Primary Care Diabetes 17 (2023) 401–407

Contents lists available at ScienceDirect

Primary Care Diabetes

journal homepage: www.journals.elsevier.com/primary-care-diabetes

Prevalence, clinical features and complications of common forms of Maturity Onset Diabetes of the Young (MODY) seen at a tertiary diabetes centre in south India

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ARTICLE INFO

Keywords:
Monogenic diabetes
Maturity-onset diabetes of the young
MODY
HNF1A-MODY
MODY3
HNF4A-MODY
MODY 1
ABCC8-MODY
MODY 12
Diabetes complications
Asian Indians
India
South Asians

ABSTRACT

Background: Maturity Onset Diabetes of the Young (MODY) is a form of monogenic diabetes caused by mutations in single genes, affecting adolescents or young adults. MODY is frequently misdiagnosed as type 1 diabetes (T1). Though several studies from India have reported on the genetic aspects of MODY, the clinical profile, complications and treatments given have not been reported so far, nor compared with T1D and type 2 diabetes (T2D).
Aim: To determine the prevalence, clinical features, and complications of common forms of genetically proven MODY seen at a tertiary diabetes centre in South India and compare them with matched individuals with T1D and T2D.
Methods: Five hundred and thirty individuals identified as 'possible MODY' based on clinical criteria, underwent genetic testing for MODY. Diagnosis of MODY was confirmed based on pathogenic or likely pathogenic variants found using Genome Aggregation Database (gnomAD) and American College of Medical Genetics (ACMG) criteria. The clinical profile of MODY was compared with individuals with type 1 (T1D) and type 2 (T2D) diabetes, matched for duration of diabetes. Retinopathy was diagnosed by retinal photography; nephropathy by urinary albumin excretion > 30 μg/mg of creatinine and neuropathy by vibration perception threshold > 20 v on biothesiometry.
Results: Fifty-eight patients were confirmed to have MODY (10.9%). *HNF1A*-MODY (n = 25) was the most common subtype followed by *HNF4A*-MODY (n = 11), *ABCC8*-MODY (n = 11), *GCK*-MODY (n = 6) and *HNF1B*-MODY (n = 5). For comparison of clinical profile, only the three 'actionable' subtypes - defined as those who may respond to sulphonylureas, namely, *HNF1A, HNF4A* and *ABCC8*-MODY, were included. Age at onset of diabetes was lower among *HNF4A*-MODY and *HNF1A*-MODY than *ABCC8*-MODY, T1D and T2D. Prevalence of retinopathy and nephropathy was higher among the three MODY subtypes taken together (n = 47) as compared to T1D (n = 86) and T2D (n = 86).
Conclusion: This is one of the first reports of MODY subtypes from India based on ACMG and gnomAD criteria. The high prevalence of retinopathy and nephropathy in MODY points to the need for earlier diagnosis and better control of diabetes in individuals with MODY.

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https://doi.org/10.1016/j.pcd.2023.04.004
Received 30 September 2022; Received in revised form 17 March 2023; Accepted 7 April 2023
Available online 11 April 2023

1. Introduction

Monogenic diabetes refers to a group of rare genetic disorders characterised by diabetes caused by mutation of a single gene. Maturity Onset Diabetes of the Young (MODY) is the most common type of monogenic diabetes and results from mutation of genes related to beta-cell function. MODY is a clinically and genetically heterogeneous group of disorders characterised by varying clinical phenotypes of diabetes affecting adolescents or young adults before the age of 25 years [1,2]. MODY is frequently misdiagnosed as type 1 diabetes (T1D) leading to unnecessary insulin treatment [3].

A total of 14 subtypes of MODY have been described, the most common of which are *HNF1A*-MODY (MODY3), *GCK*-MODY (MODY2), *HNF4A*-MODY (MODY1), *HNF1B*-MODY (MODY5), and *ABCC8*-MODY (MODY12). Rarer subtypes include *NEUROD1*-MODY (MODY6), *IPF1/PDX1*-MODY (MODY4), and *INS*-MODY (MODY10). Other purported forms of MODY such as BLK-(MODY 11), PAX4-(MODY9), KLF11-(MODY7), and APPL1-(MODY14) have subsequently been unclassified as true MODY [4]. The clinical criteria for diagnosis of MODY were first proposed by Tattersall and Fajans in 1975 [5]. However, these criteria are not specific enough to discriminate MODY from type 2 diabetes (T2D) or T1D. With the introduction of molecular genetics in the 1990s, our understanding of the phenotype and genotype of MODY have improved considerably [6].

