ANALYSIS OF THE EFFECTS OF DIFFERENT DIETARY INTERVENTIONS ON MANAGEMENT OF DIABETES MELLITUS: A META-ANALYSIS

Thesis in partial fulfilment of the requirement for the degree of Master of Science

In

Biotechnology

By

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Under the supervision of

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to

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Certificate

This is to certify that thesis entitled "**Analysis of the Effects Of different dietary Interventions on management of Diabetes Mellitus: A Meta-Analysis**", submitted by **Pradeep Singh** in partial fulfilment for the award of degree of **Master of Science** in **Biotechnology** to Jaypee University of Information Technology, Waknaghat, Solan has been made under my supervision.

Dr. Jitendraa Vashistt

Associate Professor

Candidate's Declaration

I hereby declare that the work presented in this thesis entitled "**Analysis of the Effects Of different dietary Interventions on management of Diabetes Mellitus: A Meta-Analysis**" in partial fulfilment of the requirements for the award of the degree of **Master in Science** in **Biotechnology** submitted in the Department of Biotechnology & Bioinformatics**,** Jaypee University of Information Technology, Waknaghat is an authentic record of my work carried out over a period from August 2022 to May 2023 under the supervision of **Dr. Jitendraa Vashistt** (Associate Professor, BT&BI).

The matter embodied in the thesis has not been submitted for the award of any other degree or diploma.

(Student Signature)

Pradeep Singh

This is to certify that the above statement made by the candidate is true to the best of my knowledge.

(Supervisor Signature)

Supervisor Name: Dr. Jitendraa Vashistt

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ACKNOWLEDGEMENT

I take this opportunity to express my gratitude to numerous people who has supported me and encouraged me to carry on my work efficiently.

First and foremost, I would like to express my heartfelt gratitude and appreciation to my project supervisor, **Dr. Jitendraa Vashistt** for his guidance, assistance, and supervision throughout my dissertation work. His expertise and knowledge contributed a major part in making this project a success. I thank him for giving insightful advice and suggestions and for continuous source of inspiration.

I would also like to take this opportunity to thank **Dr**. **Sudhir Kumar Syal,** Head of the department of Biotechnology and Bioinformatics, Jaypee University of Information Technology for his knowledge and support in making this project and for allowing me to work on such a diverse project.

I would express my gratitude towards our PhD Scholar Monika Chaudhary for her endless help in every step of the way. I would also like to extend my thanks to the lab technicians and other staffs of the department for their invaluable help and support.

Finally, I must acknowledge with due respect the constant support and patience of my parents.

Pradeep Singh (217807)

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ABBREVIATION	FULL FORM
CVD	Cardiovascular diseases
T1D	Type-1 Diabetes
T2D	Type-2 Diabetes
DKA	Diabetic Ketoacidosis
FFA	Free-Fatty Acids
LADA	Latent Autoimmune Diabetes in Adults
MUFA	Mono-unsaturated fatty acids
PUFA	Poly-unsaturated fatty acids
RDA	Recommended Dietary allowances
TEE	Total energy expenditure
BMR	Body metabolic rate
PAL	Physical activity level
HbA1c	Glycated hemoglobin
FBG	Fasting blood glucose
LDL	Low-density lipoprotein
HDL	High-density lipoprotein
TG	Triglycerides
BMI	Body mass index
RCTs	Random clinical trials
GI	Glycaemic index
ADA	American diabetes association

LIST OF FIGURES

LIST OF TABLES

Abstract

Diabetes mellitus has become one of the most prevalent metabolic disorders worldwide. For the management of diabetes mellitus, many dietary interventions have been proposed. However, each management process has some limitations. Therefore, we performed a meta-analysis on the various widely utilized dietary interventions to overcome the problems associated with diabetes mellitus and their management. Information was extracted from earlier reports for the Low-carbohydrates diet, Mediterranean diet, and low-glycaemic index diet. Inclusion and exclusion criteria were used to select the relevant studies and data was extracted based on selected variables. We calculated the combined mean for pooled effect and compared the effects. On the basis of observations on the mean reductions in selected diabetic variables, our study has proposed a well-suited and effective moderate carbohydrate diet having food of low-glycemic index that could help in the better management of diabetes mellitus.

Chapter 1

INTRODUCTION

1.1 Diabetes

Several studies conducted in developing nations, including India, have reported disease burden, i.e., undernutrition and overnutrition among urban populations (NNMB report,2017). Overweight, obesity, Hypertension, insulin resistance, diabetes mellitus, other cardiovascular diseases (CVDs), cancers, and other diet-related chronic non-communicable (NCD) diseases have been increasing in epidemic proportion among urban populations. Nutrition transition, sedentary behavior, unhealthy lifestyles, and high-risk behaviors generally account for the rise in NCD incidences. Furthermore, demographic and health transitions, epigenetic, and gene-environmental interactions, and maternal and childhood malnutrition are major contributors to the rise in the occurrence of NCDs in India [1].

Type-2 Diabetes mellitus (T2D) is now a major public healthcare concern worldwide, with the disease's occurrence predicted to reach 380 million people by the year 2025 [International diabetes federation]. Type-2 diabetes imposes several physical, societal, and financial consequences. Those with Type 2 diabetes mellitus, for instance, can have a 10-year shorter lifespan when opposed to those without the illness, due to a greater chance of both macrovascular and microvascular problems. As the disease's global incidence rises, so does the need for and expense of Type 2 diabetes mellitus healthcare. According to studies, efficient hyperglycemia management has been one of the best indicators of lower yearly healthcare expenses in people with Type 2 Diabetes [2]. Type 2 diabetes mellitus has multiple alternative expenses in addition to obvious societal costs and a person's health. This included lost efficiency for organizations and lost money for both management and staff as a result of severe illness that causes absence from initial resignation, untimely death, and work. Given the high health, societal, and economic costs of Type II diabetes mellitus, it is evident that developing effective strategies for reducing and managing the illness is important [3].

For the management of diabetes mellitus various dietary interventions were made and many random clinical trials (RCTs) were conducted. Some of the diets which were found effective in the management of diabetes are the Mediterranean diet, low-carbohydrate diet, and low glycaemic index diet.

In our meta-analytical study, we will be collecting data from RCTs conducting an interventional study on low-carbohydrate, Mediterranean, and low-glycemic index/load diets. Data extraction will be based on diabetic variables such as glycated hemoglobin (HbA1c), fasting blood glucose (FBG), triglycerides (TG), low-density lipoprotein (LDL), and body mass index (BMI). All the data collected were converted into the same units. There is a need to make an effective diet containing macro and micronutrients for the management of diabetes.

1.2 Current Scenario of Diabetes mellitus

Around **537M** adults between the age of 20-79 years are diagnosed with diabetes mellitus i.e., out of 10 individuals one person is diabetic. This number is predicted to rise **643 M** by 2030 and **783M** by the end of the year 2045 [4].

Diabetes Mellitus has a significant worldwide and rising impact, particularly in developing countries such as India, owing mostly to the rising incidence of obesity and unhealthy food and lifestyle. Diabetes Mellitus was estimated to affect 77M people in India in 2019, with this figure anticipated to climb to more than 134M by the end of the year 2045 [4]. Around 57% of people are still not diagnosed. T2D accounts for most of the cases resulting in multiple organ failures, which are roughly classified as CVDs. These problems are a key reason for increased early disease and mortality in diabetes, resulting in shortened lifespans and huge economic and other diabetes expenses on the Indian health system. Diabetes health factors include a poor diet, age, race, obesity and physical inactivity, behavioral patterns, and family history as well as Controlling glucose levels, blood lipid levels, and blood pressure, which can help to avoid the development of diabetic issues. Diabetes diagnosis and control is a serious hurdle in India because of many challenges and hurdles such as shortage of a participatory strategy, collected information, understanding of diabetes mellitus, its health conditions and consequences, availability of healthcare settings, access to inexpensive drugs, and so on. To combat diabetes and decrease T2D-related complications issues in India, proper health awareness and main preventive measures at both the personal and community level are required [3].

Condition of diabetes mellitus in India:

In India, the occurrence of diabetes and altered FBG was 9.3% and 24.5%, respectively. 45.8% of people with diabetes were conscious of it, 36.1% were still on medication, and 15.7% had it in management [5]. More than three-quarters of individuals (84.0%) sought advice from allopathic clinicians and 78.8% sought therapy for diabetes mellitus [5]. Adults with high cholesterol and high blood pressure had higher therapy, consciousness level, and management. The occurrence of high FBG and diabetes is more among adults, but treatment and management awareness remain poor in India. To control diabetes mellitus in India, various measures such as medication persistence, counseling services, increased knowledge, and enhanced preventiveness are required [5].

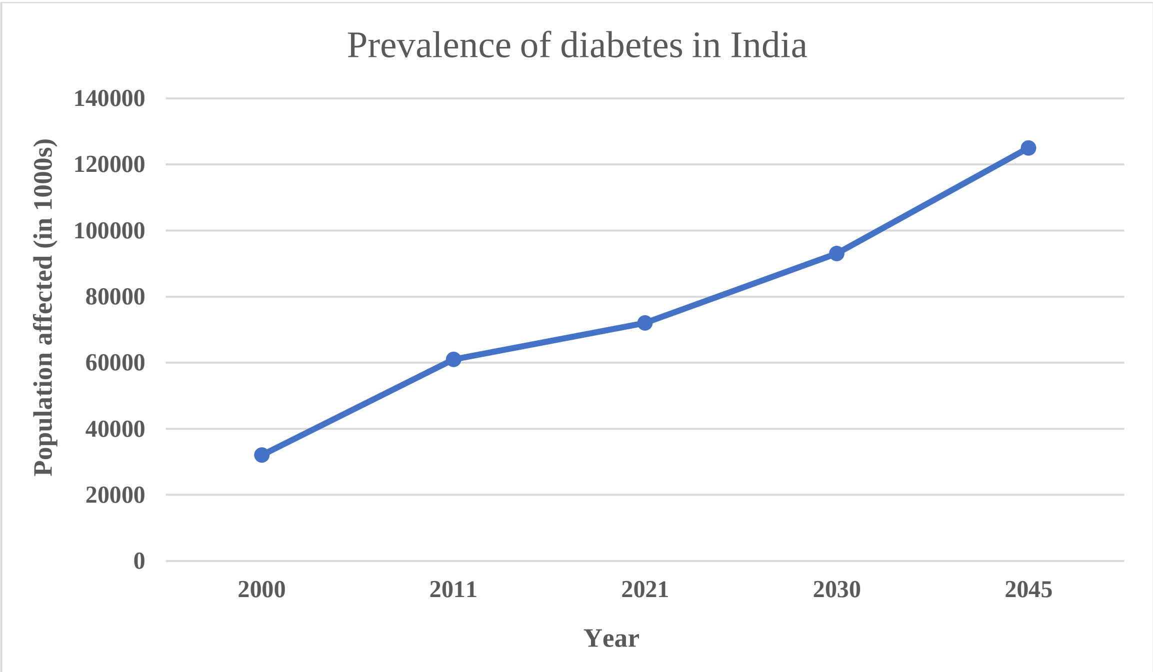

Figure 1. The current prevalence of diabetes in India, and the projected values for the same for the years 2030 and 2045 [4].

OBJECTIVES

- To perform literature search on available databases for RCTs for selected dietary interventions in case of diabetes mellitus.
- To compare the nutritional composition of different dietary interventions.
- To compare the effects of different dietary interventions on Glycaemic Control and Anthropometric measures in diabetic patients.
- To implement the best possible nutrient composition for making an effective traditional Indian diet plan for diabetic patients.

Chapter-2

LITERATURE REVIEW

2.1 OVERVIEW

Diabetes mellitus is a diverse set of multivariate, multiple-gene inheritance disorders described by a rise in FBG due to a lack of or total absence of insulin [6]. Diabetes is the major reason for adult blindness and disability, as well as heart attacks, nerve damage, renal failure, and strokes [6]. The vast proportion of diabetes cases is characterized by T1D or T2D also known as insulin-dependent and insulin-independent diabetes respectively.

2.2 Type-1 Diabetes

Around ten percent of 20M Americans who are diabetic have T1D [Centers for disease control and prevention]. A complete insulin shortage produced by an auto-immune assault on pancreatic cells by T-cells distinguishes the condition. Insulitis occurs when the beta cells get invaded. This autoimmune assault on cells gradually depletes the beta-cell frequency over the period. Complications begin rapidly once 80-90% of the insulin-producing cells are killed. At this stage, the pancreas is not able to appropriately react to sugar consumption, needing insulin treatment to re-establish glycemic control and prevent dangerous ketoacidosis. Cell death can be triggered by an external factor that is which can be due to viral infection or can be due to heredity factor which enables them to recognize as non-self and causes cell death [6]. Type 1 diabetes patients have essentially no functioning cells and are not able to react to fluctuations in flowing sugars or sustain constant insulin production.

