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NEW PERSPECTIVE WITH GLICLAZIDE MR ON SCREENING AND MANAGEMENT OF MODY PATIENTS IN INDIA

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ABSTRACT

Maturity-onset diabetes of the young (MODY) is a genetically heterogeneous group of monogenic endocrine disorders characterized by autosomal dominant inheritance and pancreatic β-cell dysfunction. Currently, 14 MODY subtypes have been identified, with differences in incidence, clinical features, diabetes severity and related complications, and treatment response. This type of diabetes is mostly misdiagnosed as either type 1 or type 2 diabetes mellitus because it is difficult to differentiate between these forms of diabetes due to clinical similarities, the high cost of genetic testing, and lack of awareness. The correct diagnosis for individuals with MODY is of utmost importance, as the applied treatment depends on the gene mutation or is subtype-specific. Sulphonylureas, specifically Gliclazide, has emerged as the drug of choice for MODY patients. This review will discuss the importance of screening in MODY patients and its management and the status of MODY patients in India.

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INTRODUCTION

The most commonly recognized diabetes mellitus includes type 1 diabetes, an autoimmune disorder, and type 2 diabetes, a polygenic disorder influenced by genetics and environment. However, now, it is understood that more than just two forms of diabetes exist, although hybrid forms occur much less frequently.[1]

As per the new classification system based upon dysfunctional β-cells, diabetes can be classified into the following types[2]-

- Type 1 diabetes
- Type 2 diabetes

- Hybrid forms
- Hyperglycaemia during pregnancy
- Unclassified diabetes
- Other specific types include monogenic diabetes

The monogenic diabetes subclass can be further sub-divided into the following subtypes-

- Monogenic defects in insulin action
- Other genetic syndromes associated with diabetes
- Monogenic defects of β-cell function- Clinical manifestation of monogenic defects in β-cell function include maturity-onset diabetes of the young (MODY).

Maturity-onset diabetes of the young (MODY) and its screening

MODY is a monogenic type of diabetes resultant from single-gene mutations. It is characterized by mild hyperglycemia, autosomal dominant inheritance, early onset of diabetes (<25 years), insulin resistance, and preservation of endogenous insulin secretion.[3] The genes involved are crucial for the development, functioning, and regulation of β cells. They can cause glucose sensing and insulin secretion disorders. Fourteen MODY subtypes have been identified thus far, each characterized by a distinct gene mutation.[3] MODY is often misdiagnosed by type 1 or type 2 diabetes; however, MODY can be distinguished from other types of diabetes based on the age at which the disease first manifested. Apart from age, other clinical distinguishing features that differ from type 1 diabetes patients include C-peptide concentration, hs-CRP, lipid levels and polyuria. It is currently suggested that genetic tests for MODY be performed when paediatric diabetes is diagnosed, together with modest hyperglycemia and absence of all four islet autoantibodies (antibodies against GAD, insulinoma antigen-2, zinc transporter and insulin)[2]. The standard approach for diagnosis of MODY includes the sequential screening of the first three common MODY genes, which include hepatocyte nuclear factor 1α (HNF1A), hepatocyte nuclear factor 4α (HNF4A) and Glucokinase (GCK).[4] The diagnosis of MODY has significant implications for diabetes management. The principal pathogenic defect in MODY is impaired insulin secretion, so (unlike patients with type 1 diabetes) 99% of patients with MODY will not have islet cell autoantibodies, and most will show endogenous insulin secretion for some years after diagnosis. As a result, these patients do not require insulin therapy.[5] Thus, in patients with GCK-MODY (a subtype of MODY), the glucose-lowering therapies are ineffective due to a higher basal glucose level.[6] On the other hand, patients with HNF1A- or HNF4A-MODY (a subtype of MODY) are highly responsive to low-dose sulfonylureas due to the increased pancreatic insulin secretion.[7]

A UK population study highlighted the importance of the correct diagnosis of MODY. Following genetic diagnosis for MODY, patients with GCK-MODY, who were inappropriately treated at the time of diagnosis, could stop this treatment without any effect on HbA1c levels. However, only 58% of HNF1A/HNF4A-MODY patients, who were also treated inappropriately in the past, could change the treatment to sulfonylurea/diet alone.[8] Thus, screening of MODY and subsequent selection of treatment modality is critical for the management of MODY patients.

