Review Article

Maturity Onset Diabetes of the Young: The Indian Scenario

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ABSTRACT

This review attempts to summarize the literature findings of Matured Onset Diabetes in Young which is known as MODY, highlighting the perspective of the Indian population. This article provides a gist of the prevalence, clinical features, methods of diagnosis and probable treatment methods of the disease having an updated list of references of all recent published articles available in the public domain. An increasing number of people worldwide, including India is being misdiagnosed as Type 1 or Type 2 Diabetes in spite of having MODY. Faulty eating habits, sedentary life style and mismanagement of stress and poor work-life balance is causing the chronic disease on the rise. Misdiagnosis results in delay of the actual treatment of the disease. Uncontrolled blood sugar levels for a very long time may lead to several macrovascular and microvascular complications. This review aims to bring an awareness among people to understand the characteristics of the disease, the possible ways of managing the disease and the precautions to be taken in order to prevent it. The possible reasons and probable solution for the problem of the alarming increase of the disease in India is being discussed here.

Key words: MODY, India, Type 1 Diabetes, Type 2 Diabetes, Misdiagnosis, Management.

INTRODUCTION

Diabetes is a metabolic disease having clinical characteristics of chronic hyperglycaemia due to defective insulin secretion and/or action. Low levels of insulin cause prolonged rise in blood sugar which causes polydipsia, polyuria, polyphagia, blurred vision and weight loss. If left untreated, it may cause diabetic keto acidosis, stupor coma and even death. It is called as the epidemic of the century.[1] Diabetes is one of the oldest diseases known, reported in Egyptian manuscripts around 3000 years ago. People having diabetes suffer from short term and long term complications which may be fatal.[2] It has been reported that approximately 415 million people in the World are living with diabetes currently.[3] Maturity Onset Diabetes Mellitus of the young, abbreviated as MODY is a heterogeneous disease resulting due to genetic mutations which causes dysfunctioning of β-cell of pancreas.[2] Tatersall *et al.* reported in 1974 MODY in a family having mild clinical characteristic of Diabetes Mellitus.[4] Heterozygous mutations of glucokinase gene were recognized in 1992 as the cause of MODY.[5] The clinical characteristics of MODY include common Type I and Type II diabetes symptoms.[6]

LITERATURE REVIEW AND SEARCH STRATEGY

A thorough literature search was done for relevant articles in databases like Science Direct, Pubmed, Cochrane library, Medline, Embase and general google search. Search terminologies used included but were limited to Diabetes review, treatments for diabetes, incidence and prevalence of Diabetes in India and the world and Diabetic complications. Relevant articles which were suitable for writing this review were included

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while old articles dated in 1980 or before were excluded since the medical treatments have evolved a lot in recent times. Articles having information on other chronic diseases like hypertension were not included in this review. Research papers containing both positive and negative outcomes have been taken into consideration in order to make this review non-biased. Articles published after the year 2000 have been referred in order to make this review an updated one.

INDIAN PERSPECTIVE

As per International Diabetes Federation, Atlas India is the second largest country in the World having Diabetic patients. 62 million people are affected presently and the Figure is expected to rise by more than one hundred million by 2030. Type 1 and Type 2 diabetes are common in India accounting for greater than 95% of the cases. MODY was reported in India in 1985.[7]

The number of Type 2 Diabetes Mellitus cases in India is exponentially increasing since the last 30 years. 8-10 percent and 15 percent of the population of India are having Type 2 Diabetes and pre diabetes respectively. MODY cases in India are also often misdiagnosed as Type 1 Diabetes Mellitus and wrongly treated with insulin.[8]

MODY is reported to occur in 1-2% of diabetic cases. Owing to high cost of genetic testing and similar clinical characteristics with Type 1 and Type 2 Diabetes, it is often misdiagnosed.[9]

The disease Diabetes causes deterioration in Quality of Life. They have problems with freedom to eat and drink; living conditions and reaction of people.[10]

TYPES OF DIABETES

The following are the types of the disease:

1. **Type 1 Diabetes Mellitus:** It is also called as Autoimmune type 1 diabetes constituting about 5-10% of diabetic patients. 80-90 percent of children and young adults are diagnosed with this type of diabetes. It results due to destruction of pancreatic β cells. Type 2 Diabetes Mellitus: It is the most common type of Diabetes Mellitus affecting adults between 40 and 59 years of age.

2. **Monogenic Diabetes:** This is caused due to genetic defects in β cells of pancreas. MODY is a category of this disease which affects adults less than 25 years of age.

