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EFFECT OF PHARMACOLOGICAL AND NON-PHARMACOLOGICAL THERAPY IN TYPE2 DIABETES MELLITUS - A REVIEW

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Abstract

Diabetes Mellitus is a complex metabolic disorder that is characterised by hyperglycemia and impaired insulin secretion, with or without insulin resistance. Polyuria, Polydipsia, Polyphagia, fatigue, and Weight loss are the most common clinical manifestation of Diabetes Mellitus. The causes of type 2 diabetes are multi-factorial and include both genetic and environmental elements that affect beta-cell function and tissue (muscle, liver, adipose tissue, and pancreas) insulin sensitivity. In type 2 diabetes, either the body does not produce enough insulin or the cells ignore the insulin. It usually begins as insulin resistance, a disorder in which the cells do not use insulin properly. As the need for insulin rises, the pancreas gradually loses its ability to produce it. Diabetic Ketoacidosis, Hyperosmolar Hyperglycaemic State, CVD, Nephropathy, Retinopathy, and Neuropathy are some of the complications that are experienced due to the chronic progression of the disorder.

Treatment for people with diabetes includes Medical Nutritional Therapy (MNT), physical activity, weight loss, Oral Anti-Hyperglcaemic Agents (OHA) and Insulin therapy where ever required. Medical Nutritional Therapy is the diet plan that is framed to achieve euglycaemia in patients by considering their lifestyle and their preferences. Insulin therapy includes consideration of insulin based on the patient's requirement to achieve euglycaemia.

Pharmacological therapy includes treatment with OHA drug classes like Biguanides,

Sulphonylureas, Meglitinides, Thiazolidinediones, Alpha-glucosidase Inhibitors, DPP-4 Inhibitors, SGLT-2 inhibitors. Euglycaemia can be achieved by proper combination of pharmacological therapy, Medical Nutritional Therapy with necessary lifestyle modifications.

KEYWORDS: **β**-cell dysfunction, Insulin Resistance, Hyperglycaemia, Medical Nutritional Therapy, OHAs, Lifestyle Modifications.

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INTRODUCTION:

Diabetes Mellitus (DM) is a complex metabolic disorder that is characterized by chronic hyperglycemia along with impairment in protein or lipid metabolism. An Egyptian physician identified it in 1500 BC, but the term "Diabetes Mellitus" was coined in 1675 (from the Greek word "Diabetes," which means "siphon" or to pass through – and the Latin word "Mellitus," which means "sweet"). In 2000, the total number of people with DM was 171 million, with a prevalence of 2.8%. By 2030, it is thought to rise to 360 million, with a prevalence of 4.4%. In India, 31.7 million people were diagnosed with DM in 2001, and that number is estimated to rise to 79.4 million by 2030**.** But the actual number will be higher than the estimated levels.

The most common symptoms are well-known and include polyuria (increased frequency of urination), polydipsia (excessive thirst), polyphagia (excessive eating), unexplained weight loss, and fatigue. Blurred vision, candida, foot ulcers, and urinary tract infections can be observed with chronic progression. Genetics, age, body weight, ethnic background, and lifestyle are the common risk factors. The risk of the development of DM in children is highwhen their mother is a diabetic patient, but the risk is low when their father is a diabetic

patient**.** This metabolic disorder is caused either by the inability of the pancreatic **β**-cells (**β**-cells dysfunction) to meet the insulin requirement or by the inability of the tissues or

muscles to take up the produced insulin (insulin resistance)and in both ways in some cases. Changes in -cell function, insulin resistance, and even pre-existing chronic inflammation willall have an effect on glucose metabolism, and continued disruption will lead to the development of diabetes-related macro- and microvascular complications. The high amountof glucose in the blood for a long time will damage the normal structure and function of the micro- and macrovasculature, which ultimately leads to micro- and macrovascular complications. The Islet of Langerhans, which constitutes around 1% of the pancreas, is the