The earliest study from India on MODY was published in 1985, however the classification of MODY was based on clinical criteria therefore it is possible that many of those cases actually had T2D [7]. Since 2009, several reports on MODY have been published from India but they mostly deal with the genetic aspects of MODY and the clinical features of various MODY subtypes, especially response to treatment or development of complications, have not been reported [8–13]. Recent papers recommend reporting genetic variants using American College of Medical Genetics and Genomics (ACMG) criteria and Genome Aggregation Database (gnomAD) to identify pathogenic and likely pathogenic variants. This paper is one of the first from India to report on the prevalence of MODY based on the above-mentioned criteria and to compare its clinical features, including complications of diabetes, with T1D and T2D as seen at a tertiary care diabetes centre in south India.

2. Methods and data collection

The data for this analysis was derived from electronic medical records (it is a retrospective prospective cohort from the year 1992–2022) of a large tertiary care diabetes centre in Chennai in southern India. At the time of their first visit/registration to the centre, every patient is given a unique identification number, to enable detailed tracking of each patient record over time. Once the registration procedure is completed, patients are seen by a dietitian or diabetes educator, who takes a detailed medical history including current medications and family history of diabetes including a pedigree chart. Anthropometric measurements, lab and diabetes complications assessments are done using standard protocols [14].

A total of 530 participants were identified based on the modified clinical criteria of Tattersall and Fajans [5]. This included age at onset of diabetes below 30 years of age, absence of ketosis, family history of diabetes in at least three generations and response to oral hypoglycaemic agents. All 530 participants underwent genetic testing and MODY was diagnosed based on gnomAD [15] and ACMG criteria [16] as described in the *Definitions* below.

The medical records of the genetically proven MODY participants were reviewed. Demographic details, including age at diagnosis, age at first visit, duration of diabetes and current treatment regimen, and anthropometric details were extracted. Individuals with T1D and T2D were matched according to their respective disease durations to the genetically proven MODY group. For each individual MODY, two T1D and two T2D individuals were selected in the ratio of 1:2.

Anthropometric measurements included height and weight. Height was measured in centimetres using a stadiometer and weight was measured using a traditional spring balance and recorded to the nearest 0.1 kg. Body mass index (BMI) was calculated using the formula: weight (kg)/height squared (m^2). Blood pressure was recorded in a rested seating position in the right arm using a mercury sphygmomanometer and rounded off to the nearest 2 mmHg. Two readings were taken 5 min apart and the mean of the two readings was used.

Plasma glucose was estimated by the glucose oxidase method, serum cholesterol by CHOD-PAP method, triglycerides by glycerol phosphate oxidase-peroxidase-amidopyrine (GPO-PAP) method [17], HDL cholesterol by direct immunoinhibition, and low-density lipoproteins cholesterol was calculated using the Friedewald equation [18]. Blood urea was measured using the glutamate dehydrogenase (GLDH) UV kinetic method and serum creatinine by Jaffe kinetic method. All analyses were carried out on Beckman Coulter AU2700 (Fullerton, CA) biochemistry analyzer [17]. Glycated haemoglobin (HbA1c) was estimated by high-performance liquid chromatography using the Variant II Turbo (Bio-Rad, Hercules, CA) [17]. The fasting and stimulated (post-breakfast) C-peptide levels were estimated by chemiluminescence method on a Siemens ADVIA lentaur XPT immunoassay analyzer at the time of first registration at the centre. The stimulated C-peptide values were obtained after providing a standard breakfast and the postprandial blood sample was drawn at 90 min as previously described [19]. Urine albumin concentration was assessed in a fasting urine sample by immunoturbidometric assay [(Beckman Coulter AU2700 (Fullerton, CA)] [17].