3. **Gestational Diabetes:** Hyperglycaemia due to Type 2 diabetes during pregnancy is known as gestational diabetes. Risks associated with it are macrosomia, caesarean delivery, pre term birth and preeclampsia.[1] Gestational diabetes generally occurs in the second or third trimesters of pregnancy and usually did not have the disease before.

INCIDENCE AND PREVALENCE

It has been reported that more than 400 million people worldwide is suffering from Diabetes.[11]

Around 80% of people living in low income and middle income countries are suffering from Diabetes. 439 million people are expected to have the disease by 2030. Majority of Diabetes cases are Type II, the rest are Type I.[12]

The Western Pacific Region has the highest number of diabetic adults (37.5%).

Type I Diabetes is called as the Disease of Wealth as an increasing number of western countries are having the disease. Diabetes is expected to increase in huge numbers in the regions of Asia, Africa and Middle East.[13]

As many individuals as 80 percent of young population having diabetes are misdiagnosed as having Type I or Type II diabetes. It is a common form of monogenic disease, affecting 1-2% of diabetics in Europe. Genetic mutations also result in many cases of MODY in UK.[4]

6.5% of Norwegian children having diabetes have been reported to have MODY.[14]

One of the most well-known forms of monogenic diabetes is MODY. Neonatal diabetes occurring before six months of age is also categorized here. It is suspected in individuals having positive family history, lack of risk factors of type 2 diabetes, type 1 diabetes markers, auto-antibodies and levels of C-peptide assay should be investigated to conclude MODY diabetes.[15]

MODY is well available among people of Europe and United Kingdom. Prevalence of the disease in South America, Africa, Asia and Middle East is not known. Further research regarding this is required.[16]

MODY is also reported in Asian Indians.

MODY is also reported in European countries of Greece, Denmark, Czech Republic, Netherlands, United Kingdom, Italy, Spain, Germany and Austria.[9]

MODY has also been reported in school going children in Japan.[17]

POSSIBLE CAUSES OF THE DISEASE

Type 2 Diabetes Mellitus mainly results due to genes, insufficient physical activity, sedentary habits, excessive smoking and drinking.[12]

The most common causes of MODY are mutations of glucokinase (causes MODY 2) and genes of hepatocyte nuclear factor (HNF) 1A/4A (causes MODY 1 and MODY 3). The former is mild, asymptomatic and normal glucose levels; while the latter cause a gradual destruction of pancreatic β cells and hyperglycaemia which may result in microvascular complications.[4]

As per a reported study, smoking was associated with risk of Diabetes Mellitus.[18]

Figure 1 Represents pictorially the major causes for MODY in India.

PATHOPHYSIOLOGY

Insulin insensitivity due to insulin resistance which results in reduced insulin production and β-cell damage. Glucose transport ratio gets reduced in liver, muscle and fat cells. This in turn causes more fat breakdown and hyperglycaemia.[12]

MODY is caused by a group of monogenetic form of the disease. High blood sugar levels causes stress in β cells which causes cell death. It is generally inherited in autosomal dominant way affecting families having diabetes for many generations.[14]

Diabetic patients with MODY have symptoms of early onset of Diabetes and do not have features of autoimmunity and insulin resistance.[19]

Single gene mutation of the pancreatic β-cells causes the endocrine disorder which results in MODY.[16]

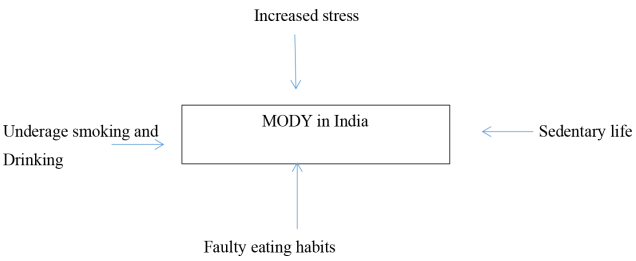

Figure 1: Possible causes of the Disease in India.

Mutations of 14 genes have been identified till date which causes MODY.[20]

Genetic mutations causing MODY have been observed in *HNF1B, INS, NEURO1, PDX1, PAX4, ABCC8, GCK, HNF1A, HNF4A, KCNJ11, KLF11, CEL, APPL1* and *BLK*.[21]

Genetic mutation of the gene HNF1A is a common cause of MODY. It is a polymorphic gene having over 1200 pathogenic and non-pathogenic variants.[22]

In MODY only insulin secretion is impaired, insulin action is not affected.[23]

Pharmacological treatment is not usually required for the glycemic control of MODY.[24]

