Review Article

Biomarkers: Tools for Discriminating MODY from Other Diabetic Subtypes

Parveena Firdous[1], Kamran Nissar[1,2], Shariq Rashid Masoodi[3], Bashir Ahmad Ganai[1]

[1]Centre of Research for Development (CORD), University of Kashmir, Srinagar, Jammu and Kashmir, [2]Department of Clinical Biochemistry, University of Kashmir, Srinagar, Jammu and Kashmir, [3]Department of Endocrinology, SKIMS, Srinagar Jammu and Kashmir, India

Abstract

Maturity Onset Diabetes of Young (MODY), characterized by the pancreatic β-cell dysfunction, the autosomal dominant mode of inheritance and early age of onset (often ≤25 years). It differs from normal type 1 and type 2 diabetes in that it occurs at a low rate of 1-5%, three-generational autosomal dominant patterns of inheritance and lacks typical diabetic features such as obesity. MODY patients can be managed by diet alone for many years, and sulfonylureas are also recommended to be very effective for managing glucose levels for more than 30 years. Despite rapid advancements in molecular disease diagnosis methods, MODY cases are frequently misdiagnosed as type 1 or type 2 due to overlapping clinical features, genetic testing expenses, and a lack of disease understanding. A timely and accurate diagnosis method is critical for disease management and its complications. An early diagnosis and differentiation of MODY at the clinical level could reduce the risk of inappropriate insulin or sulfonylurea treatment therapy and its associated side effects. We present a broader review to highlight the role and efficacy of biomarkers in MODY differentiation and patient selection for genetic testing analysis.

Keywords: Biomarker, diabetes, diagnosis, MODY, obesity, treatment

Introduction

Diabetes is a highly prevalent heterogeneous disease and one of the primary causes of mortality and morbidity.[1] The appropriate treatment and timely diagnosis is a foundation in disease management to defer or put off the hyperglycemia associated complications. The diagnosis is mainly corresponding to the discrimination of T1D and T2D based on the hyperglycemia.[2] The updated guidelines of American Diabetes Association,[3] 2012 recommend diabetes classification into four categories *viz* T1D (Type 1 diabetes), T2D (Type 2 diabetes), gestational diabetes and other specific forms of diabetes.[3] The "other specific forms" contain the very uncommon and rare form of monogenetic diabetes termed Maturity- onset diabetes of young (MODY).[4] This discrete form of non-insulin dependent familial diabetes initially reported by Tattersal[5], 1974 in young adults and children does not fit the diagnosis based on hyperglycemia due to its mixed clinical presentation.[5,6] MODY represents a combination of genetic, metabolic, and clinical heterogeneity. MODY has 14 subtypes depending upon the involvement of genes and their mutations (deletion, splice-site, non-sense, etc.). MODY is usually misdiagnosed and inappropriately tagged as T2D or T1D due to its mixed clinical presentations.[7] However, MODY is most appropriately discriminated from other diabetic forms by molecular diagnosis testing.[8] MODY is diagnosed using three marker genes: hepatocyte nuclear factor 4 alpha (HNF4α), hepatocyte nuclear factor 1 alpha (HNF1α), and glucokinase (GCK).[9] Molecular genetic testing has led to the identification of MODY causing genes, associated mutations and distinct clinical phenotypes.[10] The usage of molecular diagnostic testing that is relying on nonspecific clinical characteristics like family history, age of onset, etiology do not exhibit realistic levels of sensitivity and preciseness.[11] Nowadays, there has been an increased drive to recognize cheap, sensitive, widely accessible and

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Address for correspondence: Prof. Bashir Ahmad Ganai, Centre of Research for Development (CORD), University of Kashmir, Srinagar - 190 006, Jammu and Kashmir, India.
E-mail: bbcganai@gmail.com

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specific biomarker that is superior in differentiating MODY from other types of diabetes.[12] This review highlights the use of biomarkers for improving diagnosis and clinical selection of MODY subjects for molecular identification. The various biomarkers [Table 1, Figure 1] suggested as screening tools for distinguishing and discriminating MODY mutations are:

1. hsCRP (High-sensitivity C-reactive protein): as a marker of MODY3 (HNF1α)

When it comes to distinguishing MODY3 from T2D, it has an accuracy of 80%, but only 75% when it comes to other types of diabetes.[13,14] McDonald *et al*.[26] (2011) used a lower hsCRP cut-off of 0.55 mg/l to distinguish MODY3 from MODY1 (caused by transcription factors HNF1α and HNF4α) with 70% specificity and 71% sensitivity.