site of insulin production. The majority of the insulin is produced by the **β**-cells which are

activated by glucose. When there is a high level of glucose in the blood, the beta cells are activated to produce insulin. Hyperfunctioning of **β**-cells can be observed when a high level of glucose is present in the blood circulation for a long time. This hyperfunction will eventually wear out the **β**-cells ultimately causing **β**-cell dysfunction. A high level of body fat also predisposes to diabetes. This is the reason obesity is a major risk factor for the

development of DM. High lipid levels will lead to the deposition of fat content on the tissues (lipotoxicity), which reduces the sensitivity of the insulin, ultimately leading to a reduction in glucose uptake. This reduction in insulin sensitivity is also known as insulin resistance.

Lipotoxicity also elevates the **β**-cell dysfunction. The decrease in **β**-cell function observed in

type 2 diabetes mellitus (T2DM) is not caused by auto-immune destruction, as seen in type 1 diabetes mellitus.

PHARMACOLOGICAL THERAPY:

Pharmacological treatment for T2DM includes oral antihyperglycemic agents (OHAs) and insulin.

Oral antihyperglycemic agents (OHAs)

OHAs include drug classes like biguanides, sulfonylureas, meglitinides, thiazolidinediones, alpha-glucosidase inhibitors, and dipeptidyl peptidase-4 inhibitors. Sulfonylureas and meglitinides

are insulin secretagogues because they primarily stimulate the release of stored insulin. Thiazolidinediones are regarded as **insulin sensitizers.**

Biguanides:

The most commonly used biguanide, Metformin, activates the AMP-activated protein kinase (AMP-K), whose activation leads to a reduction in hepatic gluconeogenesis**.** The reduction in gluconeogenesis aids the uptake of glucose in the peripheral tissues**.** It also reduces the intestinal absorption of glucose. Functioning beta cells are not a concern when considering metformin therapy. Unlike other OHAs, metformin does not cause weight gain**.** On the contrary, several studies have proposed that metformin has reduced triglyceride and LDL levels**,** which is due to the elevated fatty acid metabolism caused by the activation of AMP-K(AMP-K is an agonist of lipid and glucose metabolism)**.** Anorexia, nausea, diarrhea, and abdominal discomfort are the common side effects observed with metformin therapy**.** An open-label study conducted by Biswabandhu Bankura et al. with a sample size of 111 newlydiagnosed DM patients to evaluate the effect of metformin shows that 92% acceptance can be attained with a significant reduction in the average values of BMI (from 25.01 kg/m-2 to

23.91 kg/m-2), FBG (from 182.3 mg/dl to 114 mg/dl), PPBG (from 277 mg/dl to 156 mg/dl), and HbA1c (from 9.36% to 6.72%)[1]**.** Defronzo Ralph et al. conducted a randomized, blindfolded, controlled study to evaluate the efficacy of metformin in moderately obese patients with Non-Insulin Dependent Diabetes Mellitus (NIDDM). A significant reduction in mean FBG (189+5 mg/dl) and HbA1c (7.1+0.1%) was observed in the group receiving metformin therapy compared to the placebo group with mean FBG (244+6 mg/dl) and HbA1c (8.6+0.2%). Reduction in the lipid parameters like serum Total Cholesterol (TC), Low-Density Lipoprotein (LDL), and Triglycerides (TG) was observed in the metformin group[2] demonstrating the drug's weight reduction ability.