The study was approved by the Institutional Ethics Committees (IEC) of both participating institutions (Madras Diabetes Research Foundation IEC approval dated 06 March 2018, Deakin Ethics Approval number-2019–060). Written informed consent was obtained from all participants aged 18 years or over and assent was obtained from participants less than 18 years of age (in addition to parental consent).

3. Definitions

Diabetes was defined when the fasting plasma glucose (FPG) level was $\geq$ 126 mg/dl (7.0 mmol/l) and/or 2-h post-load glucose level $\geq$ 200 mg/dl (11.1 mmol/l) [20], if there was a self-reported diagnosis of diabetes treated by a physician, or if they were on medications for diabetes.

3.1. MODY

The sequencing was done at the time of first presentation whenever possible. However, in some cases it was done later if they fulfilled the clinical criteria of MODY. The different subtypes of *MODY* were diagnosed based on genetic analysis and presence of specific mutations for these subtypes.

Briefly, genomic DNA was isolated from whole blood and the quality and quantity assessed spectrophotometrically. Direct sequencing of DNA amplified with published primers [21–25] was carried out on the ABI 3500 Genetic Analyzer (Applied Biosystems, Foster City, CA) using the Big Dye terminator V3.1 chemistry. Resulting sequences were compared with the public databases (NCBI: HNF4A-NM_000457, GCK-NM_000162, HNF1A-NM_000545, HNF1B-NM_000458, and ABCC8-NM_000352). The Genome Aggregation database (gnomAD) was used to study the functional consequence of the variant [15] and the American College of Medical Genetics and Genomics (ACMG) guidelines were used to assess the clinical significance of genetic variants. Specifically, causal variants (mutation) were diagnosed only if they were classified as pathogenic or likely pathogenic [16]. Those with variants of uncertain significance, benign or likely benign were excluded.

Type 1 *diabetes (T1D)* was defined by abrupt symptoms of polyuria, polydipsia, or unexplained weight loss, history of diabetic ketoacidosis (DKA), lack of insulin reserve as shown by absent fasting and stimulated C-peptide (<0.3 pmol/ml), and requirement of insulin from the time of

diagnosis for control of hyperglycaemia [26].

Type 2 *diabetes (T2D)* was defined by the absence of ketosis, good beta-cell functional reserve as evidenced by stimulated C-peptide (>0.6 pmol/ml), absence of pancreatic calculi (on X-ray abdomen) and good response to oral hypoglycaemic agents for more than two years [26].

Hypertension was defined as self-reported history of physician-diagnosed hypertension, if participants were on medications for hypertension or had a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg [27].

Dyslipidaemia was defined as hypercholesterolaemia, if total cholesterol was ≥ 5.8 mmol/L (≥200 mg/dL), hypertriglyceridemia, if triglyceride levels were ≥ 1.69 mmol/dL (≥150 mg/dL) or if the individual was on lipid lowering medications. High LDL cholesterol was diagnosed if LDL cholesterol was ≥ 2.6 mmol/L (≥100 mg/dL). Low HDL cholesterol was diagnosed if the HDL-C value was < 1.0 mmol/L (<40 mg/dL) in males and < 1.3 mmol/L (<50 mg/dL) in females [28].

3.2. Microvascular complications

Assessments for diabetes complications were done annually, or whenever possible, using the following methods:

3.3. Retinopathy

Comprehensive ocular examination included visual acuity measurement, intraocular pressure measurement, slit-lamp examination of the anterior segment, and fundus examination after dilatation using direct and indirect ophthalmoscopy by retina specialists. Digital retinal (fundus) colour photography was done using a mydriatic conventional desktop fundus camera (FF 450 Plus camera; Carl Zeiss, Jena, Switzerland) after mydriasis. The modified Early Treatment Diabetic Retinopathy Study (ETDRS) grading system was used to grade diabetic retinopathy [29] [30].

3.4. Nephropathy

Nephropathy was diagnosed by the presence of albuminuria (consecutive assessment by two or more urine samples) and defined as urinary albumin excretion ≥ 30 μg/ mg of creatinine [31].