Two key concepts support the relationship between hsCRP levels and MODY:

a) The CRP gene encodes a protein with specific HNF1α binding sites, and SNPs in HNF1α transcription factors have been linked to CRP levels in different populations.[27,28]

b) While MODY and T2DM have some clinical similarities, certain pathophysiological conditions, such as cardiovascular disease and obesity, are only seen in T2DM and not in MODY.

hsCRP has been shown in a number of studies to be a less reliable biomarker for distinguishing HNF1α -MODY without sequence analysis.[29,30] The hsCRP assay is undeniably inexpensive and widely available, but it does have limitations:

a) Because CRP is always elevated in inflammatory conditions, its utility as a potential biomarker is limited.

b) A number of medications, including aspirin, statins, and beta-blockers, have been shown to reduce CRP levels by 20-30%.

If hsCRP is used alone to distinguish MODY3 from other types, there will be a lot of unnecessary genetic testing and false-positive rates.[31-33] The hsCRP assay must be combined with other clinical tests to provide clear discrimination.

2. GAD (glutamic acid decarboxylase), IA-2A (insulinoma antigen-2), IA-2β: Discrimination of T1 autoimmune diabetes from MODY

T1D is characterized clinically by autoimmune processes such as the appearance of islet-specific auto-antibodies and auto-reactive T cells, and is caused by the autoimmune destruction of pancreatic β-cells. Autoantibodies are important markers for detecting ongoing β–cell destruction and the progression of T1D.[34,35] T1D is the most common type of diabetes in children and adolescents, accounting for more than 90% of all cases of diabetes. Other types of diabetes, such as MODY or young-onset type 2, are frequently misdiagnosed as T1D and thus necessitate insulin therapy. Incorrect insulin therapy causes a slew of side effects.[7,36] In a number of studies, increased levels of ICA (islet-specific antibodies) were found to be a predictive marker for distinguishing T1D from young-onset diabetes. Glutamic acid decarboxylase (GAD) and IA2 islet autoantibodies are important markers for distinguishing T1D from other types of MODY (young-onset diabetes). GAD and IA2 antibodies are found in 1% of MODY cases and 80% of autoimmune T1D cases.[26] Seissler *et al*.[37] 1998 used recombinant antigens to confirm the presence of IA-2, GAD65, and IA-2 autoantibodies in T1D patients.