Insulin Secretagogues:

Sulfonylureas get bound to the pancreatic islet cell Sulfonylurea Receptor 1(SUR1) where the binding results in the closure of ATP-sensitive potassium channels in the **β**-cell membrane. This closure causes depolarization, which leads to an increase in the intracellular calcium concentration. This increase in calcium concentration stimulates the release of insulin from the vesicles**.** To have a biological effect, sulfonylureas must have functional **β** cells**.** Tolbutamide and chlorpropamide belong to the first generation of sulfonylureas, and glibenclamide, glipizide, gliclazide, and glimepiride belong to the second generation. Weight gain and hypoglycemia are common adverse effects. However, due to the shorter elimination half-life, second-generation sulfonylureas are preferred over

first-generation sulfonylureas**.** A study conducted by Bianca Hemmingsen et al. to assess the effect of sulfonylurea monotherapy for T2DM patients shows a mean reduction in the HbA1c levels of 1.01% among the patients treated with sulfonylureas[3]**.** Goldberg RB et al. conducted a study to assess the dose response of glimepiride in NIDDM patients. The study

shows that a reduction in HbA1c of about 1.9% and 1.8% was achieved with the dosing of 8 mg and 4 mg glimepiride, respectively[4].

The mechanism of action of meglitinides is similar to that of sulfonylureas, but they differ in the site of action (receptors), time of onset, and extent of action**.** When compared with sulfonylureas, meglitinides exhibit faster and higher production of insulin, which promotes rapid reduction in blood glucose levels**.** Nateglinide and

repaglinide are the drugs used in this class. Hypoglycemia and weight gain are the most common adverse effects**.** Nausea, vomiting, and diarrhoea are the common side effects. With a sample size of 576 T2DM patients, Thomas Marbury et al. conducted a randomised prospective multicenter,

double-blind, parallel-group study to compare repaglinide and glyburide. The mean reduction in HbA1c was found to be similar in both the repaglinide (0.08 + 0.07%) and glyburide (0.1 +0.11%) groups, but the reduction in FBG is relatively higher in the repaglinide group (9.5 +

3.0 mg/dl) when compared with the glyburide group (6.4 + 4.1 mg/dl). A higher degree of reduction in HbA1c and FBG was observed in the pharmacologically naive patients than in the patients who had previously been treated with OHAs[5]**.**

Thiazolidinediones:

Glitazones is another name for thiazolidinediones. Glitazones bind to the PPAR-$\boldsymbol{\gamma}$ receptor (found primarily in the adipose tissue, **β**-cells) leading to the production of heterodimers with a retinoid-X receptor. Heterodimers bind to the response element of the genome, resulting in the activation of genetic material that potentiates the insulin action and also suppresses the nuclear pathways that inhibit the insulin action**.** The activation of PPAR-$\boldsymbol{\gamma}$ blocks the release of free fatty acids. The blockage of fatty acid production also enhances insulin sensitivity**.**

The pre-produced fatty acids will escape from muscle, liver, and islet cells and be taken up by the adipose tissue**.** Pioglitazone, rosiglitazone are the most commonly used glitazones. Weight gain and edema are the most common adverse effects. A Diabetes Outcome Progression Trial (ADOPT), a randomized, controlled, multi-center, double-blind clinical trial conducted by Kahn SE et al., shows that monotherapy failure was 15% with rosiglitazone, which was less when compared to 21% failure with metformin and 34% failure with glyburide. But a higher percentage of mean weight gain was observed in rosiglitazone monotherapy (4.8 kg) than in glyburide therapy (1.6 kg) and metformin therapy (-2.9 kg)[6]**.** A study conducted by Micheala Diamant et al. shows that monotherapy trials of pioglitazone and rosiglitazone prescribed in the range of 15–45 mg and 2–8 mg, respectively, have resulted in a mean reduction of HbA1c of 1.5% and 1.6% when compared with the placebo group**.**

α-glucosidase inhibitor:

Acarbose is the most commonly used alpha-glucosidase inhibitor. Acarbose decreases the digestion of carbohydrates by altering glucosidase activity**.** Acarbose inhibits the

α-glucosidase enzyme (present in the small intestine and the pancreatic **β**-amylase, which is

responsible for the breakdown of complex starches into monomers), resulting in a significant reduction in the conversion of complex carbohydrates to a simple form (i.e., glucose)**.**

Flatulence and diarrhoea are the most common adverse effects**.** A multicentered,

double-blind, placebo-controlled trial was conducted by Robert F. Coniff et al. to assess the reduction of HbA1c by different doses of acarbose in NIDDM patients. The reduction in

