2753-8818/74/2024.LA18822

T2DM with weight management and blood sugar regulation [39]. The viscous fiber originated from certain vegetables, legumes and fruits, mixes with body fluids to form gelatinous substance in the intestine, aiming to stabilize postprandial blood sugar and insulinemic fluctuations, improve lipid profile. As the non-water-soluble fibers, normally found in legumes, whole grains, seeds, tubers show a similar effect. This form of fibers remains intact in the digestive tract and directly reach the colon, which add complexity to the digestive process and slow down the digestion rate. They can be fermented by the gut microbiota to form short chain fatty acid (SCFA) which trigger hormones for fullness, take peptide YY and ghrelin as examples to be released. Hence, providing satiety and avoiding cravings.

On the other hand, the free sugar, especially for high-fructose corn syrup and sucrose in many processed food and sugar-sweetened beverages (SSBs) is the central issue for T2DM. Fructose with the highest sweetness among all naturally occurring sugar, is indeed the main risk, significantly increase prevalence of metabolic disease, especially for diabetes and CV. Study shows fructose distinctly damaged insulin signaling, fasting glucose and insulin and increase body weight [38]. Fructose presents a different metabolic pathway than glucose, which is normally metabolize in the liver and convert to fatty acid and triglycerides, known as lipogenesis. The lipid tends to accumulate in the liver, which interfere with signal transmission of insulin receptor, hence damage insulin response. The hepatic lipid accumulation also promotes oxidative stress and systemic inflammation which further damage glucose metabolism. It is suggested by WHO that for diabetic patients to cut off or limit fructose intake to 5% of total daily calories would be beneficial to glucose and insulin regulation.

In terms of starches, choosing the correct starch food is essential which can be found in breads, grains, beans, cereal products, potatoes, etc. Depending on the component of the starch the food contains, and the rate and completeness of hydrolysis, the GI (glycemic index) will change differently. For example, starches from white rice, bread can be easily digested, thus brings negative effect on the blood glucose, however, for starches found in legumes, green bananas, and uncooked or cooked and cooled potatoes, are consider as resistant starch. This type of starch exerts a similar function compared to dietary fibers as they contain a large component of amylose, other than amylopectin. Since they are hardly be metabolized in the upper digestive tract which decrease caloric density of food, amount of glucose release into circulation and the requirement of insulin.

*2.1.4. Dietary Suggestion*. There are many popular diet regimens related to T2DM, such as Low Carbohydrate Diet approach (LCD) which reduce carbohydrates intake to 26% or less of daily energy intake and Very Low Carbohydrate Diet for a restriction (VLCD) to 10% or less. Although these diet approaches do show benefits to blood glucose, weight management, hunger, hepatic fat storage control [39], in long term consideration, worries like starvation ketosis, dyslipidimia, and gallstones may arise due to prolong period of long-term deprivation of carbohydrates, high intake of lipid, and damaged metabolic health. There is no standard carbohydrates intake restriction advice for patients with diabetes, but it is recommended that to start to consume less than 25% of daily intake [40].

What more important is the quality of carbs, eat more nutrition-dense type, such as whole grains found in brown rice, quinoa, and whole wheat, etc. [40]. And non-starchy vegetables which is high in fibers, such as tomatoes, broccoli, and kale. And keep away from unhealthy carbohydrates derived from refined grains and processed food with free sugar, for example, white rice, noodles, different types of desserts and snacks. Considering low-calorie sweeteners such as stevia, sucralose, may be an alternative approach because they may not provide an immediate rise in blood sugar, but it remains unclear for longer term effect. Overall, even though carbohydrate is directly link to blood glucose level, it is not rational to stop its consumption by a large quantity, remaining a balance sustainable and beneficial diet is optimal.

### *2.2. Fat*

Fat is a type of lipid, which is a Dietary fat is the overall daily consumption of fat in our food, which then broken down into fatty acid and glycerol, which then enter the bloodstream and store as triglycerides, acting as a fuel provider and energy depot, especially under the circumstances of fasting.

DOI: 10.54254/2753-8818/74/2024.LA18822

It provides the highest energy among macronutrients which is 9cal/g. The main function of fatty acid is to help the absorption of various type of vitamins and nutrients, production of hormones and cell signaling molecules, construction of cell membrane. At the same time, they are distributed under the skin, around the internal organs, acts as a thermal insulation and protective pad, also maintains body temperature. Different types of fat also influence cholesterol level, which affect the incidence of CDV. In this case, lipid exerts a substantial benefit in maintaining body's function and integrity.