Table 1: Biomarkers used for discrimination MODY from other diabetic subtypes

Biomarker	Description	Specificity/sensitivity	References
hsCRP	The accuracy for differentiating MODY3 from T2DM is 80%, while its accuracy is 75% when compared with other diabetes types	MODY1 , MODY3 from T2D and T1D	Besser *et al*.[13,14], 2011
GAD65	GAD65 isoform in combination with other islet autoantigens accurately discriminates MODY from T1D , thus avoids the risk of inappropriate insulin therapy and its associated side effects	GAD65 exhibit antigenicity in T1D	Morran *et al*.,[15] 2010
UCPR	Discriminates HNF4α-MODY, HNF1α-MODY from the autoimmune T1D Invalid for Discriminating MODY from T2D	MODY1/MODY3/ GCK-MODY from T1D	Besser *et al*.[16] 2013
IA-2A	IA-2A acts as a specific prognostic markers for type 1 diabetes with >70% detection rate at disease onset	T1D from young-onset diabetes	Decochez *et al*.,[17] 2002
IA-2β	In nearly all individuals IA-2β auto-antibodies are found together with IA-2A	T1D from young-onset diabetes	Hawkes *et al*.,[18] 1996
IAA	Occurs in >70% diabetic patients during childhood and is less prominent in diabetic cases having clinical onset after puberty	Biomarker for T1D	Achenbach *et al*.,[19] 2010
ZnT8	Occur in about 70% T1D cases, but only in association with other β-cell auto-antibodies	Young-onset diabetes from T1D	Achenbach *et al*.,[20] 2009
GP30	Lower in MODY patients that harbor detrimental HNF1α alleles	HNF1α-MODY	Juszczak *et al*.,[21] 2019
Sulfonylurea	HNF1α/HNF4α MODY subjects achieved the HbA1c ≤7.5% on diet/ Sulfonylurea alone	Invalid	Shepherd *et al*.[22] 2018
ApoM	The HNF1α is regulating ApoM protein expression. Lower plasma ApoM occurs in HNF1α-MODY patients	HNF1α-MODY	Richter *et al*.,[23] 2003
HDL	Low HDL levels occur in T2D patients when compared with young-onset diabetes	HNF1α-MODY GCK-MODY, and T1D	Mcdonald *et al*.,[24] 2012 Fendler *et al*.,[25] 2011

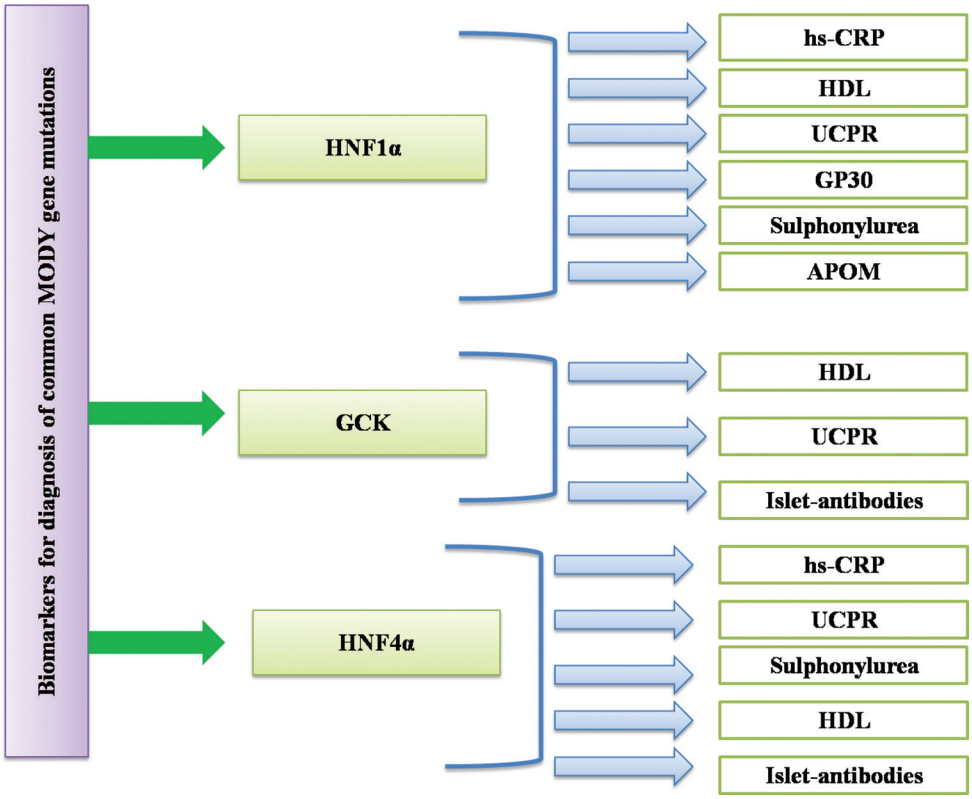

Figure 1: Representative diagram of currently used biomarkers for discriminating most common MODY types *viz* HNF1α, GCK, and HNF4α