HbA1c was 0.45% with 100 mg, 0.40% with 200 mg, and 0.77% with 300 mg dosing, and weight reduction was also observed in all three doses (-0.19 kg for 100 mg, -0.80 kg for 200 mg, and -0.45 kg for 300 mg)[7]**.** Jorge L. Gross et al. conducted a meta-analysis of 18 trials to assess the efficacy of drug classes when used as a third agent in the pharmacotherapy of T2DM patients who

are already taking metformin and sulfonylureas. A direct meta-analysis of this study shows a lesser reduction in HbA1c (-0.6%) for acarbose as the third agent when compared with thiazolidinediones as the third agent (-1.15%). But a 2.4 kg increase in weight was observed with thiazolidinediones, and a 0.96 kg decrease in weight was observed with acarbose[8].

Dipeptidyl Peptidase - 4 inhibitors:

DPP-4 inhibitors are otherwise regarded as gliptins. This class of drugs exerts pharmacological action by influencing incretin activity. Dipeptidyl peptidase inactivates incretins like Glucagon Like Peptide -1 (GLP-1) and Glucose-dependent Insulinotropic Peptide (GIP). Gliptins inhibit the activity of Dipeptidyl peptidase, thereby potentiating the action of incretin, which increases the endogenous insulin response to high glucose levels in the blood. Sitagliptin, Vildagliptin, and Saxagliptin are the most common drugs used in this class. The most common side effects are urinary tract infections and gastrointestinal discomfort. A multicentered, randomized, double-blind, parallel-group trial conducted by Andre J. Scheen et al. to compare the safety and efficacy of saxagliptin and sitagliptin when prescribed in combination with metformin showed a slightly higher reduction of HbA1c in the sitagliptin plus metformin group (0.62%) when compared with the saxagliptin plus metformin group (0.52%). Although numerically greater reductions were achieved with sitagliptin, saxagliptin met the predefined non-inferiority criteria for HbA1c lowering, and a slightly higher reduction in FBG was observed in sitagliptin than saxagliptin[9]. Similar results were observed in a comparative study conducted by Asti et al.[10].

Insulin

Insulin preparations are used in treating DM patients as they exhibit (or mimic) actions similar to those of insulin, which is naturally produced in the body. In the 1970s and 1980s, insulin produced from the pancreas of pigs and cows was purified and used. Porcine insulin, insulin from the pig's pancreas, is one of the few animal-derived insulin preparations used at present as it is very similar to human insulin (the only difference is the presence of one amino acid at the B30 position of the insulin B chain). Now, newer insulin preparations are manufactured using recombinant DNA technology (rDNA technology) by inserting synthetic genes at desired sites. At present, human insulin analogues are considered for treatment rather than animal-derived preparations. Based on the duration of action, insulin preparations are classified into three groups: short-acting insulins, intermediate-acting insulins, and long-acting insulin.

Short-acting insulin consists of normal human insulin and rapid-onset insulin analogues which contain a minor amount of zinc for stability and safety enhancement. Human insulin and rapid-acting insulin must be administered 45 minutes and 15 minutes before food, respectively, to achieve the desired therapeutic outcome. Regular insulin is a zinc-insulin crystalline product that is available in various concentrations. These insulins are produced by enzymatic modification of porcine insulin. The absorption rate is higher when injected in the

deltoid muscle or abdomen than in the thighs or buttocks. Fast-acting insulin analogues are soluble insulin preparations in which the insulin will enter the circulation within 10 minutes after subcutaneous administration. Maximal action is attained within 2 hours and declines after 4–8 hours, with the duration of action being 2–5 hours. Absorption time for Insulin analogues like insulin lispro, insulin aspart, and insulin glulisine is

shorter when compared to non-analogues. Differences in pharmacokinetic parameters can be observed with insulin analogues because they are ready to be absorbed, unlike human insulin, which needs to be broken down for absorption. In insulin lispro, a proline at B28 is reversed with lysine at B29**.** In insulin aspart, proline is substituted by aspartic acid at B28**.** In insulin glulisine, asparagine is exchanged with lysine at position B3 and lysine with glutamic acid at position B29**.**