*2.2.1. Type and Source*. Dietary fat can be divided based on their distinct chemical structures and impact to human health, it can be sorted into Saturated fatty acid (SFA), monosaturated Fatty acid (MUFA), polyunsaturated fatty acid (PUFA), and Trans-fat.

**Saturated fatty acid (SFA)**: as the name suggested, all the carbon atoms relate to the hydrogen atoms with no double bond in the fatty acid chain, which gives a characteristic structure of long chain and straight orientation allows the fatty acid to pack closely, making SFA to be solid at room temperature. This type of fat gains its bad reputation because it can raise the level of serum LDL cholesterol, which is strongly related to CVD. Therefore, in Dietary Guidelines for Americans, it is suggested to reduce the intake of SFA less than 10% of daily calories [41]. SFA often found in animal products, including red meat and dairy products, but also found in coconut, palm and kernel oil used for cooking and processed food.

**Unsaturated fatty acid (UFA):** Depending on the number of double bonds between carbon atoms the fatty acid chain contains, UFA can be divided into monounsaturated and polyunsaturated.

**Monounsaturated fatty acids (MUFA):** includes single double bond in their hydrocarbon chain, mostly in cis configuration with the hydrogen atoms on the same side of the double linkage between carbons. Different from SFA, the presence of unique carbon-carbon bond gives MUFA its bend shape which make it to have a higher fluidity and melting point, and their state depends on the temperature. The most typical form of MUFA in diet is oleic acid (OA; 18:1n–9), also known as omega-9 fatty acid with the double located at the $9^{th}$ carbon from the methyl (CH3) terminal. Other less abundant includes palmitoleic acid (PO; 16:1n–7) and stearidonic acid (C18:1 Δ6) [42]. MUFA mostly found in plant-based food, such as avocados, certain nuts, and vegetables oil (olive, canola, and peanut oils). Conversely to SFA, this type of fat known as healthy fat as they exert their benefits to cardio-metabolic disease and help to control inflammation response done by the immune system [42].

**Polyunsaturated fatty acid (PUFA):** Chemically, two or more double bond presents in the fatty acid chain, which makes it to be liquid all the time at room temperature. Specifically, PUFA is vulnerable to oxidation, and the severity of lipid peroxidation has a positive relationship with the number of double bond the hydrocarbon chain contains as it provides more active sites for election donation. In this case, storing foods that is high in PUFA in a proper way, such as use a container, or a refrigerator is crucial. Generally, there are two types: omega-3 and omega-6 fatty acids. Omega-3 can be categorized into alpha linolenic acid (ALA) derived mostly from plants source (flaxseeds, seeds, seaweeds and soybeans) Eicosapentaenoic acid (EPA), and Docosahexaenoic acid (DHA) largely found in marine products, such as oily fish. ALA is the produce of the other two, meaning it considers as essential. So that our body system cannot create it but must be acquired from eating and supplements. Similarly, there are three types of Omega-6: linoleic acid (LA); arachidonic acid (AA); and gamma-linolenic acid (GLA). Among them, LA is the one that is necessary to obtain via the dietary channel and mainly from nuts (almond, walnut), seed (sunflower, chia seed, pumpkin seeds), oil flaxseed oil, soybean oil). AA and GLA primarily obtained from animal products and certain seeds respectively. Both Omega-3 and Omega-6 play essential roles in maintaining health. They help with cell membrane construction, acts as gene expression regulators, cognitive process and skin health. Distinctly, Omega-6 promotes inflammation processes and blood clotting by producing eicosanoids increasing platelet aggregation and constricting blood vessels respectively. Omega-3 has a counteract effect, which aid in an anti-inflammatory, lower blood pressure. Also, retinal protection function. In this case, it is optimal to balance the consumption of Omega-3 and Omega-6 for controlling inflammation and overall welling-being [43,44].