IA-2A autoantibodies are extremely specific prognostic markers for T1D, with a detection rate of more than 70% at disease onset.[17] IA-2A autoantibodies occur in conjunction with β-cell autoantibodies. When digested with trypsin, the islet antigens yield two fragments of 40-kDa (termed IA-2ic or ICA512ic) and 37-kDa (termed phogrin or IA-2).[38,39] Rabin *et al*.,[40] 1994 demonstrated the presence of ICA512 as a diabetes-specific marker with a relationship to protein tyrosine phosphatases.[40] Johansson *et al*.[41] (2017) discovered a 6.5% MODY prevalence in diabetic children with negative autoantibodies in their study.[41] IA-2β autoantibodies are found in nearly all people, along with IA-2A, but IA-2β is rarely used as a primary test.[18] GADA, ZnT8A, and IA-2A were the most cost-effective islet auto-antibodies for distinguishing T1D from MODY (Carlsson *et al*. 2020). In comparison to European patients (60–70%), the frequency of IA-2A was reported to be much lower in Indian T1D cases (15 percent -25%).[42,43] Using GADA and IA2A autoantibodies, a relatively higher frequency (45%) of Idiopathic T1D cases was reported in a North-Indian study.[44] GAD has an enzymatic activity through two key protein isoforms (GAD65, GAD67) that catalyse the synthesis of the inhibitory neurotransmitter g-aminobutyric acid (GABA). The two protein isoforms share 65% homology but differ in their distribution (GAD 65 occurs in synaptic like vesicles on chromosome 10, GAD67 occurs in the cytosol of β-cells on chromosome 2) and translational regulation. Regardless of the elevated expression of GAD67 in β- islet cells, only GAD65 exhibits antigenicity in T1D.[45] Because GAD auto-antibodies are more commonly found in the early preclinical stages, their early occurrence and ease of evaluation for anti-GAD auto-antibodies make them more reliable for early screening of T1D.[46] The GAD65 isoform, in conjunction with other islet autoantigens, distinguishes MODY from T1D and avoids the risks associated with inappropriate insulin therapy.[15]

3. Insulin autoantibodies (IAA) and zinc transporter-8 (ZnT8): discriminating T1 diabetes from young-onset diabetes

In addition to GAD and IA-I2, insulin autoantibodies (IAA) and zinc transporter-8 (ZnT8) are important biomarkers for distinguishing T1D from young-onset diabetes. ZnT8 was identified as a T1 diabetes autoimmune marker after extensive research and screening of over-expressed islet-cell specific molecules.[47] Insulin autoantibodies (IAA) were found in T1D patients prior to starting insulin therapy.[48] Exogenous insulin stimulates antibodies against insulin peptides, with proinsulin and insulin being the most common targets of islet autoimmunity. The IAA occurs in more than 70% of diabetic patients during childhood, with a lower prevalence in diabetic cases with clinical onset after puberty. The immunization patterns differ depending on the affinity and epitopic uniqueness/specificity of IAA, with high-affinity IAA serving as a highly predictive biomarker for T1 diabetes.[18] ZnT8A auto-antibodies are found in approximately 70% of type 1 diabetic patients, but only in conjunction with other β-cell auto-antibodies. Autoimmunity to the carboxyl-terminal of ZnT8 is associated with the development of Type 1

diabetes.[19] The target of ZnT8A is influenced by specific amino acids (arginine, glutamine, or tryptophan at 325) encoded by distinct polymorphic variants of the SLC30A8 gene, which encodes ZnT8.[49] Females had a higher frequency of ZnT8A than males, according to Vipin *et al*.[50] [2021].