Diagnosis

T1D often manifests itself during adolescence or childhood and signs arise abruptly. Individuals with T1D have a rapid outbreak of polydipsia (extreme thirst), polyphagia (extreme hunger), and polyuria (frequent urination), which is often induced by sickness or stress. These problems are usually followed by a reduction in weight, weakness, and fatigue. The diagnosis of T1D is done by glucose test done at fasting in which FBG levels are checked. An FBG of more than 125mg/dl is said to be diabetic [WHO 2016]. [Note: FBG levels between 100 and 125 mg/dl are termed impaired and a person will be called pre-diabetic.]

Fasting is described as not eating for at least 8 hours minimum. When the clinical diagnosis of type 1 diabetes is questionable, testing for circulating islet-cell antibodies is advised [6].

2.2.1 Metabolic changes in T1D

T1DM metabolic disorders are induced by insulin insufficiency, which has a substantial influence on metabolism in 3 major tissues: adipose tissue, liver, and muscle.

Ketoacidosis and Hyperglycemia:

Untreated T1D is characterized by high levels of blood glucose and ketone bodies. High blood glucose levels result from increased hepatic glucose synthesis via gluconeogenesis mixed with reduced regional consumption (adipose tissue and muscle have the GLUT-4 transporter;). Ketosis is triggered by a rise in Fatty acids mobilization from fat cells, as well as a rise in liver F.A-oxidation and the production of ketone bodies. [Note: Acetyl coenzyme A is a ketogenesis substrate as well as an allosteric regulator of the gluconeogenic enzyme pyruvate carboxylase]. Diabetic ketoacidosis(DKA), a kind of metabolic disorder, strikes when twenty to forty percent of recently diagnosed T1D patients can return if the patient gets unwell or fails to follow medication. Diabetic Ketoacidosis is managed with electrolyte and fluid replacement, as well as short-term insulin doses which are used to control hyperglycaemic conditions and to not let the body go into hypoglycaemic conditions [6].

Hypertriglyceridemia:

Some Fatty acids that saturate the liver can be eliminated by oxidation or ketones production. These extra FA are transformed into TAG, which is packed and released in the form of very low-density lipoproteins(VLDLs). After a meal, intestinal epithelium cells manufacture small size fatty molecules, known as chylomicrons from dietary fats. Since lipoprotein lipase breakdown in fat tissue blood capillaries is limited in diabetics (when insulin concentrations are insufficient), circulating VLDLs and chylomicrons levels are high, leading to hyper triacyl glycerolemia [6].

2.3 Type–2 Diabetes

Approximately 90-95% of adults in India having Diabetes are diagnosed with Type-2 Diabetes [7].

T2D usually appears gradually without visible symptoms. To diagnose the illness, regular screening tests are routinely utilized. But polydipsia and polyuria can last for multiple weeks in persons with type II diabetes. Although polyphagia is feasible, it is unusual [6].

Patients with T2D have both dysfunctional pancreatic beta-cells and insulin resistance arising due to lifestyle changes and changes in dietary habits. Although in T2D, hyperglycaemic conditions are often controlled by small insulin doses for the management of HbA1c levels below 7%. T2D is often milder than T1D metabolic abnormalities since insulin release in T2D, while insufficient, does inhibit ketogenesis and halt the course of DKA [6]. The existence of hyperglycemia—that is, an FBG of 126 mg/dl or higher—is the most prevalent foundation for identification. Viruses and bacteria do not induce pathogenesis nor Anti-inflammatory antibodies.

[Note: hyperglycemia, dehydration, and altered mental status, all are acute complications of type 2 diabetes in older adults.

T2D is distinguished by insulin resistance, low insulin levels, and high sugar levels.

Resistance to Insulin

Insulin resistance is the diminished ability to absorb insulin by muscle, adipose tissue, and liver. The capacity of the muscle, adipose tissue, and liver to react correctly to typical (or elevated) insulin levels in the blood. Insulin resistance is characterized by unregulated gluconeogenesis and decreased glucose adsorption by adipose tissue and muscle.

2.3.1 Obesity causing insulin insensitivity

Obesity is one the most predominant cause of the development of resistance towards insulin. Due to malfunctioning of insulin-producing beta-cells, in hyperglycaemic conditions body produces a high amount of insulin to compensate for the amount of glucose in the blood or to control the hyperglycaemic conditions. Figure 2 illustrates, that insulin production in obese persons is 2-3 times greater than in healthier ones. This high insulin conc attempts to compensate for the hormone's reduced impact (due to insulin resistance), resulting in blood sugar levels equivalent to those seen in lean people.

Obesity is the predominant cause of T2D, and 80-90% of those who have it are obese or overweight. Obese persons require unusually high quantities of insulin to keep their blood sugar levels appropriate because obesity induces insulin sensitivity.

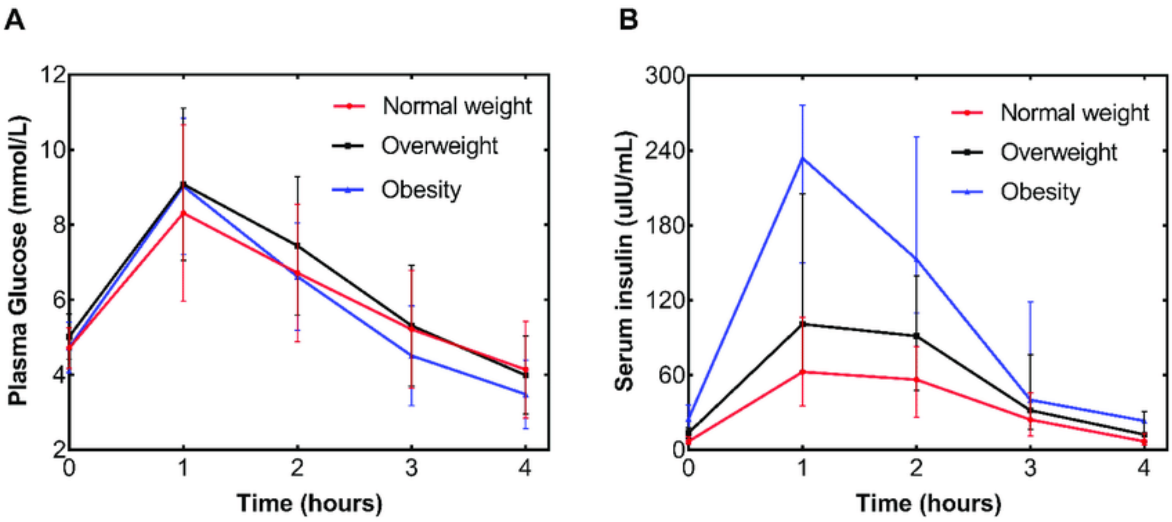

Figure 2. Level of blood glucose and insulin among normal and obese individuals

Insulin resistance causing T2D

Type 2 diabetes is not caused solely by insulin resistance. T2D develops in insulin-resistant individuals with reduced -cell activity. Insulin resistance and the accompanying risk of acquiring T2D are widespread in the aged, obese persons, and those who are not physically active. With elevated insulin release, these individuals are not able to appropriately compensate for insulin resistance [6].

Causes of insulin resistance

Insulin sensitivity develops when one gains weight and gets better as one loses weight. This suggests that fat storage contributes to the emergence of insulin resistance. Fat tissue is both a secretory and an energy reserve organ. Fat cells release regulatory chemicals like adiponectin and leptin, which can be the reason for developing insulin insensitivity. Furthermore, obesity-related Free fatty acids levels have connected to the evolution of insulin resistance [6].

[Note: Lipolysis produces FFAcids in insulin-resistant adipocytes].

Beta-cells defectiveness

In T2D, the pancreas initially preserves mere beta-cells activity, resulting in levels of insulin fluctuation from higher or lower than normal. Nevertheless, as time passes, the cell gets less functioning and is not able to release enough insulin to control high blood sugar level conditions. Insulin levels are higher in obese T2D patients than normal T2D patients. As a result of the disease's natural progression, the ability to manage hyperglycemia with intracellular insulin secretion declines (Figure 3). The harmful effects of prolonged hyperglycemia and raised Free fatty acids may hasten the deterioration of beta-cell function.

Fig. 3, Progression of type-2 diabetes and the factors associated.

2.3.2 Metabolic Alterations in T2D

Hyperglycaemia

Hyperglycaemic condition is achieved by elevation in gluconeogenesis, with a decrease in glucose use. Production of ketone bodies is probably negligible or absent in T2D patients because insulin reduces hepatic ketogenesis [6].

[Note: Metformin, an oral medication used to treat type-2 diabetes, hinders hepatic gluconeogenesis]

Dyslipidemia

Fatty acids are translated to triacylglycerols in the liver, where they are bundled, and secreted as VLDL. Following a meal, intestinal mucosal cells synthesize chylomicrons from dietary lipids. Because diabetes patients have poor lipoprotein-lipase breakdown in adipose tissue and muscle, blood chylomicron and very low-density lipoprotein concentrations are elevated, leading to a condition called hypertriacylglycerolemia. T2D has also been associated with low HDL levels.

2.4 Gestational Diabetes

Gestational diabetes occurs when your blood sugar levels rise during pregnancy. Each year, it affects approx. 10% of pregnant women in the United States. Undiagnosed pregnant women are at risk. There are two types of gestational diabetes.

Women with A1 can manage their condition through diet and exercise. People with type A2 should take insulin or another medication, such as metformin. Gestational diabetes disappears after delivery. However, it can harm a child's health and increase our risk of developing type

2 diabetes later in life. The person can also take preventive measures to protect the health of h imself and his children [8].

Cause of Gestational diabetes

During pregnancy, the placenta produces hormones that cause a build-up of glucose in your blood. Normally, your pancreas produces enough insulin as per our needs. However, if you are resistant to insulin, the blood sugar levels increase and you develop gestational diabetes.

2.5 Type 1.5 Diabetes

LADA (Latent Autoimmune Diabetes in Adults) holds properties from both t1d and t2dm. LADA is diagnosed in adulthood and, like type 2 diabetes, develops gradually. However, apart from type II diabetes, LADA (latent autoimmune diabetes in adults) is an autoimmune disorder that cannot be reversed through dietary and lifestyle changes. In the case of type 1.5 diabetes, your beta cells stop working much faster than when you have type II. Damage to your pancreas caused by antibodies against BETA- cells can cause type 1.5 diabetes. Family background of autoimmune conditions, for example, may also play a role. When the pancreas is destroyed in type 1.5 diabetes, the body, like in type 1, destroys pancreatic beta cells.

2.6 Diagnosis of Diabetes Mellitus

Blood glucose measurement: Doctors collect blood samples after individuals have not eaten overnight to examine blood sugar levels. Diabetes is detected when FBG levels exceed 6.9 mmol/L (125 mg/dL). Nevertheless, samples of blood collected after persons have eaten can also be used. It is typical for blood glucose levels to rise after eating, although levels should not rise significantly. Diabetes is diagnosed when a randomized blood glucose concentration exceeds 11.0 mmol/L (199 mg/dL).

Haemoglobin A1C: Haemoglobin is the oxygen-carrying red material found in RBCs. When plasma is subjected to high amounts of glucose levels over time, glucose clings to hemoglobin and creates glycosylated hemoglobin. Diabetes may be detected using hemoglobin A1C readings. Diabetes is diagnosed when the hemoglobin A1C level is 6.5% or above. Individuals have prediabetes if their reading is between 5.7-6.4 [Centers for disease control and prevention].

Glucose tolerance test: People do this test after fasting, having a sample of blood obtained to assess their FBG level. A specific amount of solution containing sugar is then given to drink and then after 2-3 hours, blood glucose levels are tested. Several blood samples are obtained over the following 2-3 hrs and examined to see if the blood sugar levels climb to excessively high levels.

2.7 Role Of Nutrition

As India is undergoing nutritional changes, resulting in an excess amount of calories, trans-fat, simple sugars, saturated fats, and a lack of fiber. Obesity, metabolic syndrome, diabetes, and cardiovascular disease have all increased as a result of such dietary changes and sedentary lifestyles (CVD). The average Indian diet was found to be higher in saturated fats, carbohydrates, and trans-fat, and lacks good cholesterol, protein, monounsaturated (MUFA), omega fats fat (n-3 PUFA), and fiber [9]. However, there is a wide variation in total fat intake(saturated), with the wealthy ingesting 3 times extra fat than the rural population(poor) in India. In South Asians, these nutritional inequities are linked to diabetes, dyslipidemia, and insulin resistance, all of which lead to CVD.