DOI: 10.54254/2753-8818/74/2024.LA18822

**Trans-fatty acid (TFA):** TFA is under the category of UFA. They are considered as the unhealthy fat. TFA is mostly industrial processed because of the desire of transforming UFA to SFA. To produce TFA, partial hydrogenation is the way where hydrogen atoms are added to some of the double bond, and the double bond transforms from cis form to transform (the hydrogen atoms oppose each other), creating a more linear shape. The purpose is to change to a more solid state, increase the shelf life by preventing oxidation. Not surprisingly, TFA is mostly found in processed food, such as cakes, cookies, potatoes chips, microwaved popcorn. Besides, products from ruminants (beef, lamb, and dairy products) do contain a little amount of naturally occurring TFA because of their distinct microbiota in their stomach. There are many health risks related to TFA, such as cause an unfavorable LDL/HDL ratio, increased visceral fat deposition, promote inflammation, contributing to the prevalence of cardio-metabolic disease, such as coronary heart disease, arteriosclerosis, T2DM, Non-Alcoholic Fatty Liver Disease (NAFLD), etc. [45].

*2.2.2. Fats and T2DM*. Patients with T2DM often consider as overweight and obese with hypertriglyceridemia, disbalance between level of VLDL, LDL and HDL. Since a high-fat diet is directly related to these issues and cause related complications, it is crucial to understand the interaction between different types of fats and T2DM. Both animal experiments and human experiments have shown that excessive total fat intake can reduce the body's sensitivity to insulin, leading to insulin resistance and glucose metabolism [46]. In addition, the total fat intake can also make the plasma free fatty acids (free fatty acid, FFA) level increase. The sustained high levels of FFA can inhibit peripheral tissue insulin stimulated glucose intake, reduce the hepatocyte insulin receptor for insulin binding, lower receptormediated degradation acceleration and liver sugar utilization. All these contribute to peripheral hyperinsulinemia and insulin resistance [47].

*2.2.3. Dietary Suggestion*. Different types of fat intake may be more important for T2DM compared to total dietary fat intake, which either be beneficial or harmful to patients with T2DM. Foods with high in animal fat, saturated fat and trans-fat will exacerbate dyslipidemia, increased body mass index (BMI) and obesity which are crucial factors in the progressive development of insulin resistance, which ultimately leads to T2DM and several complications. However, higher intake of vegetables fats, unsaturated fat found in sources like olive oil, avocados, and fatty fish may improve cholesterol metabolism, lowering LDL cholesterol and help with insulin sensitivity. Hence, it becomes crucial to transformed saturated and trans fats into healthier unsaturated fats can contribute to better overall metabolic health, reduce inflammation, and support weight management efforts, which assist in prevent and mitigate T2DM. When processing food, it is essential to give priority to unsaturated fatty acids such as olive oil and reduce consumption of foods rich in high cholesterol and saturated fatty acids, such as animal skin, viscera, and egg yolks.

*2.3. Protein.*

Protein is one of the macro-nutrients that couples with various physiological functions and its metabolism is crucial for maintaining overall body health. Chemically, it is the product of translation and made by amino acids, and their structure can be divided into primary, secondary, tertiary, and quaternary. Proteins have various functions which cannot be accomplished by carbohydrates and fats, and there is different form of protein with special functions, such as enzyme, hormonal proteins, immunoglobulins, and movement proteins, etc. They can contribute to muscle contraction, growth, construction and repair of tissue, also clotting of blood, etc. Nutritionally, protein provides 4cal/g and are made up of 20 different amino acids, among them, nine of which are essential (Histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine, they must be obtained from the dietary pathway because the body cannot synthesize them. Some non-essential amino acids are conditionally essential, meaning our body cannot synthesize in a sufficient amount or they are originated from essential amino acid [48].

DOI: 10.54254/2753-8818/74/2024.LA18822

*2.3.1. Source and type*. The major source of protein can be divided into animal-based (eggs, fish, meat and poultry) and plant based (legumes and grains). Since proteins are absorbed in the form of amino acid, the food contains all the A.A with an optimal proportion that our body need is known as 'complete' and is mostly from animal products. On the contrary, vegetable proteins contain a relatively lower nutritional value which need to cooperate with other plants-based protein in the diet, especially for vegetarian, to get enough protein profile and nutrients. For example, combining grains with lysine-rich food, such as legumes (peas and beans) to have proper protein synthesize, enzyme function, and calcium absorption.