4. Fucosylated plasma glycans- GP30 as a marker of HNF1α - MODY3

The plasma Nglycome GWAS identified transcription factor HNF1α as a key regulator of plasma protein fucosylation.[51] N-glycosylation is a post-translational protein modification defined as the enzymatic addition of glycans (complex sugar moieties) to the N-terminus of a nascent polypeptide chain.[52] MODY-causing HNF1α transcription factor has been implicated in the modification of plasma N-glycans containing antennary fucose.[53] HNF1α functions as a transcription factor for fucosyl transferases, which encode genes in liver hepatocytes.[51] Fucosylated GP30 plasma glycans were found to be low in MODY patients with detrimental HNF1α alleles.[20] The GP30 is more specific as a biomarker for HNF1α deleterious mutations than hs-CRP (80% vs. 69%).[20]

5. C-peptide and Sulfonylurea

C-peptide, a 31-amino-acid cleavage product of proinsulin, is a widely used parameter for assessing pancreatic β-cell function.[54,55] Because of its slower degradation rate (half-life of 20–30 min) than insulin (3–5 min), C-peptide serves as a stable test parameter for measuring β-cell fluctuations. In contrast to insulin, C-peptide has minimal hepatic clearance but is steadily metabolized in the peripheral circulation, whereas insulin is metabolized and cleared in a variable manner.[56]

The C-peptide is a useful marker for distinguishing MODY patients from autoimmune T1 diabetes.[57] In autoimmune T1 diabetes, residual insulin secretion from pancreatic β-cells is typically observed during the first two years of disease progression and completely disappears after five years, resulting in low C-peptide values, whereas in MODY and T2DM, C-peptide is conserved for a longer time period.[58] Because there is no direct β-cell destruction in MODY, endocrine functioning is still observed after years of disease evolution. As a result, visible serum C-peptide levels outside of the honeymoon phase may be used to diagnose MODY. The random C-peptides obtained 6 months after initial diagnosis aid in the differentiation of antibody-negative patients who require further MODY genetic testing from those who do not, but further confirmation is needed in large population-based studies. In clinical practice, the UCPCR (urinary C-peptide creatinine ratio) is being used as a new biomarker for measuring β-cell function.[13,14] UCPR is used to distinguish MODY 1 (HNF4α-MODY) and MODY 3 (HNF1α-MODY) diabetes from autoimmune T1 diabetes.[59] Besser *et al*.[13,14] (2011) found that the median UCPCR for T1 diabetes was 0.02 nmol/mmol, whereas HNF1/4α patients had a UCPCR of 1.72 nmol/mmol. Their findings demonstrated 96% specificity and 97% sensitivity in distinguishing MODY1/MODY3 from T1D. If diabetes has been present for more than two years, UCPCR 0.7 nmol/mmol is thought to be an effective marker for distinguishing MODY1/MODY3 with 100% sensitivity and 97% specificity.[16] The UCPCR, while effective in distinguishing T1D from MODY, is ineffective in distinguishing MODY and T2D.

Prior to the description of MODY-causing gene mutations, sulfonylurea sensitivity was reported. Sulfonylurea is prescribed to MODY patients regardless of the MODY mutations involved. Bowman *et al*.[60] (2012) reported Sulfonylurea sensitivity in 8% of patients with the ABCC8- MODY12 mutation, but negative results for HNF1α/HNF4α mutations.[60] In their study, Shepherd *et al*.[22] (2018) found that 36% of patients with HNF1α/HNF4α MODY mutations achieved HbA1c 7.5% on diet/Sulfonylurea alone (Shepherd *et al*. 2018).[22] However, sensitivity to Sulfonylurea is not a valid criterion for subject selection for genetic testing.[61]

6. Apolipoprotein M (ApoM) and HDL (High-Density Lipo-proteins)

The *ApoM* gene on chromosome 6p21.3 at the *MHC class III* region encodes the human Apolipoprotein M (ApoM), a 26 kD novel lipoprotein.[62] ApoM shares structural similarities with the lipocalin family and is found primarily in HDL.[62] HNF1α directly regulates ApoM protein expression levels by binding to the promoter region of the *ApoM* gene and activating transcriptional activity through certain conservative sites (103 to 88).[23] HNF1α-MODY patients had significantly lower plasma ApoM levels.[23] Cervin *et al*.,[63] 2010 found that only MODY3 women had 10% lower serum ApoM levels, with no significant differences from T2DM.[63]