Intermediate-acting insulins are insoluble, cloudy suspensions of insulin with protamine(isophane insulin) or zinc (Lente insulin), whose action peaks 4–8 hours after entering circulation. Isophane insulin (NPH) contains an equivalent amount of protamine and native insulin in water for injection with a phosphate buffer**.** Biphasic insulin also belongs to this class. The duration of action for this class of insulin is in the range of 12 to 18 hours.

Long-acting insulins are insoluble insulin analogues developed using rDNA technology.

The duration of action is about 24 hours in this class of insulin, where peak plasma concentration is attained within 6–12 hours. Significant peaks cannot be observed in this class of insulin, as it has a flat action profile. Insulin Glargine, Insulin Detemir, and Insulin Degludec belong to the class of long-acting insulins. In insulin detemir, myristic acid is attached to lysine at the B29 position, and threonine is detached from B30**.** In insulin glargine, asparagine is replaced by glycine at position B21 in the insulin A chain, and two arginine residues are added to the carboxyl terminal of the B chain**.** In insulin degludec, threonine at B30 is deleted and B29 is conjugated to hexadecanedioic acid**.**

Injections and insulin pens are the most commonly used devices for the administration of insulin. Insulin pumps (open loop systems) and closed loop systems are also available, but they require a person with a considerable degree of knowledge in handling to continuously monitor the functioning.

Subcutaneous (SC) and Intravenous (IV) routes are the common routes of administration for insulin. Devices like insulin pens are commonly preferred due to the easy subcutaneous administration of the medication by patients without any help, but the major drawback is that the medication will be delivered to the systemic circulation rather than the portal circulation, which may cause a small dip in the desired outcome. Intravenous insulin delivery should be considered in patients with Diabetic Ketoacidosis (DKA) and patients who are about to undergo surgery. But a small proportion of patients still use a syringe with insulin from a vial as insulin therapy. Insulin preparation must be kept away from sunlight, and heat and must not be refrigerated, except for vials and cartridges. Insulin pens must be stored based on the insulin preparation present inside. Hypoglycemia, edema, and lipohypertrophy are the most common adverse effects experienced with insulin therapy.

The suggested pattern of use of anti-hyperglycemic agents by the ICMR (2018guidelines)[11]

- After diagnosis, lifestyle modification should be suggested.
- If the HbA1c level is less than 9% then metformin monotherapy should be considered(if metformin is contraindicated, then monotherapy of other classes of OHAs should be considered). If the HbA1c has not reduced to the desired level, then dual therapy with metformin and either sulfonylureas or DPP-4 should be considered. If the HbA1chas reduced to the

desired level, then the patient must be monitored at regular intervals for assessment of efficacy and the development of side effects.

- If HbA1c is higher than 9% and the patient is symptomatic, then insulin therapy should be considered with or without OHAs.
- If HbA1c is higher than 9% and the patient is asymptomatic, dual therapy with metformin and other OHAs (first choices are sulfonylureas and DPP-4 inhibitors and second choices are α-glucosidase inhibitors, glinides, thiazolidinediones as add on

with metformin) should be considered. If HbA1c has reduced to the desired level, the

patient must be monitored at regular intervals for assessment of efficacy and the development of side effects. If HbA1c has not been reduced to the desired level, then insulin therapy should be combined with dual therapy or even triple therapy of OHAs with insulin therapy in the worst cases.

- Complications like diabetic retinopathy or nephropathy indicate the long-term prevalence of DM. As a result, insulin therapy should be considered on a regular basis. In the case of diabetic ketoacidosis, insulin therapy should be considered for a brief period until euglycemia is attained.