*2.3.2. Relationship with T2DM and insulin resistance*. Leucine is the only ketogenic amino acid in animals, which is the amino acid that plays a major role in regulating protein metabolism. It can activate mTOR, promote the phosphorylation of p70S6, and then promote protein synthesis. In the state of insulin resistance, the hyperactivated serine/chromine kinase and its downstream substrate ribosomal protein S 6 kinase 1 (Ribopsomal S6 kinase 1, S6K1) can block the insulin signaling pathway through negative feedback regulation, leading to a glucose metabolism disorder [49]. On the one hand, protein can stimulate the gastrointestinal tract to produce satiety signals such as cholecystokinin and glucagon-like peptide, delaying gastric emptying, inhibiting appetite and reducing the potential of developing obesity; on the other hand, protein can play the same effect as glucose in improving insulin sensitivity and stimulating its synthesis, while inhibiting the secretion of glucagon to achieve the effect of reducing blood glucose. Therefore, for patients with T2DM with mainly insufficient insulin secretion, a high protein diet benefits to cell regeneration and tissue repair, and thus reduce body damage in diabetic patients.

*2.3.3. Dietary Suggestion*. It is optimal to cooperate protein with other two macronutrients, like high fiber-carbohydrates and healthy lipids. This is because it can reduce patients' glycated albumin, lowering blood sugar level and limit the demand of insulin. It is important to consume in a moderate level to avoid kidney problem as T2DM as the high-risk group of developing nephropathies. Moreover, when considering protein products, it is always important to reflect on other components that may affect the overall well-being. For example, reduce the intake of red meat with high saturated fat, industrialized dairy products with added sugar (protein bars, flavored yogurts) and caloric-dense food (nuts and seeds), they can lead to weight gain, cardiovascular disease, and eventually insulin resistance. Foods like fish, whole milk with calcium and vitamin D, egg white provides sufficient vitamins and minerals and plant-based protein, such as peas, bean, and whole grains with high fiber content help to stabilize the blood sugar and regulate general well-being [50].

## 3. Conclusion

T2DM is a worldwide epidemic, bringing a huge anxiety and health issues to people, especially when it comes to cardiovascular disease. Unhealthy diet and a sedentary lifestyle have been identified as basic modifiable risk factors for T2DM. The major possible contributor would be rapid urbanization and the rampant availability of westernized processed foods containing lots of refined carbohydrates, saturated and trans fats, and added sugars have dramatically transformed the current food environment. Various dietary patterns are linked to the incidence of Type 2 diabetes (T2DM). Since a diet comprises a complex interplay of foods and nutrients, future research should focus on dietary scores that encompass all critical aspects of a healthy diet known to influence T2DM risk. This method could offer a more accurate prediction of disease risk compared to studying individual foods and nutrients individually. Therefore, it is very important to determine the optimal diet to provide accurate advice on diabetes prevention. However, not all studies reported sufficient details regarding macronutrient or micronutrient content, or prescribed and reported energy intakes, including a nutrient-restricted ad libitum diet, which limits the interpretation and transferability of the results. Therefore, evidence from clinical practice is often used to identify safe and effective methods to enhance the interpretation of the available data through individual patient data meta-analysis.

DOI: 10.54254/2753-8818/74/2024.LA18822

As T2DM onset is primarily due to excessive weight gain in individual, focusing on how people acquired and consumed energy in a daily basis is the key. A balanced and healthy diet with choosing the right carbs, fats, and proteins only solve one aspect of regulating blood sugar levels, support weight management, and provide essential nutrients. Additionally, cooperating exercise to regulate an appropriate energy expenditure, combining aerobic exercise (walking, swimming and running) and resistant training (weightlifting, push-ups) and flexibility and Balance Exercises (yoga, pilates). These increase the usability of glucose for muscle tissue, thus lowering blood glucose, which also can increase cell's response to insulin by increasing more insulin receptors. Also, aiding in weight management by reducing fat depositions, especially around organs that is directly linked to insulin resistance and obesity. Overall, it is worthy to mention that is not a single type of nutrients that is directly related to lower the risk of T2DM, but the nutritional quality and the quantity consumed is the matter of affect. Understanding the metabolism, the sources of different macronutrients, how they work together with each other in a diet and rise different body responses related to T2DM, will provide optimized and individualized dietary plans for patients. The main goal is to assist with blood glucose level, improve insulin responses, and reduce the incidence of complications involved, paving the way for T2DM prevention and regulation.