Treatment with Sulphonylureas in MODY patient

The finding of the UK nationwide prospective study of treatment change in MODY suggests that in individuals with HNF1A/HNF4A-MODY with a longer duration of diabetes (>11 years) at the time of genetic test, rather than ceasing current treatment, a sulfonylurea should be added to existing therapy, particularly in those who are overweight or obese and have a high HbA_{1c}.[8]

Studies have suggested that MODY caused by HFN mutations, i.e., HNF1A/HNF4A (MODY1, MODY3 and MODY5), responds exceptionally well to sulfonylureas. Thus, suggesting the use of sulphonylureas as a first-line treatment before metformin in patients with MODY because these patients do not have insulin resistance; metformin, as an insulin sensitizer, is better suited for patients with type 2 diabetes. Because of this, a crossover trial of Gliclazide and Metformin in 36 patients, either with diabetes caused by HNF-1alpha mutations or type 2 diabetes who were matched for body-mass index and fasting plasma glucose, was carried out. Participants were randomized to metformin or Gliclazide for 6 weeks and then crossed over to the alternative treatment following a 1-week washout period between treatments. Patients with HNF-1alpha diabetes had a 5.2-fold greater response to Gliclazide than metformin (fasting plasma glucose reduction 4.7 vs 0.9 mmol/L, p=0.0007). Thus, Gliclazide was significantly more effective in lowering fasting plasma glucose in patients with MODY3 than in patients with T2DM. In contrast, metformin was slightly (but not significantly better) in the T2DM than in the MODY3 group. Additionally, Gliclazide increased β-cell function by 55% in patients with T2DM; the increase was 310% in patients with MODY3.[5,9]

These findings demonstrated that the cause of hyperglycaemia changes the response to hypoglycaemic drugs; HNF-1α diabetes has marked sulphonylurea sensitivity. This pharmacogenetic effect is consistent with models of HNF-1α deficiency, which show that the β-cell defect is upstream of the sulphonylurea receptor. Thus, the genetic basis of hyperglycaemia has critical implications for patient management.[9]

Treatment of MODY in Indian population

Indian population shows a marked difference in the type 2 diabetes profile compared to the global profile. The Indian population profile differs from that in Western populations, with respect to the tendency to develop insulin resistance at a younger age, lower body mass index, and a high prevalence of several high-risk genetic polymorphisms.[10] Similarly, the MODY patient profile is expected to differ vastly from the western population.[11] Genomic data from South India reported that MODY3 was the most prominent subtype (as it is elsewhere), followed by MODY12, which is associated with a mutation in ABCC8. MODY12 is rarely found in European populations.[12]

This study highlighted the difference in the genetic profile of MODY patients in India and the need to undertake a nationwide study to identify the genetic profile of MODY patients in India. This is highly critical as the MODY subtype can impact treatment modality selection which will determine the management of diabetes in MODY patients in India.

In view of these urgent clinical implications, a Pan-India MODY study has been undertaken between November 2019 and October 2021. There are two parts to this study. The first part aimed to carry out the comprehensive genetic screening of Indian MODY patients. This will help to identify the prevalent subtypes in Indian MODY patients. Further, the study investigates the feasibility, reliability and efficacy of genetic testing on salivary samples. Collecting salivary samples than blood, especially in children, is far more convenient and has far-reaching implications.

The second part of the study aimed to evaluate the clinical efficacy (primary objective) and safety (secondary objective) of Gliclazide MR 60 mg in MODY1, MODY3 or MODY12 patients.[5] The results of this study will help to establish the treatment modality of MODY patients in India. The Pan-India MODY study is expected to provide important information about the prevalence of MODY and the effect of treatment with Gliclazide MR 60 mg in patients with MODY. This study is

expected to delineate the prevalence of MODY in India. It could contribute to the development of a standardized salivary diagnosis test. It will also provide new valuable data on the efficacy and safety of gliclazide MR in specific MODY subtypes.