Adult T2D is frequently associated with higher plasma triglyceride levels and lower HDL (high-density lipoprotein) levels, a condition known as diabetic dyslipidemia. Lower fasting triglyceride levels have been reported in HNF1α-MODY patients.[64] Sulfonylureas cause insulin exocytosis by directly binding to the SUR1 subunit of KATP channels, causing channel closure. HNF1α-MODY patients have normal HDL levels, just like non-diabetic individuals. When compared to MODY, T2D patients had significantly lower HDL levels.[24] As a result, HDL levels are not particularly effective as a biomarker. Fendler *et al*.[25] (2011), on the other hand, hypothesized the use of HDL as a potential biomarker for differentiating T1D, GCK-MODY, and HNF1-MODY.

Discussion

Insulin deficiency or receptor insensitivity is a critical factor in all types of diabetes. Insulin is the primary hormone that regulates the uptake of glucose from the blood into most cells in the body, particularly the liver, adipose tissue, and muscle[65] [Figure 2]. MODY also has the same insulin action mechanism. The clinical characteristics of MODY are more similar to those of early-onset T2D, making it difficult to distinguish on the basis of clinical diagnostic features. However,

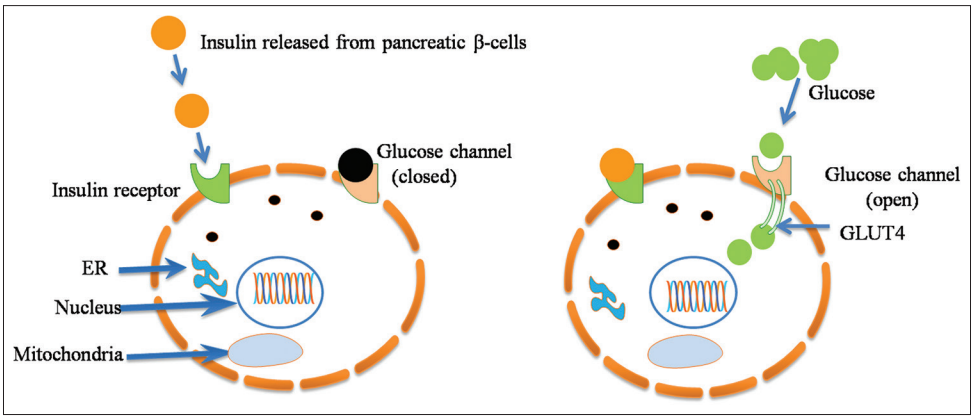

Figure 2: Role of Insulin: The figure depicts the entry of glucose *via* the GLUT4 transporter into the skeletal muscle/adipose tissue cells as a result of the action of insulin released by β-cells. Initially, the glucose channel is closed in the absence of insulin; however, when insulin binds to the cell surface insulin receptor, the glucose channel opens, allowing glucose to enter the cell *via* the GLUT4 transporter and be metabolized *via* the glycolytic pathway. The figure was created by using Motifolio Toolkit (https://www.motifolio.com)

in the absence of clinical signs such as metabolic syndrome, obesity in cases of early-onset diabetes increases the likelihood of having T2D rather than MODY.[64] Obesity, on the other hand, has been reported among young adults and adolescents, linking the occurrence of obesity with MODY as well.[66] However, clinical presentations differ even among subjects with the same MODY subtype or among subjects with different MODY types. The clinical characteristics of HNF1α (the most common MODY type) range from symptomatic hyperglycemia to overt insulinopenia with ketosis and hyperglycemia. HNF1α-positive MODY patients have higher serum ghrelin and HDL levels, as well as lower hsCRP levels, when compared to T1D and T2D patients.[67] GCK-MODY patients have mild fasting hyperglycemia, whereas HNF4α-MODY patients have foetal Macrosomia. HNF1β-MODY subtype is associated with renal diseases and urinary tract anomalies. MODY subtypes differ not only in clinical profiling and distribution, but also in pathophysiology and treatment options, as we discussed in our previous publication.[9] As a result, the clinical manifestations of MODY subtypes differ greatly from one another [Table 2], necessitating the use of accurate clinical-based biomarkers for accurate diagnosis.