3.5. Neuropathy

Biothesiometry was used to assess neuropathy. A single observer measured the vibration perception threshold (VPT) at the great toe in a standardised manner. Neuropathy was diagnosed if the VPT was ≥ 20 V [32].

4. Statistical analysis

The data is represented as mean (SD) for normally distributed continuous variables and median with interquartile range (IQR) for highly skewed continuous variables and as n (%) for categorical data. One way ANOVA / Kruskal Wallis test (non-parametric) for continuous variables as appropriate and Chi square test for categorical variables. $p < 0.05$ was considered as statistically significant. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS, Inc., Windows V 25.0, Chicago).

5. Results

Among 530 individuals with clinical characteristics suggestive of MODY who underwent genetic testing, 58 were confirmed to have one of the MODY subtypes using ACMG criteria and gnomAD criteria. Thus, the pick-up rate for MODY at our centre was 10.9% among all individuals with "clinically suspected" or "possible" MODY. Of the confirmed MODY cases, 25 had *HNF1A*-MODY (53.2%), 11 had *HNF4A*-MODY (23.4%), 11 had *ABCC8*-MODY (23.4%), 6 had *GCK*-MODY (10.7%) and 5 had *HNF1B*-MODY (8.9%). As *GCK*-MODY is a mild form of MODY which does not require pharmacotherapy and *HNF1B*-MODY has a different phenotype with genitourinary and other pathology and does not usually respond to oral drugs, these two subtypes were not considered for further analysis. Thus, the rest of this paper will only focus on "*actionable MODY*" subtypes defined as those subtypes which show response to sulphonylureas namely *HNF1A*-MODY, *HNF4A*-MODY and *ABCC8*-MODY. Fig. 1 shows the flow chart of clinical selection of the MODY participants for this study.

Table 1 shows the clinical profile of the three MODY subtypes as well as T1D and T2D included as controls. Female predominance is observed among all MODY subtypes; *HNF1A*-MODY (56%), *HNF4A*-MODY (92%) and *ABCC8*-MODY (67%). Parental consanguinity was reported among twelve participants (five among *HNF1A*-MODY, four among *HNF4A*-MODY and three among *ABCC8*-MODY). The median age at diagnosis of diabetes was higher among *ABCC8*-MODY as compared to *HNF1A*-MODY and *HNF4A*-MODY (24.7 vs. 15.4 and 18.5 years) respectively. The BMI of individuals with MODY was intermediate between those with T1D and T2D.

The fasting plasma glucose and glycated haemoglobin values in the MODY subtypes were intermediate between T1D and T2D. The fasting and stimulated C-peptide values were lowest among T1D followed by MODY and then T2D. After identification as MODY, all individuals were treated with either sulfonylurea alone (or with sulfonylureas plus insulin in those with longer duration of diabetes) and all three subtypes including ABCC8-MODY showed response to sulfonylureas. The prospective A1c values before the MODY screening and after treatment with SU for HNF1A-MODY, HNF4A-MODY and ABCC8-MODY were 9.2 vs.8.1%; $p < 0.005$; 8.6 vs.8.1; $p = 0.894$ and 7.6 vs. 7.1; $p < 0.005$ respectively. Treatment for other comorbidities including dyslipidemia, hypertension or both was higher among individuals with T1D and T2D as compared to those with MODY.

The three MODY subtypes were combined (n = 47) to compare the prevalence of microvascular complications to T1D and T2D , matched for duration of diabetes (Table 2). Retinopathy screening was done in 30 MODY of whom 17 (56.7%) had retinopathy, which was higher than in T1D and T2D. Nephropathy screening was done in 32 MODY of whom 10 (31.3%) had nephropathy which was also higher than in T1D and T2D. Neuropathy screening was done among 24 MODY and its prevalence was lower (4.2%) than among T1D (13.6%) and T2D (17.5%).

6. Discussion

This study reports on the clinical profile and microvascular complications of a cohort of MODY patients, diagnosed based on gnomAD and ACMG criteria at a tertiary referral diabetes centre in south India. The significant findings of the study are: *HNF1α*-MODY, *HNF4α*-MODY and *ABCC8*-MODY are the common subtypes in India which respond to sulphonylureas and they all have a female predominance. The prevalence of retinopathy and nephropathy was higher among MODY when compared to T1D and T2D matched for duration of diabetes while the prevalence of neuropathy was lower.