DIAGNOSIS

Glycosylated Hemoglobin, also called as HbA_{1c} provides the integrated glycaemic index of 120 days lifespan of RBC. A value of more than 6% HbA_{1c} indicates Diabetes. For well controlled diabetes, HbA_{1c} value should be kept below 6.5%.[25]

Proper diagnosis of MODY is required in order to differentiate it from the other types of diabetes. In the United States, a large volume of young adults were diagnosed with MODY by molecular methods. Prior to that, they were mistakenly given treatments for Type 1 or Type 2 diabetes.[4]

As per the SEARCH study conducted on youth, 36% of MODY patients having mutated gene variants were misdiagnosed as having Type 1 diabetes and only 19% of them received appropriate treatment.[26]

Islet antibodies GADA, 1A-2A, HLA, IAA, ZnT8A, HbA_{1c} and C-peptide are collected during diagnosis. Serum C-peptide from random blood sugars are measured. MODY is diagnosed by identifying pathogenic or likely variants in the genes.[6]

Genetic testing is possible since the 1990s for identification of genes causing MODY.[24]

Molecular genetic testing to detect MODY include single or multi gene serial gene-targeted testing and chromosome microarray or exome sequencing analysis called as comprehensive genomic testing.[27]

Once a patient gets genetic diagnosis of MODY, genetic testing may be offered to other family members in order

to rule out genetic predisposition. This phenomenon is called cascade testing.[28]

Since MODY diabetes is a genetic disease, DNA analysis of family members of patients may be done.[22]

C-peptide assay may be conducted for suspected MODY individuals like onset before 45 years of age, absence of β-cell autoimmunity and insulin resistance. This assay characterises the functioning of pancreatic β-cells. Insulin treatment is not required if its level is more than 200 pmol/L following 3 years of insulin treatment.[17]

India is making rapid advances in genetic testing. Molecular genetic testing is available in the country for diagnosis of MODY.[7]

However, in Asian diabetics, rate of detection of autoantibodies is low and is expensive.[23]

TREATMENT

Insulin is used to treat Type I diabetes mellitus. It is also used as an add on therapy with oral hypoglycaemic agents for the treatment of Type II diabetes. Types of insulin's used include long and intermediate acting insulin's like Neutral protamine Hagedorn (NPH), lente and ultralente insulin. They cause irregular absorption, hypoglycaemia may result at the peak time of action.

Most of the MODY patients do not require treatment due to the characteristics of mild hyperglycaemia and no long term microvascular complications. Progressive β-cell damage require treatment with low dose sulphonylurea.[29]

MODY due to mutations of HNF4A and HNF1A genes require treatment with oral hypoglycaemic agents like sulphonylureas. Medical treatment involves the practice of "Precision Medicine". It refers to the knowledge and application of one's intuition, susceptibility and etiology of disease and treatment response. Low carbohydrate diet may be followed as the HbA1c values for these individuals come in the non-diabetic range. When glucose control becomes ineffective after many years, diet and oral hypoglycaemic agents may be used for the disease management.[30]

Insulin lispro and as part are rapid acting in nature. Insulin glargine is a long acting peak less insulin.[12]

Low dose insulin may be used for the treatment of MODY.[20]

The following is a Table (Table 1) representing oral hypoglycaemic agents which may be used for the treatment of MODY:[31-35]

MANAGEMENT OF THE DISEASE

Maintaining a healthy body weight, BMI of within 25 kg/m^2, consumption of high fibers, regular exercise and cutting down of unsaturated fats, trans-fats and foods having a high glycaemic index are essential for managing the disease properly.[12]

A diabetic diet may be used to control hyperglycaemia in pregnancy.[36]

Yoga and meditation is non pharmacological way of managing the chronic disease. A literature study reported that practice of meditation for six months lowered blood sugar and improved the HbA1c value of diabetic patients.[37]

COMPLICATIONS DUE TO DIABETES

Type 1 and Type 2 diabetes is associated with chronic macrovascular complications like stroke, peripheral vascular disease and coronary heart disease; and microvascular complications like diabetic neuropathy, retinopathy and amputation of lower extremities. Acute complications associated with Diabetes are diabetic ketoacidosis, lactic acidosis, hypoglycaemia and hyperosmolar state. Diabetic patients are at an increased risk of having infections like tuberculosis, urinary tract infection, hospital acquired postoperative infection and tropical diseases. They are also at risk of suffering from anxiety, dementia, eating disorders, and psychiatric disorders like mental illness, dementia and major depressive disorders.[3]

In a reported study conducted in France, proteinuria, retinopathy and peripheral neuropathy occurred in 4-6% of MODY individuals.[4]