A prospective, open-label, observational study conducted by Sonam Dolma et al. with 150 patients to assess the prescription pattern of medications in the treatment of T2DM shows that insulin therapy is the most prescribed therapy at the study site with 60.66% because the majority of DM patients in the study had co-morbidities and rapid onset of action was required in those patients. Among the frequently prescribed antidiabetic therapies, dual therapy was the most common with a 53.33% prescription, followed by monotherapy with a 50% prescription. Triple therapy was rarely prescribed, with a prescription rate of 8%. The study states that ICMR guidelines were followed while framing the drug therapy. The average number of drugs per prescription in this study is 1.95, which is slightly higher when compared to the WHO recommended range of drugs per prescription (1.6–1.8)[12]. Another cross-sectional, observational study conducted to assess the prescription pattern of OHAs at private OPD by Piparva Kiran et al. with a sample size of 349 patients shows that dual therapy (32.09%) was the most commonly used pattern of prescription, followed by triple therapy (23.2%) and five drug therapy (21.2%) at the study site. The average number of drugs prescribed per prescription is 3.34, which is high when compared to the WHO's recommended normal range (1.6–1.8)[13]. According to Divya Singh et al.'s drug utilisation study, dual therapy is the most prescribed pattern at the study site, with 46.06% prescription, followed by monotherapy (30.33% prescription) and triple therapy (23.59% prescription). The average number of OHAs prescribed per prescription is 2.18, which is higher than the normal range (1.6–1.8) recommended by WHO[14]**.** All of the studies mentioned above show that the average number of drugs prescribed per prescription is higher than the normal range, indicating that the possibility of developing drug-drug interactions, drug-food interactions, and adverse effects is higher than normal, which must be addressed as soon as possible.

NON-PHARMACOLOGICAL THERAPY:

The non-pharmacological management of diabetes mellitus should include individualised Medical Nutritional Therapy (MNT) and appropriate lifestyle modification**.**

MEDICAL NUTRITIONAL THERAPY (MNT) OR DIETARY MODIFICATION:

Medical Nutritional Therapy entails developing a meal plan that takes into account the individual's preferred foods and eating habits in order to match the required nutritional values and achieve the desired outcome**.** Over the past decades, there has been a drastic change in the pattern of dietary modification, mainly in terms of carbohydrates. When insulin was yet to be developed, a very low-calorie diet with very low carbohydrate and high-fat content was recommended**.** Following the discovery of insulin and the observed increase in cardiovascular complications caused by diabetes, a diet high in carbohydrates and low in fat (HCLF) was recommended**.** High carbohydrates mean that 55–65% of the energy contribution is from carbohydrates. The Research Society for the Study of Diabetes in India (RSSDI) recommends an individualised MNT with high carbohydrate, fiber, and low-fat content. For maximum therapeutic outcomes, carbohydrates should have a low glycemic index and should not be refined**.** The glycemic index measures the ability of carbohydrates to raise blood glucose levels**.** The glycemic load is calculated by multiplying the carbohydrate content (in grams) by the glycemic index of the food item and dividing it by 100.

Mohan et al. found that brown rice consumption resulted in a significant reduction in glucose level due to the low GI and relatively higher fibre content in brown rice than in white rice[16]. A 121-patient RCT was carried out to compare the effects of a high-fiber wheat diet versus a low-GI legume diet. The low-GI legume diet resulted in a greater reduction in HbA1c than the high-wheat-fiber diet. The low-GI legume diet also reduced total cholesterol and triglyceride levels[17]**.** A meta-analysis of 14 RCTs revealed that HbA1C levels were significantly reduced by foods with a low GI when compared to foods with a high GI[18]**.** A study conducted on the effect of consumption of low GI desserts on anthropometric parameters in patients with type 2 diabetes mellitus by Argiana et al. shows that consumption of desserts made of food items with a low GI will aid in maintaining the normal blood sugar level[19]**.**