2.8 Food and Nutrient Intake of Urban Population of India

Food consumption:

Cereals comprised the majority of the urban population's diet. The intake of root and tuber crops was relatively high in West Bengal, Assam, Bihar, and the Andaman and Nicobar Islands. Similarly, consumption of millet was high in Maharashtra, Gujarat, and Karnataka. The average cereal and millet intake was 320 g/CU/day, which was less than the RDI [NNMB report,2017]. While the consumption of legumes and pulses was approximately 42g/CU/day, it was comparable to the ICMR recommended level [10]. GLV, dairy-based products, sugar, and jaggery intake were all found lesser than the Recommended daily intake (Figure 4).

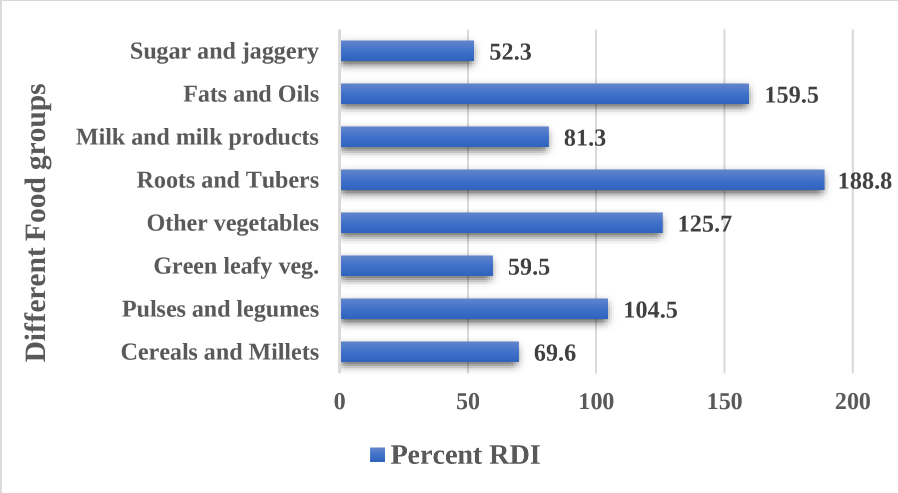

Fig 4. Average household consumption of foodstuffs as % recommended dietary intake

Nutrition Intake

The average consumption of macro-nutrients like energy as well as protein, and micro-nutrients such as iron, thiamine, and niacin, was found to be less than the RDA, whereas riboflavin and Vitamin A intake had been grossly inadequate. The consumption of total folate and Vitamin C was adequate (Figure 5) [10].

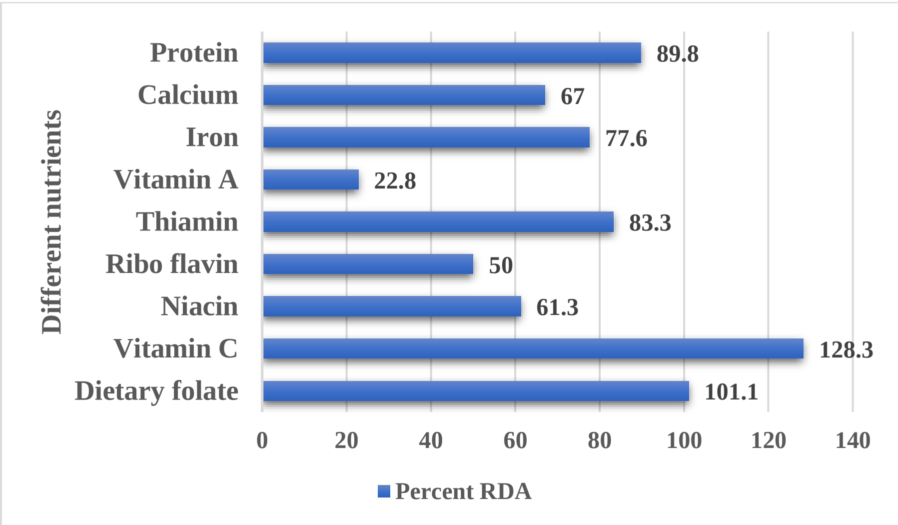

Figure 5. Average Household consumption of Nutrients as % Recommended dietary Allowances

2.9 Prevalence of Obesity and Overweight in Urban Adults

When compared to their male counterparts (34%), more urban women (44%) were found to be overweight or obese. (Fig. 6) The overall prevalence of overweight/obesity (BMI 25) among urban men was 34%, with Rajasthan (42.6%) having the highest prevalence, accompanied by Puducherry (42.5%) and Tamil Nadu (35.3%), and West Bengal and Uttar Pradesh having the lowest (21%). Overweight/obesity was most prevalent in the regions of Puducherry (59.8%) and Tamil Nadu (54.19%). Overweight/obesity was lowest in Uttar Pradesh (29.7%), followed by New Delhi (52.3%), Gujarat (52.2%), and Kerala (52.1%). Almost 11% of adult females had chronic energy deficiency [NNMB report,2017].

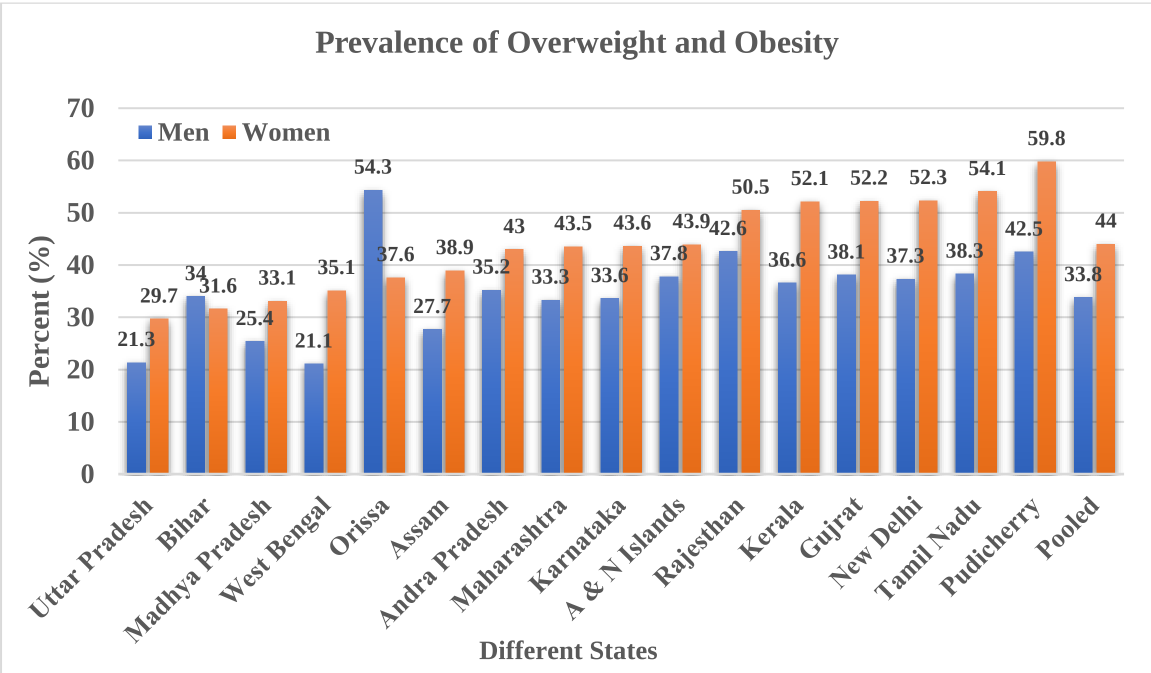

Figure 6. Percent prevalence (%) of Overweight and Obesity in Urban Adults

Table 1. Mean energy (E), protein, carbohydrate, and fat consumption and percentages from various dietary categories among Indian urban adults [11].

Food groups	Intake		Energy		Protein		Fat		Carbohydrate	
	(g)	(%)	(Kcal)	(%)	(g)	(%)	(g)	(%)	(g)	(%)
Cereals and Millets	293.4	33.7	998	51.4	26.3	47.5	2.9	5.6	212	73.4
Pulses and Legumes	38.6	4.4	119	6.1	8.2	14.8	0.8	1.6	19	6.6
Fats and Edible Oils	29.5	3.4	266	13.7	0	0	29.5	57.2	0	0
Meat, Poultry, Fish and Sea foods	32.1	3.7	104	5.4	6.4	11.6	2.1	4.1	0	0
Milk and Milk products	120.7	13.9	99	5.1	4.2	7.6	6	11.6	8	2.8
Nuts and Oil seeds	8.9	1	39	2	0.8	1.4	3.6	7	1	0.3
Vegetables	92.2	10.6	29	1.5	1.9	3.4	0.3	0.6	4	1.4
Roots and tubers	87.5	10	53	2.7	1.4	2.5	0.2	0.4	11	3.8
Fruits	51.6	5.9	22	1.1	0.5	0.9	0.2	0.4	4	1.4
Others	116.8	13.4	215	11.1	5.7	10.3	6	11.6	31	10.7
Total	871.3	100	1943	100	55.4	100	51.6	100	289	100

Table 2. Summary of RDA for Indians (ICMR-NIN,2020)

GROUP	CATEGORY	ENERGY (Kcal/d)	ENERGY (Kcal/kg/d)	CARBOHY DRATE (gm)	FATS (gm)	DIETARY FIBRE (gm)	PROTEIN RDA (gm/d)	PROTEIN RDA (gm/kg/d)
	Sedentary work	2110	32	90	25	30		
MEN (65kg)	Moderate work	2710	42	110	30	40	54.0	0.83
	Heavy work	3470	53	130	40	50		
	Sedentary work	1660	30	80	20	25		
Female (55kg)	Moderate work	2130	39	90	25	30	45.7	0.83
	Heavy work	2720	49	100	30	40		

The total energy required or the total energy expenditure (TEE) is calculated by multiplication of (BMR) to (PAL) [ICMR,NIN report,2020]:

$$TEE = BMR \times PAL$$

Table 3. Summary of RDA for Indians, ICMR, NIN (2020)

NUTRIENTS	Required amount for men	Required amount for women	NUTREINTS	Required amount for men	Required amount for women
Calcium(mg)	1000	1000	Niacin(mg)	18	14
Magnesium(mg)	440	370	Vitamin B6(mg)	2.4	1.9
Iron(mg)	19	29	Folate(ug)	300	220
Zinc(mg)	17	13.0	Vitamin B12(ug)	2.2	2.2
Iodine(ug)	150	150	Vitamin C(mg)	80	65
Thiamine(mg)	1.8	1.7	Vitamin A(ug)	1000	840
Riboflavin(mg)	2.5	2.4	Vitamin D(IU)	600	600

2.10 T2D control with a dietary approach

T2DM has reached pandemic proportions in the world today. Carbohydrate restriction and weight loss have been found in clinical research to ameliorate obesity, hyperglycemia, and T2DM in persons with obesity-related T2DM [13].

Diabetes is heavily influenced by diet. Meal depends on the calories it has which is determined by gender, weight, height, age, occupation, and other factors.

Whether you're attempting to avoid or treat diabetes, your dietary requirements are nearly identical to everyone else's, so no special meals are required. Even a 5% to 10% weight loss will help you decrease your sugar levels, cholesterol levels, and blood pressure.

Reducing weight and eating healthy can also improve your attitude, energy, and overall sense of well-being. Even if you've already been diagnosed with diabetes, it's never too late to make a change. Diabetes symptoms can be reduced or even reversed by eating better, becoming more fit and healthy, and decreasing weight [14].

Dr. Frederick Madison Allen treated diabetes with a fasting approach and a step-by-step reintroduction of macro and micronutrients to discover the threshold at which high blood sugar formed. The average diabetic diet suggestion using this approach was 70% fat, 18% protein, only 8% carbs, and 4% alcohol [13].

Foods to focus on for diabetic person:

1. SALT: The salt ratio for a diabetic diet should be low as it can raise blood pressure.
2. SUGAR: Sucrose, a kind of table sugar, solely comprises calories and carbs. You also require calcium to metabolize sucrose. Inadequate sucrose intake may cause calcium to be leached from the bones. Replace sucrose with natural sugars such as honey, jaggery, etc. [14]
3. FATS: Fried items should be avoided. Good fats should be included as they help in absorbing fat-soluble vitamins (Avocado).
4. DAIRY: Low-fat milk should be used.
5. HIGH GI INDEX FOODS: Foods with high glycemic index should be avoided. (White bread, rice)
6. LOW-FAT MEAT: A leaner source of protein should be included in the diet for non-veg, such as fish, and high-fat meat such as red meat should be avoided.