The widespread application of next generation sequencing methods in MODY has helped to identify various MODY subtypes and has increased the knowledge about the interpretation and understanding of genetic variation in diabetes[33]. However, in this paper, we chose to report only the commoner types of MODY because Misra et al. [34] reported HNF1α-MODY, HNF4α-MODY, GCK-MODY, ABCC8-MODY as common causes of MODY with well-established evidence. Also, we focussed on the three subtypes of MODY which were "actionable" (i.e. they respond to sulphonylureas) as this will help in successful adoption of precision diabetes approach [35].

In the current paper, we have used modified Tattersal and Fajans criteria which is largely adapted from the original criteria to initially identify possible MODY cases. A recent review on rarer MODY subtypes

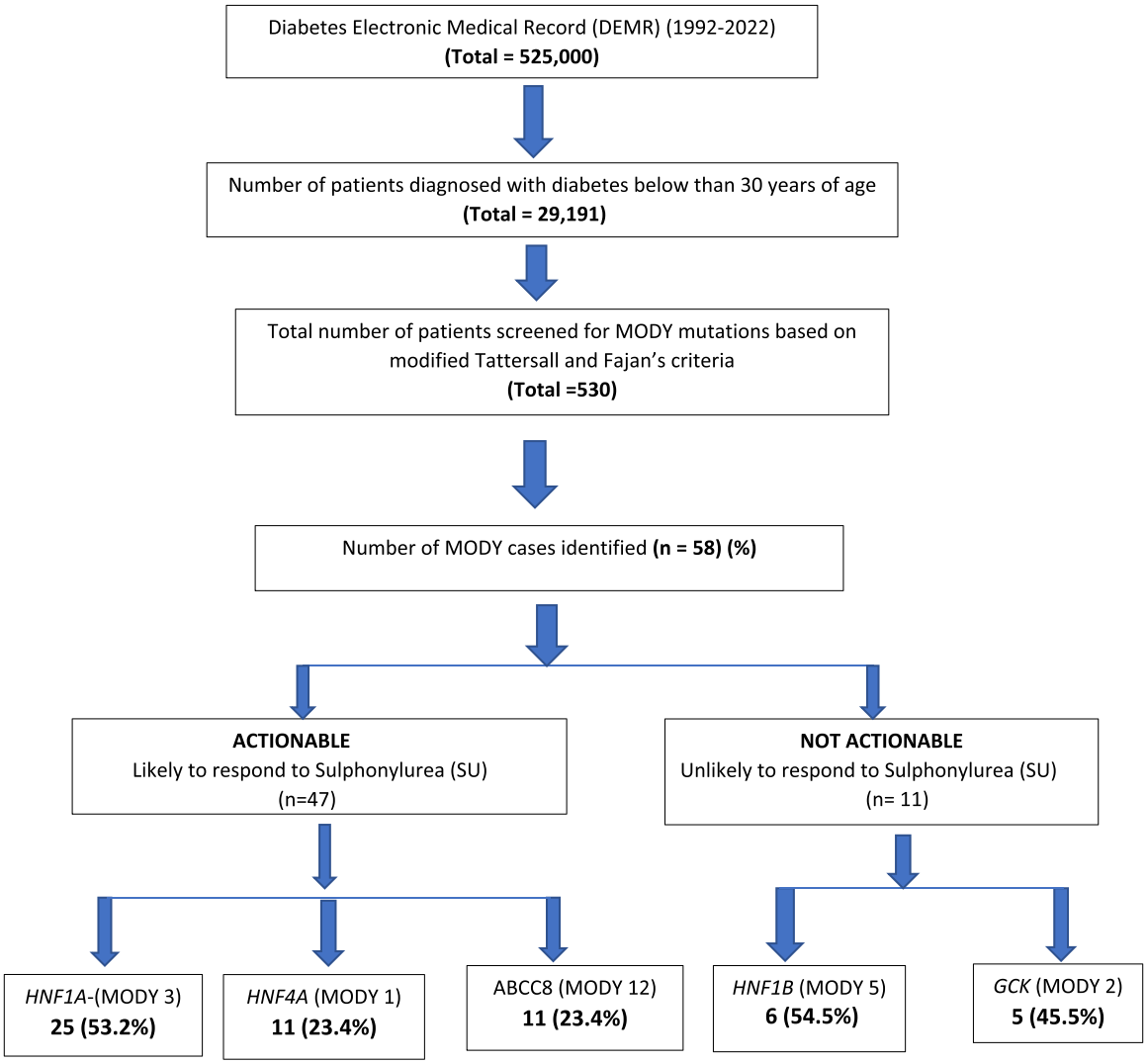

Fig. 1. Flowchart of screening Maturity Onset Diabetes of the Young (MODY).

also reported that modification of the original criteria has been adopted across the globe [4]. Strict adherence to the traditional criteria may miss some MODY patients as the clinical picture of MODY is now changing with rising obesity rates globally [36]. Updated diagnostic criteria are also available from the European Molecular Genetics Quality Network-MODY group which can be used for criteria selection [37].

The study finding that *HNF1A*-MODY is the most common subtype of MODY is similar to the findings reported from the UK [1]. *GCK*-MODY, which is a very common subtype in the UK, Australia, Japan, and the USA, was however less common in our population [38–40]. This is likely because, *GCK*-MODY, being a milder form of MODY, does not get referred to tertiary diabetes centres like ours which treat more severe forms of diabetes [26]. Our results also show a female predominance among MODY participants, which is similar to the findings of a recent study from Australia [41] and UK [42] and a systematic review done among *HNF1A*-MODY participants [43].