CONCLUSION

MODY is an early-onset, autosomal dominant form of non-insulin-dependent diabetes. There are around 14 subtypes of MODY, classified on a genetic basis. It has been seen that different genetic subtype of the MODY can exhibit varied sensitivity towards the treatment modality selected. Thus, the genetic diagnosis of MODY is exceptionally critical and can transform patient management. Studies show that MODY patients exhibit a highly sensitive response to the sulphonylureas, specifically, Gliclazide. Therefore, Gliclazide has been suggested to be taken as the first-line treatment in certain types of MODY patients, as they do not respond to metformin treatment.

Further, unlike the western population, the genetic profile of the Indian population differs significantly. The PAN India MODY study results are expected to provide the genetic profile of the Indian MODY patients and the efficacy and safety of Gliclazide in Indian MODY patients. Increasing awareness about MODY is essential for timely and optimal management of the disease, preventing complications in patients affected and early diagnosis in their asymptomatic family members.

REFERENCES

1. Laura S. Hoffman, Tamaryn J. Fox, Catherine Anastasopoulou, Ishwarlal Jialal. *Maturity Onset Diabetes in the Young*.; 2021. Accessed February 22, 2022. www.ncbi.nlm.nih.gov/books/NBK532900
2. Skoczek D, Dulak J, Kachamakova-Trojanowska N. Maturity onset diabetes of the young—new approaches for disease modelling. *International Journal of Molecular Sciences*. 2021;22(14). doi:10.3390/ijms22147553
3. Tshivhase A, Matsha T, Raghubeer S. Diagnosis and Treatment of MODY: An Updated Mini Review. Published online 2021. doi:10.3390/app
4. Doddabelavangala Mruthyunjaya M, Chapla A, Hesarghatta Shyamasunder A, et al. Comprehensive Maturity Onset Diabetes of the Young (MODY) Gene Screening in Pregnant Women with Diabetes in India. *PLOS ONE*. 2017;12(1):e0168656. doi:10.1371/journal.pone.0168656
5. Khunti K, Hassanein M, Lee MK, Mohan V, Amod A. Role of Gliclazide MR in the Management of Type 2 Diabetes: Report of a Symposium on Real-World Evidence and New Perspectives. *Diabetes Therapy*. 2020;11(S2):33-48. doi:10.1007/s13300-020-00833-x
6. Chakera AJ, Steele AM, Gloyn AL, et al. Recognition and Management of Individuals With Hyperglycemia Because of a Heterozygous Glucokinase Mutation. *Diabetes Care*. 2015;38(7):1383-1392. doi:10.2337/dc14-2769
7. Gardner D, Tai ES. Clinical features and treatment of maturity onset diabetes of the young (MODY). *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*. Published online May 2012:101. doi:10.2147/DMSO.S23353
8. Shepherd MH, Shields BM, Hudson M, et al. A UK nationwide prospective study of treatment change in MODY: genetic subtype and clinical characteristics predict optimal glycaemic control after discontinuing insulin and metformin. *Diabetologia*.

2018;61(12):2520-2527. doi:10.1007/s00125-018-4728-6

9. Pearson ER, Starkey BJ, Powell RJ, Gribble FM, Clark PM, Hattersley AT. Genetic cause of hyperglycaemia and response to treatment in diabetes. *The Lancet*. 2003;362(9392):1275-1281. doi:10.1016/S0140-6736(03)14571-0
10. Gujral UP, Pradeepa R, Weber MB, Narayan KMV, Mohan V. Type 2 diabetes in South Asians: similarities and differences with white Caucasian and other populations. *Annals of the New York Academy of Sciences*. 2013;1281(1):51-63. doi:10.1111/j.1749-6632.2012.06838.x
11. Shah A, Kanaya AM. Diabetes and Associated Complications in the South Asian Population. *Current Cardiology Reports*. 2014;16(5):476. doi:10.1007/s11886-014-0476-5
12. Mohan V, Radha V, Nguyen TT, et al. Comprehensive genomic analysis identifies pathogenic variants in maturity-onset diabetes of the young (MODY) patients in South India. *BMC Medical Genetics*. 2018;19(1):22. doi:10.1186/s12881-018-0528-6