2.11 Different dietary approaches for the management of Diabetes mellitus

Control of T2D requires lifestyle changes and self-management abilities. Improvements in eating habits are among the most important lifestyle adjustments and difficulties for diabetes patients. For quite some time, diabetic patients have been advised to follow the conventional fraction-controlled diet high in carbohydrates; nevertheless, other diets are now also being evaluated on this group of people. Numerous strategies are used by diabetic patients to manage their blood sugar levels. The long-term dietary plan a person selects, together with exercise and medicine, has a crucial impact on the quantity of insulin required and the total blood glucose changes that an individual encounters during the day. Diabetes must be well managed to lower medical expenses, improve quality of life, and avoid both small and major consequences.

Type 2 diabetes must be properly treated using self-monitoring skills in an attempt to help avoid complications. A healthcare provider can educate patients about diabetes methods for self-management such as diet and nutritional counseling or medical nutrition treatment (MNT), diabetes fundamentals, plasma glucose monitoring, managing medications, and exercising. The objectives of MNT for people who have diabetes include encouraging and supporting healthy eating habits, achieving, and maintaining body weight targets, achieving specific glycaemic conditions, blood pressure, and cholesterol targets, and delaying or preventing complications associated with diabetes.

Managing body weight is crucial for lowering the risks associated with diabetes. Therefore, these dietary suggestions begin by taking energy levels and weight reduction techniques into account. By itself, sports and fitness only have a minimal impact on reducing weight. Yet, exercising should be advised because it helps to maintain weight loss over the long term, lowers blood sugar levels quickly, and improves sensitivity to insulin without requiring weight loss. The typical diets for losing weight initially contribute to a loss of 0.5-1kg/week and contain 500–1,000 lesser calories than are thought to be required for weight retention. With these diets, many individuals can lose weight up to 10% of their starting weight in about six months, but without ongoing care and monitoring, most people gain back the weight they have lost. When people with T2D consume less than 800 calories per day, they lose a significant amount of weight and have quick changes in their lipid and glucose levels [24]. Weight gain is typical when exceptionally low-calorie dietary habits are ended and independently chosen meals are reinstated.

One of the main objectives of diabetes treatment is to manage blood sugar levels to return to normal or close to normal levels. Since dietary carbohydrates are the main driver of postprandial glucose levels, nutritional and dietary treatments that lower these fluctuations are crucial in this regard. Diets lower in carbohydrates were found to be beneficial in controlling post-prandial hyperglycaemic conditions. However, foods richer in carbs are essential sources of minerals, fiber, vitamins, and energy, and they also contribute to the flavor of our diets. As a result, these items are crucial parts of a healthy diet for those who have diabetes.

The nutritional content of meals may be estimated using several techniques, such as carbohydrate measurement, the system of exchange, and experience-based estimating. Many people use the experience to assess and meet post-meal glucose goals with a wide range of healthy foods by evaluating pre and postprandial glucose.

2.12 Nutrient recommendation

Carbohydrate recommendation

Following a meal, blood glucose concentration is primarily influenced by how quickly glucose enters the bloodstream (through digestion and absorption) and leaves (through circulation). Typical insulin glandular response regulates postprandial blood sugar levels in response to eating carbohydrates, but in individuals who have diabetes, malfunctions in insulin action, secretion of insulin, or both interfere with the control of postprandial glucose. Postprandial blood sugar levels are influenced by both the amount and kind of source of carbs present in the meal.

- For optimal health, one should consume carbohydrates mainly from vegetables, fruits, whole grains, and legumes.
- To achieve control of glycaemic levels, tracking carbohydrate measurement remains a crucial method.
- Sucrose-containing meals should be avoided as they can elevate blood sugar levels, or if added into meals should be compensated with insulin or antidiabetic drugs.
- High-fiber foods are recommended for diabetic patients.

Diabetic patients are advised to consume different fiber-containing foods such as fiber-rich cereals, vegetables, legumes, and whole-grain products as they can provide minerals, vitamins, complex carbohydrates, and other crucial elements for a healthy diet.

Cholesterol and Dietary fats recommendation

The primary goal for diabetic patients is to limit the amount of trans fats, saturated fats, and cholesterol in their diets to lower the risk of developing cardiovascular diseases. Trans fats and saturated fats are the main elements for the elevated levels of LDL (low-density lipoprotein). Reduction in the saturated and trans-fat levels in the diet helps in the reduction in the total plasma and LDL cholesterol levels. Reduction in the saturated fats in diets has shown a reduction in high-density lipoprotein (HDL) levels. The increased amount of LDL levels has shown a high chance of cardiovascular risk.

- Limit the number of saturated fats to less than 7% of total calories consumed.
- Limit the amount of trans fat in the diet.
- Limit the amount of cholesterol to less than 200mg/day.

- Two or more servings containing polyunsaturated fatty acids are recommended.

Protein recommendation

The recommended protein intake for a healthy diet is about 10-30% of protein of total energy intake. The recommended dietary allowance for protein is 0.8gm of protein per kilogram of body weight per day. High PDCAAS (protein digestibility-corrected amino acids) scores and the provision of all 9 EAAs are indicators of high-quality protein sources. Poultry, fish, cheese, soy, and Meat are a few examples.

- For diabetic individuals' protein intake should be between 15-25% of total energy consumed throughout the day.
- Currently, it is not advised to lose weight using a high-protein diet. It is uncertain how long-term protein intake beyond 20% of calories may affect controlling diabetes and its consequences. these diets may result in a temporary weight reduction and improved glycaemic condition, it is unknown whether these advantages last over the long term.

Several diets are commonly recommended for the management of Diabetes mellitus. Below are a few examples of diets: -

The mediterranean diet

This diet emphasizes whole, unprocessed food like fruits, vegetables, whole grains, legumes, nuts, and seeds, as well as healthy fats like olive oil, nuts, and fatty fish. It has been found to improve hyperglycaemic conditions and the prevalence of diabetes.

DASH diet

The Dietary approach to stop hypertension (DASH) diet is a low-salt diet that emphasizes adding whole grains, vegetables, protein-rich foods, fruits, and low-fat food products in their meals. This diet has been found to lower blood pressure and Blood Sugar control in diabetic patients.

Vegan diet

A vegan diet comprises all the food items based on plants. All the products related to animals such as dairy-based products, eggs, and meat are excluded from the diet. A vegan diet is found to be having a positive effect on controlling the risk of CVDs.

Low-Carbohydrates diet

A low-carbohydrate diet limits carbohydrate intake and emphasizes protein and fat sources, such as meat, fish, eggs, nuts, and seeds. This diet has been shown to improve blood sugar control and reduce the need for diabetes medications in some people with type 2 diabetes.

Low-G.I/Load diet

The low-G.I diet focuses on choosing foods with a low glycaemic index, which means they cause a slower and smaller rise in blood sugar levels. Foods with a low glycaemic index include whole grains, fruits, vegetables, and legumes.

FOODS	GLYCAEMIC INDEX ± S. D	FOODS	GLYCAEMIC INDEX ± S. D
GLUCOSE	103 ± 3	Ragi	104 ± 1
RICE	78 ± 4	Red gram	43 ± 4
White wheat Bread	75 ± 2	Green gram	42 ± 4
Wheat chapati	62 ± 3	Bengal gram	37 ± 5
White boiled Rice	70 ± 4	Masoor dal	42 ± 3
Brown boiled Rice	68 ± 4	Mixed dal	43 ± 6
Barley	24 ± 2	Chocolate	40 ± 3
Instant oats Porridge	79 ± 3	Popcorn	65 ± 5
Rice Porridge	78 ± 9	Soft drinks/ Soda	59 ± 3
Millet Porridge	67 ± 5	Honey	61 ± 3
Sweet Corn	52 ± 5	Vegetable soup	48 ± 5
Corn flakes	81 ± 6	Khichadi (steamed)	57 ± 3
Kidney beans	44 ± 3	Rice + Chickpeas	54 ± 1
Potato (boiled)	78 ± 4	Rice + Green gram	68 ± 18
Carrot (boiled)	39 ± 4	Rice + Red gram	64 ± 6
Milk (full fat)	39 ± 3	Pasta	45 ± 4
Milk (skimmed)	37 ± 4	Orange	43 ± 3
Chickpeas	28 ± 9	Banana	51 ± 3
Soya beans	16 ± 1	Pineapples	59 ± 8
Lentils	32 ± 5	Mango	51 ± 5
Muesli	57 ± 2	Watermelon	76 ± 4
Dates (raw)	42 ± 4	French-fries	63 ± 5
Sweet potato (boiled)	63 ± 6	Ice-cream	51 ± 3
Yogurt	41 ± 2		
Bajara	55 ± 13		
Jowar	77 ± 8		

Table 4. Glycaemic index of some common Indian food

Low-fat diet

A low-fat diet emphasizes lean protein sources, such as poultry and fish, and limits consumption of high-fat foods, such as oils and fatty meats. This diet was found to improve blood glucose control and reduces the risk of heart disease in people with diabetes.

Ketogenic diet

A ketogenic diet comprises of very low-carbohydrate diet in which most of the macronutrient composition is of fats that is about 40-50% and protein at 25-35%. Most of the foods in the keto diet comprise healthy fats containing MUFA and PUFA. This diet is found effective in reducing weight and triglycerides levels. Also been found to be effective in lowering FBG levels and diabetic medications.

The TLC diet

The American Heart Association recommends the Therapeutic Lifestyle Changes (TLC) diet as a low-saturated fat, low-cholesterol dietary strategy to help lower blood cholesterol levels and lessens the risk of CVDs. In contrast to reducing saturated fat, trans fat, and cholesterol, it emphasizes fruits, vegetables, whole grains, lean protein sources, and low-fat dairy products.

The American Diabetes Association (ADA) diet

The ADA diet places a strong emphasis on portion management and a healthy amount of fats, proteins, and carbs. While limiting the consumption of saturated and trans fats, added sugars, and sodium, it promotes the consumption of whole grains, fruits, vegetables, lean protein sources, and low-fat dairy products.

Out of these diets available for the management of diabetes, we have selected a few most effective diets having a good impact on diabetic patients which are the Mediterranean diet, low-carbohydrate diet, and low-glycemic index/load diet. we have discussed the diabetic variables being under the influence. The most prevalent form of diabetes, type 2, has an established risk factors:

Body Weight

T2D is more likely to strike fat or overweight people than healthy-weight people. This is because extra body fat, especially in the belly, might prevent the body from using insulin as it should, resulting in insulin resistance and high blood sugar levels.

After eating, a person's body converts the meal into glucose, which is subsequently carried into the cells to produce energy. A hormone called insulin aids in the transport of glucose from the circulation to the cells. When a person has insulin resistance, their cells stop responding to insulin, allowing glucose to stay in circulation and raise blood sugar levels.

T2D risk can be lowered by maintaining a healthy BMI with a balanced diet and frequent exercise. Losing weight and changing to a healthy lifestyle can also help control diabetes and lower the risk of complications in people who have already received a diagnosis. It's crucial to remember, though, that weight reduction should always be accomplished under the advice of a healthcare practitioner in a healthy and long-lasting manner.

Being overweight or obese increases the chance of acquiring type 2 diabetes as well as other health issues including heart disease, high blood pressure, and some forms of cancer. But in terms of diabetes risk, body weight alone is not the only factor to consider. Another crucial factor is the distribution of body fat. Visceral fat, which is extra body fat that is in the belly, increases the risk of type 2 diabetes compared to other types of body fat. This is so because visceral fat, compared to fat in other parts of the body, is more metabolically active and can affect how well insulin works. Age, certain ethnic origins, and a family history of diabetes are other variables that might raise the risk of type 2 diabetes. However, healthy body weight can be maintained through a balanced diet and consistent exercise, which can also help lower the risk of developing diabetes and enhance general health and well-being.

Weight control can be a key component of diabetes care for those who have already received a diagnosis. Losing weight can increase the body's ability to use insulin more effectively, lessen the need for diabetic drugs, and lessen the chance of consequences including heart disease and nerve damage. To create a safe and efficient weight reduction strategy that takes into consideration their unique demands and health state, diabetics must collaborate with their healthcare team.