## References

[1] Sipra A., & Bhandari P. 2023 *Diabetes.* (StatPearls Publishing) https://www.ncbi.nlm.nih.gov/books/NBK551501/

[2] Park S. Y., Gautier J. F., & Chon S. (2021). Assessment of Insulin Secretion and Insulin Resistance in Human. *Diabetes Metab. J.*, 641-54. https://doi.org/10.4093/dmj.2021.0220

[3] Nakrani M. N., Winelands R. H., & Anjum F. (2024). *Physiology, Glucose Metabolism*. (StatPearls Publishing) https://www.ncbi.nlm.nih.gov/books/NBK560599/

[4] American Diabetes Association Professional Practice Committee Diabetes Care (2024). *2.* Diagnosis and Classification of Diabetes: Standards of Care in Diabetes-2024*. Diabetes Care,* 47(1), S20-42. https://doi.org/10.2337/dc24-S002

[5] Heritier J., & Roden M. (2023). Diabetes mellitus: definition, classification, diagnosis, screening and prevention. *Wien. Klin. Wochenschr.*, 135, 7-17. https://doi.org/10.1007/s00508-022-02122y

[6] Parker, E. D. & et al. (2024). Economic Costs of Diabetes in the U.S. in 2022. *Diabetes Care.* 47(1), 26-43. https://doi.org/10.2337/dci23-0085

[7] Zhang, P., & et al. Global economic burden of diabetes and its implications. *Lancet Diabetes Endocrinol.,* 5(6), 404-05. https://doi.org/10.1016/S2213-8587(17)30100-6

[8] Patel M. R., Piette, John D., Resnicow, K., Kowalski-Dobson, Theresa H., & Michele M. D. (2016). Social Determinants of Health, Cost-related Nonadherence, and Cost-reducing Behaviors Among Adults with Diabetes: Findings from the National Health Interview Survey. *Med Cate.* 54(8), 796-803. https://doi.org/10.1097/MLR.0000000000000565

[9] Dieleman, Joseph L., & et al. (2016). US Spending on Personal Health Care and Public Health, 1996-2013. *JAMA*, 316(24), 2627-46. https://doi.org/10.1001/jama.2016.16885

[10] O'Connell, Joan M., & Spero M. M. (2019). Understanding the Economic Costs of Diabetes and Prediabetes and What We May Learn About Reducing the Health and Economic Burden of These Conditions. *Diabetes Care*, 42(9), 1609-11. https://doi.org/10.2337/dci19-0017

[11] Chawla S. P. S., Kaur S., Bharti A., Garg R., Kaur M., Soin D., Ghosh A., & Pal R (2019). Impact of health education on knowledge, attitude, practices and glycemic control in type 2 diabetes mellitus. *J. Family Med. Prim. Care*, 8(1), 261-68. https://doi.org/10.4103/jfmpc.jfmpc_228_18

[12] Geneva: World Health Organization (2019). *Classification of diabetes mellitus.* CC BYNC-SA 3. 0 IGO.

DOI: 10.54254/2753-8818/74/2024.LA18822

[13] American Diabetes Association (2021). 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021. *Diabetes Care*, 44(1), S15-S33. https://doi.org/10.2337/dc21S002

[14] Lucier J., & Dulebohn S. C. (2023). *Type 1 Diabetes*. (StatPearls Publishing). https://www.ncbi.nlm.nih.gov/books/NBK507713/

[15] Rich, Stephen S., Catherine C. C. & et al. (2018). *Genetics of Type 1 Diabetes.* (National Institute of Diabetes and Digestive and Kidney Diseases) https://pubmed.ncbi.nlm.nih.gov/33651545/

[16] Solis-Herrera C., Triplitt C., Reasner C., & et al. (2018). *Classification of Diabetes Mellitus.* https://www.ncbi.nlm.nih.gov/books/NBK279119/

[17] Goyal R., Singhal M., &Jialal I. (2023). *Type 2 Diabetes.* (StatPearls Publishing) https://www.ncbi.nlm.nih.gov/books/NBK513253/

[18] Ismail L. & et al. (2021). Association of risk factors with type 2 diabetes: A systematic review. *Comput. Struct. Biotechnol. J.,* 19, 1759-85. https://doi.org/10.1016/j.csbj.2021.03.003

[19] Solis-Herrera C., Triplitt C., Reasner C., et al. (2018). *Classification of Diabetes Mellitus.* (South Dartmouth) https://www.ncbi.nlm.nih.gov/books/NBK279119/

[20] Galicia-Garcia U. & et al. (2020). Pathophysiology of Type 2 Diabetes Mellitus. *Int. J. Mol. Sci. ,* 21(17) 6275. https://doi.org/10.3390/ijms21176275.

