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REVIEW ARTICLE

PATHOPHYSIOLOGY AND MANAGEMENT OF MODY: A REVIEW

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ABSTRACT

Maturity Onset Diabetes of Young (MODY) is ahereditary form of diabetes mellitus and is caused due to mutations in autosomal dominant gene and isreferred to as Monogenic diabetes. It may be confuses to be a disease Latent Autoimmune Diabetes of Adult (LADA). But LADA has a slower progression to insulin dependence as age progresses while MODY has childhood onset and occurs later in life. MODY variant forms include MODY 2 and 3 which are most common forms. Children and adolescents with MODY may have fasting hyperglycemia at diagnosis and these patient presents with typical microangiopathic and macroangiopathic complications with similar degree of hyperglycemia In retrospect we can now recognize that this category covered a heterogeneous collection of disorders which included cases of dominantly inherited diabetes, still call MODY today. As in 20th century the concept and understanding of MODY has become refined and debatable, hence the pathophysiology and management has been explored through literature in this review.

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INTRODUCTION

MODY[(1)] refers to hereditary forms of diabetes mellitus due to mutations in autosomal dominant gene (Barry, 2008) disrupting insulin production, often referred to as Monogenic diabetes (Yorifuji *et al*., 2004; Edghill *et al*., 2006) MODY 2 and 3 are most common forms (Tattersall, 1974) MODY was originally applied to any child or young adult who had persistent, asymptomatic hyperglycemia without progression to diabetic ketoacidosis. Many of these patients were treated with sulfonylureas with varying degrees of success (Tattersall, 1998; Whiting, 2011; Ogurtsova *et al*., 2017; Tattersall, 1998) Since the 1990s, the concept of MODY have become refined and narrower. It is now used as a synonym for dominantly inherited monogenic defects of insulin secretion at any age. The prevalence is 70-110 per million population. 50 percent of first degree relatives will inherit the same mutation. Patients present with a strong family history of diabetes and onset of symptoms is in the 2nd to 5th decade. There are two types of clinical presentation: Significant hyperglycemia with signs and symptoms of diabetes- Polydipsia and Polyuria. In contrast, most of them have no signs and symptoms and diagnosed accidently during testing for glucose or presence of mild hyperglycemia during a routine GTT for pregnancy. Many cases of MODY are initially assumed to be more common forms of diabetes- type 1 in young patient and not overweight, type 2 if the patient is overweight or gestational diabetes if the patient is pregnant. These facts gave us an impetus to explore the pathophysiological basis and management of patients of MODY in today's context.

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MATERIALS AND METHODS

In order to have a systematic review of pathophysiology and management of MODY in 21st Century, the literature data available from index citations. Pub Med and National Library of Medicine US was analyzed and studied to understand and discuss the pathophysiology and management of MODY in todays context.

DISCUSSION

Epidemiology: MODY appears to be more common in Indians of which 27 percent of MODY patients had autosomal dominant inheritance. According to International Diabetes Federation 2011, India is second with regard to prevalence. Nearly 62 million people affected at present and this number is expected to rise to more than 100 million by 2030 (Tattersall, 1998). Another systematic literature review was conducted on the prevalence of diabetes from studies conducted from 1990 to 2015 in which 540 data were reviewed of which 196 sources were selected. In 2015, estimated people with diabetes were 415 million in which 75% people were living in low and middle income countries. The predicted increase in the percentage of people with diabetes for 2040 was 642 million

(Tattersall, 1998; A missense TCF1 mutation in a patient with MODY- 3 and liver adenomatosis, 2011; Dhavendra Kumar, 2008). A review on MODY was given by Fajans and Conn in which they stated that tolbutamide could improve carbohydrate tolerance in young non obese diabetic patients by showing carbohydrate intolerance in 45 patients diagnosed under age 25 had not progressed after up to 16 years on sulfonylureas and nearly all these subjects had a first degree relative with diabetes. In 1974, Tattersall described three families in which diabetes, although diagnosed in adolescence could be treated with sulfonylureas and was dominantly inherited.

Clinical presentation in patients of MODY: Patients with MODY might be presented with following presentation-Mild to moderate hyperglycemia (130-250 mg/dl) before 30 years but can be seen in persons under 50 years (Steele, 2014). Similar history of diabetes may be present in first degree relatives. There is absence of obesity and other metabolic syndrome such ashyperlipidemia, PCOD and hypertension (Ogurtsova, 2017; Neve, 2005). Presence of liver adenoma or hepatocellular carcinoma is found in MODY type 3 (Ogurtsova, 2017; Tattersall, 1998; Raeder, 2006).

Pathophysiology: MODY is an autosomal dominant disorder with an onset before age of 25 years and most commonly in childhood/ adolescence with a primary defect in function of beta cells. Children and adolescents with MODY may have fasting hyperglycemia at diagnosis. Most people are not obese. Most of them presents with typical microangiopathic and macroangiopathic complications with similar degree of hyperglycemia. One form is due to mutations of glucokinase gene. In some cases, there are significant differences in the activity of mutant gene product that contribute to variations in the clinical features of diabetes. Only one abnormal gene is required to produce the disease. The severity of disease is influenced by the presence of a second normal allele. However, people with two abnormal alleles have been identified. Most common forms are MODY 2 and 4. MODY 2 include severe congenital insulin deficiency resulting in neonatal diabetes mellitus due to deficiency of homozygous glucokinase. About six cases have been reported worldwide and all have required insulin treatment shortly after birth. The condition does not seem to improve with age. In case of MODY 4, there is congenital absence of pancreas, termed pancreatic agenesis, involves deficiency of both endocrine and exocrine functions of pancreas. Homozygous mutations in other forms have not yet been described. Those mutations for which homozygous form has not been described may be rare, may result in clinical problems or may be lethal for a fetus and not result in a viable child.

Management: MODY cases may make up to 5% of presumed type 1 and type 2 diabetes cases while the goals of management are the same. In some forms of MODY, appropriate standard treatment is required (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003; Urbanova *et al*., 2014; Schover, 2009). Sulfonylureas are effective as demonstrated in a mouse model of MODY suggested that reduced clearance of sulfonylureas stands behind their therapeutic success in human MODY patients but Urbanova *et al.* found that human MODY patients respond differently to mouse model and there was no decrease in clearance of sulfonylureas. The principle treatment goals is to keep blood sugar as normal as possible and minimizing other risk factors.

The tools for management are similar for all forms of diabetes-blood testing, diet changes, physical exercise, oral hypoglycemic agents and insulin injections. In MODY cases, the first resort of oral hypoglycemic agents are sulfonylureas (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997; Galler *et al*., 2010). These patients are more sensitive to sulfonylureas.

Conclusion

Early diagnosis, treatment withsulfonylureas, diet control and life style modification are effective in providing quality life to MODY patients. Patients with MODY less often suffer from obesity and insulin resistance than those with ordinary type 2 diabetes and in type 2 diabetes insulin sensitizers are preferred over sulphonylureas.

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