HbA1C (Glycated hemoglobin) levels

Glycated hemoglobin (HbA1C, glycohemoglobin) is a form of hemoglobin that is chemically linked to sugar which can be monosaccharides, including fructose, galactose, and glucose, which are spontaneously linked to hemoglobin when present in the bloodstream. Since glucose is most likely to bind to the hemoglobin than the other two monosaccharides, it has been used as a major source of energy by our body.

To accurately depict the actual (non-enzymatic) mechanism, the name ‘glycated hemoglobin’ is recommended over glycosylated hemoglobin.

HbA1c is typically evaluated to identify the three-month normal glucose level, but it can also be used to diagnose diabetes mellitus and monitor a patient's glycaemic control if they already have the disease. The test is restricted to a three-month average since RBC typically lives for four months. Since different red blood cells have different lifespans, the test is only used with a three-month limit.

Blood cells' cell membranes change because of glycated hemoglobin’s rise in highly reactive free radicals. Blood flow is hampered as a result of blood cell aggregation and increased blood viscosity. Glycated hemoglobin may also harm cells by causing inflammation, which leads to the development of atherosclerotic plaque (atheroma). Free-radical accumulation encourages the stimulation of Fe^{2+}-hemoglobin into aberrant ferryl hemoglobin (Fe^{4+}-Hb) through Fe^{3+}-Hb. Because Fe^{4+} is unstable, hemoglobin’s specific amino acids interact with it to restore Fe^{3+} to its oxidation state. Through cross-linking processes, hemoglobin molecules group together to form hemoglobin clumps (multimers), which promote cell death and the escape of Fe^{4+}-hemoglobin into the sub-endothelium and matrix of arteries and veins. The endothelium of blood vessels becomes more permeable as a result, and pro-inflammatory monocyte adhesion proteins are produced. These proteins encourage the accumulation of macrophages on the surfaces of blood vessels, which eventually culminate in the formation of damaging plaques [6].

The normal range for HbA1c in adults without diabetes normally is between 4% and 5.6%. The desired range for HbA1c in diabetics, however, may change based on age, the course of diabetes, and other medical issues. For most persons with diabetes, the ADA generally suggests a goal HbA1c level of 7% or lower.

Reaching and maintaining a desired HbA1c level can assist in lowering the risk of complications from diabetes, including nerve damage, renal disease, and eye issues. Healthcare professionals can also modify treatment regimens as necessary to enhance blood sugar management by routinely checking HbA1c levels.

Fasting blood glucose (FBG) levels

A blood test known as the fasting blood sugar level is performed after a person has fasted for a set amount of time, usually at least for eight hours. It is a typical test used to identify and track diabetes, as well as evaluate how well blood sugar is being managed overall.

Normal fasting blood glucose levels in adults without diabetes normally fall between 70 to 99 milligrams per deciliter (mg/dL) of blood. For most persons with diabetes, the American Diabetes Association (ADA) advises a goal FBG level of fewer than 100 mg/dL. FBG in the range of 100-125 mg/dl comes in the range of pre-diabetes, which means blood glucose level is higher than normal but not much that it can come under the category of diabetes. FBG level of more than 125mg/dl is said to be diabetic.

Fasting blood glucose levels that are routinely over the desired range may be a sign of diabetes or a sign that a patient needs to adjust their medication or way of life to better regulate their blood sugar.

It's crucial to remember that variables including stress, sickness, certain drugs, and other medical conditions might have an impact on fasting blood glucose levels. To monitor blood sugar management and diagnose diabetes, healthcare professionals may combine fasting blood glucose levels with additional tests like HbA1c, oral glucose tolerance tests, or random blood glucose checks.

Overall, fasting blood glucose levels are an effective tool to manage diabetes and must be used in combination with other metrics like HbA1c, blood glucose self-monitoring, medication management, and lifestyle changes to achieve and sustain target blood sugar levels and lower the risk of complications related to diabetes.

Triglycerides (TG) levels

Triglycerides are a form of fat that the body stores in fat cells and is present in the blood. They are one of the primary elements of human fat and are crucial to the process of metabolizing energy. When we eat, the body transforms the extra calories into triglycerides and stores them in our fat cells. However, if we consume extra calories than our bodies require, our triglyceride levels may rise and cause health issues. The normal range for triglycerides level is less than 150 mg/dl. Triglycerides are considered borderline when the triglyceride level ranges between 150 mg/dl to 199 mg/dl. Triglycerides level is considered high when it reaches above 200 mg/dl [6].

A high-carbohydrate and sugar-rich diet, binge drinking, obesity, and some medical disorders including diabetes and hypothyroidism are just a few of the things that can raise triglyceride levels. Cardiovascular disease, which can result in heart attack and stroke, is a risk factor for high triglyceride levels.

General health and disease prevention must keep triglyceride levels in check by a nutritious diet, frequent exercise, and keeping a healthy weight. For people with extremely high levels of triglycerides, medication may occasionally be administered to assist decrease them.

Abnormal triglyceride levels can be caused by foods, especially those heavy in saturated fat or carbohydrates that have undergone extensive processing. These high-calorie, simple-to-digest meals provide a more rapid release of energy, which is subsequently transformed into triglycerides and accumulated in fat cells.

High triglyceride levels are a sign of poorly managed type 2 diabetes as well. High levels of triglycerides are also associated with low thyroid hormone levels, liver, and renal problems. hypertriglyceridemia is a term used to describe a hereditary propensity to elevated triglyceride levels in some persons.

It is advised to make lifestyle changes such as eating a nutritious diet, exercising frequently, losing weight, and drinking less alcohol to reduce triglyceride levels. Drugs like statins or fibrates could also be administered in specific circumstances. A lower-calorie diet and frequent exercise can be used to treat high triglyceride levels. Alcohol consumption should also be reduced. This lifestyle-based approach is the best strategy to reduce triglyceride levels. The use of omega-3 fish oils may also lower triglyceride levels.

Low-density lipoprotein (LDL) levels

A form of cholesterol that is frequently known as "bad" cholesterol is low-density lipoprotein (LDL). LDL is a tiny, dense particle that can build up in artery walls and cause the development of plaques that can restrict or obstruct blood flow. This might make cardiovascular conditions like heart attacks and stroke more likely.

The liver produces LDL, which is then carried by the blood to other bodily tissues. It is utilized to create several hormones and is an essential part of cell membranes. LDL may still be a potential factor for cardiovascular disease if levels become too high.

A diet heavy in saturated and trans fats, as well as several medical disorders including diabetes and hypothyroidism, frequently results in high LDL levels. LDL levels can also be influenced by genetics.

A nutritious diet, frequent exercise, and keeping a healthy weight are among lifestyle changes that can lower LDL levels. Some people may also be given statins or other medications to decrease their LDL levels. Overall, keeping an eye on LDL levels is crucial for preventing cardiovascular disease, and people should collaborate with their doctor to create a personalized strategy for achieving and maintaining appropriate LDL levels.

LDL makes up the majority of your body's cholesterol. High-density lipoprotein, or "good" cholesterol, makes up the remaining portion. LDL is transported by HDL to your liver, where it is eliminated from your system. High HDL concentrations may offer protection from heart attacks and strokes.

Normal LDL levels are said to be ≤100 mg/dl. LDL levels between 100-129 mg/dl are said to be near-optimal or near-borderline levels. The level range between 130- 159 mg/dl is said to be borderline high. LDL level of range 160-189 mg/dl is said to be a high level of LDL levels. LDL level above 190 mg/dl is said to be very high and is found at risk for developing cardiovascular diseases such as strokes [6].

High LDL cholesterol levels can raise the risk of cardiovascular disease in those with diabetes, who are already at a higher risk. Diabetes frequently results in an altered lipid profile, with higher LDL-cholesterol and triglyceride levels and a reduction of HDL-cholesterol.

Insulin insensitivity, a sedentary lifestyle, and bad food choices are some of the common contributors to high LDL levels in diabetics. Atherosclerosis is a disorder where fatty plaques build up in the arterial walls, which can limit or obstruct blood flow. Increased LDL cholesterol levels can play a key risk factor in the development of this illness.

Controlling blood sugar levels in diabetes by medication and lifestyle changes can help lower the risk of CVD. Additionally, controlling other risk factors is crucial to lowering the risk of heart disease, including high LDL cholesterol levels. People with diabetes should engage with their healthcare practitioner to create a personalized strategy to reach and maintain appropriate LDL levels since monitoring LDL cholesterol levels is a crucial part of preventing cardiovascular disease.

Chapter-3

METHODOLOGY

3.1 Data sources and searches

The literature search was performed for published studies using electronic databases: PubMed and Google Scholar for (RCTs) until December 2022 using a predefined search strategy. Key search terms included diabetes, atherogenic, Low- Carbohydrates, Mediterranean, and Low-Glycaemic Index (GI),

Furthermore, reference lists from the studies were also screened to search for additional relevant studies.

3.2 Study selection

Inclution Criteria

Studies were included in the analysis when they are found to follow the inclusion criteria

1. RCTs of different dietary approaches:
    a. Low-carbohydrate (LC) diet (<30% carbs).
    b. Mediterranean diet
    c. Low glycaemic index/Load diet.
2. A minimum intervention period of 3 months and a maximum of 1 year were taken into study.
3. Patients of age ≥18 years, diagnosed with T2D.
4. The primary outcome is glycaemic control and anthropometric measurements.

Exclusion Criteria

The following studies were excluded:

1. Intervention is only based on dietary supplements or the effect of single foods.
2. RCTs include pregnant women, children, obese adults, and patients with abnormal glucose metabolism.
3. RCTs with an exercise or medication included in the intervention or control group.
4. RCTs with high-calorie restriction.

Selected studies were pre-examined by abstract before data extraction.

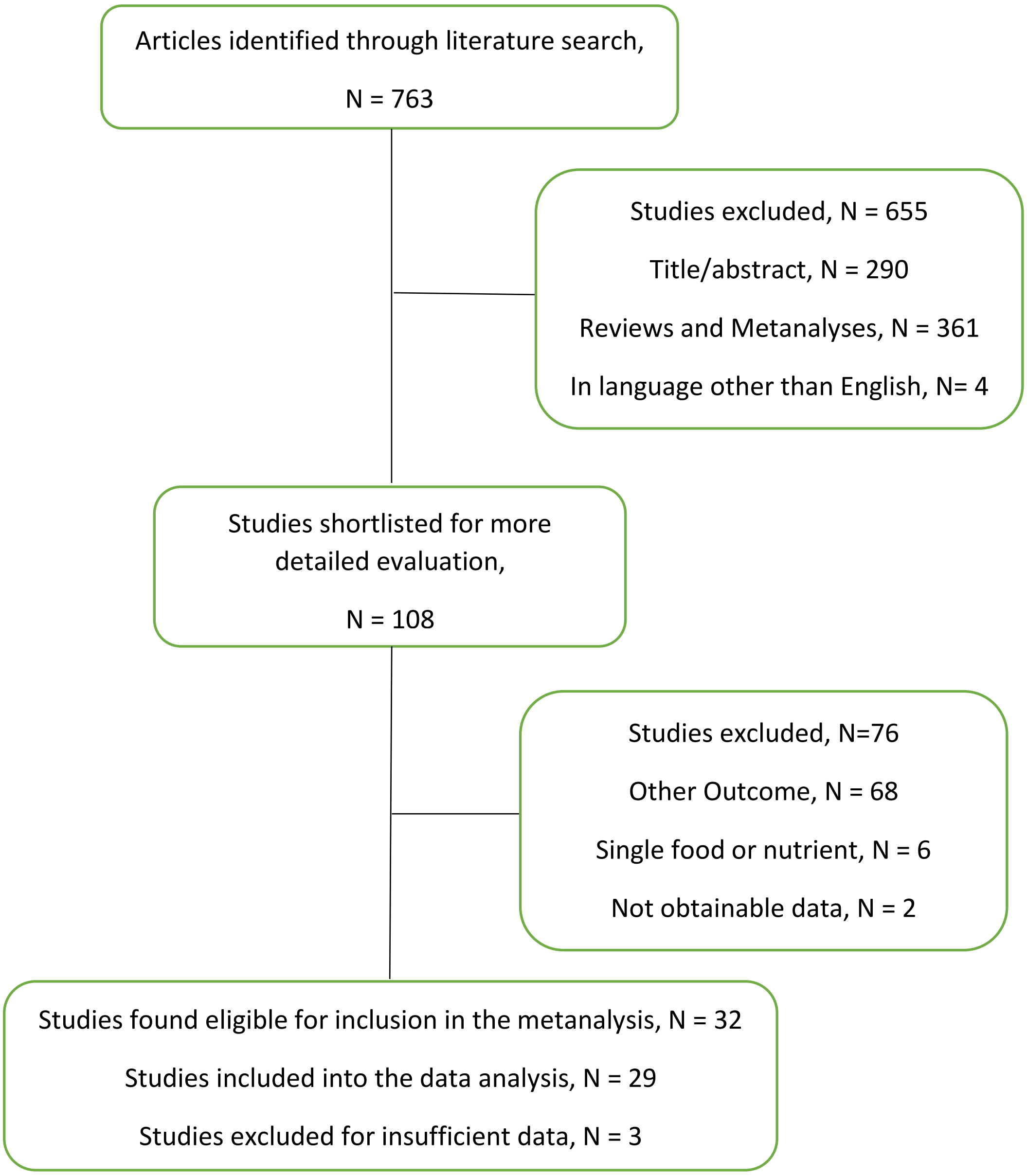

Figure 7. Process of Study Selection for the Meta-analysis

3.3 Data Extraction

After the determination of study selection, the following characteristic data is extracted: first author, publication year, the origin of study, Study design(RCT: parallel or cross-over), population size, duration, mean BMI, mean baseline HbA1c(%) levels, mean baseline Triglycerides level, mean baseline LDL levels, mean baseline Fasting blood glucose level (FBG), description of interventions, control group, type of diet (energy restricted, iso caloric), dropouts. Outcome data include post-intervention values for glycaemic control, FBG, triglycerides, LDL levels, and anthropometric measures.