Dietary fibres are carbohydrate polymers that consist of more than third-degree polymerization. Because they cannot be digested or absorbed by the small intestine on their own, they require bacterial fermentation for breakdown. Soluble fibre are beneficial in the management of DM as they increase the viscosity of the intestinal content, which delays emptying and decreases the absorption of other macronutrients, resulting in a reduction in blood sugar levels with reduced cholesterol levels due to the elevated production of bile[20]**.**

Although a reduction in carbohydrate content in the DM diet is a long-held belief, historic data from studies of the High Carbohydrate, High Fibre (HCHF) diet conducted in India proves the beneficial effect of the HCHF diet over other diets. Recent research supports the benefits of a long-term HCHF diet in weight loss and glycemic control, as well as a lower risk of cardiovascular disease (CVD) development**.** A retrospective study was conducted in

California to determine the effect of the HCHF diet for 7 days. Weight loss and improved metabolic profiles were observed in the study population[21]**.**

A study was conducted on 28 East Asian Americans and 22 Caucasian Americans to compare the effects of the traditional Asian diet and the Western diet. Improved insulin sensitivity and reduced total cholesterol levels were identified while consuming the

Asian diet, as the Asian diet is traditionally high in carbohydrates, and fibre and low in fat content[22]. A 21-day RCT was conducted to compare the HCHF diet with the standard DM diet, and a significant reduction was found in Fasting Blood Glucose (FBG), Postprandial Blood Glucose (PPBG), HbA1c, total cholesterol levels in patients who were in the HCHF diet group[23]. A meta-analysis of 15 RCTs that compared HCHF with a placebo in DM patients shows that HCHF is more effective in the reduction of FBG and HbA1c than the placebo group[24].

In DM patients with renal insufficiency or with other kidney diseases, RSSDI recommends protein consumption in the range of 0.6–0.8 g/kg of body weight, and plant-sourced protein must be preferred over animal protein in DM patients with renal disorders, as it avoids the phosphate, sodium, and potassium imbalances. Restricted protein intake is suggested as it lowers the risk of a decline in glomerular filtration rate and creatinine clearance. The addition of salt must be limited to 5 g per day to avoid burdening the kidneys. The major limitation in the recommendation of salt restriction is that sodium plays an important role in glucose metabolism and also improves insulin sensitivity. A meta-analysis of several RCTs, which was done by Pedrini et al. to evaluate the effect of dietary protein restriction on the progression of diabetic and nondiabetic renal disease intake, shows that protein restriction has a beneficial effect in DM patients with renal insufficiency[25]. The potassium and phosphorus content of the foods prescribed in the diet must be considered while framing the diet plan for DM patients who have advanced-stage kidney diseases.

RSSDI recommends the addition of fibre to a cardio-protective diet for the management of DM patients with cardiovascular complications. High intakes of dietary fibre have a positive impact on DM patients with cardiovascular complications. High fibre intake decreases cholesterol levels, which in turn reduces the risk of cardiovascular disease development. There is enough evidence that emphasises the impact of the type of fat consumed on the outcome of CVD. Plant oils containing unsaturated fatty acids like Monounsaturated fatty acids (MUFAs) and Polyunsaturated fatty acids (PUFAs) should be added to the diet in place of saturated fatty acids, as unsaturated fatty acids have a positive impact on the reduction of cardiovascular complications in DM patients. A PREDIMED study shows that the replacement of oils with saturated fatty acids with oils with PUFA in a classic Mediterranean diet has reduced the risk of developing cardiovascular complications in high-risk populations[26]. A study demonstrates that the HCHF diet with the use of oil-containing unsaturated fatty acids has a protective effect against the development of DM-associated cardiovascular complications[27].