The pickup rate for MODY from this study was 10.9%. However, studies from the United Kingdom reported a higher pick-up rate of 23% [44] and France 17.9%[45]. In contrast, lower rates were reported from USA (8%) [46], Iran (6%) [47] and a study from Kerala (India) (6.6%) [48]. The lower pickup rate of MODY in India compared to Europe could be because T2D presents at a much lower age in India.

All MODY patients in our study, after diagnosis of MODY, were treated with sulphonylureas or in those with longer duration of diabetes, with sulphonylureas and insulin. The MODY sequencing was done in most cases at the time of first visit to the centre but in certain cases it was done later, during the follow up visit of the patient, occasionally after several years as the treating physician may not have thought of MODY earlier. Some of the latter cases were categorised in our records as "Clinical MODY" but they were treated as type 2 diabetes (T2D). As sulphonylureas are also used extensively for treatment of T2D in India, in some of these MODY cases, no major treatment changes may have occurred over the years, even after the genetic diagnosis was made as they were already in sulphonylureas. In some cases, however who would have been treated with metformin , sulphonylureas were added after the diagnosis of MODY was confirmed for improving the glycaemic control. Initially we were using Sanger Sequencing and looking for MODY genes one at a time e.g., HNF1A, HNF4A, GCK, HNF1B, etc. Since 2014, a monogenic diabetes panel has been used and testing using Next Gen Sequencing was introduced at our centre. This speeded up the genetic testing.

The Expert Forum on Monogenic Diabetes recently overviewed the treatment for monogenic diabetes and suggested that *HNF1A*-MODY and *HNF4A*-MODY respond to low doses of inexpensive oral sulfonylurea medications which leads to improved glycemic control [49]. We report in this paper that *ABCC8*-MODY also responds to sulphonylureas and we believe that this is not that well described in the literature.

Our study reports a high frequency of microvascular complications,

Table 1
Clinical characteristics of mody, t1d and t2d participants matched for disease duration.