Diagnosis and discrimination are critical for disease management, optimizing treatment options, and improving quality of life. The timely diagnosis of MODY is critical for predicting extra-pancreatic features, disease course, and testing relatives (first degree) who are 50% likely to inherit the specific MODY mutation. The personalized drugs may perhaps have a greater clinical impact on disease management, if MODY types might have been discriminated from each other and from other diabetes forms. As a result, identifying subjects with MODY diabetes is critical for ensuring appropriate treatment therapy. The advancement in molecular genetics has led to the introduction of next-generation sequencing (NGS) that efficiently performs the diagnosis and discrimination of monogenetic diabetes. However, the correct diagnosis of MODY is still deferred due to limited knowledge and huge genetic testing expanses. Over the last decade, numerous non-genetic biomarkers have been studied to aid in patient selection for genetic testing analysis. hsCRP is a promising biomarker for distinguishing HNF4α-MODY and HNF1α-MODY from T2 diabetes. There is a need for efficient, inexpensive, and readily available biomarkers that could refine patient selection for genetic testing using clinical details, improving the cost-effectiveness of early diagnosis, treatment options, and overall disease management.

Limitations of MODY Biomarkers

The MODY biomarkers undeniably aid in subject selection for genetic testing in order to avoid expenses and unnecessary treatment options, but they are associated with drawbacks that limit their potential to be used alone for subject selection. These limitations are listed in tabular form [Table 3].

Conclusion

Clinical laboratories are unquestionably transitioning from first-generation genetic analysis to NGS in order to simultaneously analyse patients for a variety of genetic mutations that occur in monogenetic diabetes. NGS panels have the potential to become widely available to patients with further development and adoption. Although molecular diagnostic testing is advantageous, it is critical to identify patients who are more likely to benefit than those whose disease is diagnosed using traditional and less extensive methods. As a result, the ongoing evolution of MODY biomarkers and clinical molecular testing will be reflected in clinical laboratory investigations, improving MODY diagnostic capabilities.

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Table 2: Various clinical manifestations that occur in all 14 known MODY types, as well as their distribution in body tissues

MODY Type	Clinical Manifestations	Tissue Distribution
HNF4α-MODY	Neonatal macrosomia and hyperinsulinemic hypoglycemia	Insulinoma cells
	Low levels of triglycerides and apolipoproteins[68]	Pancreatic β-cells,
	Impaired Glucagon secretion	Intestines
	Microvascular complications particularly in kidneys and retina	Kidneys
	Sulfonyl sensitivity	Liver
	Fanconi syndrome with nephocalcinosis and hypercalciuria in Arg76Trp mutations carriers[69]	
	Fasting hyperglycemia is mild.	Pancreatic β-cells
	It is usually managed through diet and does not necessitate the use of medications.	Liver
	Microvascular complications are less common.	
	There are no additional pancreatic associations.	
HNF1α-MODY	The kidneys and the retina are involved in the macro and microvascular complications caused by defective insulin secretion	Liver Pancreatic islets
	Renal transport impairment, resulting in a lower renal glucose absorption threshold	Kidneys
	Glycosuria	
	Sensitivity to sulphonyl urea	
PDX/IPF-MODY	In the homozygous condition, it causes pancreas agenesis and neonatal diabetes; in the heterozygous condition	Pancreatic β-cells
	It causes mild diabetic complications such as reduced insulin secretion and uncontrolled glucose maintenance	
	Azoospermia, renal cysts, uterine anomalies, and other genital and urinary system malformations	
HNF-1β-MODY	Hyperuricemia	Gut
	Exocrine dysregulation	Thymus
	Anomalies of the female genitalia	Liver
	Males with azoospermia	Lung
	Diabetes management necessitates the use of insulin	Thymus
	It causes renal deformities, such as RCAD (Cystic renal disease)	Kidney
	Birth weight reduced	Bile ducts
	Pancreatic hypoplasia and atrophy	
NEUROD1-MODY	Causes diabetic complications in adults, neonates, and children	Intestines
	Various levels of hyperglycemia are represented	CNS
	Mild to severe microvascular complications, such as proliferative retinopathy and kidney failure, can occur	Neurons Pancreatic Endocrine cells
	Result in neurological abnormalities	
KLF11-MODY	It's similar to T2D	Ubiquitously expressed
	Atrophy of the pancreas	
	Exocrine dysfunction	
	Decreased insulin sensitivity	
	Mild hyperglycemia.	
CEL-MODY	Diabetes with autosomal dominance	Lactating mammary gland cells
	Exocrine and endocrine dysfunction in the pancreas	Pancreas
	Lipomatosis	
PAXA4-MODY	It is extremely uncommon	Embryonic germ cells in mammals
	The occurrence of progressive hyperglycemia	
	Ketoacidosis	
INS-MODY	It is extremely uncommon	Pancreas
	Requires insulin or sulphonylurea for glucose management	Limbs
	Occurrence of diabetes after 20 yrs of age	Eyes
BLK-MODY	Extremely uncommon; increased penetrance with higher BMI	Muscle,
	Some people are obese	Ovary
		Pancreatic islets
		Testis
		Spleen
		Muscle lymphoblastoid cell lines