3.4 Quality Assessment

The quality of each included study was assessed against specific criteria outlined in the Cochrane Handbook for Systematic Intervention Reviews (Risk of Bias Assessment Tool by the Cochrane Collaboration). The following sources of bias were assessed: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and staff), attribution bias (incomplete outcome data), and reporting bias (selective reporting).

Studies were classified as low-risk, unclear-risk, and at high risk by detailed study of the intervention for selection, allocation, outcome data, etc. for generation of risk of bias graph Revman 5 tool was used.

3.5 Data synthesis and analysis

Given that cross-sectional studies are generally useful for generating hypotheses, but less reliable in concluding, particularly for highly variable diseases such as diet and behavior-altering diseases, studies were set apart by design. Therefore, only prospective studies and clinical trials were included.

To produce the combined (pooled) effect of the interventional studies, data were extracted and converted into the same units, the combined mean was calculated using the population size of the study and the mean effect of the intervention. Below represents the formula used to calculate the combined mean,

$$X_c = \frac{N_1X_1 + \ N_2X_2 \ ... + \ N_nX_n}{N_1 + N_2 .. + N_n}$$

Where Xc is the combined mean, N is the population size and X is the mean of the population.

For every different intervention, i.e., Low-carb diet, Mediterranean diet, and Low glycaemic index/Load diet, studies are collected and checked for the business and a separate graph is drawn representing the percent studies at low risk, unknown risk, and high-risk.

3.6 Statistical analysis

Meta-analysis was conducted separately for each dietary intervention (Low- carbohydrates, Mediterranean, low GI) by using Revman5 software (Cochrane Information Management System) (https://training.cochrane.org/online-learning/core-software/revman) and the good quality data was taken from trials of each intervention. The combined mean was calculated and presented in terms of the combined mean effect in their reduction values.

Chapter - 4

RESULTS

4.1 Study selection

From the electronic search at different databases (PubMed, Google Scholar), we identified 427 studies for low- carb interventional studies, 292 studies for the mediterranean diet, and 44 studies for low-glycaemic index diet. 13 studies were also identified additionally from the references of reviews and other meta-analytical studies.

Studies were selected for further analysis for selection by abstract reading. From the abstracts of these studies, a total of 57 low-carbohydrate, 37 mediterranean, and 13 low-GI interventions were selected for full-text analysis.

Futher, studies were excluded from the study when the intervention-selected population was non-diabetic or only obese or prediabetic. Only those studies are selected which were having diabetic patients in their intervention. Some studies which were having small children <18 years were also excluded from the study.

Studies were also selected according to the duration, i.e., studies that are of less than 3 months or 12 weeks are excluded and studies that are of more than 1 year are also excluded. Post-intervention data is collected by checking the number of subjects who completed the intervention duration successfully and entered the analysis stage for an intervention.

In low-carbohydrates intervention studies, a total of 14 studies are selected for data extraction and metanalysis [15-28]. Most of the studies collected had approximately 15%-20% of carbs in their intervention study. most studies have low-fat calorie-restricted diets in their control group. Some studies have a Conventional calorie-restricted diet for the control group and in a few studies, they have a high carb or ADA diet in the control group.

In Mediterranean diet intervention studies, a total of 9 studies were selected for data extraction and metanalysis [29-37]. Most studies have the usual diet as a control. Some intervention studies have low- a fat diet as a control group.

In Low-glycaemic index/load intervention studies, a total of 6 studies were selected for data extraction and metanalysis [38-43]. In most intervention studies they have a high glycaemic index/load diet in control. Few studies have a high carb or low- fat diet in the control group.

4.2 Study biasness

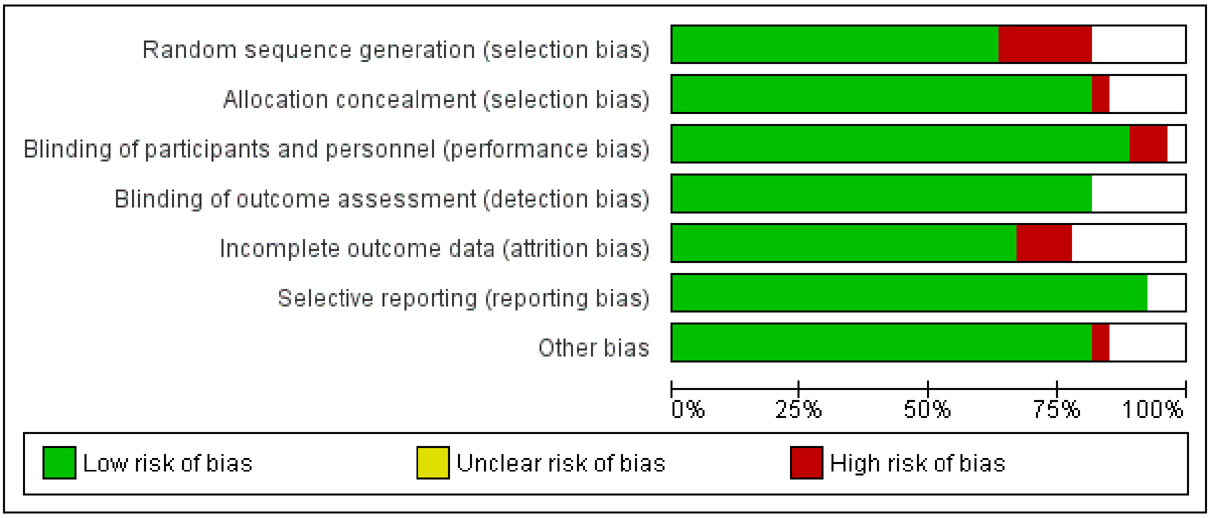

Figure 8. Graph showing risk of biasness

Some of the RCTs included in the meta-analysis were shown as interventions through ads or pamphlets. Allocation to the intervention group or the control group was controlled by computerized randomly allocated. Few of the studies have not provided complete data.

4.3 Study Participants

In low carbohydrate interventional studies, a total of 946 participants entered the final analysis of the post-intervention results in a total of 14 studies. A total of 76 participants were excluded from the final analysis as they were unable to continue the intervention, withdrawal due to death, and any other circumstances. Intervention studies have participants from both sexes having an age <18 years.

In Mediterranean diet intervention, a total of 2246 participants entered the final analysis of the post-intervention results in a total of 9 studies. A total of 37 participants were excluded from the final analysis as they were unable to continue the intervention, withdrawal due to death, and any other circumstances. Intervention studies have participants from both sexes having an age <18 years.

In Low- glycaemic index/load intervention, a total of 657 participants entered the final analysis of the post-intervention results in a total of 6 studies. A total of 8 participants were excluded from the final analysis as they were unable to continue the intervention, withdrawal due to death, and any other circumstances. Intervention studies have participants from both sexes having an age <18 years.

4.4 Intervention

In low carbohydrate diet intervention, studies have 15-20% of carbs, 30-35% protein, and 40-45% healthy fats mainly comprising PUFA and MUFA. Studies have calorie restriction for men and women both of 1400 kcal/d and 1600 kcal/day for men and women respectively. Diets were assessed in intervals and made followed by the intervention heading group. Lectures and health benefits of low carb diet and the healthy eating pattern is made known to the group. Regular health check-ups and analysis is done timely.

In Mediterranean diet intervention, studies have 40-45% of carbs, 25-30% protein, and 25-30% healthy fats mainly comprising PUFA and MUFA. Studies have calorie restriction for men and women both of 1400 kcal/d and 1600 kcal/day for men and women respectively. Diets were assessed in intervals and made followed by the intervention heading group. Lectures and health benefits of low carb diet and the healthy eating pattern is made known to the group. Regular health check-ups and analysis is done timely.

In Low-glycaemic index/load intervention, studies have incorporated carbohydrates containing foods having a glycaemic index of <55 (most of the foods included having a low glycaemic index of <55, but few foods included having moderate glycaemic index), 25-30% protein and 25-30% of healthy fats mainly comprising of PUFA and MUFA. Intervention studies have included foods that are high in fiber such as whole grains for slow release of glucose. Studies have calorie restriction for men and women both of 1400 kcal/d and 1600 kcal/day for men and women respectively. Diets were assessed in intervals and made followed by the intervention heading group. Lectures and health benefits of low carb diet and the healthy eating pattern is made known to the group. Regular health check-ups and analysis is done timely.

4.5 Meta-analyses of selected data

4.5.1 Glycaemic control (HbA1c)

Low-carbohydrate diet. Data from 14 interventional studies was collected and combined mean is calculated. There was a significant decrease in the HbA1c levels in the low carbohydrates group. The mean reduction is calculated for 3 months, 6 months, and 12 months. Combined mean at 3 months interval was found to be -0.62 % [15,16,18]. Combined mean at 6 months interval was found to be -0.48 % [15,20-23,25,26]. Combined mean at 12 months of interval was found to be -0.40 % [15,16,21,25-27].

Mediterranean diet. Data from 9 studies was collected and combined mean is calculated. There was a significant decrease in the HbA1c levels in the Mediterranean diet group in intervention of 1 year. The mean reduction is calculated for 3 months, 6 months, and 12 months. The Combined mean at 3 months interval was found to be -0.16% [29,31,32]. Combined mean at 6 months intervals was taken from a single study and found to be -0.25% [34]. Combined mean at 12 months of the interval was found to be -0.10% [29,31,36,37].

Low- glycaemic index/load diet. Data from 6 studies were collected and a combined mean is calculated. There was a significant decrease in the HbA1c levels in the low-glycaemic index diet. The mean reduction is calculated for different time intervals of 3 months, 6 months, and 12 months. Combined mean at 3 months interval was found to be -0.41% [38,39]. Combined mean (CM) at 6 months intervals was taken from a single study and found to be -0.50% [41]. Combined mean at 12 months of the interval was also taken from a single study and found to be -0.35% [42].

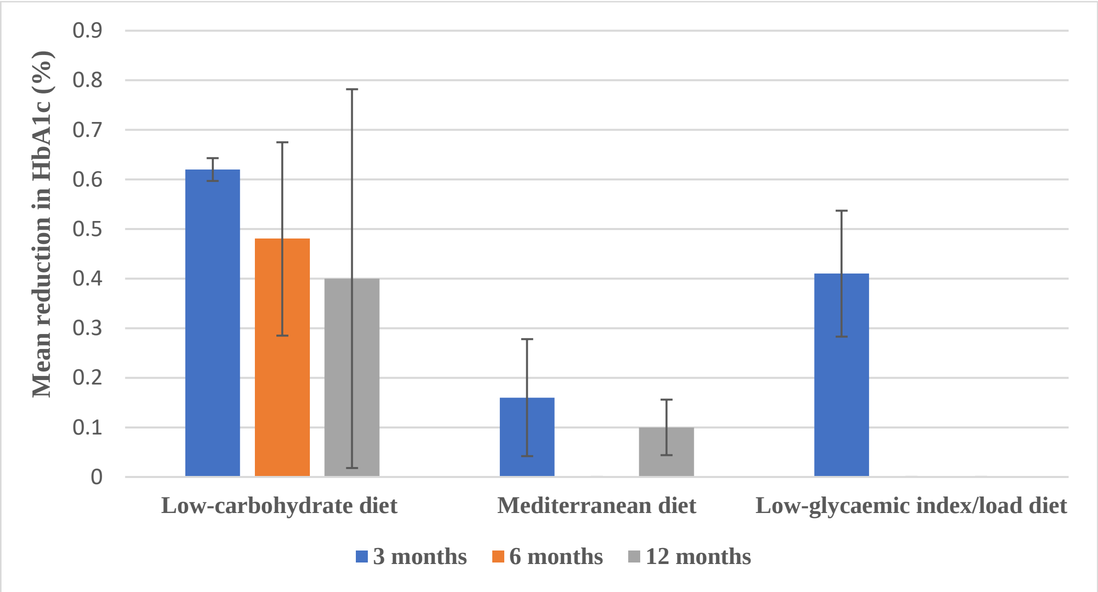

Figure 9. The mean reduction in HbA1c (%) levels in different dietary intervention

The error bars in the figure represents the standard deviation in the mean reduction values. Size of the error bars shows the heterogeneity in the data.