[21] Modzelewski R., & et al. (2022). Gestational Diabetes Mellitus-Recent Literature Review. *J. clin. med.*, 11(19), 5736, https://doi.org/10.3390/jcm11195736

[22] Kopylov, A.T., Papysheva, O., Gribova, I., & et al. (2020). Molecular pathophysiology of diabetes mellitus during pregnancy with antenatal complications. *Sci. Rep.,* 10, 19641. https://doi.org/10.1038/s41598-020-76689-9

[23] Quintanilla R. B. S., Vadakekut E. S., & Mahdy H. (2024). *Gestational Diabetes*. (StatPearls Publishing)https://www.ncbi.nlm.nih.gov/books/NBK545196/

[24] Tracy L., Setji, Ann J., Brown, Mark N., Feinglos. (2005). Gestational Diabetes Mellitus, *Clin. Diabetes*, 23(1), 17–24. https://doi.org/10.2337/diaclin.23.1.17

[25] Evert, Alison B. & Boucher J. L. (2014). New Diabetes Nutrition Therapy Recommendations: What You Need to Know. *Diabetes Spectr.*, 27, 121-30. https://doi.org/10.2337/diaspect.27.2.121

[26] Institute of Medicine (2000). The Role of Nutrition in Maintaining Health in the Nation's Elderly: Evaluating Coverage of Nutrition Services for the Medicare Population. (Washington, DC, National Academies Press)

[27] Alison B. E., Jackie L. B., Marjorie C., Stephanie A. D., Marion J. F., Elizabeth J. M., Joshua J. N., Robin N., Cassandra L. V., Patti U., & William S. Y. (2013). Nutrition Therapy Recommendations for the Management of Adults with Diabetes. *Diabetes Care*, 36 (11), 3821-42. https://doi.org/10.2337/dc13-2042

[28] American Diabetes Association (2021). 13. Children and Adolescents: Standards of Medical Care in Diabetes-2021. *Diabetes Care*, 44(1), S180-99. https://doi.org/10.2337/dc21-S013

[29] Abdullah A., Peeters A., de Courten M., & et al. (2010). The magnitude of association between overweight and obesity and the risk of diabetes: a meta-analysis of prospective cohort studies. Diabetes Res. *Clin. Pract.*, 89(3), 309-19. https://doi.org/10.1016/j.diabres.2010.04.012

[30] Eckel R. H., Kahn S. E., Ferrannini E., & et al. (2011). Obesity and type 2 diabetes: what can be unified and what needs to be individualized? *Diabetes Care*, 34(6), 1424-30. https://doi.org/10.2337/dc11-0447

[31] Fridman M., Lucas M. E., Paprocki Y., Dang-Tan T., Iyer N. N. (2020). Impact of Weight Change in Adults with Type 2 Diabetes Mellitus: A Literature Review and Critical Analysis. *Clinicoecon Outcomes Res.*, 12, 555-66. https://doi.org/10.2147/CEOR.S266873

[32] Esposito K., Maiorino M. I., Ciotola M., & et al. (2009). Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: a randomized trial. *Ann. Intern. Med.*, 151, 306-14. https://doi.org/10.7326/0003-4819-151-5200909010-00004

DOI: 10.54254/2753-8818/74/2024.LA18822

[33] Pi-Sunyer X., Blackburn G., Brancati F. L., & et al. (2007). Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the Look AHEAD trial. *Diabetes Care*, 30, 1374-83.