Contd...

Table 2: Contd...

MODY Type	Clinical Manifestations	Tissue Distribution
ABCC8-MODY	Rare with clinical phenotype similar to HNF1α/HNF4α	Pancreatic β-cells
KCNJ11-MODY	Uncommon	Muscle cells
	Clinical phenotype that is heterogeneous	Pancreatic β-cells
	Neonatal diabetes is caused in homozygote's	neurons
APPL1-MODY	Some patients are Obese/Overweight	Heart Elevated expression in skeletal muscles
	Young-onset diabetes/adult-onset diabetes	Pancreas
		Ovary

Table 3: The limitations of using various MODY distinguishing biomarkers

MODY Biomarkers	Limitations
HsCRP	Inflammatory conditions cause an increase in hsCRP levels.
	Variability varies according to method and laboratory conditions.
	Reduction in hsCRP with the use of certain drugs such as Asprin, Statins, β-blockers, and so on.
C-peptide	Individual to individual variability is high.
	Identifiable C-peptide levels in T1D cases diagnosed before the age of five years
ApoM	Inadequate diagnosis precision.
	The ApoM assays are in extremely short supply.
Sulphonylurea	Sensitivity issues
HDL	Ineffective at distinguishing MODY from T2D.
UCPCR	Ineffective at distinguishing MODY from T2D.
Fucosylated plasma glycans- GP30	Exhibits high sensitivity only in the case of HNF1α MODY and not in other MODY types
Auto-antibodies (IA-2A, IA-2β, IAA)	T1D is distinguished from young-onset diabetes, but MODY is not distinguished from other forms of young-onset diabetes (negative predictive for testing MODY)
GAD65	T1D is only distinguished from other types of young-onset diabetes.

Author contribution

Parveena Firdous, conducted the literature review, conceptualized, prepared and revised the manuscript. Kamran Nissar, peer-reviewed the literature search, provided technical inputs. Shariq Rashid Masoodi and Bashir Ahmad Ganai provided technical inputs throughout the process and critically reviewed the manuscript. All authors approved the final version of the manuscript.

Highlights

- Introduction of MODY
- hsCRP, GAD, IA 2A and IA-2β as discriminatory tools for MODY from T1 autoimmune diabetes
- GP30 as marker of MODY3
- C-peptide and Sulfonylurea sensitivity
- Importance of diagnostic and discriminatory power of biomarkers.

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Conflicts of interest

There are no conflicts of interest.

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