Variables	MODY (n = 47)								p value
	HNF1A-MODY (n = 25)		*HNF4A*-MODY (n = 11)		*ABCC8* -MODY (n = 11)		T1D (n = 86)	T2D (n = 86)	
Sex -Male n (%)	11 (44%)		1 (8%)		4 (33%)		49 (57%)	55 (64%)	0.015
Female n (%)	14 (56%)		11 (92%)		7 (67%)		37(43%)	31 (36%)	
Age at diagnosis (years)	17.1 ± 6.0		18.9 ± 5.5		21.4 ± 6.7		19.9 ± 5.8	25.2 ± 4.7	< 0.001
Age at baseline visit (years)	20.4 ± 7.8		25.5 ± 11.4		20.6 ± 25.2		24.1 ± 10.1	29.5 ± 8.5	< 0.001
Duration at baseline visit (years)	2.4 ± 3.4		4.5 ± 6.3		11.3 ± 15.5		4.4 ± 7.7	4.4 ± 7.7	0.126
Height (cm)	158 ± 11		156 ± 11		163 ± 9		162 ± 10	166 ± 9	0.001
Weight (kgs)	53.4 ± 11.2		55.2 ± 14.0		57.9 ± 11.4		53.4 ± 13.2	74.3 ± 14.7	< 0.001
Body mass index (kg/m2)	21.4 ± 3.7		22.3 ± 3.7		21.7 ± 4.3		20.0 ± 3.6	27.0 ± 4.7	< 0.001
Systolic blood pressure (mm Hg)	108 ± 11		120 ± 17		130 ± 14		111 ± 15	120 ± 14	< 0.001
Diastolic blood pressure (mm Hg)	72 ± 7		76 ± 9		81 ± 9		72 ± 8	79 ± 9	< 0.001
Hypertension	1 (4%)		4 (36%)		1 (9%)		10 (12%)	25 (29%)	0.003
Fasting plasma glucose (mg/dl)	204 ± 79		149 ± 49		155 ± 101		234 ± 127	189 ± 73	0.007
Glycated Haemoglobin (%)	9.0 ± 2.4		8.3 ± 1.6		7.1 ± 1.5		10.2 ± 2.8	9.4 ± 2.1	0.001
Serum Cholesterol (mg/dl)	172 ± 41		179 ± 41		152 ± 32		168 ± 41	181 ± 49	0.266
Serum triglycerides (mg/dl)*	95(66)		98(79)		117(11)		86(51)	146(106)	< 0.001
LDL Cholesterol (mg/dl)	110 ± 29		113 ± 32		94 ± 31		102 ± 34	106 ± 39	0.651
HDL Cholesterol (mg/dl)	41 ± 12		42 ± 7		41 ± 9		46 ± 11	39 ± 9	< 0.001
Blood urea (mg/dl)	20 ± 5		24 ± 5		26 ± 7		24 ± 14	22 ± 8	0.587
Serum creatinine (mg/dl)	0.6 ± 0.1		0.6 ± 0.1		0.7 ± 0.1		0.8 ± 0.4	0.7 ± 0.3	0.195
C-peptide (Fasting) pmol/ml	0.54 ± 0.22		0.57 ± 0.25		0.63 ± 0.34		0.35 ± 0.25	1.00 ± 0.47	< 0.001
C-peptide (Stimulated) pmol/ml	1.09 ± 0.44		1.33 ± 0.50		1.79 ± 0.38		0.50 ± 0.46	2.14 ± 1.03	< 0.001
Parental history n (%)	25 (100%)		11 (91.6%)		9 (90%)		32 (37.2%)	67 (77.9%)	< 0.001
One or both parents	19(76.0)		7(70.0)		6(85.7)		34(39.5)	30(34.9)	
Three generation diabetes									
Current treatment	**Before**	**After**	**Before**	**After**	**Before**	**After**	0	11 (13%)	< 0.001
history n (%)	-	20(80.0)	-	8(74.0)	-	9(81.8)	0	28 (32%)	
Sulfonylurea alone							0	24 (28%)	
Sulfonylurea plus Metformin	-	-	-	-	-	-	0	9 (10%)	
Metformin alone	-	-	-	-	-	-	0	14 (17%)	
Other oral drugs	6(24.0)	-	4(36.4)	-	5(45.4)	-	86 (100%)	0	
Oral drugs plus Insulin	13(52.0)	5(20.0)	4(36.4)	3(26.0)	2(18.2)	2(18.2)			
Only insulin	6(24.0)	-	3(27.3)	-	2(18.2)	-			
Other treatment n (%)	2(18.2)		2(8.0)		1(9.1)		8(9.3)	14(6.3)	0.350
Dyslipidemia	-		-		1(9.1)		3(3.5)	7(8.1)	
Hypertension	1(9.1)		-		-		3(3.5)	7(8.1)	
Both									

Data presented as mean (SD) or n (%), * median along with IQR (Interquartile Range).