Higher body fat, high intra-abdominal visceral fat, and ectopic fat deposition predispose to the development of metabolic comorbidities in South Asians. RSSDI recommends a 5–10% reduction in body weight in DM-obese patients by moderate calorie restriction and changes in the diet pattern with exercise. An individualized low-carbohydrate, low-fat, high-protein diet can help DM obese patients lose weight. Leila Azadbakth et al. conducted a randomised dietary trial with 63 obese women to see how a high-protein weight-loss diet affected weight and cardiovascular risk. A greater reduction in weight and waist circumference was observed in the group on a high-protein diet[28]. Samaha Frederick F et al. conducted a study to

compare the effects of a low-carbohydrate diet versus a low-fat diet. Relatively high weight loss and a greater reduction in triglyceride, FBG, and HbA1c levels were observed in the group with a low-carbohydrate diet than in the group with a low-fat diet[29].

EXERCISE MANAGEMENT PROGRAM (EMP) OR LIFESTYLE MODIFICATION:

Exercise management programs have a positive impact on the management of DM. It is thought that exercise elevates the energy requirement of the skeletal muscles, where the requirement is quenched by the glucose produced via glucose transporter 4 (GLUT 4).

Aerobic exercise, passive exercise, endurance exercise, and resistance exercise are the different types of exercise that have a beneficial effect on management. Aerobic exercise improves the functioning of the Cardiovascular System (CVS) and Respiratory System (RS) as they enhance their functioning to match the oxygen requirement. Aerobic exercise includes brisk walking, jogging, running, and swimming**.** As the name suggests, resistance exercises are exercises that must be performed against resistance. Weight lifting is a common example of resistance exercise. Resistance exercise increases CVS and RS functioning and enhances muscle and bone strength**.** Endurance exercise improves CVS functioning by enhancing the functioning of various large groups of muscles, whose enhancement increases the oxygen requirement that is met by the CVS. Passive exercise requires the use of instruments or another person's help**.** Other than these types of exercises, yoga also has a positive impact on achieving glycemic control**.**

A multicenter RCT was conducted by Balducci et al. with a sample size of 606 patients to examine the impact of different intensities of aerobic and resistance exercise. The finding was that both high- and low-intensity aerobic and resistance training are effective in the management of DM and also significantly reduce the risk of developing CVD in DM patients[30]. An RCT conducted by Van Dijk et al. on 40 people to examine the effect of resistance and endurance exercise in the management of DM shows that both resistance and endurance exercise can be included in exercise management programs for achieving enhanced glycemic control. An RCT with a sample size of 18 DM patients conducted by Bello AI et al. to identify the beneficial effect of aerobic exercise revealed that aerobic exercise can reduce FBG, PPBG, and lipid parameters in DM patients**.** Skoro-Kondza L et al. conducted an exploratory RCT with 59 DM patients to estimate the impact of yoga on glycemic control and found that yoga has a positive impact on HbA1c levels in DM patients**.**

J.D. Goldhaber-Fiebert et al. studied the effect of walking on diabetes in 75 diabetic patients in a randomised controlled pilot study. Walking was found to reduce FBG, PPBG, and CVD risk factors in DM patients, demonstrating the beneficial effect of walking in DM patients**.**

DISCUSSION:

At present, pharmacological therapy is mostly preferred for the management of blood glucose in the vast majority of patients. The dependence on pharmacological therapy for management requires more drugs than the suggested normal range to achieve euglycemia,

which may produce some undesired side effects, adverse effects, and interactions

(drug-drug). The studies mentioned above also prove the same. By prescribing the most appropriate drug at a suitable dose while considering the patient's body

condition, the risk of developing undesired effects can be significantly reduced. Verifying the possible drug interactions and also substituting the combination therapy with fixed-dose combination drugs might have a significant effect. In the non-pharmacological aspect, MNT has demonstrated a positive impact on management, but the degree of compliance will be higher when the MNT is framed according to the patient's preference. Combining the most appropriate pharmacological therapy with individualised non-pharmacological therapy is the key to achieving a normal blood glucose level. Continuous monitoring at regular intervals will assist in identifying the risk of developing any unwanted effects as well as the level of adherence to the therapy.

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