[34] Holesh J. E., Aslam S., Martin A. (2024). *Physiology, Carbohydrates*. (StatPearls Publishing) https://www.ncbi.nlm.nih.gov/books/NBK459280/

[35] Bonsembiante L., & et al. (2021). Type 2 Diabetes and Dietary Carbohydrate Intake of Adolescents and Young Adults: What Is the Impact of Different Choices? *Nutrients,* 13(10), 3344. https://doi.org/10.3390/nu13103344

[36] Stanhope K. L., Schwarz J. M., Keim N. L., Griffen S. C., Bremer A. A., Graham J. L., Hatcher B., Cox C. L., Dyachenko A., Zhang W., & et al. (2009). Consuming fructose-sweetened, not glucosesweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. *J. Clin. Investig.*, 119, 1322-34. https://doi.org/10.1172/JCI37385.

[37] Wheatley S. D., & et al. (2021). Low Carbohydrate Dietary Approaches for People With Type 2 Diabetes-A Narrative Review. *Frontiers nutr.,* 8, 687658. https://doi.org/10.3389/fnut.2021.687658

[38] Johnston, C. A., & et al. (2013). The Role of Low-calorie Sweeteners in Diabetes. *Eur. Endocrinol.*, 9(2), 96-8. https://doi.org/10.17925/EE.2013.09.02.96

[39] National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Food and Nutrition Board, Committee to Review the Process to Update the Dietary Guidelines for Americans, (2017). *Redesigning the Process for Establishing the Dietary Guidelines for*

[40] *Americans. (*Washington (DC): National Academies Press (US)) https://www.ncbi.nlm.nih.gov/books/NBK469839/

[41] Mashek, Douglas G., and Chaodong W. (2015). *MUFAs*. *Adv. Nutr.*, 6(3), 276-7. https://doi.org/10.3945/an.114.005926

[42] Duan H., & et al. (2023). Polyunsaturated Fatty Acids (PUFAs): Sources, Digestion, Absorption, Application and Their Potential Adjunctive Effects on Visual Fatigue. *Nutrients,* 15(11), 2633. https://doi.org/10.3390/nu15112633

[43] Dhaka V., & et al. (2011). *Trans fats-sources, health risks and alternative approach - A review*. *J. Food Sci. Technol.,* 48(5), 534-41. https://doi.org/10.1007/s13197-0100225-8

[44] Manco M., Calvani M., Mingrone G. (2004). Effects of dietary fatty acids on insulin sensitivity and secretion. *Diabetes Obes. Metab.*, 06, 402-13. https://doi.org/10.1111/j.14628902.2004.00356.x

[45] Kharroubi I., Ladriere L., Cardozo A. K., & et al. (2004). Free fatty acids and cytokines induce pancreatic betacell apoptosis by different mechanisms: roke of nuclear factor-kappaB. *Endocrinology,* 145(11), 5087-96. https://doi.org/10.1210/en.2004-0478

[46] Zhang T., Zhang H., Li Y., Li S., Fernandez C., Bazzano L., He J., Xue F., & Chen W. (2017). Long-term Impact of Temporal Sequence from Childhood Obesity to Hyperinsulinemia on Adult Metabolic Syndrome and Diabetes: The Bogalusa Heart Study. *Sci Rep.*, 23(7), 43422. https://doi.org/10.1038/srep43422

[47] Asgari S., Khalili D., Mehrabi Y., & et al. (2021). Letter to the editor regarding "Nationwide prevalence of diabetes and prediabetes and associated risk factors among Iranian adults: analysis of data from PERSIAN cohort study". *Diabetes Ther*, 13(1), 217-9. https://doi.org/10.1007/s13300-021-01186-9

[48] ABDEF-AZIZ A. K., PALLAVICINI I., CECCACCI E., & et al. (2020). Tuning mTORC1 activite dictates the response of acute myeloid leukemia to LSD1 inhibition. *Haematologica*, 105(8), 2105-17. https://doi.org/10.3324/haematol.2019.224501

[49] Tian S., Xu Q., Jiang R., Han T., Sun C., & Na L. (2017). Dietary Protein Consumption and the Risk of Type 2 Diabetes: A Systematic Review and Meta-Analysis of Cohort Studies. *Nutrients*, 9(9), 982. https://doi.org/10.3390/nu9090982.

DOI: 10.54254/2753-8818/74/2024.LA18822

[50] Zhang, P., & et al. (2017) Global economic burden of diabetes and its implications. *Lancet Diabetes Endocrinol.,* 5(6), 404-5. https://doi.org/10.1016/S2213-8587(17)30100-6.