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Low-Dose Glimepiride and Metformin Fixed-Dose Combination in treating Maturity-Onset Diabetes of the Young Type (MODY): A Cross Sectional Survey

Maturity-onset diabetes of the young (MODY) is a monogenic disorder characterized by an autosomal dominant inheritance, absence of insulin resistance and beta-cell autoimmunity and is a rare type of diabetes that can be difficult to diagnose, leading to frequent cases of misdiagnosis [1, 2]. The incidence rate is 1–6% among the population with diabetes, with a higher prevalence among the pediatric population [1, 3]. Modern sulfonylureas such as glimepiride can be the first-line treatment of MODY. In a cross-sectional Pan-India survey in October 2022, the authors assessed the perspective and attitude of healthcare practitioners (HCPs) about the use of low-dose sulfonylurea (SU) and metformin fixed-dose combination (FDC) for treating MODY (Tab. 1). The study involved 130 HCPs, including endocrinologists, diabetologists, and clinical practitioners (South: 72, East: 21, West: 9 and North: 29).

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In real-life practice, most HCPs (64%) encountered less than five patients with MODY in a month. Molecular diagnosis is a critical tool for accurate diagnosis and individualized patient management. However, more than 50% of the HCPs did not often consider genetic testing to diagnose MODY due to the lack of availability of facilities, unwillingness of patients, lack of awareness and cost issues. Clinicians need to be familiarized with the pathogenesis and various biomarkers for MODY for timely diagnosis and interventions.

Impaired glucose-stimulated insulin secretion in patients with MODY can be attributed to reduced uptake of glucose by β-cell. This results in low levels of intracellular ATP, leaving the K_{ATP} channels open, preventing insulin release. Glimepiride belongs to the class of modern SU that acts by closing the KATP channels in β-cells, which causes depolarization with the subsequent influx of calcium and insulin secretion [1, 2]. Study findings have demonstrated that SU is an effective and safe treatment option for neonatal diabetes [4]. Bacon et al. [5], in 2015, demonstrated that majority of the patients with HNF1A-MODY who underwent sulfonylurea therapy were able to maintain a good glycemic control. In MODY patients, the treat-to-target approach is emphasized to achieve a previously determined target within a stipulated time period. A study [2] that

evaluated the efficacy of glimepiride with or without linagliptin found a significant mean dose reduction of 0.7 mg with the treat-to-target approach. Given the high efficacy of sulfonylureas in patients with MODY demonstrated in clinical studies, a clinically relevant dose reduction has been suggested [1].

More than 80% of the HCPs preferred a low dose of modern SU (glimepiride) with or without metformin FDC for treating their MODY cases. The most recommended dose of glimepiride by HCPs was 0.5 mg (62%). Glimepiride 1.5–2 mg was preferred in about 4% of the cases. Older generation SUs are associated with hypoglycemia and weight gain. However, modern SUs such as glimepiride provide effective glycemic control, with minimum risk of hypoglycemia and weight gain and with proven CV safety [6, 7]. Obesity and physical activity can affect insulin activity among MODY patients. Shepherd and Hattersley, in 2004, found that the transition to sulphonylureas had a positive impact on lifestyle and self-perception, but support was neccesary for these patients to adjust to the new treatment regime [8]. Most HCPs (75%) opined that low-dose modern SU (glimepiride) and metformin FDC, along with diet and lifestyle modifications, plays an important part in the management of MODY cases [1].

Table 1. Questionnaire to assess the knowledge of healthcare practitioners about the diagnosis and treatment of MODY

	Questions	Responses N (%)				
	No. of patients	< 5	5–10	10–20	> 20	
1	How frequently do you encounter Maturity-Onset Diabetes of the Young Type (MODY) patients in your routine clinical practice? (N = 130)	83 (64)				
	28 (21.5)	10 (7.7)	9 (7)			
		Routinely	Sometimes	Rarely	Not using	
2	In your clinical practice, how often do you use genetic testing to diagnose MODY patients? (N = 130)	22 (17)	38 (29)	48 (37)	22 (17)	
		Cost	Unwillingness	Issue with availability	Lack of awareness and knowledge	All the above
3	In your opinion, what barriers do you frequently encounter while performing genetic testing for MODY patients? (N = 130)	2 (1.5)	16 (12.3)	26 (20)	17 (13)	69 (53)
		Low-dose modern SU	Low-dose modern SU and metformin	DPP4i and SU combination	DPP4i and metformin combination	Insulin
4	Optimal therapeutic management (first line of treatment) for your MODY patients includes which of the following? (N = 131)	31 (23.6)	74 (56.4)	19 (14.5)	1 (0.7)	6 (4.5)
		Yes/very likely	Sometimes	May or May not	Not likely	
5	How likely are you to prescribe low-dose modern sulfonylurea & metformin FDC in your newly diagnosed MODY patients? (N = 129)	86 (67)	29 (22.4)	9 (7)	5 (3.8)	
		Glimepiride 0.5 mg	Glimepiride 1 mg	Glimepiride 1.5 mg	Glimepiride 2 mg	
6	If yes, what is your preferred choice of low-dose modern sulfonylurea (glimepiride) dose for treating MODY patients? (N = 126)	78 (62)	38 (30)	5 (4)	5 (4)	
		Very effective	Somewhat effective	Not effective		
7	How effective do you find diet and lifestyle modification in treating your MODY patients? (N = 130)	99 (76)	29 (22.3)	2 (1.5)		

DPP4i — dipeptidyl peptidase-4 inhibitor; SU — sulfonylurea

According to the authors' study, modern SUs, especially the low dose glimepiride and metformin FDC are the commonly used treatment modality in treating MODY patients. However, there is a need to improve awareness about the use of low-dose modern SU as a potential treatment modality for treating MODY cases.

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