Both microvascular and macrovascular complications occurring in MODY patients were found to be similar to that of Type 1 and Type 2 diabetic patients.[5]

MODY genes damage insulin production which causes hyperglycaemia resulting in damage to eyes, nerves, kidneys and blood vessels. The disease will get detected upon routine testing as long term diabetic complications do not develop in MODY.[38]

Table 1: Summary of anti-diabetic drugs

Class of Drugs	Drugs under the category	Mechanism of Action	Major Adverse events
Sulphonylureas	Tolbutamide, Clorpropamide, Gliclazide, Glipizide, Glibenclamide, Glimepiride	Stimulates insulin secretion from β-cells of pancreas, decreases hepatic clearance of insulin	Hypoglycaemia
α-Glucosidase Inhibitors	Acarbose, Miglitol, Voglibose	Delays absorption of carbohydrates from small intestine; lowers blood glucose	Gastrointestinal disturbances
Biguanides	Metformin, Phenformin	Decreases hepatic glucose production, intestinal glucose absorption, improves insulin sensitivity	Nausea, diarrhoea, abdominal cramps, appetite loss
Thiazolidinediones	Pioglitazone Rosiglitazone	Decreases insulin resistance by activating PPARγ receptors	Cardiovascular toxicity, risk of bone fracture, bladder cancer
Sodium Glucose Co-transporter-2 inhibitors	Dapagliflozin Canagliflozin Empagliflozin Ipragliflozin	Inhibits SGLT2 in proximal convoluted tubule, prevents reabsorption and promotes excretion of glucose in urine	Urinary infection, vulvitis and vaginitis (women), balanoposthitis and balantis (men)
DPP-4 Inhibitor	Sitagliptin Vildagliptin Saxagliptin Linagliptin Alogliptin Dutogliptin Gemigliptin	Inhibits the enzyme DPP-4 which regulates activity of glucagon-like-peptide and glucose-dependent insulinotropic peptide	Extremity pain

As per a reported literature, patients having GCK-MODY have mildly raised blood sugar concentration. This usually does not require treatment and don't lead to complications associated with diabetes.[26]

Another published literature reported that microvascular and macrovascular diabetic complications are rare in MODY due to GCK. Hyperglycaemia treatment is not necessary for MODY unless for pregnancy. The treatment depends on the genotype of foetus and how it responds and senses maternal hyperglycaemia.[36]

DISCUSSION

General guidelines to manage diabetes involve physical exercise, maintenance of healthy body weight, abstaining tobacco and alcohol use. Families having positive family history may prevent it by consuming diet rich in fiber and grains, choosing healthy polyunsaturated fats like fish, nuts and vegetable oils; limiting sugar and red meat consumption. Well controlled diabetes may delay and prevent the occurrence of Diabetic complications.[40]

As per published literatures, many Indians regularly consume alcohol. The age of drinking is going down considerably. Many teenage people in India have started abusing alcohol.[40]

Yoga originated in India more than 5000 years ago. It helps to balance the mind, body emotions. It regulates eating patterns and helps in the management of eating disorders. Yoga and meditation have been reported in published literatures to be helpful in managing stress and for controlling diabetes.[41]

CONCLUSION AND FUTURE PROSPECTIVE

Several hospitals are available in India for exclusive treatment and care of Diabetic patients.

MODY which occurs in young adults and even teenagers are becoming widely prevalent in India currently. This is occurring due to the increased number of students and young professionals for mismanaging stress, sedentary lifestyle, consumption of fast food and unchecked abuse of tobacco and alcohol. People in India should be counselled about stress management and practice yoga and meditation. They should be warned about the dangers and health hazards of underage smoking and drinking. Further, children and adolescents should be encouraged to participate in outdoor activities and sports instead of spending too much time on mobile phones, television and other electronic gadgets.

Physicians practicing in India should take adequate care not to misdiagnose MODY as Type 1 or Type 2 Diabetes. MODY is having good pancreatic β-cell functioning does not need insulin treatment. Improper diagnosis and treatment of MODY may cause uncontrolled glycaemic levels for several years, resulting in complications at a later stage.

Further, the molecular genetic testing in India for the diagnosis of MODY is expensive considering the economy of India. These tests may be made available to common people at a subsidised rate.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

MODY: Matured Onset Diabetes of the Young; **HNF:** Hepatocyte Nuclear Factor; **HbA1c:** Haemoglobin A1c; **NPH (insulin):** Neutral Protamine Hagedorn; **SGLT2:** Sodium Glucose Co-transporter-2; **DPP-4:** Dipeptidyl Peptidase-4.

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