4.5.2 Weight loss

Low- carbohydrate diet. Data from 14 studies were collected and combined mean is calculated. There was a significant decrease in the weight loss in the low carbohydrates group, instead best weight reduction is seen in the low carbohydrate intervention group. The mean reduction is calculated for different time intervals of 3 months, 6 months, and 12 months. Combined mean at 3 months interval was found to be -4.41 kg [15,16,18,19]. Combined mean at 6 months intervals was found to be -5.24 kg [15,19-26]. Combined mean at 12 months of the interval was found to be -4.93 kg [15,16,19,21,27,28].

Mediterranean diet. Data from 9 studies were collected and combined mean is calculated. There was a significant decrease in weight loss in the Mediterranean diet group but lower than the low-carbohydrate intervention group. The mean reduction is calculated for different time intervals of 3 months, 6 months, and 12 months. Combined mean at 3 months interval was found to be -5.35kg [30,32,33]. Combined mean at 6 monthly intervals was taken from a single study and found to be -2.74 kg [34]. Combined mean at 12 months of the interval was found to be -4.27 kg [29,35,36].

Low- glycaemic index/load diet. Data from 6 studies were collected and combined mean is calculated. The reduction in weight loss in the Low- glycaemic index/load diet group is found to be less. The mean reduction is calculated for different time intervals of 3 months, 6 months, and 12 months. Combined mean at 3 months interval was found to be -4.37 kg [38-40]. Combined mean at 6 monthly intervals was taken from a single study and found to be -2.5 kg [41]. Combined mean at 12 months of the interval was found to be -3.80 kg [42,43].

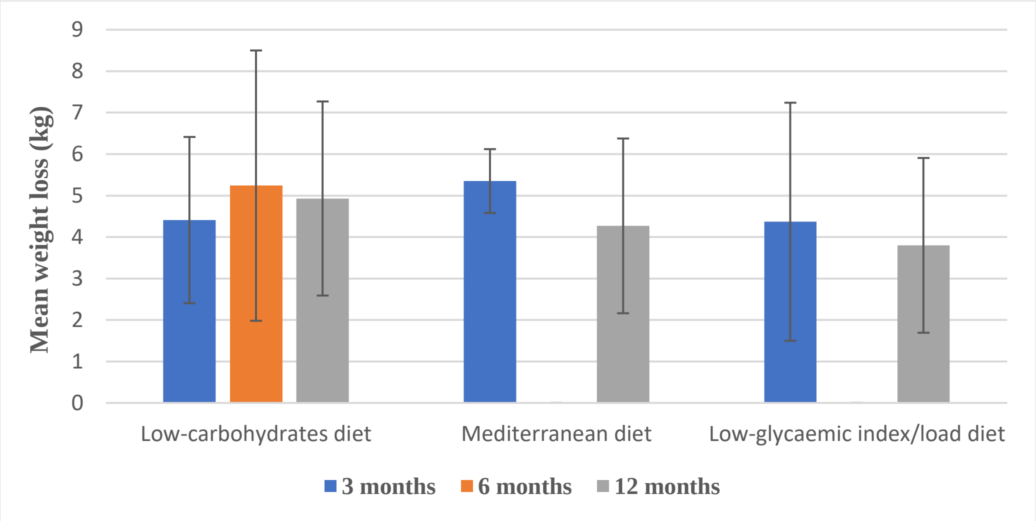

Figure 10. Mean weight loss (kg) in different dietary interventions

The error bars in the figure represents the standard deviation in the mean reduction values. Size of the error bars shows the heterogeneity in the data.

4.5.3 Fasting blood glucose (FBG) levels

Low-carbohydrate diet. Data from 14 studies were collected and combined mean is calculated. There was a significant decrease in FBG levels in the low carbohydrates group then in MD and low-glycaemic index diet. The mean reduction is calculated for different time intervals of 3 months, 6 months, and 12 months. Combined mean at 3 months interval was found to be -11.4 mg/dl [16-18]. Combined mean at 6 months interval was found to be -16.94 mg/dl [19,21,24-26]. Combined mean at 12 months of the interval was found to be -17.19 mg/dl [21,26,27].

Mediterranean diet. Data from 9 studies were collected and combined mean is calculated. There was a significant decrease in the FBG levels in the Mediterranean group during an intervention of 12 months, but only one study was found for a 12-month intervention. The mean reduction is calculated for different time intervals of 3 months, 6 months, and 12 months. Combined mean at 3 months interval was found to be -3.41 mg/dl [29,30,32]. Combined mean at 6 months intervals was taken from a single study and found to be -4.77 mg/dl [34]. Combined mean at 12 months of the interval was also taken from a single study and found to be -63 mg/dl [35].

Low- glycaemic index/load diet. Data from 6 studies were collected Combined mean is calculated. There was a significant decrease in the FBG levels in the low-glycaemic index diet. The mean reduction is calculated for different time intervals of 3 months, 6 months, and 12 months. Combined mean at 3 months intervals was found to be -8.65 mg/dl [38-40]. Combined mean at 6 months interval was taken from a single study and found to be -11.1 mg/dl [41]. No 12 months study was found reporting the effect of a low-glycaemic index diet on FBG levels.

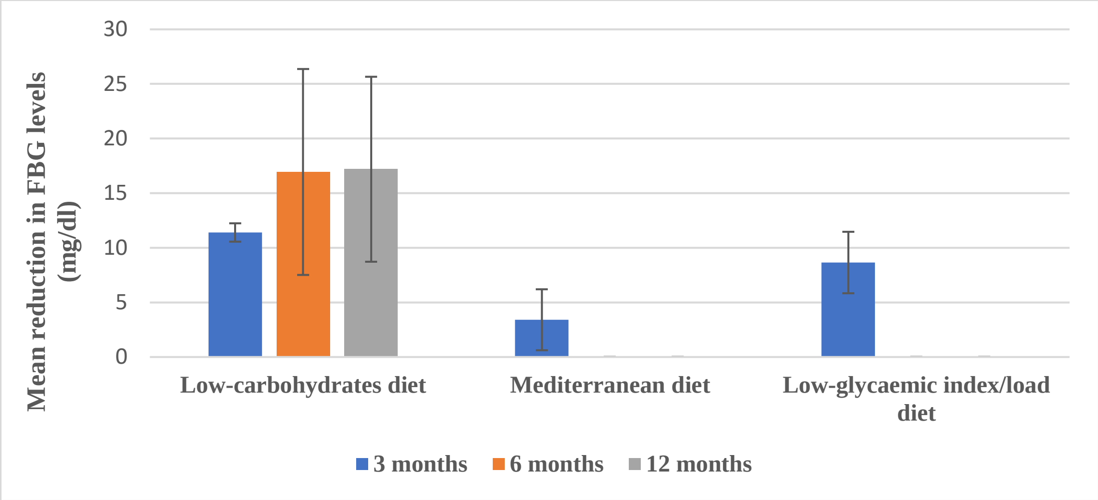

Figure 11. The mean reduction in FBG levels (mg/dl) in different dietary interventions

The error bars in the figure represents the standard deviation in the mean reduction values. Size of the error bars shows the heterogeneity in the data.

4.5.6 LDL levels

Low carbohydrate diet. Low carbohydrate diet has been found to reduce the levels of LDL levels but not significantly. Data from 14 studies is extracted, and the mean reduction value is calculated for different time intervals of 3 months, 6 months, and 12 months. Combined mean at 3 months intervals was found to be -4.53 mg/dl [16-18]. Combined mean at 6 months intervals was found to be -5.63 mg/dl [15,17,20-25]. Combined mean at 12 months of interval was found to be -3.76 mg/dl [15,17,21,25,26].

Mediterranean diet. Mediterranean diets have been found to reduce LDL levels more significantly when compared with low carbohydrate diet. Data from 9 studies are extracted, and the mean reduction value is calculated for different time intervals of 3 months, 6 months, and 12 months. Combined mean at 3 months intervals was found to be -4.83 mg/dl [30-33]. Combined mean at 6 months intervals was found to be -2.55 mg/dl [34]. Combined mean at 12 months of the interval was found to be -5.81 mg/dl [29,31,35,36].

Low-glycaemic index diet. A low-Glycaemic index diet is found not that much useful in reducing LDL levels than the Mediterranean diet and low-carbohydrates. Data from 6 studies are extracted, and the mean reduction value is calculated for different time intervals of 3 months, 6 months, and 12 months. Combined mean at 3 months intervals was found to be -

10.09 mg/dl [38-40]. Combined mean at 6 months intervals was taken from a single study and found to be -1.6 mg/dl [41]. Combined mean at 12 months of interval was found to be -2.14 mg/dl[42,43].

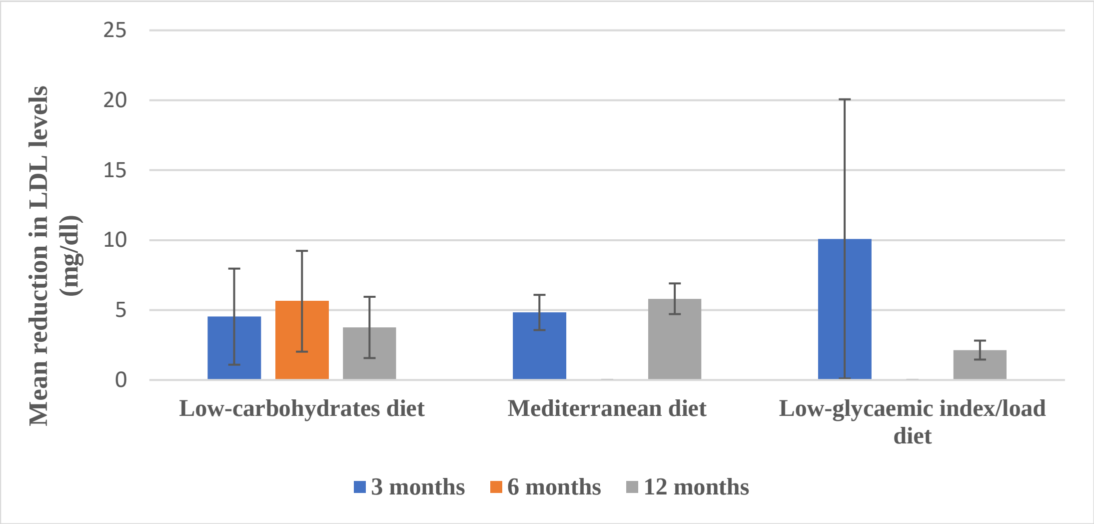

Figure 12. The mean reduction in LDL levels (mg/dl) in different dietary interventions

The error bars in the figure represents the standard deviation in the mean reduction values. Size of the error bars shows the heterogeneity in the data.

4.5.7 Triglycerides levels

Low-carbohydrates diet. A low-carbohydrate diet is found to be very effective as it is showing a significant reduction in the levels of triglycerides. Data from 14 studies is extracted, and the mean reduction value is calculated for different time intervals of 3 months, 6 months, and 12 months. Combined mean at 3 months intervals was found to be -30.77 mg/dl w [16-19]. Combined mean at 6 months interval was found to be -32.57 mg/dl [15,17,19-26]. Combined mean at 12 months of the interval was found to be -26.64 mg/dl [15-17,19,21,25-28].

Mediterranean diet. The mediterranean diet has also been found effective for reducing the triglycerides level significantly. Data from 9 studies are extracted, and the mean reduction value is calculated for different time intervals of 3 months, 6 months, and 12 months. Combined mean at 3 months interval was found to be -5.89 mg/dl [29,30,32,33]. Combined mean at 6 months intervals was taken from a single study and found to be -16.77 mg/dl [34]. Combined mean at 12 months of the interval was found to be -14.17 mg/dl [29,35].