Table 2
Prevalence of complications among mody compared to type-1 and type-2 diabetes participants.

Complications	MODY[#] (n = 47)	T1D (n = 86)	T2D (n = 86)	p value
Duration of diabetes* (years)	1.0 (6.0)	1.0 (6.0)	1.0 (6.0)	0.625
Retinopathy (%)	56.7% (n = 17/30)	35.7% (n = 25/70)	32.8% (n = 21/64)	0.071
Nephropathy (%)	31.3% (n = 10/32)	26% (n = 20/77)	22.8% (n = 18/79)	0.647
Neuropathy (%)	4.2% (n = 1/24)	13.6% (n = 9/66)	17.5% (n = 14/80)	0.256

[#]Includes *HNF1A*-MODY, *HNF4A*-MODY and *ABCC8* -MODY12.
*shown as median with IQR.

particularly retinopathy among MODY. Nephropathy was also observed among MODY participants. This is in accordance with a recent review that stated that microvascular complications which involve the retina and kidney are, as common, if not more common, in MODY as in T1D and T2D [50]. Velho [51] reported among French families, a higher prevalence of proliferative retinopathy (21%) among *HNF1A*-MODY as compared to other MODY subtypes. Isomaa et al. [52] reported that the risk of microvascular complications among *HNF1A*-MODY was associated with poor glycemic control and longer duration of diabetes. A recent literature review [43] reported prevalence of retinopathy among patients with *HNF1A*-MODY as 21.3%, similar between Asian and non-Asian patients though the Asian patients were reported as having higher HbA1c values.

This is one of the first papers from India to report the clinical profile and complications among genetically proven MODY diagnosed using ACMG and gnomAD criteria. The next step is to identify and report the clinical variables which will help to screen for MODY among the Indian population. The most established model developed by Shields et al. [42] is widely used. However, new models are being developed and recently a Chinese model has been developed based on clinical variables identified for their population [53]. We are trying to develop a clinical model for MODY screening in India and this paper is a step in that direction.

The strength of this paper is that it is the first report from India on MODY subtypes that responds to sulphonylureas classified using strict ACMG and gnomAD guidelines criteria. Earlier studies have often included variants of unknown significance or benign variants. It also describes the clinical and biochemical profile as well the complications in MODY from India and compares it with matched groups of T1D and T2D. It is also one of the first to report on the clinical profile of *ABCC8*-MODY. This provides important insight into the clinical profiles of these MODY subtypes in the Indian population. However, one of the limitations of our study was that it was done at a tertiary care private diabetes centre in south India which restricts the generalisation to the whole population of India. However, the centre is a national nodal centre for

monogenic diabetes recognised by the Indian Council for Medical Research (ICMR) and therefore does receive samples from patients all over the country (www.monogenicdiabetes.in).

The small sample size is yet another limitation. However, as MODY is a very uncommon form of diabetes, obtaining very large numbers of MODY is extremely difficult. Further, the family history of diabetes reported is based on the information given by participants and not by testing of family members, Finally, the microvascular complications screening could not be conducted on all participants due to financial and other constraints.

In summary, we present the clinical profile of MODY participants at our centre. The fact that microvascular changes are common among MODY underscores the need for earlier detection and better glycemic control of individuals with MODY. It is particularly important to identify the "actionable" subtypes, *HNF1A*-MODY, *HNF4A*-MODY, and *ABCC8*-MODY, as they can respond to sulfonylureas and this can be life changing to these patients who are often wrongly diagnosed as T1D and administered unnecessary insulin treatment.

Declaration of Competing Interest

M/s Serdia Pharmaceuticals and M/s Servier are manufacturers of Gliclazide used in treatment of MODY.

Acknowledgements

This research is a part of AR's doctoral research work. Her work is supported under Deakin India Research Initiative (DIRI) scholarship. The authors would like to thank Serdia Pharmaceuticals, India for providing financial assistance in genetic testing of some of the MODY participants in this project.

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