Low-glycaemic index/load diet. Low-glycaemic index diets have been found significantly effective in reducing triglycerides level but not better than the Mediterranean diet and low-carbohydrates diet. Data from 6 studies are extracted, and the mean reduction value is calculated for different time intervals of 3 months, 6 months, and 12 months. Combined mean at 3 months intervals was found to be -16.91 mg/dl [38-40]. Combined mean at 6 months intervals was taken from a single study and found to be -3.5 mg/dl [41]. Combined mean at 12 months of the interval was found to be -19.23 mg/dl [42,43].

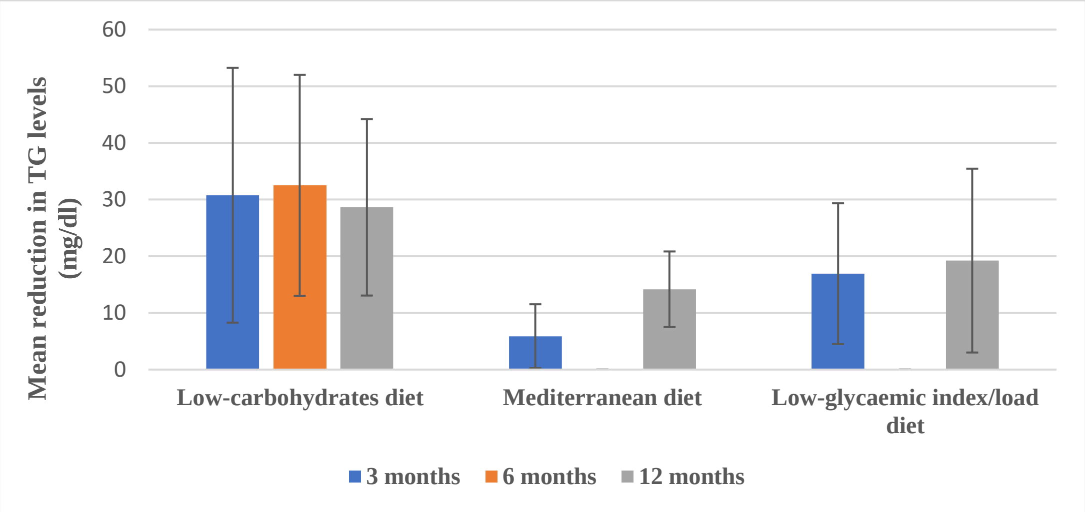

Figure 13. The mean reduction in TG levels (mg/dl) in different dietary interventions

The error bars in the figure represents the standard deviation in the mean reduction values. Size of the error bars shows the heterogeneity in the data.

4.5.8 Studies excluded

Studies not fulfilling the complete inclusion criterias were excluded from our meta-analysis. The study by Ramon Estruch et. al compared two different Mediterranean diets with low-fat diet in which they made two groups following the intervention, one in which they introduced and checked the effectiveness of a single food. The first group consumed a diet having extra virgin olive oil (EVOO) and the second group consumed nuts for healthy fats. Furthermore, the studies reporting the intervention on non-diabetic obese subjects, the studies on effectiveness of intervention diet on adherence to diabetes, and the studies on the unavailability of the data required for meta-analysis were excluded.

Two studies were excluded from the meta-analysis as the studies or random clinical trial was not having a control group for comparison.

Discussion

As diabetes has become one of the most prevalent diseases, many studies have been published on the management of diabetes. Many dietary interventions have been developed for the management of diabetes, some of which are the Mediterranean diet, low-carbohydrate diet, ketogenic diet, low-glycaemic index diet, American diabetic association diet (ADA), vegetarian diet, or vegan diet. Out of these diets, many RCTs have been conducted checking the efficiency of different dietary interventions, out of which low-Carbohydrates, Mediterranean, low-glycaemic index/load, and ketogenic diet have been found to be effective for the management of diabetes. Many RCTs have been conducted checking the effect of a Very low-carbohydrate ketogenic diet (VLCKD) on the diabetic population, which shows that a ketogenic diet can be beneficial for fast weight reduction, also lowers the blood glucose levels and a significant reduction in the LDL and TG levels [13]. However, in several instances, the VLCKD has been found harmful in case of improper management body which leads to ketoacidosis (as the concentration of ketone bodies increases due to less availability of carbohydrate or glucose for energy), therefore it is not advisable for prolong usauge of this diet. Moreover, studies suggest the other alternate to the ketogenic diet as it can be harmful and hard to follow in the long term.

Eating a diet with lower carbohydrates was one of the initial therapies for diabetic complications long before the function of insulin became known and intravenous insulin became available. A low-carbohydrates diet consists of 25% of carbohydrates, 35% of protein, and fats at 40%. Controlling dietary carbohydrate portions effectively lowers high blood glucose because dietary carbohydrates are the main macronutrient that affects blood glucose levels. The main principle behind the low-carb concept is that weight can be reduced and improved by reducing insulin, the main hormone that causes fat storage, anabolic, cardiometabolic performance. Because low-carb foods are low in carbohydrates, they have often been found to be effective at lowering blood sugar and controlling hyperglycemia. Other than that, a lower carbohydrate diet is found effective in pushing the body into the glucose-starving phase which can induce ketosis, the process is found effective in reducing weight reduction, reduction in total cholesterol levels, and reduction in triglycerides levels. Many RCTs conducted checking the efficiency of a low-carbohydrates diet for the management of diabetes and found that the intervention is helpful in the management of diabetes as it effectively lowers the HbA1c levels, fasting blood glucose levels, and reduced the use of medications. A meta-analytical study by Yan Meng et al., shows that LCD is beneficial in better glycaemic control and has a positive effect on HDL and TG levels [49]. Some of the foods included in low-carbohydrate intervention studies are meals containing Quinoa, eggs whites, tofu, Oatmeal, spinach, broccoli, fish, tomatoes, lentils, black beans, nuts, and seeds, cheese, milk, etc. interventions were used excluding baked products, fast foods, white rice, potato chips, soda drinks, etc. Also, a meta-analytical study by Joshua Z Goldenberg et al., states that a longer-term usage of LCD is still a limitation [50].

Whole grains, fruits, nuts, seeds, and vegetables, as well as other plant-based foods, were generally the foundation of the Mediterranean diet. These include vitamins, minerals, antioxidants, and a sizable quantity of fiber. Another important benefit of the Mediterranean diet is the consumption of healthy lipids, especially olives, almonds, and fatty fish such as salmon and sardines. These sources are often used to replace saturated fat and trans-fat in fatty meats and cheeses, as they are rich in heart-healthy MUFAs (monounsaturated fatty acids). Consumption of dairy products is likewise modest. Mediterranean diet has a macronutrient composition of carbohydrates at 50-60%, protein at 15-20%, and fats at 30%. Some of the food groups included in the intervention of MD are nuts and seeds, olive oils, avocados, cheese, yogurt, whole grains, fish and sea food, beans, peas, fruits, and green leafy vegetables, etc. intervention excluded food which commonly are refined sugar, trans fat, highly processed food stuff, added sugar.

The Modern Mediterranean Diet Pyramid recommends daily, weekly, and monthly food types and frequency. Fruits, vegetables, grains (mostly whole), olive oil, beans, nuts, legumes, seeds, herbs, and spices are essential elements of every meal. Fish and seafood should be eaten more often, at least twice a week. Eat chicken, eggs, cheese, and yogurt in moderation every day and every week. He rarely eats meat and sweets. Med Diet Pyramid also provides insight into the balance of many different foods and emphasizes the balance of energy and energy consumption from food through daily activities. Individual foods and portions should be adjusted to the individual's needs. It provides a whole food model, rather than referring to a single food or food. It is not a dietary restriction that refers to or excludes certain foods or foods; thus, preventing nutritional deficiencies associated with prolonged dieting. The focus is on nutrition over quantity: saturated fat versus saturated fat, whole carbs versus carbs, or sugar. It has variety, taste, and toughness, so it is easy to digest. The model also favors whole foods over processed foods, which increases the healthy micronutrient and antioxidant content of these foods [44]. The MD has been found effective in reducing fasting blood glucose levels, and

Hba1c levels. Mediterranean diet along with calorie restriction has been found effective in losing weight and reducing risks for cardiovascular diseases. A meta-analytical study by Efi Koloverou et al., suggests that an MD can be a choice for the primary prevention of diabetes [47]. Instead, then focusing on only one food or vitamin, the entire dietary pattern is offered. Since it is not a restrictive diet that emphasizes or excludes nutrients or foods, nutritional deficits associated with prolonged restrictive diets can be avoided. Instead, focusing on the number of nutrients, unsaturated vs saturated fats and whole versus processed carbohydrates or sugar are addressed. It is simple to follow since it gives variety, flavor, and fullness. The diet also advocates natural foods over processed ones, which can maximize the number of micronutrients and antioxidants in these meals that are good for your health.

Mediterranean diet has been found positively effecting in management of diabetes mellitus in various ways, such as improvement in blood sugar control, weight loss, reduced need for medication, improved lipid profile, increased satiety and fullness, improved insulin sensitivity, and lower risk of hypoglycemia. A meta-analytical study by Katherine Esposito et al., has shown that a Mediterranean diet is helpful in better glycaemic control and can be beneficial in the overall management of T2D [48]. Most importantly MD is highly customizable and sustainable. Also, it does not have any potential drawbacks as a very low carbohydrate diet has of the body going under diabetic ketoacidosis. It's easy to follow because it's versatile, delicious, and perfect. The diet also encourages eating whole foods rather than processed foods, which increases the amount of micro-nutrients and antioxidants in foods.

G.I. indicates how rapidly a diet can increase blood sugar levels. The glycaemic index is a ranking of how rapidly your blood sugar levels rise after consuming each carbohydrate-based meal and beverage. Different carbs undergo digestion and absorption at different rates. Pure glucose, which has a Glycaemic Index of around 100, is typically used as the reference for the GI index, which ranges from 0 to 100. Low-GI foods, such as most legumes, unsweetened milk, fruits and vegetables, nuts, legumes, certain whole-grain cereals, and bread, contain slowly digested carbs that have a GI rating of 55 or below. According to research, adopting low-GI meals can especially help type 2 diabetics control their long-term blood glucose (HbA1c) levels.

Most food groups in a meal included have a glycaemic index of <55 that is having a low glycaemic value. Very few food groups included in the intervention have a glycaemic index of <70. No food groups were added to the meals having a high glycaemic value. Some of the food groups included in the interventional studies are whole grains products, apples, kiwi, broccoli, lentils, beans, brown rice, low-fat milk, soy products, fish, olive oil, etc. food group which are excluded are white bread, white rice, potatoes, mango, or food groups having high GI value. Most of the foods included in the low- glycaemic index intervention has a high amount of fiber in the nutritional content. As of now, no RCTs were found to check the effectiveness of interventions having different fiber content and their effectiveness on the management of diabetes mellitus.

A meta-analytical study by L.M. Goff et al., has shown that a Low-G.I diet was found effective in reducing LDL and total cholesterol levels and does not affect HDL cholesterol and triglycerides levels [51]. Another study by Lukas Schwingshackl et al., has shown that a low-G.I diet has shown a positive effect on TG levels and HOMA index, but no effect is seen on anthropometric measurements of the participants such as body weight and waist circumference [52].

Chapter - 5

CONCLUSION

In our meta-analysis, we found that the diets with low-carbohydrate and a low-glycemic index/load are effective in reducing body weight, low-density lipoproteins, and triglycerides levels. Both diets helped reduce fasting blood glucose levels as well in diabetic patients.

Our study suggests that, when the diet is considered for diabetic patients, a moderate carbohydrate diet with slight calorie restriction will be beneficial. Foods to be included in the meals should first be checked for glycaemic index, as only those food groups should be added which are having low to moderate glycaemic index. Carbohydrates should be <40% (less than 200gm/day). Protein should be 1gm/kg/day as recommended by recommended dietary allowances. Healthy fats should be included in the diet as they contain mono-unsaturated fatty acids and poly-unsaturated fatty acids which maintain a good ratio of low-density lipoproteins and high-density lipoproteins. Also, a diabetic person should have six small meals rather than three big meals, as big meals will have a high glycaemic load, leading to hyperglycaemic conditions.

In conclusion, through are meta-analysis, we proposed important interventions regarding dietary intake that could be beneficial in the better management of diabetes.

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